FINAL DECISIONS & REASONS FOR DECISIONS BY DELEGATES OF THE SECRETARY TO THE DEPARTMENT OF HEALTH AND AGEING

MAY 2012

The following delegates' final decisions and reasons on scheduling matters relate to applications referred to

- the February 2012 meeting of the Advisory Committee on Chemicals Scheduling (ACCS) [**ACCS#4**];
- the February 2012 meeting of the Advisory Committee on Medicines Scheduling (ACMS) [**ACMS#5**]; and
- the October 2011 meeting of the Advisory Committee on Medicines Scheduling (ACMS) [**ACMS#4**];

Notice under subsections 42ZXZS 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 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 Regulations. This notice also provides the reasons for each decision and the date of effect of the decision.

Matters referred to ACCS#4 and ACMS#5

Delegates' interim decisions on advice and recommendations from the ACCS#4 and ACMS#5 were published on 26 April 2012, accessible at www.tga.gov.au/industry/scheduling-decisions-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 further public submissions on interim decisions for matters referred to ACCS#4, or ACMS#5 are also available at www.tga.gov.au/industry/scheduling-submissions.htm.

In accordance with subsection 42ZCZR of the Regulations, if a delegate makes an interim decision on an application, that delegate may make a final decision confirming, varying or setting aside the interim decision only after considering any further valid submissions.

Implementation

The SUSMP and its amendments are available electronically at the ComLaw website, a link to which can be found at www.tga.gov.au/industry/scheduling-poisons-standard.htm.

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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
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
INN	International Non-proprietary Name
ISO	International Standards Organization

LC_{50}	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.
LD_{50}	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])
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
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

FINAL DECISIONS ON MATTERS REFERRED TO AN ADVISORY COMMITTEE

1. MATTERS INITIALLY REFERRED TO ACCS#4 – FEBRUARY 2012

1.1 CYFLUFENAMID

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Cyflufenamid – seeking advice on a proposal to capture in Schedule 6.

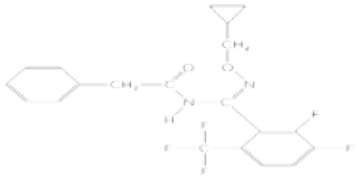
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for cyflufenamid with a cut-off to Schedule 5 for preparations containing 5 per cent or less of cyflufenamid. The Committee also recommended an implementation date of no more than 6 months after delegate's final decision (i.e. 1 September 2012).

BACKGROUND

Cyflufenamid belongs to the amidoxime group of fungicides with activity against all strains of cereal powdery mildew including those resistant to demethylation inhibitor, strobilurin-type and benzimidazole-type fungicides. The mode of action of cyflufenamid was unknown.

The IUPAC name for cyflufenamid is (*Z*)-*N*-[α-(cyclopropylmethoxyimino)-2,3-difluoro-6-(trifluoromethyl)benzyl]-2-phenylacetamide and the structure is:



XXXXX submitted data to the APVMA seeking approval of the active ingredient cyflufenamid and registration of a new fungicide product, XXXXX. The product was proposed to be used in cucurbits and grapes as a protectant fungicide against powdery mildew.

The Office of Chemical Safety (OCS) Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for cyflufenamid. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required.

SCHEDULING STATUS

Cyflufenamid was not specifically scheduled. There were no entries that would capture cyflufenamid as a derivative, nor any group entry that would capture cyflufenamid.

SUBMISSIONS

The OCS Report recommended that, based on the toxicity profile, cyflufenamid be listed in Schedule 6 with no cut-off. Other evaluator's conclusions included:

- The ADI for cyflufenamid was established at 0.03 mg/kg bw/d based on a NOEL of 4.14 mg/kg bw/d in a 52-wk dietary study in dogs, by applying a 0.7* times oral absorption correction factor and a 100-fold safety factor, to account for inter- and intra-species variation. The NOEL was based on elevated alkaline □hosphatise (ALP) levels in both sexes and adrenal vacuolation and hypertrophy in females.
- The ArfD for cyflufenamid was established at 0.07 mg/kg bw, based on the maternal and foetal NOEL of 10 mg/kg bw/d in a rabbit developmental study, applying a 0.7 times oral absorption correction factor and using a 100-fold safety factor to account for potential intra- and inter-species variation. The NOEL was based on decreased body weight gain and food consumption in dams and minor skeletal variations/abnormalities in foetuses.

Toxicology

Absorption, distribution, metabolism and excretion in mammals	
Rate and extent of oral absorption	Rapid absorption. T_{max} = 1–4 h; a minimum of 70% of oral low dose (10 mg/kg bw) absorbed in rats.
Dermal absorption (triple-pack methodology)	1% (5% emulsion-in-water [EW] formulation) human 8% (0.25 g/L dilution of cyflufenamid) human 16% (0.0156 g/L dilution of cyflufenamid) human
Distribution	Extensive in rats. Highest detected concentrations in kidney, muscle, fat, liver, GI tract.
Potential for accumulation	No evidence for accumulation in rats. > 80% elimination in excreta by 24 h after final dose in repeat-dose (14 d) experiment, with essentially complete elimination in excreta 168 h after final dose. Residual dose in rat carcass < 1%.
Rate and extent of excretion	Rapidly excreted in rat; > 95% eliminated in excreta by 48 h after single dose. Higher urinary excretion of radiolabel in males compared to females.
Metabolism	Extensive; numerous metabolites in urine, faeces and bile. Processes involved include hydrolysis, amidine reduction, deamination, di-hydroxylation/methoxy conversion, mono-hydroxylation, cleavage of cyclopropylmethoxy moiety and glucuronide conjugate, cyclisation and isomerisation.
Toxicologically significant compounds (animals, plants and environment)	Cyflufenamid (NF-149); 149-F, 149-F1, 149-F6, 149-F-3-OH-4-OH-B, 149-F-3-OH-B and 149-F-4-OH-B, 149-F4B and associated glucuronide conjugate, 149-F12 and 149-E-FB. Impurities CPMOH and CPCA in cyflufenamid TGAC.
Toxicologically relevant compounds for residue definition	Cyflufenamid (NF-149); 149-F, 149-F1, 149-F6, 149-F11, 149-(E)-FB.

*The evaluator later indicated that there should not be an absorption correction factor on the ADI.

Acute toxicity	
Rat oral LD_{50}	> 5000 (mg/kg bw)
Mouse worst oral LD_{50}	> 5000 (mg/kg bw)
Rat dermal LD_{50}	> 2000 (mg/kg bw)
Rat inhalation 4-hr LC_{50}	> 4760 (mg/m^3)
Skin irritation	Not irritating
Eye irritation	Slight irritant
Skin sensitization	Not sensitising (Guinea pig)
Short-term toxicity	
Target/critical effect	Liver (organ weight changes, clinical chemistry changes, histopathological change [hypertrophy]) across species (rats, mice and dogs). Brain (reversible vacuolation, myelin oedema and thinness in myelin membranes) at high doses (1500 ppm) in dogs. Thymus (involution/atrophy) at high doses (1500 ppm) in dogs.
Lowest relevant oral NOEL	6.5/7.5 mg/kg bw/d (males/females) 13-wk dog study. Based on organ weight and histopathology changes in liver, clinical pathology alternations at higher doses in dogs.
Lowest relevant dermal NOEL	1000 mg/kg bw/d (4-wk rat study) the highest dose tested.
Genotoxicity	Non-mutagenic/genotoxic *in vitro* with and without ±S9, and did not cause genotoxicity or DNA damage *in vivo.*
Long-term toxicity and carcinogenicity	
Target/critical effect	Histopathological changes in kidney (male) and liver (female) in rat. Reduced body weight gain, liver weight increase and histopathological change in liver, heart and lungs in mouse. Adrenal vacuolation and hypertrophy (females) and elevated ALP levels (both sexes) in dogs.
Lowest relevant NOEL	4.14/4.41 mg/kg bw/d (males/females) in dog (1 yr). 62.8/75.5 mg/kg bw/d (males/females) in mouse (78 wk). 4.4/5.5 mg/kg bw/d (males/females) in rat (2 yr).
Carcinogenicity	Thyroid adenoma/carcinoma in male rats at highest dose tested, but of limited relevance to humans. Pancreatic islet cell carcinoma in female mice at highest dose but noting the absence of a clear sequential progression (e.g. over-stimulation leading to hyperplasia through to neoplasm), this marginal finding in one sex is considered likely incidental and not treatment-related. Hepatocellular adenomas in male mice at highest dose. However, compared to the historical control range the observed slight increase in benign liver tumours in males only at the top dose level was seen at a dose level that produced a 25.1% decrease in body weight gain over the study period. Consequently, the observed incidence of benign liver tumours in one sex only were of limited relevance as they were only observed above the historical control range at a dose level substantially exceeding the maximum tolerated dose (MTD).

Reproductive toxicity	
Reproduction target/critical effect	Reproductive parameters unaffected by treatment. Evidence of treatment-related toxicity (increased liver and thyroid weights, decreased body weight gain) observed in both generations.
Lowest relevant reproductive NOEL	Parental NOEL: 250 ppm (18.0/19.9 mg/kg bw/d). Offspring NOEL: 250 ppm (18.0/19.9 mg/kg bw/d). Fertility NOEL: 800 ppm (57.4/65.7 mg/kg bw/d).
Developmental toxicity	
Developmental target/critical effect	Maternal: Decreased food consumption, increased liver weights, decreased body weight gain. Foetal: Increased frequency of minor skeletal variations/abnormalities and delayed ossification above control frequencies.
Lowest relevant developmental NOEL (mg/kg bw/d)	Maternal (rat): 100, Foetal (rat): 1000 (limit dose), Maternal (rabbit): 10, Foetal (rabbit): 10,
Neurotoxicity	No effects. Not neurotoxic in subchronic neurotoxicity study in rats.

Summary	**NOEL (mg/kg bw/d)**	**Study**	**Comments**
ADI (0.03 mg/kg bw/d)	4.14	1-yr dog study (adrenal vacuolation and hypertrophy in females)	0.7 oral absorption correction factor, 100-fold safety factor for inter-/intra-species variation.
ARfD (0.07 mg/kg bw)	10	Rabbit developmental toxicity study (increased skeletal variations/delayed ossification)	0.7 oral absorption correction factor, 100-fold safety factor for inter-/intra-species variation.
NOEL for OHS Risk Assessment (4.55 mg/kg bw)	6.5	13-wk dog toxicity study (organ weight/histopathology changes in liver, clinical pathology changes)	0.7 oral absorption correction factor, 100-fold safety factor for inter-/intra-species variation and for brain vacuolation observed at high doses (> 65 mg/kg bw/d) that was reversible 26-wk after cessation of treatment.

Vacuolation

- In repeat-dose studies in dogs, vacuolation in the brain (identified as myelin oedema under electron microscopy, along with occasional thinness in myelin membranes) was observed at high doses (1500 ppm), but was reversible after a 26-wk recovery period.
- The evaluator raised concerns regarding this vacuolation. Although no neurological or behavioural changes were identified in affected animals the mechanism associated with myelin oedema and thin myelin membrane formation was not identified. While noting that the observed brain vacuolations in a 13-wk dog study were not seen in a 52-wk dog study, (doses administered were possibly not at sufficiently high levels to trigger this endpoint) the brain vacuolation findings were seen at ~70 mg/kg bw/d in a sub-chronic study.
- On the basis of the absence of mechanism together with an extended 26-wk recovery period for reversibility of effects, the delegate sought advice from the ACCS as to whether these effects were of sufficient toxicological significance as to warrant a Schedule 6 listing. The

delegate noted that the brain lesions were reversible (albeit slowly) and were seen at dose levels substantially higher than the NOEL.

Study details

- In a 13 wk sub-chronic dietary study, dogs (4/sex/dose) were administered with 0, 150, 500 or 1500 ppm of cyflufenamid.
- Histopathology revealed treatment-related brain vacuolation in the neuropile near the thalamus and cerebrum at 1500 ppm, vacuolation and enlargement of hepatocytes at ≥ 500 ppm, thymic involution and atrophy at all doses (but considered toxicologically significant at 1500 ppm only) and abnormal spermatogenic cells in 1500 ppm. Additionally, sporadic but possibly treatment-related histopathology findings in the prostate (retardation in acinar development at 150 and 1500 ppm), ovary (arrested follicular development at 1500 ppm), uterus (reduced myometrium/endometrium at 1500 ppm) and cervix (decreased cervical diameter at 1500 ppm) were observed. A NOEL was established at 150 ppm (equivalent to 6.5/7.5 mg/kg bw/d in M/F), based on organ weight, clinical pathology and histopathological changes in the liver of animals at ≥ 500 ppm.
- The evaluator concluded that dogs administered at 1500 ppm presented with clear signs of treatment-related effects and that these effects were toxicologically significant and adverse when considered as a whole. Dogs administered at 500 ppm exhibited a smaller selection of treatment-related symptoms to those observed in 1500 ppm animals. The findings at 500 ppm were considered treatment-related and likely toxicologically adverse, suggesting that the liver was a target organ of toxicity. Dogs administered at 150 ppm presented with higher relative liver weights in females and reduced acinar development in one male. No histopathological changes were identified, and no other treatment-related symptoms were identified in other examined endpoints. While it was possible that the effects described were treatment-related, it was unlikely that the effects were toxicologically significant.
- In a separate chronic study, dogs (4/sex/dose) were administered with 0, 30,120 and 480 ppm of cyflufenamid for 52 wk. A slight increase in the severity of focal vacuolation of the zona glomerulosa in adrenals was observed in male animals administered 480 ppm (~17 mg/kg bw/d). Additionally, a slight increase in the severity of epithelial vacuolar degeneration was observed in male animals administered 120 and 480 ppm. The evaluator considered the vacuolation in zona glomerulosa in adrenals of males administered 480 ppm was unlikely to be treatment-related due to the lack of a dose response and evidence of the finding in control animals at a similar incidence. The evaluator also asserted that the findings of vacuolation in zona glomerulosa in adrenals in a single animal at a severity greater than seen in controls (i.e. moderate) was unlikely to be toxicologically significant.

Carcinogenicity

- Carcinogenicity studies demonstrated an increased frequency of hepatocellular adenomas in mice and thyroid adenomas/carcinomas in rats; however, these neoplastic findings occurred at a defined threshold dose and were considered to be of limited relevance to humans based on the proposed modes of action (non-genotoxic mitogenic stimulation for hepatocellular

adenomas and disruption of the HPT axis-mediated hormonal balance for thyroid adenoma/carcinomas).

Reproductive and developmental

- Cyflufenamid was negative in *in vitro* and *in vivo* mutagenicity and/or genotoxicity studies, and *in vitro* mutagenicity studies using a range of cyflufenamid metabolites and impurities.
- There was no reproductive or developmental toxicity observed at doses that were not maternotoxic.

Product

Toxicity end point	Toxicity of Product
Rat oral	Low toxicity (LD_{50} > 5000 mg/kg bw)
Mouse oral	Low toxicity (LD_{50} > 5000 mg/kg bw)
Rat dermal	Low toxicity (LD_{50} > 2000 mg/kg bw)
Rat inhalational	Low toxicity (LC_{50} > 4410 mg/kg bw)
Rabbit skin irritation	Moderate irritant
Rabbit eye irritation	Slight irritant
Skin sensitisation	Not sensitising

- In a skin irritation study, 6 male rabbits were administered with 0.5 mL of the product. Clear, well-defined, moderate or severe erythema was observed in all test animals for up to 7 d after exposure. At 72 h, 5 rabbits exhibited moderate erythema with one animal exhibiting severe erythema. Very slight to slight oedema was also observed during this period. Desquamation of the *stratum corneum*, evidenced as dryness and sloughing of skin, was also observed in all animals from day 4 (96 h post-treatment). Gradual resolution of these symptoms was observed, with resolution in four animals by d 10 of the study, but slight erythema was still observed at study termination in two animals.
- In an eye irritation study, rabbits (5 males and 1 female), were administered with 0.1 mL of the product. No corneal damage or iridial irritation was observed. Hyperaemia of blood vessels resulting in a diffuse crimson colouration of the conjunctivae was observed in all animals. Increased swelling was observed in one animal. Resolution of symptoms was completed by the 72 h observation. The evaluator indicated that under the conditions of this study the product was a slight eye irritant.
- The evaluator asserted that in the absence of repeat dose studies with the product, no cut-off was applicable. Additionally, the evaluator asserted that the moderate skin irritation seen in rabbits with the product meet Schedule 6 criteria. The evaluator verbally advised the meeting, however, that after further consideration the OCS now supported a low concentration cut-off to Schedule 5 for preparations containing 5 per cent or less of cyflufenamid.
- The delegate sought the ACCS's advice on whether the moderate skin irritancy of the product (noting that irritancy was absent for the active cyflufenamid) was likely to be a function of the formulation excipients, and the impact of such a determination on whether a scheduling cut-off to exempt status was warranted.

- Members agreed that the moderate skin irritant potential of the product could be due to the vehicles present in the product.

Exposure

· The product was intended for professional use only. Bystander exposure would be possible, but would be expected to be limited based on the proposed use pattern and crop targets (grapes and cucurbits). Potential routes of bystander exposure would be dermal, inhalational and ocular during or immediately after a spraying event, while dermal exposure would be the most likely route for re-entry. Adherence to good agricultural practice would minimise potential exposure. The evaluator asserted that risk to the public from accidental exposure from overspray/spraydrift would likely be minimal.
· Farmers and their employees would be the main users of the product. Workers may be exposed to the product when opening containers, mixing/loading, application and cleaning up spills and equipment. In this case, the main route of exposure to the product and diluted spray would be dermal and inhalational, although ocular exposure was also possible during application of the dilute spray.
· The evaluator noted that in the absence of exposure data for the proposed mode of application, the Pesticide Handler Exposure Database (PHED) Surrogate Exposure Guide (1998) was used to estimate potential worker exposure.

MOE* for workers using cyflufenamid when applied to cucurbits

Estimates	Gloves	Mixer/loader dermal	Applicator dermal	Mixer/ loader Inhalation	Applicator Inhalation	Total MOE*
Estimate 1	No clothes	7347	31264	192628	312369	5666
	N	8093	101525	192628	312369	7052
	Y	1005888	103046	192628	312369	52380
Estimate 2	No clothes	183672	1474	4815688	6148	1181
	N	202321	3015	4815688	6148	2002
	Y	25147198	5104	4815688	6148	2787
Estimate 3	No clothes	183672	2687	4815688	73150	2554
	N	202321	20137	4815688	73150	14603
	Y	25147198	56447	4815688	73150	31612

* Based on a NOEL of 4.55 mg/kg bw/d. Estimates are for workers wearing long pants and long sleeved shirt (single layer of clothing), except the 'no clothes' scenario, where no PPE is used. MOE values were based on person of 70 kg bw, 1% dermal absorption factor during mixing/loading, 16% dermal absorption during application, and a 100% default inhalational absorption factor.

MOE* for workers using cyflufenamid when applied to grapes

Estimates	Gloves	Mixer/loader dermal	Applicator dermal	Mixer/ loader Inhalation	Applicator Inhalation	Total MOE*
Estimate 4	No clothes	6334	571	166058	44282	516
	N	6977	3438	166058	44282	2161
	Y	867145	5156	166058	44282	4470

* Based on a NOEL of 4.55 mg/kg bw/d. Estimates are for workers wearing long pants and long sleeved shirt (single layer of clothing), except the 'no clothes' scenario, where no PPE is used. MOE values were based on person of 70 kg bw, 1% dermal absorption factor during mixing/loading, 16% dermal absorption during application, and a 100% default inhalational absorption factor.

- Based on the repeat dose risk assessment for each application method proposed for cucurbits and grapes acceptable Margin of Exposure (MOE) values (>100) were estimated even when the 'no clothes' scenario was selected.

Re-entry and re-handling risk

- The MOE estimate for workers re-entering treated areas to conduct high exposure activities was considered acceptable on day zero after treatment (i.e. MOE > 100) for cucurbits and grapes – for very high exposure activities in grape crops this was 414, while for high exposure activities in cucurbit crops the MOE was 3978.
- However, as the applicant indicated that the product would be used in glasshouses for cucurbit crops, re-entry to these enclosed areas should be restricted until the spray had dried and/or dissipated, and thorough ventilation of the enclosed area had occurred.

Applicant's Response to the Evaluation Report

The applicant was provided a copy of the evaluation report for comments and advised that they did not accept the evaluator's recommendation for a Schedule 6 listing with no cut-off for cyflufenamid. The applicant also indicated that they intended to provide further comments during the public submission period. The applicant specifically noted the following:

- The oral absorption correction factor, which was normally not considered in the calculation of ADI, was considered in the calculation of the 0.03 mg/kg ADI. The ADI would be 0.04 mg/kg (i.e. 4.14/100=0.04) if this absorption correction had not been applied. Asserted that the lower ADI might have an impact in other countries.
- Questioned why all the metabolites were regarded as "toxicologically significant compounds" and requested the definition for estimating toxicologically significant compounds in Australia.
- Indicated that the metabolites proposed as relevant compounds were metabolites which had acute oral toxicity and bacterial mutation result data and questioned why these metabolites were considered as relevant compounds.
- Members noted the issues identified by the applicant to relate to APVMA registration matters rather than scheduling.

Pre-meeting Submissions

Three submissions were received. XXXXX.

XXXXX

Advised that they were aware of the data submitted in the application and argued that this data supported a Schedule 5 classification. Further asserted that cyflufenamid had a unique mode of action for control of diseases in cucurbit and grape crops and that this active would be an invaluable tool for managing fungicide resistance.

XXXXX

Argued in support of a Schedule 5 classification based on the toxicological data and large MOE's in the evaluation report. Noted the evaluation report's moderate skin irritation finding for the product and asserted that the safety directions would be adequate to reduce the dermal exposure of spray operators, thereby minimising the potential for skin irritation.

XXXXX

The applicant provided further comments that were not detailed in the evaluation report i.e. had not had the benefit of being assessed by OCS. Specifically:

ADI

- Noted that the ADI from the OCS report was 0.03 while this was established in the EU and Japan as 0.04. This difference was largely due to the OCS applying an extra 0.7 x oral absorption factor.
- Asserted that an ADI was usually established based on the results of long-term animal studies of repeated dietary administration of a test substance. In the case of several animal studies on different effects, the lowest NOAEL was usually taken. A digestive tract absorption rate was not used for establishment of the ADI, because consumer exposure to residual substance in crops is via the same route as in the animal studies.
- Asserted that a 0.7 oral absorption factor should not be considered in establishing the ADI.

Members again noted that this issue appeared more related to APVMA registration matters than scheduling.

Vacuolation

- Agreed that cyflufenamid caused brain lesions and myelin oedema in dogs, but noted that it did not do so in rats (chronic/ oncogenicity and subchronic neurotoxicity studies) nor mice (oncogenicity study).
- XXXXX.
- Also noted the conclusion of European Food Safety Authority (EFSA):

- In a 90-d dog study, dogs showed brain vacuolation of the white matter of cerebrum and thalamus at relatively high doses (76 mg/kg bw/d). The brain vacuolation did not disrupt neurologic functions and was reversible. The effect was treatment-related as well as duration and dose dependant.
- Cyflufenamid did not cause signs of neurotoxicity in a 90-d rat neurotoxicity study, and vacuolation was absent from a 52-wk dog study.

· Asserted that the above indicated that the observed brain vacuolation issue was not a factor in the scheduling consideration; therefore believed that cyflufenamid best fit the set of factors relevant to Schedule 5.

XXXXX

· XXXXX reviewed available data relating to the neurotoxicology and metabolism of cyflufenamid (up to 2004) which was also independently reviewed by a panel of neurotoxicologists and neuropathologists who considered the potential risk to humans from the intended agricultural use of cyflufenamid.
· The panel also reviewed histopathological slides (including special stains) and electron micrographs of the dog brains. XXXXX.
· The panel also advised whether there were any additional experiments likely to be helpful in understanding the pathogenesis of the lesion and useful in assessing its potential risk to humans. In particular, they considered the scientific value of an autoradiography study with dog brain XXXXX. The panel did not believe that such a study would provide information able to help assess the relevance of the brain lesion to humans.
· The panel concluded:
  - The available data on the nervous system was impressive and well suited to evaluate the neurotoxicity of cyflufenamid.
  - The dog brain lesion was unique in their experience, affecting the oligodendrocytes and causing oedema of myelin in the white matter in certain areas of the brain. Several approaches for exploring its pathogenesis were suggested but these were deemed to represent academic research and do not affect the risk assessment of cyflufenamid. For instance, the panel suggested that it might be worth finding out if cyflufenamid was a carbonic anhydrase inhibitor, since oligodendrocytes show high activity of that enzyme and certain experimental inhibitors have caused white matter damage.
  - There was a clear NOEL for neurotoxicity.
  - Rats and mice were unaffected.
  - XXXXX.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (c) toxicity.

Liver and neurotoxic potential

Members noted cyflufenamid's effect on the liver, such as changes in weight and histopathology, and questioned whether these effects were significant. It was also noted that these effects were common when these occur during detoxification through liver. The Committee agreed these effects were not particularly serious.

Members raised concern regarding neurotoxic potential of cyflufenamid and the use of the substance in commercial situations where repeated application of this substance would be a norm. The Committee noted that as the MOE was 5000, neurotoxicity was not a concern.

Vacuolation

Members agreed that vacuolation was an issue and extensively discussed its effects with regards to scheduling. Members noted that vacuolation was species specific - this was only observed in dogs but not other exposed animals (i.e. rats and mice). It was also noted that affected animals showed significant neuropathological symptoms. It was asserted that this effect was not associated with clinical findings and there were no physical or behavioural changes. Members further noted that vacuolation was observed only at higher doses and that this effect was reversible.

Members noted that European Food Safety Authority and the UK Pesticides Safety Directorate's (PSD) Advisory Committee on Pesticides (ACP) had also considered the vacuolation effect and concluded that while this was a unique effect, vacuolation was not a serious concern. Some Members argued that as cyflufenamid had low acute toxicity and vacuolation was not a serious concern, a Schedule 5 listing for cyflufenamid was appropriate.

Members raised further concerns that the mechanism for the myelin oedema and thin membrane formation was not identified. Similarly the extended recovery period was of concern. Committee Members generally agreed that this uncertainty was sufficient to warrant a Schedule 6 parent entry. Members agreed that since vacuolation was species specific, non-persistent and did not give rise to clinical signs, it did warrant support for consideration of a low concentration cut-off.

Members argued that the data for the product provided sufficient reassurance to allow support for a cut-off to Schedule 5 for preparations containing 5 per cent or less of cyflufenamid. The Committee noted that the vacuolation was only observed at higher concentrations and was not of concern for preparations containing 5 per cent cyflufenamid. The OCS evaluator verbally advised that while a cut-off was not initially considered, further consideration of the data supported a low concentration cut-off to a Schedule 5 for preparations containing 5 per cent or less of cyflufenamid.

Other issues

Members considered the delegate's and applicant's concern regarding the evaluator's use of an absorption correction factor in the calculation of ADI. The Committee agreed that this issue was a regulatory matter that could be explored between the applicant and the APVMA. The evaluator indicated that in general the absorption correction factor was not included in the calculation of ADE and the absorption correction factor was inadvertently included in the calculation of the ADI.

Members noted but did not support alternative resolutions on this matter.

DELEGATE'S CONSIDERATION OF ACCS ADVICE

The delegate noted the ACCS Member's recommendation to include cyflufenamid in Schedule 6 with a cut-off to Schedule 5 for preparations containing 5 per cent or less cyflufenamid. The delegate particularly noted that this recommendation was mainly based on the neuronal vacuolation effect of cyflufenamid seen in dogs. The delegate considered the toxicity profile of cyflufenamid and indicated that apart from its vacuolation effect, cyflufenamid in general had low toxicity potential.

Vacuolation

The delegate noted that ACCS Members extensively considered the neuronal vacuolation effects observed in the brains of dogs. It was noted that some Members concluded that vacuolution was not a sufficiently serious issue to influence scheduling and, based on its otherwise low acute toxicity potential, supported a Schedule 5 listing for cyflufenamid.

The delegate also considered concerns raised by some ACCS Members that there was uncertainty regarding the mechanism and human significance of the neuronal vacuolation effect, especially the myelin oedema and thin membrane formation. The Delegate noted that this concern resulted in the final ACCS advice that a Schedule 6 listing is more appropriate for cyflufenamid. The delegate noted that the neuronal vacuolation effect appeared to be the only concern that led the ACCS to recommend a Schedule 6 listing for cyflufenamid.

The delegate noted the various sub-chronic and chronic toxicity studies indicated that neuronal vacuolation was possibly species specific, with the effect only observed in dogs and not in other exposed animal species. The delegate further noted that in repeat-dose studies in the dog, vacuolation in the brain was observed at high doses, but was reversible after a 26-wk recovery period and that the vacuolation was not observed in the longer 52-wk dog study. The delegate further noted the ACP's and EFSA's view that the neuronal vacuolation seen in dogs was not of significant toxicological concern for humans. The delegate therefore decided that vacuolation was not concern to warrant a Schedule 6 entry for cyflufenamid and decided to set-aside the ACCS recommendation. Based on the overall toxicology profile of cyflufenamid, the delegate determined to list cyflufenamid in Schedule 5.

The delegate agreed the ACCS recommendation for an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012) was appropriate.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate has decided to create a Schedule 5 entry for cyflufenamid. The delegate also decided an implementation date of no more than six months after the delegate's final decision (i.e. September 2012).

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to include cyflufenamid in Schedule 5.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACCS;
- scheduling factors for inclusion in Schedule 5[1]; and
- section 52E of the *Therapeutic Goods Act 1989*.

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

The final decision to schedule cyflufenamid in Schedule 5 included the following reasons:

- the toxicity profile of cyflufenamid is consistent with that of a substance listed in Schedule 5.
- Although neuronal degeneration was observed in some of the dog studies (but not all), it lacked a definitive mechanism. The significance of these findings for scheduling purposes was therefore questionable.
- No other studies showed significant neuronal toxicity, along with the submissions made about the relevance of this toxicity to humans, the ACCS advice and recommendation to list cyflufenamid in Schedule 6, with a cut-off to Schedule 5 for preparations containing 5% or less was not accepted.

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

- Cyflufenamid is intended to be included in pesticide products whose use will be regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA).
- The APVMA regulatory process will complement the labelling and access controls associated with listing flonicamid in Schedule 5.
- A scheduling cut-off from Schedule 5 was not considered appropriate given the likely similarity of the toxicological profiles of cyflufenamid and its proposed products.

SCHEUDULE ENTRY

Schedule 5 – New entry

CYFLUFENAMID

1.2 DIETHYLPHTHALATE AND DIMETHYLPHTHALATE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Diethylphthalate (DEP) and dimethylphthalate (DMP) – seeking advice on a proposal to consider scheduling when used in leave-on cosmetics. Particular consideration will be given to the recommendation from the National Industrial Chemicals Notification and Assessment Scheme's (NICNAS) DEP priority existing chemical assessment report to prohibit more than 0.5 per cent of DEP in body lotion type use pattern, i.e. longer duration leave-on preparations that might be applied to large areas of skin, through inclusion in Appendix C. A copy of the NICNAS DEP report is accessible at www.nicnas.gov.au/Publications/CAR/PEC/PEC33.asp. In addition to the NICNAS recommendations, consideration might also extend to introducing a parent entry for DEP (such as in Schedule 6 or Schedule 7) and whether the current parallel scheduling of DEP and DMP (in Appendix C) should be maintained. As DMP was not addressed in the NICNAS DEP report, comment was particularly sought from industry on existing DMP usage in leave-on cosmetics.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that body lotion preparations for human use containing more than 0.5 per cent diethylphthalate or dimethylphthalate be added to the existing prohibited uses in the respective Appendix C entries for diethylphthalate and dimethylphthalate. The Committee recommended an implementation date of within 6 months of the delegate's publication of final decisions (i.e. 1 September 2012).

BACKGROUND

DEP and DMP are members of the phthalic acid chemical group known as phthalates.
DEP has been use as a solvent and/or vehicle for fragrance in perfumes, cosmetics, personal care products and nail polishes, as well as an alcohol denaturant in toiletries, detergents and insecticides. DEP has also been used as a plasticiser in plastic tools, automotive parts, tooth

brushes, food packaging and medical tubing as well as in soft plastic toys and child care articles. It has also been used in non-polymer uses such as dye application agents, adhesives and sealants. DMP shares many of the properties of DEP, although there is some variability in use pattern (e.g. DEP is used more frequently in cosmetics than DMP).

DEP and DMP were two of nine phthalates that the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) declared as Priority Existing Chemicals (PEC) for public health risk assessment in March 2006. The decision for declaration was based on:

- ubiquitous use of phthalates as solvents and plasticisers in industrial and consumer products;
- consumer products being potentially significant sources of repeated and long-term exposure of the public through their use in cosmetic and personal care products and toys;
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from exposure; and
- current overseas activities including reassessment and review of the use of phthalates in certain consumer products.

NICNAS referred a recently completed DEP PEC Report which contained a scheduling recommendation (a NICNAS PEC Report on DMP has yet to be completed). A delegate agreed that this was a matter for scheduling consideration and that advice from the ACCS was needed. In referring this matter to the ACCS, the delegate:

- Noted the existing DEP and DMP Appendix C exemption cut-offs (0.5 per cent) and sought ACCS's advice on whether the exposure associated with the proposed use pattern for leave-on body lotions would be sufficiently similar to exposure associated with sunscreens or personal insect repellents as to warrant retention of a cut-off at 0.5 per cent.
- Sought advice on appropriate wording for any amendment to the Appendix C entry that would give effect to restricting only cosmetic uses that could involve large-scale application to the human body.

Relevant previous scheduling considerations

In August 2000, the National Drugs and Poisons Schedule Committee (NDPSC) considered the scheduling of DMP as a result of an APVMA application to register a personal insect repellent. The NDPSC noted with concern effects on the development of male offspring exposed to DMP in late gestation or during puberty. In considering this matter, the NDPSC was informed that because of the lack of toxicity data on DMP, toxicity data on DEP had been drawn upon. The NDPSC decided to foreshadow inclusion of DMP in either Schedule 7 or Appendix C.

In May 2001, the NDPSC foreshadowed entries in Appendix C for DMP and DEP when used in sunscreens or personal insect repellents for human use. This would exclude the bulk of cosmetic products for which there was no concern.

In August 2001, the NDPSC confirmed that sunscreen and insect repellent products containing DMP and DEP were of concern as a substantial amount could be repeatedly and directly applied to large areas of the skin for an extended period. The NDPSC considered whether a cut-off limit could be set to allow for low, incidental concentrations in products. Members were advised that application of a 10-fold safety factor to the NOEL resulted in a lower value of 5 mg/kg bw/d for short-chain phthalates and that exposure at or below this level was unlikely to present a risk. It was therefore suggested that 0.5 per cent would be an appropriate cut-off as the systemic exposure of children from preparations containing 0.5 per cent or less of DEP or DMP when applied to the skin was unlikely to exceed 5 mg/kg bw/d. The NDPSC recognised that this was a conservative approach, but agreed that a cut-off of 0.5 per cent was appropriate.

SCHEDULING STATUS

DEP and DMP in sunscreens or personal insect repellents for human use are listed in Appendix C with a low concentration exemption cut-off of 0.5 per cent.

SUBMISSIONS

Application

The NICNAS PEC Report indicated that measures were needed to minimise the risk of reproductive effects of DEP in adults and children. NICNAS therefore recommended listing DEP in body lotion preparations at greater than 0.5 per cent in Appendix C as this should limit public exposure, particularly young children. This recommendation was based on the following findings from the PEC report:

- There was widespread use of body moisturisers in infants or young children who were considered sensitive to DEP-induced reproductive toxicity. This toxicity may have serious long-term health effects if the exposure to DEP was high and within a critical window of development.
- A cautious approach to the potential risks was warranted, given the level of uncertainty regarding both health effects and the levels of exposure for different population groups.
- Margin of Exposure (MOE) calculations indicated that use of 0.5 per cent or less of DEP in body lotions would be protective for the public, particularly young children.

DEP Toxicology

Absorption and distribution

- DEP was rapidly and almost completely absorbed following oral or inhalation exposure. No information was available concerning differences in oral absorption between adult and immature animals or between animals and humans. Bioavailability of 100 per cent was assumed for these routes.
- Bioavailability via dermal absorption was not likely to exceed 10 per cent.

- Tissue distribution was widespread including foetal tissues but there was no evidence of accumulation. DEP was rapidly metabolised and excreted, predominantly via the urine with monoethyl phthalate (MEP) as the main metabolite.

Acute toxicity

Acute toxicity	
Rat oral LD_{50}	> 5600 – 31000 mg/kg bw.
Rabbit oral LD_{50}	1000 mg/kg bw.
Rat dermal LD_{50}	> 11000 mg/kg bw.
Guinea pig dermal LD_{50}	3000 mg/kg bw.
Rat inhalation LC_{50}	7.5 mg/L.
Mouse inhalation LC_{50}	4.9 mg/L.
Rat skin irritation	Slight irritant.
Rabbit eye irritation	Slight irritant.
Skin sensitization	Non-sensitiser (Magnusson and Kligman method).

- DEP had low acute toxicity via all routes and low skin and eye irritation potential. There were case reports of sensitisation to perfumes and plastic articles in patients with dermatitis and other skin diseases although DEP was not considered a skin sensitiser. Members noted that the oral LD_{50} value in rabbits (1000 mg/kg bw), aligned with a Scheduling Policy Framework (SPF) Schedule 6 factor. Members noted that there was no discussion in the PEC report to reconcile this rabbit LD_{50} value with the conclusion that DEP had low acute toxicity.

Repeat toxicity

- Repeated exposure to DEP in rodents caused increased liver and stomach weights in a 16-wk dietary exposure study.
- A weak association between liver toxicity and peroxisome proliferation had been reported for DEP in some studies, but the mechanism for digestive organ enlargement was not confirmed in the critical 16-wk study. The evaluator concluded that these effects could not be excluded from consideration and were relevant to humans for the risk assessment. A conservative NOAEL of 0.2 per cent in the diet (150 mg/kg bw/d) was established based on dose-dependent increased relative liver weight in females and increased stomach weight in males at 1 per cent in the diet (LOAEL of 750-770 mg/kg bw/d).

Genotoxicity and carcinogenicity

- Available data did not support a genotoxic or carcinogenic potential for DEP.

Reproductive and developmental

- Reproductive toxicity associated with DEP had been examined in multigeneration studies in rats and mice, in studies on testicular function, in prenatal and postnatal developmental toxicity studies, and in studies on possible modes of action.
- DEP did not appear to be a potent testicular toxin in animal studies. Evaluations of potential DEP toxicity to the developing male rat reproductive system had consistently found no effect on testis weight or testis morphology at doses up to 1016 mg/kg bw/d. However, reduced testosterone production and altered Leydig cell ultrastructure following DEP exposure had been reported.
- In a critical two-generation study, reduced testosterone levels were observed in F0 male rats at a dose of 197 mg/kg bw/d. In addition, there was a slight but statistically significant dose related increase in the frequency of abnormal and tailless sperms in the F0 and F1 generations, although there was no effect on fertility. Based on this study, a NOAEL of 40 mg/kg bw/d was established.
- There was no evidence of foetal or neonatal toxicity after perinatal exposure to DEP at oral doses up to 3200 mg/kg bw/d. None of the effects observed with transitional phthalates (C4-6 backbone) were noted. However, decreased pup weight at weaning and developmental delay (delayed onset of vaginal opening and pinna detachment) were reported in high dose rats in the critical two-generation study. The NOAEL for developmental effects was 197 mg/kg bw/d. The NOAEL for maternal liver and kidney effects was 197 mg/kg bw/d.
- In other prenatal exposure rat studies at 3200 or 5600 mg/kg bw/d, an increased frequency of skeletal variations such as rudimentary cervical and/or lumbar ribs was reported, although these effects generally occurred at or above maternally toxic doses. The increase in supernumerary ribs (either cervical or lumbar) was one of the common anomalies seen in developmental toxicity studies in rodents. In view of the lack of conclusive evidence to assign the skeletal defects to maternal toxicity, these skeletal variations in rodents were interpreted as indicative of slight developmental effects.
- Available epidemiological studies did not provide sufficient evidence for a causal relationship between exposure to DEP (measured as urinary MEP) and possible health effects.
- Overall, elements of a plausible mode of action for the effects of DEP on the developing male reproductive system (e.g. reduced testosterone and sperm levels and sperm quality) were considered likely to be paralleled in rats and humans if the exposure level of DEP was high enough and within a critical window of development.

Human studies

- When human sperm suspensions were incubated with DEP (33, 330, 3300 μmol/L), sperm motility was dose-dependently decreased with a statistically significant difference from the control (approximately 10 per cent) observed at 3300 μmol/L.
- In a 2-wk single-blind study, 26 healthy young men were given one wk of daily whole body topical applications of a cream containing 2 per cent DEP vs. a similar 1-wk application of

vehicle cream. There were no statistically significant differences in serum levels of reproductive or thyroid hormones.

- A statistically significant negative correlation between semen DEP levels (0.64 to 3.11 μg/mL) and sperm concentration was reported in a population of 300 healthy men from rural/urban areas in India. Other measured parameters such as sperm motility, abnormal sperm, depolarized mitochondria, reactive oxygen species, lipid peroxidation and DNA fragmentation index showed no correlation with DEP.

Exposure and Risk

The physiochemical properties of phthalates that impart usefulness as plasticisers also permit their migration and leaching from polymer materials. The potential for leaching from plastics and a variety of consumer products, including cosmetics, together with reproductive toxicity profile of phthalates in general, have led to concerns over the potential for health impacts from exposure to DEP.

Public health risks from DEP exposure were assessed using an MOE approach for two exposure scenarios:

- use of toys and child care articles by children; and
- use of cosmetic products by the general population.

NICNAS advised that the uncertainties inherent in the characterisation of risk for DEP uses (discussed below) arose mainly from inadequate data and included:

- absence of DEP-specific data for migration from polyvinyl chloride (PVC);
- absence of Australian-specific data on children's mouthing behaviours and DEP content in toys and child care articles;
- Australian data on the use patterns of consumer products were not available to allow a precise exposure assessment for cosmetics – conservative plausible assumptions such as daily use of all cosmetics containing DEP were used;
- there was a high degree of uncertainty associated with cosmetic exposure estimates in newborns and infants, as it was not known whether DEP was being used in baby lotions or creams – it was possible that general moisturisers may also be used in newborns and infants;
- information related to use pattern and/or DEP levels in personal care products for babies and children was not available;
- the significance of the observed toxicity in animals, particularly the reproductive effects, to the human population; and
- lack of adequate epidemiological studies for determining the health effects of DEP in children following repeated exposure.

Exposure from toys and child care articles

- Two routes of exposure of children to DEP were considered – dermal exposure during normal handling of toys and child care articles and oral exposure during mouthing, sucking and chewing of these products.
- Studies conducted overseas indicated that children's mouthing behaviour, and therefore the potential for oral exposure, was maximal in the period between 6 and 12 m of age.
- Given the low acute toxicity, low eye and skin irritation and sensitising potential for DEP, the risk of adverse acute effects for children arising from handling toys was negligible.
- Health risks for children were estimated for both systemic toxicity and reproductive/developmental effects, both of which are potentially associated with repeated handling and mouthing of toys containing DEP. The MOEs were derived by comparing the dose at which no adverse effects were observed in experimental systems (the NOAEL) with the estimated internal DEP doses for children. In both cases, the risk estimates for DEP-induced effects on the liver, stomach and the reproductive system derived MOEs above 10,000 for both the worst-case and typical exposure scenarios of toy use by children. MOE greater than 100 in risk characterisation is usually regarded as an indication of low concern.
- The evaluator concluded that the risk of DEP-induced adverse effects from the use of toys and child care articles by children was negligible.

Cosmetics

- The main route of exposure to DEP from use of cosmetics in the general population was through dermal contact. Inhalation exposure was also possible from products applied as aerosols. Information did not indicate use of phthalates in products most prone to accidental oral ingestion such as toothpastes, mouthwashes, lipsticks and lip-glosses.
- Depending on the type of product, dermal contact with cosmetics and personal care products could be limited to specific areas of the body or it could be more extensive, covering large areas of the trunk as well as the face. In the absence of Australian specific data, a worst-case exposure scenario of daily use of combined cosmetic products was derived based on European use patterns of cosmetics.
- Given the low acute toxicity, low irritation and sensitising potential for DEP, the risk of adverse acute effects for consumers exposed to DEP through cosmetics was very low.
- The potential risks from cosmetic use were related to long-term exposure through repeated use, especially of leave-on products. The internal dose of DEP from daily use of various DEP-containing cosmetic products was estimated to be 285 µg/kg bw/d, considering a "worst-case" scenario of daily use of all cosmetic products.
- The MOE derived for general systemic toxicity was greater than 500 indicating low concern in the general population from daily use of combined cosmetic products containing DEP.
- The MOE for reproductive effects for the general population in the reasonable worst-case scenario was 140, which indicated an adequate safety margin.
- The health risk to children (12 months or under) was estimated from use of personal care products containing DEP applied over large areas of the body. Based on the estimates for use of body lotions or moisturisers containing 0.25 per cent DEP (the maximum level

reported in Australia), the MOE derived for reproductive toxicity was 400 (average), which indicated an adequate safety margin.

- The only area of potential concern identified for both adult and children's use of cosmetics was in relation to the use of body lotions or moisturisers. For adults, 0.5 per cent DEP in body lotions would reduce the MOE for reproductive toxicity in the reasonable worst-case scenario from 140 to 118 which was still an adequate safety margin. For children, 0.5 per cent DEP in body lotions would reduce the MOE for reproductive toxicity from 400 to 200, which was an adequate, albeit reduced, safety margin.

Calculated MOE in the general population for critical health effects of DEP from estimated aggregate exposure to cosmetic products

Toxicity endpoints	NOAEL mg/kg bw/d	MOE for reasonable worst-case exposure scenario
Reproductive (effects on testosterone & sperm)	40	140
Repeated dose (liver & stomach effects)	150	526

Calculated MOE in the general population for reproductive effects (reduced testosterone and abnormal sperm) from estimated aggregate exposure to cosmetic products

Varying concentrations of DEP in body lotions				
	#0.25%	0.5%	0.75%	1%
$D_{int,derm}$ (μg/kg bw/d)	252.7+32.4	306.3+32.4	359.8+32.4	413.4+32.4
MOE	140	118	102	90

#upper limit of DEP reported for body lotions in Australia.

- Overall, the risk estimates for general systemic toxicity indicated low concern for both children and the general population from use of cosmetic products containing DEP at the current reported levels. The risk estimates for reproductive / developmental toxicity also indicated low concern even though the MOEs were lower for these endpoints. A note of caution was identified in relation to the use of one type of cosmetic products used in infants or young children, namely, body lotions or moisturisers, where an increase in the DEP content above 0.5 per cent could reduce the safety margin to unacceptable levels.

Cumulative exposure

- The effect of cumulative exposures could arise from use of cosmetics containing multiple phthalates acting on the same biological targets, from the effects of other components in a mixed phthalate used in toys and child care articles, and from combined exposure scenarios or multiple sources.
- Risks from cumulative exposure to DEP and DEHP for the two scenarios (toys and cosmetic use) was not likely to be higher than that for DEP alone as risk management measures have been implemented for use of DEHP in toys and cosmetics.

International controls

Europe

- In March 2007, the European Commission's Scientific Committee on Cosmetic Products and Non-food Products (SCCNFP) was requested to review the safety of phthalates (including DEP) in cosmetic products. The SCCNFP's opinion was that new studies on DEP published later than 2003 did not provide sufficient new information to change previous safety assessment of DEP in cosmetics such that:
  - DEP has been registered with the European Chemicals Agency with no additional authorisation required for continual use; and
  - DEP was not listed in Annex 1 of Dangerous Substances Directive 67/548/EEC, relating to the classification, labelling and packaging of substances and mixtures.

US

- DEP was not subject to any restrictions for use in toys, child care articles or cosmetics. DEP was not included in the US Enviromental Protection Agency's (US EPA) 2009 phthalate action plan. However, DEP was included in a screening-level hazard characterisation of Phthalate Esters Category released in 2010 under the US EPA High Production Volume Challenge Program.
- The US Consumer Product Safety Commission was reviewing the potential effects on children's health of all phthalates and phthalate alternatives used in children's toys and child care articles, including DEP. Reports over the next 18 m will determine whether to continue an interim ban on DINP, DIDP, and DnOP; and whether additional bans on phthalates or phthalate alternatives were needed. The phthalates' endocrine disrupting effects and the cumulative effects of exposure to multiple phthalates from all sources, including personal care products, would also be examined.

Canada

- In Canada, DEP was considered to be of moderate priority for further work following Canada's 2008 categorization of approximately 23,000 substances on its Domestic Substances List.

XXXXX

DMP

- The public health risk posed by DMP had not been assessed by NICNAS and there was currently no data available to XXXXX upon which to base any DMP scheduling recommendations.
- It was recommended that consideration of scheduling DMP for use in body lotion be deferred until NICNAS undertook a full health risk assessment for DMP – planned to commence during 2012.

February 2012 Pre-meeting Submissions

A submission was received from XXXXX which advised that:

- XXXXX had received feedback from XXXXX on the use of DEP and DMP in cosmetic products indicating that these substances were not being used in Australia XXXXX.
- Feedback from XXXXX international XXXXX indicated that DEP and DMP were important solvents for certain types of products.
- Reiterated the point from the PEC Report that in the EU, there were no limitations on the use of either DEP or DMP in cosmetics. Noted that the latest Scientific Committee on Consumer Products (SCCP) opinion on DEP and DMP use concluded that the use pattern for these substances did not indicate a risk to the health of consumers (http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_106.pdf).
- While XXXXX indicated that they were not currently using DEP or DMP in their products, as products containing DEP and DMP were available in the EU, these products might be considered for future import.
- Requested that the Committee consider the international uses of these substances and future potential uses in Australia.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

Members generally agreed that the NICNAS PEC Report had raised sufficient concerns as to warrant the prohibition of some uses of DEP. While there were few current international controls, Members generally agreed that this probably reflected the low level of use in existing products rather than any active endorsement that DEP was not of concern.

Several Members, while agreeing with the need for some type of control, noted the broad use of DEP and the potential for large unintended regulatory impact. Members therefore focused on developing scheduling specific to the identified risk through discussion of several issues: scope; parent entry; cut-off; DMP; and implementation. Members also noted, but did not support, alternative resolutions on this matter.

Scope

Members questioned whether any scheduling should be specific to body lotions, or whether the identified concern should be more broadly reflected i.e. application of longer duration leave-on preparations to large areas of an infant's skin. Members noted that this was not a clear cut issue, and that any entry would need to balance capture of concerning products with the need to avoid or minimise unintended regulatory impact. The challenge was capturing the right set of products.

A Member noted that it was not exactly clear what products needed to be captured. While the NICNAS PEC Report articulated the concern from all over body use in infants, it did not provide specific examples of products. Industry input had also indicated little use in Australian products of this type. Another Member noted that trying to word a schedule entry with a condition such as 'intended for application to large areas of skin' would raise some interpretation and enforcement challenges for authorities.

Members generally agreed that a specific entry, rather that a descriptive entry, would be more appropriate. A Member was concerned, however, that if the wording were limited to 'body lotions', people might try to avoid the scheduling intent by referring to their product as a body cream/ointment etc. A Member noted that DEP could potentially be in nappy rash creams or in a perfume or deodorising product or solid fragrance intended for use on infants. A Member also noted some rinse-off or volatile products had higher concentrations of DEP and that some nail polishes had significant DEP content.

A Member noted that the matter was somewhat simplified by recalling that the concern was use on infants, and than many personal and cosmetic products were unlikely to be for all over body use in infants e.g. nail polishes. Similarly, the concern was linked to a long duration of exposure i.e. not concerned with use in perfumes or similar volatile products.

Members noted that products intended for large areas of skin were likely to be lotions, or sufficiently lotion like, that it would be clear that they would be captured by intent of the scheduling entry if the term 'body lotion' were used. A Member also noted that having a specific prescriptive list of uses (creams, gels, ointments etc) might be more problematic for enforcement than just a simple reference to 'body lotions'. It was argued that a simple 'body lotion' reference would provide better flexibility for authorities to enforce the intent of the prohibition. Members agreed, noting that if it eventuated that a particular concerning use was not captured, the matter could be reconsidered at that time.

Parent entry

Members noted that the reproductive and developmental toxicity potential of DEP raised concern as to whether the broader use of DEP required scheduling in addition to specific controls on body lotions. One such suggestion, as set out in the delegate's proposal, was for a Schedule 6 or 7 parent entry.

A Member recalled the DEHP consideration (item 1.3, June 2011 reasons for delegates' decisions), which prohibited all cosmetic use of DEHP. Under that consideration process the ACCS advised the delegate that a parent entry for other uses was not necessary. While the hazard from undiluted DEHP (industrial use) may be indicative of a Schedule 7 entry, there appeared little actual risk necessitating scheduling action.

The Member noted that the toxicity of DEHP (significant reproductive toxicity concerns) was significantly higher than for DEP and that this provided some reassurance that a DEP parent entry would not be necessary.

Another Member noted that a larger population will be exposed to DEP than DEHP (given the prohibition from use of DEHP in cosmetics). Several Members argued that no particular broad risk had been identified and that imposing significant potential regulatory impact without such a concern would not be warranted. The Committee generally agreed that the need for a broad parent entry had not been established in the evidence tabled.

Cut-off

A Member noted that consideration of whether a cut-off would be appropriate relied largely on the NICNAS analysis of exposure, crucial for determining the low concentration risk. The Member asserted that the existing cut-off, 0.5 per cent, appeared consistent with the NICNAS exposure models. The Member noted that even with highly conservative assumptions, the NICNAS calculated MOEs exceeded 100 and that large safety margins were therefore built into proposed 0.5 per cent cut-off.

A Member queried whether the calculated MOEs had taken into account the potential for cumulative effects with other phthalates. Another Member noted that while combined effects may add to toxicity, it was reassuring that the biological monitoring data indicated a lower exposure than the conservative modelling, even though the biological monitoring would be expected to be somewhat upwardly skewed by environmental exposure to other phthalates. The Member commented that this suggests 0.5 per cent was an appropriate cut-off. Another Member agreed, noting that the degree of conservative assumptions might even suggest that the cut-off could safely be increase above 0.5 per cent.

A Member noted from the NICNAS PEC Report that body lotion type products in Australia appeared to contain less than 0.25 per cent DEP, so there should be little regulatory impact from setting a cut-off at 0.5 per cent. A Member queried, given the lack of concerning product on the Australian market, whether there was any risk actually being addressed by the proposed Appendix C entry. Several Members noted that there did appear to be products of this type available overseas containing higher levels of DEP that would be appropriately prohibited should import attempts be made.

Similarly, without scheduling, there would be nothing to prevent future Australian body lotions being formulated with a higher DEP content.
The Committee therefore supported extending the existing 0.5 per cent low concentration cut-off from Appendix C to body lotions.

DMP mirror scheduling

Members discussed that further scheduling of DMP wait until the completion of a NICNAS PEC Report. Several Members noted that the original scheduling of DMP drew on DEP data, and for consistency there was no benefit from delaying scheduling of DMP.

A Member noted that it was possible that any future NICNAS DMP PEC Report would end up relying on the read across of DEP data, so it was not a concern if DMP were scheduled in conjunction with DEP ahead of any NICNAS DMP PEC Report.

Implementation

Members considered whether a deferred implementation date might be warranted due to possible regulatory impact. A Member reiterated that there did not appear to be any existing Australian products which would be affected. The Committee agreed that there was no need for an extended implementation date.

DELEGATE'S CONSIDERATION OF ACCS ADVICE

The delegate concluded that the advice of the ACCS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012) was appropriate.

The delegate agreed that relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits of the substance; (b) purpose; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate has decided that body lotion preparations for human use containing more than 0.5 per cent diethylphthalate or dimethylphthalate be added to the existing prohibited uses in the respective Appendix C entries for diethylphthalate and dimethylphthalate. The delegate also decided an implementation date 1 September 2012.

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to amend the existing Appendix C entries for diethylphthalate and dimethylphthalate to include body lotion preparations for human use containing more than 0.5 per cent.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

· advice and recommendations from the ACCS;

- scheduling factors for inclusion in Appendix C[2]; and
- section 52E of the *Therapeutic Goods Act 1989*.

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

The final decision to amend the existing Appendix C entries diethylphthalate and dimethylphthalate included the following reasons:

- concentrations of dimethylphthalate above 0.5% in leave-on cosmetics could represent a health risk. Inclusion of such products in Appendix C is an effective control mechanism to prevent the use of dimethylphthalate in leave-on cosmetic products, consistent with the previous restriction on use for humans in sunscreens and insect repellents.
- Reproductive toxicity is the toxic effect noted in animal studies that drives the risk assessment. The risk assessment indicated that a cut-off at 0.5% provides an adequate margin of exposure estimate for the uses specified in the Appendix C amendment.
- The ACCS recommended that a similar Appendix C restriction be placed on the related substance, namely dimethylphthalate given the overlap in the toxicological profiles of diethylphthalate and dimethylphthalate, and that some of the toxicity data used to support the original Appendix C entries were based on this overlap in toxicity profile.

SCHEDULE ENTRY

Appendix C – Amendment

DIETHYLPHTHALATE – Amend entry to read:

DIETHYLPHTHALATE in sunscreens, personal insect repellents or body lotion preparations for human use **except** in preparations containing 0.5 per cent or less of diethylphthalate.

DIMETHYLPHTHALATE – Amend entry to read:

DIMETHYLPHTHALATE in sunscreens, personal insect repellents or body lotion preparations for human use **except** in preparations containing 0.5 per cent or less of dimethylphthalate.

1.3 FLONICAMID

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Flonicamid – seeking advice on a proposal to capture in Schedule 6 or Schedule 7.

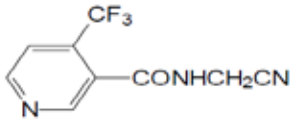
[2] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a new Schedule 6 entry be created for flonicamid with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012).

BACKGROUND

Flonicamid belongs to the nicotinoid class of insecticides. It is a novel systemic insecticide with selective activity against hemipterous, such as aphid and whitefly, and thysanopterous pests. The IUPAC name of flonicamid is ***N***-cyanomethyl-4-(trifluoromethyl)nicotinamide and the structure is:



XXXXX submitted data to the APVMA seeking approval of the active ingredient flonicamid. XXXXX.

The Office of Chemical Safety (OCS) Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for flonicamid. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required.

SCHEDULING STATUS

Flonicamid was not specifically scheduled.

INITIAL SUBMISSIONS

Application

The OCS Report recommended that, based on the toxicity profile, flonicamid be listed in Schedule 6 with no cut-off. Other conclusions included:

- The ADI for flonicamid was established at 0.01 mg/kg bw/d based on a NOEL of 10 mg/kg bw/d established in an 18-m mouse study and using a 1000-fold safety factor to account for potential inter- and intra-species variation as well as the severity of the critical health effect (pulmonary tumours).
- The ARfD was 0.025 mg/kg bw, based on a NOEL of 2.5 mg/kg bw established in a rabbit developmental study for developmental toxicity and using a default of 100-fold safety factor to account for potential inter- and intra-species variation.
- The submitted toxicology data on flonicamid was extensive and comprehensive. The data included studies on toxicokinetics/metabolism, acute, short-term, subchronic, chronic and

carcinogenicity (two species), reproduction and developmental studies, neurotoxicity and genotoxicity studies.

Toxicology

Absorption, distribution, metabolism and excretion in mammals	
Rate and extent of oral absorption	Rapid and extensive > 80 % within 24 h in the rat. T_{max}= 20-40 min at low dose (2 mg/kg) and 20-60 min at high dose (400 mg/kg) in the rat.
Dermal absorption	No data provided. Noting the molecular weight and Log $P_{ow,}$ a default 100% absorption will be assumed in the absence of data.
Distribution	Extensive in most tissues 30 min following administration to rats, with highest concentrations in the liver, kidneys, adrenals, thyroid and GI tract.
Potential for accumulation	No evidence for accumulation in rats.
Rate and extent of excretion	In rats, rapidly excreted in urine (approx 75-90%) within 24 h, faeces (approx 3-5%) within 48 h and low bilary (approx 5%).
Metabolism	In the rat, proceeds by nitrile and amide hydrolysis, N-oxidation, hydroxylation of pyridine ring. Main component in urine, faeces and bile: IKI-220 (up to 70% administered dose); main metabolites in the urine and bile: TFNA-AM (up to 27% administered dose); minor metabolites: TFNA and conjugates, TFNG-AM, TFNA-AM N oxide conjugate, OH-TFNA-AM, TFNG.
Toxicologically significant compounds (animals, plants and environment)	Parent compound.
Toxicologically relevant compounds for residue definition	Parent compound, impurity toluene.
Acute toxicity	
Rat oral LD_{50}	884 mg/kg bw in males and 1768 mg/kg bw in females.
Worst oral LD_{50} in other species	No study provided.
Rat dermal LD_{50}	>5000 mg/kg bw (no deaths).
Worst dermal LD_{50} in other species	No study provided.
Rat inhalation 4-hr LC_{50}	>3234 mg/m^3 (no deaths).
Worst inhalation LC_{50} in other species	No study provided.
Skin irritation	Non irritant.
Eye irritation	Slight irritant.
Skin sensitisation	Non-sensitiser (guinea pig maximisation test).

Short-term toxicity	
Target/critical effect	Kidney (rat, dog), liver (rat), haematopoietic system (rat, dog).
Lowest relevant oral NOEL	8 mg/kg bw/d (90-d dog oral [gelatine capsule] study). Based on frequent episodes of vomiting in males and females, an increase in thymus absolute and relative weight in males, and mortality, reduced body weight gain and minor histopathological changes in the pancrease, thymus and kidneys in females, at 20 mg/kg bw/d.
Lowest relevant dermal NOEL	No study provided.
Lowest relevant inhalation NOEC	No study provided.
Genotoxicity	Non-mutagenic/genotoxic in vitro with and without ±S9, and did not cause genotoxicity or DNA damage in vivo.
Long-term toxicity and carcinogenicity	
Target/critical effect	Rat: kidneys, liver, haematopoietic system. Mouse; lungs, liver, haematopoietic system.
Lowest relevant NOEL	7.32 mg/kg bw/d (2-yr rat). 10 mg/kg bw/d (18-month mouse).
Carcinogenicity	Pulmonary tumours seen in male and female mice. NOEL for pulmonary tumours 10 mg/kg bw/d. Not carcinogenic in male or female rats. Carcinogenic in one rodent species.
Reproductive toxicity	
Reproduction target/critical effect	**Reproductive:** No effect on reproductive parameters. **Parental:** Nephrotoxicity and increased liver, thyroid and spleen weights. **Offspring:** No treatment related findings observed.
Lowest relevant reproductive NOEL	**Reproductive NOEL**: 85.2 mg/kg bw/d (highest dose tested) **Parental NOEL**: 13.5 mg/kg bw/d based on increased absolute and relative thyroid weight in P males and increased relative liver weight in F1 males, and increased relative liver, kidney and spleen weight in F1 females together with vacuolation of the proximal tubular cells of the kidney in P and F1 females. **Offspring NOEL**: 85.2 mg/kg bw/d (highest dose tested.
Developmental toxicity	
Developmental target/critical effect	**Development (rat):** increased incidence of skeletal variations due specifically to an increased incidence of a cervical rib. **Maternal (rat):** liver and kidney. **Development (rabbit):** increased incidence of visceral malformations and variations. **Maternal (rabbit):** reduced weight gain and food consumption.
Lowest relevant developmental NOEL	**Developmental (rabbit):** 2.5 mg/kg bw/d. Based on findings of abnormal lung lobation and absent kidney and ureter seen in 2 and 1 foetus, respectively, at 7.5 mg/kg bw/d. **Maternal (rabbit):** 7.5 mg/kg bw/d. Based on an overall decrease in body weight gain over the dosing period and decreased food consumption on d 9-21 of gestation at 25 mg/kg bw/d.
Neurotoxicity	No evidence of neurotoxicity in an acute oral study and a sub-chronic oral study in the rat.

Summary	NOEL (mg/kg bw/d)	Study	Comments
ADI (0.01 mg/kg bw/d)	10	18-m dietary mouse study	Based on an increased incidence of pulmonary alveolar/bronchiolar adenoma and primary pulmonary tumours in males, with an increased incidence of hyperplasia/hypertrophy of the epithelial cells lining the terminal bronchioles, and applying a 1000 fold safety factor to additionally account for the severity of critical endpoint.
ARfD (0.025 mg/kg bw)	2.5	Rabbit developmental study	Based on abnormal lung lobation and absent kidney and ureter seen in 2 and 1 foetus, respectively, in the absence of maternal toxicity, and applying a default 100-fold safety factor.

Acute toxicity

- Flonicamid had a low acute toxicity hazard profile, with the exception of acute oral toxicity. The acute oral toxicity aligned with a Scheduling Policy Framework (SPF) factor for Schedule 6.
- In an acute oral toxicity study, rats (5/sex/dose) were administered with 625, 1250, 2500 or 5000 mg/kg bw of flonicamid. In the dose range-finding study using two to three animals/sex/dose, one of two males and both females died after administration at 5000 mg/kg bw. Two of three males and all three females died after administration at 2000 mg/kg bw, while no animals died after administration at 1000 mg/kg bw.
- At 1250 mg/kg bw, mortality occurred in all male animals and one of five female animals.
- At 625 mg/kg bw, all animals survived. Necroscopy did not reveal any gross abnormalities in animals at this dose level.

Repeat dose toxicity

- Repeat dose toxicity testing was performed using rats, mice and dogs. The primary target organs of toxicity were the liver in the rat, mouse and dog, haematopoietic system in the dog, rat and mouse, and the lungs in mice. The evaluator concluded that the observed findings, their severity and the dose levels they were observed at (excluding neoplastic findings) would not warrant a scheduling listing.

Carcinogenicity

- Long-term oral toxicity and carcinogenicity studies showed that, while flonicamid was not carcinogenic in male and female rats, it was carcinogenic in male and female mice for which an increased incidence of pulmonary tumours were observed.
  - The delegate raised concerns regarding the potential pulmonary neoplasia seen at high doses in mice and sought advice from the Committee as to whether this might warrant a Schedule 7 listing. The delegate further sought the Committee's advice on a possible mode of action (MOA) and the basis for this apparent site-specific carcinogenicity.
- Pulmonary lung tumours were observed in two 18-month dietary studies in mice. An increased incidence of alveolar/bronchiolar adenomas was seen in male and female mice in

the presence of hyperplasia/hypertrophy of the epithelial cells lining the terminal bronchioles with higher doses resulting in an increased incidence of alveolar/bronchiolar carcinoma in both sexes. A NOEL for the observed pulmonary lung tumours and associated hyperplasia was established at 10 mg/kg bw/d (in male mice). This NOEL was based on an increased incidence of pulmonary alveolar/bronchiolar adenoma and primary pulmonary tumours (i.e. alveolar/bronchiolar adenoma and carcinomas combined) in males and an increased incidence of hyperplasia/hypertrophy of the epithelial cells lining the terminal bronchioles in both sexes. The evaluator indicated that the MOA for the development of the observed lung tumours in mice had not been established. Therefore these tumours were considered relevant to humans. The evaluator, however, also noted that there was no evidence that flonicamid was an *in vivo* genotoxicant and additionally a number of flonicamid metablolites were negative in an Ames test with and without metabolic activation. Thus, while the MOA had not been established, the evaluator considered it was unlikely to be by a genotoxic mechanism.

- In a carcinogenicity study, rats (52/sex/dose) were administered with 0, 50, 100, 200 or 1000 ppm (for males) and 0, 200, 1000 or 5000 ppm (for females) of flonicamid. At study termination (week 104) a statistically significant decrease in haematocrit, haemoglobin concentration and erythrocyte count was seen in females at 5000 ppm. No statistically significant changes were seen in males at week 104. All other statistically significant changes were seen in the absence of a dose response or temporal relationship and were considered likely incidental and not treatment related. Females at 5000 ppm sacrificed after 104 week exhibited a statistically significant increase in the incidence of accentuated lobular pattern of the liver and luminal dilatation of the common bile duct. The evaluator considered that these findings were both treatment related and toxicologically significant. Additionally, in females at 5000 ppm a statistically significant increase in the incidence of eye discharge was observed in animals found dead or killed *in extremis*. The evaluator indicated that although the biological significance of this was unclear, it had no toxicological significance.
- When all macroscopic findings from each sacrifice time were combined together with findings seen in animals killed *in extremis*, statistically significant findings were still apparent in the liver of females at 5000 ppm, though this was now an increase in dark colouration of the liver as well as an accentuated lobular pattern to the liver. The evaluator asserted that although not statistically significant, the observed increased incidence in common bile duct luminal dilation in females at 5000 ppm was still treatment related and toxicologically significant.

Reproductive toxicity

No reproductive toxicity was observed in an oral 2-generation rat study.

Developmental toxicity

- An oral developmental study in rats was suggestive of a developmental toxicity potential, while in a rabbit developmental toxicity study there was evidence of developmental toxicity

(a limited number of visceral findings) in the absence of maternal toxicity, albeit in a very small number of animals.

- The delegate raised concern regarding the developmental toxicity findings. The delegate sought advice from the Committee as to whether this might possibly warrant a Schedule 7 listing.

· In a rat developmental study, at 500 mg/kg bw/d, there was no effect on bodyweight gain in dams and the findings of liver and kidney toxicity in dams at this dose was only considered to provide evidence of 'slight' (not marked) maternal toxicity. At this same dose level, an increased incidence in both the total number of foetuses and litters with skeletal variations was seen which was solely due to an increase in a single specific skeletal variation, cervical rib. No historical control data was provided to allow a more informed evaluation of the observed findings and in the absence of such data were considered to be treatment related. The evaluator considered that the observed skeletal variations were unlikely to be a secondary non-specific consequence of the observed 'slight' maternal toxicity. The evaluator, however, argued that this singular finding alone did not provide reliable evidence that flonicamid was a hazard for developmental toxicity, rather it was suggestive of a developmental toxicity potential.
· In an oral rabbit developmental toxicity study, a number of visceral malformations and variations were seen in rabbit foetuses at the top dose of 25 mg/kg bw/d, these finding were seen in the presence of marked maternal toxicity and were likely a secondary non-specific consequence of such. However, in the absence of maternal toxicity (7.5 mg/kg bw/d) there was evidence of developmental toxicity, albeit in a small number of animals (abnormal lung lobation in 2/156 foetuses [1.28 per cent] and absent kidney and ureter in 1/156 foetuses [0.64 per cent]) though these finding were very rarely seen (0.09 per cent for abnormal lung lobation) or absent from a historical database of 2177 foetuses (i.e. absent kidney and ureter). The evaluator considered that this study provided evidence, albeit limited findings in a small number of animals, of a developmental toxicity potential in rabbits.

Applicant's Response to the Evaluation Report

The applicant had seen a copy of the evaluation and informed the OCS that they accepted the findings of the report.

Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; (c) toxicity; and (e) potential for abuse.

Members noted that several neonicotionid substances, including imidacloprid, acetamiprid and thiacloprid, are listed in Schedule 5 and/or Schedule 6. A Member argued that flonicamid, while a nicotinoid, had a number of significant chemical differences from the more standard nicotinoid structure and that this might give rise to unexpected effects or risks. The Member suggested that this might justify a cautious approach to this substance.

While agreeing that the acute toxicity findings were consistent with Schedule 6, Members debated the significance of the observed carcinogenic and developmental effects and whether this might warrant inclusion in Schedule 7.

Carcinogenicity

A Member noted that the pulmonary lung tumours had been observed in a single species, the mouse. Another Member noted that a single species effect was normally less concerning than an effect observed in several species. It was also noted that the observed tumours had been with relatively high doses of flonicamid, there were no neoplastic findings of concern and flonicamid was not genotoxic. A Member reiterated the evaluator's point that the effects were still concerning enough to warrant a Schedule 6 entry because of the uncertainty arising from the lack of identified mechanism, especially without historical control data for the observed effects.

Members noted that the data indicated that only a single strain of mouse developed the pulmonary lung tumours. Members discussed how significant this specificity might be. A Member noted that effects were only observed in a single mouse strain, it did not necessarily mean that effects would not be observed in other strains. It was common to use a single strain for related toxicological studies to facilitate interpretation of results; minimising compounding factors that can arise from inter-strain variation.

Members noted the lack of identified mechanism for the observed pulmonary lung tumours and the delegate's request for views on possible mechanisms. A Member advised that there was precedent for species specific pulmonary lesions, citing the example of the active compound in Crofton Weed (9-oxo-10, 11 dehydroagerophorone) which caused lung lesions in horses but not in mice (which instead developed liver lesions). With regard to the apparent susceptibility of mice to flonicamid, the Member suggested that this might be the result of a mouse specific metabolism pathway, perhaps involving specific cell activation. The Member noted that this was speculation and that there was insufficient evidence to provide any robust underpinnings for a possible mechanism of action. A Member suggested that this uncertainty might require additional caution and suggested a Schedule 7 entry.

Several other Members argued that the uncertainty, while additional justification for requiring a Schedule 6 entry, was insufficient evidence to support Schedule 7.

Members also noted advice from OCS that the applicant had subsequently submitted more data on the mechanism of the pulmonary effects. While not yet evaluated, a preliminary review did not reveal any specific concerns beyond the current consideration. Members noted that if

significant new concerns did emerge following OCS evaluation of new data, this matter could again be referred for further scheduling consideration.

Developmental

A Member argued that, while the findings raised some questions, the data did not provide particularly reliable evidence. Several Members noted that developmental effects remained a concerning endpoint. It was generally agreed, in the absence of better evidence, that this concern reinforced the need for Schedule 6 entry but would not by itself justify a Schedule 7 entry.

Domestic exposure

Flonicamid had been used for the control of aphids in various agriculture crops. Members noted that XXXXX, the delegate was seeking specific advice from the Committee regarding toxicological concerns should a low-concentration product be submitted for registration, potentially for home-garden use.

A Member agreed that there was potential for such a use pattern to promote domestic use of a product. Another Member noted that Schedule 7 was a far greater barrier to products leaking into domestic use than Schedule 6.

A Member XXXXX and suggested that the regulatory product approval process would provide the opportunity for any concerns, such as domestic use, to be referred for a scheduling consideration.

Other Members noted the low concentration expected from use in the occupation setting and argued that domestic exposure, even without any personal protective equipment, would probably be lower again, so was unlikely to be a significant concern.

Schedule 7

Several Members questioned whether the uncertainty arising from the unknown mechanism of action for the carcinogenic effects was sufficient to shift what appeared to be a Schedule 6 substance into Schedule 7.

Other Members agreed that there was limited evidence of developmental toxicity and that the limited concerns for carcinogenicity, together with the moderate acute toxicity, could be sufficiently mitigated through listing in Schedule 6.

DELEGATE'S CONSIDERATION OF ACCS ADVICE

The delegate concluded that the advice of the ACCS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of no more than six months after the final decision (i.e. 1 September 2012) was appropriate.

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (c) toxicity; and (e) potential for abuse.

DELEGATE'S INTERIM DECISION

The delegate has decided that a new Schedule 6 entry be created for flonicamid with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012).

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to include flonicamid in Schedule 6.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACCS;
- scheduling factors for inclusion in Schedule 6[3]; and
- section 52E of the *Therapeutic Goods Act 1989*.

The delegate decided that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* include (a) risks and benefits; (b) purpose and extent of use; (c) toxicity; and (e) potential for abuse.

The final decision to schedule flonicamid in Schedule 5 included the following reasons:

- the toxicity profile of flonicamid is consistent with that of a substance listed in Schedule 6.
- The limited evidence of developmental toxicity and limited concerns for carcinogenicity, together with the moderate acute toxicity, is sufficiently mitigated through listing in Schedule 6.
- Flonicamid is intended to be included in pesticide products whose use will be regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA).
- The APVMA regulatory process will complement the labelling and access controls associated with listing flonicamid in Schedule 6.
- A scheduling cut-off from Schedule 6 was not considered appropriate in the absence of detail on the product formulations and intended uses.

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

SCHEDULE ENTRY

Schedule 6 – New entry

FLONICAMID

1.4 FORMALDEHYDE AND PARAFORMALDEHYDE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Formaldehyde and paraformaldehyde – seeking advice on a proposal to include a definition for 'free formaldehyde' to clearly encompass 'methylene glycol' (the bound hydrated form of formaldehyde created reversibly when formaldehyde is in an aqueous solution). It is proposed that 'free formaldehyde' could be defined as 'all hydrated or non-hydrated formaldehyde present in aqueous solution, including methylene glycol'. Alternatives will also be considered, including, but not necessarily limited to, the scheduling of methylene glycol under the same term as formaldehyde; or substituting 'methylene glycol (determined as formaldehyde)' for 'free formaldehyde'; or defining 'free formaldehyde' in terms of formaldehyde measured by a specific test.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

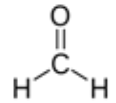
The Committee recommended that a definition be included in Part 1, Paragraph 1.(1) defining "free formaldehyde" as all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012). The Committee also recommended that a cross-reference be added to the index in the next consolidation of the SUSMP from methylene glycol to formaldehyde.

BACKGROUND

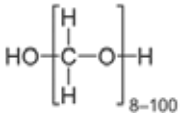
Formaldehyde is a colourless gas with a pungent, irritating odour. Paraformaldehyde is polymerised formaldehyde, usually obtained as a white powder.

Formaldehyde and paraformaldehyde are mainly used in the manufacture of formaldehyde-based resins, widely used in a variety of industries, predominately the wood industry. Formaldehyde is also used in medicine-related industries (such as forensic/hospital mortuaries and pathology laboratories), embalming in funeral homes, film processing, textile treatments, leather tanning and in a wide range of personal care and consumer products.

The IUPAC names of formaldehyde and paraformaldehyde are formaldehyde and polyoxymethylene respectively and the structures are:



Formaldehyde



Paraformaldehyde

Formaldehyde is a gas at room temperature, but it is very soluble in water. Saturated formaldehyde aqueous solutions (37 per cent formaldehyde w/v) are commonly referred to as "formalin". In aqueous solution, formaldehyde reacts rapidly and reversibly with water:

$$H_2CO_{(aq)} + H_2O \rightleftharpoons H_2C(OH)_2$$

This equilibrium strongly favours the bound hydrated form of formaldehyde, methylene glycol ($H_2C(OH)_2$), over the loosely hydrated formaldehyde ($H_2CO_{(aq)}$) – undiluted formalin has been reported to contain less than 0.05 per cent loosely hydrated formaldehyde. Methylene glycol does not have an independent existence and removal of water regenerates formaldehyde as a gas.

XXXXX has submitted a request seeking a clarification for the scheduling of formaldehyde and paraformaldehyde. A delegate agreed that this was a matter for scheduling consideration and that advice from the ACCS was needed.

Relevant scheduling considerations

In August 1991, after considering a review of the toxicology of formaldehyde, it was agreed that Schedule 6 remained appropriate for formaldehyde (with an exception for preparations containing 5 per cent or less of formaldehyde).

In November 1999, the National Drugs and Poisons Scheduling Committee (NDPSC) noted that both formaldehyde and paraformaldehyde, for most practical purposes, were the same compounds. Paraformaldehyde consists of short chain polymers of 8 to100 units of formaldehyde that readily dissociates to form gaseous formaldehyde when heated or dissolved in water. The NDPSC agreed to create entries for paraformaldehyde mirroring the formaldehyde entries.

In June 2007, the NDPSC considered recommendations from a NICNAS Priority Existing Chemicals (PEC) Assessment Report on formaldehyde. The NDPSC agreed to foreshadow further consideration to allow a broadening of the consideration to all use patterns (including human therapeutic use and non-cosmetic domestic use) rather than that stipulated in the NICNAS PEC report i.e. cosmetic use.

In October 2007, the NDPSC agreed that as formaldehyde may induce skin sensitisation and even very low concentrations of formaldehyde in solution may elicit a dermatological reaction in individuals who have been sensitised, dermal exposure should be minimised or prevented wherever possible. The NDPSC therefore decided to include an entry in Appendix C prohibiting formaldehyde in a number of preparations: oral hygiene at more than 0.1 per cent; aerosol spays for cosmetic use at more than 0.0005 per cent; nail hardener cosmetics at more than 5 per cent;

and all other cosmetics at more than 0.05 per cent unless labelled "Contains formaldehyde" in which case the prohibition limit increased to 0.2 per cent.

The NDPSC also noted that the NICNAS PEC report used "free formaldehyde" when proposing cut-off concentrations. The NDPSC agreed to adopt use of "free formaldehyde" as this more clearly reflected the risk being addressed by scheduling. The NDPSC, however, did not define a specific interpretation of "free formaldehyde". The NDPSC had noted various existing international requirements which made reference to free formaldehyde including the EU's Annex VI (List of preservatives which cosmetic products may contain) of the Cosmetics Directive 76/768/EC (EC, 1999).

- Members noted that while not stated in the minutes as such, it appeared that the NDPSC felt that industry would be clear on what was meant by "free formaldehyde" because of this existing EU and international usage.

In February 2008, the NDPSC considered post-meeting comment on the October 2007 decision. The major issue for industry was formaldehyde generators producing free formaldehyde in a product. It was noted that the example tabled for consideration would release less free formaldehyde than the Appendix C cut-off. The NDPSC also noted some assertions that a low level cut-off may be problematic due to lack of a standardised test for formaldehyde generated *in situ*. A Member asserted that this was not a reason which should influence the Committee's consideration and it was up to the industry to develop guidelines on such testing. The NDPSC therefore agreed to confirm the October 2007 decision.

SCHEDULING STATUS

Various concentrations and formulations of formaldehyde and paraformaldehyde are listed in Schedule 2, Schedule 6, Appendix C, Appendix E and Appendix F.

INITIAL SUBMISSIONS

XXXXX **Concern**

XXXXX advised that recent events relating to the regulation of certain hair straightening products (findings of high levels of formaldehyde, up to 10 per cent in some hair straightening products) had demonstrated the need for an unambiguous definition of the term "free formaldehyde". Claims had been made that methylene glycol was "bound" rather than "free" formaldehyde and therefore products containing methylene glycol were not subject to the current scheduling restrictions for formaldehyde. XXXXX was concerned that such arguments undermine the intent behind the scheduling entries of controlling the risk of sensitisation arising from excess levels of aqueous formaldehyde. NICNAS provided a letter from XXXXX to illustrate this concern. The letter:

- Claimed that no cosmetic product had ever contained formaldehyde as an ingredient and argued that only one substance can truly be formaldehyde: HCHO, Chemical Abstracts Service Registry (CAS) No. 50-00-0.
- Further argued that while methylene glycol, CAS No. 463-57-0, was also formaldehyde, methylene glycol and formaldehyde were completely different substances and should be regulated accordingly, especially given that methylene glycol was a cosmetic ingredient and formaldehyde was not.

XXXXX also noted that claims were made that some hair straightening products were "formaldehyde free" due to use of ^{13}C nuclear magnetic resonance (NMR) to show that the hair products contained methylene glycol but not measurable levels of loosely hydrated formaldehyde.

XXXXX contends that the methylene glycol/loosely hydrated formaldehyde equilibrium had no impact on the findings of toxicity studies on aqueous formaldehyde solutions, which were strong skin sensitisers. The known sensitiser, formalin, contained less than 0.05 per cent loosely hydrated formaldehyde.

XXXXX ***Recommendation***

XXXXX recommended that "free formaldehyde" be defined as being "all hydrated or non-hydrated formaldehyde present in aqueous solution, including methylene glycol", to remove any ambiguity in the formaldehyde and paraformaldehyde scheduling entries.

XXXXX believed that the above definition provides the greatest clarity. However, XXXXX was also open to consideration of alternatives, so long as it achieved an equivalent outcome. Further possibilities include:

- Defining "free formaldehyde" as being all bound hydrated (methylene glycol) or loosely hydrated formaldehyde present in aqueous solution. This differs from the above definition in referring to loosely hydrated rather than non-hydrated formaldehyde.
- Defining "free formaldehyde" in terms of formaldehyde measured by a specific test.
- Substituting "methylene glycol (determined as formaldehyde)" for "free formaldehyde" in the existing formaldehyde and paraformaldehyde entries.
- That methylene glycol be scheduled under the same terms as formaldehyde and paraformaldehyde, substituting "methylene glycol (determined as formaldehyde)" for "free formaldehyde" in all schedule and Appendix entries.

International Status

<u>EU</u>

- Restriction of formaldehyde in terms of "free formaldehyde" occurs under the Cosmetics Directive in the EU. The term "free formaldehyde" has a definition that is implicit in the

official EU test method for "free formaldehyde" (Directive 90/207/EEC http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31990L0207:EN:HTML).

- This liquid chromatography (HPLC) based method determines all aqueous formaldehyde, whether as methylene glycol or non-hydrated formaldehyde, as being "free formaldehyde". The term "free" distinguishes this aqueous formaldehyde from the available formaldehyde bound to formaldehyde donors. As such, "free formaldehyde" was essentially synonymous with "methylene glycol". The term "free formaldehyde" was used for all aqueous formaldehyde other than that bound to the donor in discussion of this method in a 2002 opinion by the EU Scientific Committee on Cosmetic products and Non-Food Products intended for Consumers (SCCNFP) (SCCNFP/586/02).

Canada

- The Canadian "Hotlist" of banned and restricted cosmetic ingredients included similar restrictions to those in the EU, but the term "formaldehyde" was used rather than "free formaldehyde".

US

- An American Chemistry Council's (ACC) position statement noted that the federal Occupational Safety and Health Administration defined formaldehyde as "formaldehyde gas, its solutions, and materials that release formaldehyde" in its Formaldehyde Standards. The ACC concluded that both formaldehyde gas and formaldehyde reacted in water determine the formaldehyde content of a product.
- The Oregon Occupational Health and Safety Division, after analysing numerous hair salon products, concluded that was scientifically correct to measure the formaldehyde content of a solution without excluding that portion of the formaldehyde that has reacted with the water to form methylene glycol.

Industry

- Prior to the inclusion of methylene glycol as an International Nomenclature of Cosmetic Ingredients (INCI) name, formaldehyde had to be listed as an ingredient in the cosmetic product if formalin was added to the formulation. The change in the INCI names allowed formulators to name the ingredient as methylene glycol, rather than formaldehyde.
- The implications for control of formaldehyde in cosmetic products were examined by the Cosmetic Ingredient Review Expert Panel which adopted a Revised Tentative Amended Safety Assessment in June 2011. This determined that the term "formaldehyde equivalents" best captured the idea that methylene glycol was continuously converted to formaldehyde and vice versa even at equilibrium, and that the same "formaldehyde equivalents" should apply to both formaldehyde and methylene glycol.

Test Methodologies

XXXXX advised that the issue of what constitutes "free formaldehyde" had not been canvassed in scientific literature, although some variations in interpretation have been evident from various test methodologies.

The EU method for determination of formaldehyde in the presence of formaldehyde donors uses HPLC to separate aqueous formaldehyde, which was predominantly in the form of methylene glycol, from the formaldehyde donor compound, and then forms a coloured derivative of formaldehyde which can be quantified. All aqueous formaldehyde, including methylene glycol, was determined as being "free formaldehyde" using this method.

Use of an NMR test method allows separate determination of formaldehyde donors, methylene glycol and loosely hydrated formaldehyde. However, an NMR test has not been adopted as a standard test by international test standard bodies. Which NMR peaks should be considered as "free formaldehyde" in an NMR test had been interpreted differently in scientific literature.

XXXXX noted that use of an NMR method which considered the methylene glycol peak as "free formaldehyde" would be consistent with the EU's HPLC method.

Other issue – Safe Work Australia

The Australian occupational controls are listed on the Safe Work Australia HSIS database. This regulates formaldehyde solutions as "Formaldehyde…%", and does not include a listing for methylene glycol or refer to free formaldehyde.

February 2012 Pre-meeting Submissions

Two pre-meeting submissions were received:

XXXXX

- Supported efforts to clarify the scheduling requirements for products containing hydrated and non-hydrated forms of formaldehyde.
- Using a specific test to determine the level of free formaldehyde may add unnecessary cost to industry when it could be easily calculated using raw material input and was not supported.
- Recommended that addition of a definition for "free formaldehyde" may be the simplest method to provide clarification.
- As the molecular weight of methylene glycol was significantly higher than formaldehyde (48 and 30 respectively), suggested that the definition also include a clarification for the calculation of free formaldehyde content in the formulation i.e. the weight of formaldehyde and not methylene glycol should be used.

XXXXX

- Noted that Australian restrictions on formaldehyde were consistent with other major regulators who also refer to "free formaldehyde". As such, any proposed definition for "free formaldehyde" should consider any existing definitions.
- Reiterated XXXXX point that the US CIR considers formaldehyde and methylene glycol as "formaldehyde equivalents" and provide a copy of the CIR's final report Formaldehyde and Methylene Glycol 12 October 2011. Both methylene glycol and formaldehyde were included in the safety standard. The CIR concluded that formaldehyde and methylene glycol were safe for use in cosmetics applied to the skin when formulated to ensure use at the minimal effective concentration, but in no case should formaldehyde equivalents exceed 0.074 per cent (w/w).
- Agreed that a definition of "free formaldehyde" should refer to both methylene glycol and formaldehyde.
- Asserted that basing a definition on a specific test method needs special consideration. In particular:

  - Referred to the following statement in a publication (Emeis et. al., 2007, 'Quantitative 13C NMR Spectroscopic Studies on the Equilibrium of Formaldehyde with Its Releasing Cosmetic Preservatives', *Anal. Chem*, vol 79, pp. 2096-2100): 'Despite many advances in analysis and the development of other measuring methods, quantitative determination of free formaldehyde simultaneously with bound formaldehyde at low concentrations in solutions, but especially in finished products, remains a problem with no satisfactory answer'.
  - Asserted that results from different methods to determine free formaldehyde could be highly variable. Referred to a comparison of results from a HPLC method and a commonly used acetylacetone colorimetric method in 100 commercial marketed cosmetics which found the acetylacetone method produced results 1.62 to 17.35 times higher than that produced by the HPLC method (Wu et. al., 2003, 'Determination of formaldehyde in cosmetics by HPLC Method and acetylacetone method', *J Food Drug Analysis*, vol 11(1), pp. 8-15). It was considered that the results from the colorimetric method reflected total formaldehyde and those from the HPLC method free formaldehyde.
  - Noted that NMR techniques had been suggested as better options, however they were also limited in that they represent the amount of non-hydrated formaldehyde molecules present in the static environment of an NMR sample tube where conditions were controlled.

- Concluded that while industry would not want to be restricted by the stipulation of a specific test from an innovation point of view, there was danger that if a test was not adequately specified erroneous results could be obtained.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (d) formulation; and (f) other matters to protect public health, i.e. clarity of controls.

The Committee generally agreed that the use of free formaldehyde in the formaldehyde and paraformaldehyde required clarification. Members indicated that the presence of higher concentrations of formaldehyde and paraformaldehyde in various cosmetic products, particularly in hair straitening products, was a concern. Members agreed that it was the intent that such products be captured by the existing entries. Members generally considered that this intent was already clear, but agreed that it would be appropriate to clarify this to assist with enforcement and to close a perceived loop hole. Members indicated a clear, unambiguous clarification was required to solve this issue.

The Committee considered whether to refer to a specific test methodology to determine free formaldehyde in the formaldehyde and paraformaldehyde entries. Members indicated that there was limited precedent for setting specific testing criteria through the scheduling. Members generally agreed that this had usually been left for industry to establish with regulators and/or enforcing authorities. In addition, such a reference may impose an ongoing requirement for the delegate to periodically review any reference to a specified test to ensure that this remains current. Members further noted it was not general practice to include methodologies in the SUSMP.

The Committee generally agreed that adding a definition in Part 1, Paragraph 1 to define free formaldehyde to include all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol was the most simple, comprehensive and practical solution to resolve this issue. The Committee also generally agreed that a cross-reference from methylene glycol to formaldehyde was required.

Other issues

Members discussed whether to recommend the delegate to communicate about this issue with Safe Work Australia. It was stated that the use pattern and issues regarding formaldehyde were significantly different in the occupational setting and that Safe Work Australia had its own regulatory measures with regard to formaldehyde. The Committee therefore agreed that this matter did not require referral to Safe Work Australia.

A Member noted that generally the IUPAC name of the substances were used in the SUSMP and questioned why in the case of paraformaldehyde the IUPAC name, polyoxymethylene, was not used. Several Members indicated that paraformaldehyde was the common name most widely used by industry.

Members noted that the Appendix C entry for aerosol sprays for cosmetic use also refers to "free formaldehyde" and agreed that a reference to formaldehyde gas was not necessary.

Members also decided that a cross-reference be added to the SUSMP index from methylene glycol to formaldehyde, to further clarify that methylene glycol was captured by the scheduling of formaldehyde.

Implementation

Members generally agreed that as this matter was just clarification, a shorter implementation period was appropriate. Another Member commented that as formaldehyde and paraformaldehyde entries were included in Appendix C, implementation should not be delayed. The Committee therefore decided that an early implementation period was appropriate (i.e. 1 September 2012). Members noted but did not support alternative resolutions on this matter.

DELEGATE'S CONSIDERATION OF ACCS ADVICE

The delegate concluded that the advice of the ACCS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of no more than six months after the final decision (i.e. 1 September 2012) was appropriate.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (d) formulation; and (f) other matters to protect public health, i.e. clarity of controls.

DELEGATE'S INTERIM DECISION

The delegate has decided that a definition be included in Part 1, Paragraph 1.(1) defining "free formaldehyde" as all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012). The delegate also decided that a cross-reference be added to the index in the next consolidation of the SUSMP from methylene glycol to formaldehyde.

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to:

- include a definition in Part 1, Paragraph 1. (1) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), describing "free formaldehyde" includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol.
- Include a cross-reference in the index from methylene glycol to formaldehyde. This change will occur as part of the next consolidation of the SUSMP.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACCS; and
- section 52E of the *Therapeutic Goods Act 1989*.

The delegate decided that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* include (d) formulation; and (f) other matters to protect public health, i.e. clarity of controls.

The final decision to include a definition in Part 1, Paragraph 1.(1) of the SUSMP for "free formaldehyde" and cross-referencing methylene glycol in the index included the following reasons:

- there were potential uncertainties regarding the meaning of the word "free formaldehyde" in the various current schedule entries. Advice provided by the ACCS was that this definition should encompass all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol and that this definition should be included in Part 1, Paragraph 1.(1) of the SUSMP.
- The ACCS advice was based on consideration of the chemistry of formaldehyde when in aqueous solution, and the availability of suitable analytical methods to quantitate its presence.
- Additional clarity for the entry is achieved by appropriate cross-referencing with methylene glycol in the SUSMP index.

SCHEDULE ENTRY

Interpretation - Part 1, Paragraph 1.(1) – New entry

"Free formaldehyde" includes all hydrated and non-hydrated formaldehyde present in aqueous solution, including methylene glycol.

SUSMP Index – New entry

METHYLENE GLYCOL

See FORMALDEHYDE

1.5 ZINC BORATE, BORIC ACID AND BORAX

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Zinc borate, boric acid and borax – proposal to consider scheduling zinc borate in Schedule 6. Consideration will be given to restricting the scheduling of zinc borate to exclude salts and derivatives. Advice will also be sought on the need to re-assess the current scheduling status of boric acid and borax (in Schedule 5), including a potential increase in scheduling to Schedule 6. There are no proposals to amend the exemptions in the current Schedule 5 entry, nor are there any proposals to reconsider the scheduling of boron compounds for human therapeutic use

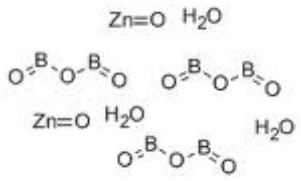
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that a Schedule 6 entry be created for zinc borate for agricultural use with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012).

BACKGROUND

Zinc borate ($2ZnO.3B_2O_3.3.5H_2O$) is one member of a class of crystalline hydrated zinc borates that span a range of B_2O_3/ZnO mole ratios from 0.25 to 5.0. Zinc borate is primarily used as a flame retardant in plastics and cellulose fibers, paper, rubbers and textiles. It is also used in paints, adhesives, and pigments. As a flame retardant, it can replace antimony trioxide as a synergist in both halogen-based and halogen-free systems. It is an anti-dripping and char-promoting agent that suppresses afterglow.

The IUPAC name for zinc borate is dodecaboron tetrazinc docosaoxide heptahydrate and the structure is:



XXXXX submitted data to the APVMA seeking approval of the active ingredient zinc borate. It was indicated that zinc borate would be used in the formulation of agricultural chemical products. XXXXX.

Members noted that the US Environmental Protection Agency (US EPA) was reviewing an application XXXXX to register zinc borate and this was expected to be finalised in 2013.

The Office of Chemical Safety (OCS) Risk Assessment Technical Report on XXXXX APVMA submission included a scheduling recommendation for zinc borate. A delegate agreed that this was a matter for a scheduling consideration and that advice from the ACCS was required. The

delegate also decided that, as the current application did not affect the therapeutic uses of boron in Schedule 4 or the exemptions allowed under that listing, this matter did not require a joint ACCS/ACMS consideration.

Previous consideration of boron/boric acid/borax – non human-therapeutic use

In January 1969, boric acid was recommended for inclusion in Schedule 5. In August and November 1974 and February and May 1975, consideration was given as to whether to allow exemptions from this entry. In addition to creating a new Schedule 4 entry for human therapeutic use (with some exceptions) it was also agreed:

- To restrict boron compounds for cosmetic use to Schedule 3 when containing 2 per cent or less of boric acid as a buffer or preservative; all other cosmetic use was Schedule 4.
- To add a boron compound parent entry to Schedule 6 with a cut-off to Schedule 5 when in soaps or detergents and an exemption for 5 per cent or less of boron.

In March and June 1976, the scheduling of boron was reconsidered and it was agreed:

- To extend the specific Schedule 5 entry for boron compounds in soaps and detergents to also include bleaches and other laundry preparations, with an exemption for 1 per cent or less of boron. This exemption was also added to the Schedule 6 parent entry.
- To delete the Schedule 3 entry for cosmetic use and capture all cosmetic use in Schedule 4 with an exception for external use preparations containing 1 per cent or less of boron.

In November 1976, the Poisons Schedule (Standing) Committee (PSC) agreed to move the boron compounds parent entry from Schedule 6 to Schedule 5 with a single exemption for 1 per cent or less of boron. In February 1977, the PSC reintroduced an exemption for soap powders, powder detergents and bleaches to the Schedule 5 entry.

In February, May and August 1982, the PSC decided to replace the Schedule 5 boron compounds entry with an entry for boric acid and borax; with the only exceptions being for:

- Preparations containing 1 per cent or less of boron.
- Hand cleaning preparations.
- When included in Schedule 4.

In May 1985, the PSC considered reports of poisonings from children eating honey-based ant baits containing boric acid. The PSC agreed that this was a concern and agreed to amend the Schedule 5 entry so that pesticide use would no longer qualify for the 1 per cent or less boron exemption. The entry was also restricted at this time to exclude salts of boric acid, although no reasons were articulated in the minutes.

Members noted that no subsequent record was located for when the May 1985 general restriction on pesticide use from qualifying for the exemption was tightened to the current limited exclusion from the exemption for insect baits only.

In May, August and November 1986 and February 1987, the Drugs and Poisons Schedule Committee (DPSC) reconsidered the Schedule 4 boron compounds entry. As a consequence, the Schedule 4 entry was reworded and no longer referred to cosmetic use.

Recent considerations of boron for human therapeutic use

Boron for human therapeutic use has been Schedule 4 (with some exemptions) since May 1975, with many subsequent scheduling considerations. The major concern was oral and dermal toxicity – in particular when used as antiseptics and for dermal use on infants (the Schedule 4 boron entry was originally intended to restrict these uses).

In February and June 2008, the NDPSC considered a NZ Medicines Classification Committee (MCC) examination of boron, including boric acid and borax, which particularly looked at appropriate exemptions from Schedule 4 for a number of therapeutic use patterns. Members also noted an evaluation of boron by XXXXX.

A Secretariat search of the Therapeutic Goods Administration's Australian Register of Therapeutic Goods located no current human therapeutic use of zinc borate in Australia.

SCHEDULING STATUS

Zinc borate is not specifically scheduled. Boron (including boric acid and borax), however, is in Schedule 4 when for human therapeutic use (with some exemptions). A general listing for boron compounds is cross-referenced to this human therapeutic boron entry through the SUSMP index. The current scheduling of uses other than human therapeutic use that relates most to zinc borate is the Schedule 5 entry for boric acid and borax. This entry, however, specifically excludes salts of boric acid i.e. does not capture zinc borate. There is also a general zinc compounds entry in Schedule 4 but this is limited to human internal use.

SUBMISSIONS

The OCS Report recommended that, based on the toxicity profile (specifically the reproductive and developmental toxicity potential of boric acid), zinc borate be listed in Schedule 6 with no cut-off. The evaluator noted the current listing of boric acid in Schedule 5. The evaluator's other conclusions included:

- Zinc borate would be used in the formulation of agricultural chemical products. The applicant had not stated whether such products were intended for food producing use; therefore, an ADI or ARfD had not been established.

The data package provided with the application comprised of five acute toxicological studies and one mutagenicity study on zinc borate. The applicant also submitted five acute toxicity studies, one sub-chronic toxicity study and three mutagenicity studies on a closely related (but not identical) hydrated zinc borate, zinc borate 4.1.1 ($4ZnO.B_2O_3.H_2O$). The evaluator considered it

was acceptable to use read-across data from both zinc borate 4.1.1 and boric acid in the absence of zinc borate data.

Suitability of boric acid data as surrogate

· Data submitted indicated that under laboratory conditions, when zinc borate was titrated against hydrochloric acid at pH 4, rapid hydrolysis occurs. Further, a US EPA scoping document reported almost complete dissociation to zinc ion and boric acid at pH 4. The evaluator therefore asserted that:

- rapid hydrolysis of zinc borate to boric acid and zinc ion would occur in the acidic stomach contents at pH 4 or less;
- for studies in rats and dogs, rat stomach pH is normally less than 4 while stomach pH is usually 2 or less in dogs;
- literature states that boric acid is not metabolised in the body due to the high energy levels required to break the boron-oxygen bond; and
- zinc is an essential trace element in the human diet while the toxicological profile of boric acid has been well investigated. It is classified as both a category 2 reproductive and developmental toxicant on Safe Work Australia's Hazardous Substances Information System (HSIS). It is therefore reasonable to assume that the boric acid (not the zinc ion) will 'drive' the repeat dose toxicity profile for zinc borate.

Toxicology – zinc borate with read-across data for zinc borate 4.1.1 and boric acid.

Absorption, distribution, metabolism and excretion in mammals	
Rate and extent of oral absorption	No information on zinc borate submitted. However, a surrogate short term oral study on zinc borate 4.1.1 qualitatively indicated absorption in the rat, as indicated by signs suggestive of slight anaemia and organ weight changes and histopathological changes in organs.
Potential for accumulation	No information on zinc borate submitted.
Distribution	No information on zinc borate submitted. However, a surrogate short term oral study on zinc borate 4.1.1 qualitatively indicated distribution as indicated by such findings as extramedullary haemopoiesis of the spleen and cortical hypertrophy in the adrenal glands.
Potential for accumulation	No information on zinc borate submitted.
Rate and extent of excretion	No information on zinc borate submitted.
Metabolism	No information re zinc borate submitted.
Toxicologically significant compounds (animals, plants and environment)	No information available to determine such compounds.
Toxicologically relevant compounds for residue definition	No information available to determine such compounds.

Acute toxicity	
Rat oral LD_{50}	>10000 mg/kg bw (Males).
Worst oral LD_{50} in other species	No information provided.
Rat dermal LD_{50}	No information provided.
Worst dermal LD_{50} in other species	>10000 mg/kg bw in rabbits (both sexes combined).
Rat inhalation 4-hr LC_{50}	No information on zinc borate submitted. However, a surrogate short term oral study on zinc borate 4.1.1 indicated a 4-h LC_{50} > 4950 mg/m^3 in male and female rats that is considered to be applicable (i.e. 'read across') to zinc borate.
Worst inhalation LC_{50} in other species	No information provided.
Rabbit skin irritation	Not an irritant.
Rabbits eye irritation	Slight eye irritant.
Skin sensitization	Non-sensitiser in guinea pigs (modified Buehler).
Short-term toxicity	
Target/critical effect	No information on zinc borate submitted. However, in a short term oral rat study with zinc borate 4.1.1 mild anaemia and extramedullary haemopoiesis of the spleen, liver toxicity, and stomach lesions were observed.
Lowest relevant oral NOEL	NOEL established for the closely related chemical zinc borate 4.1.1 whose data is considered to be surrogate for zinc borate. 15 mg/kg bw/d. Based on minimal changes in the clinical chemistry parameters ALP and ALT in males, along with and histopathological changes in the stomach (parietal cell atrophy) in both sexes at 150 mg/kg bw/d.
Lowest relevant dermal NOEL	No information on zinc borate submitted.
Lowest relevant inhalation NOEC	No information on zinc borate submitted.
Long-term toxicity and carcinogenicity	
Target/critical effect	No information on zinc borate submitted. However, in a chronic study with boric acid in rats and dogs effects on the reproductive system were seen in males.
Lowest relevant NOEL	NOEL identified for boric acid (which zinc borate dissociates to under acidic conditions). 350 ppm (male rats and dogs) though severely limited confidence can be placed in this NOEL.
Carcinogenicity	No studies submitted on zinc borate. However, chronic studies available in the rat and dog with boric acid. No increased incidence of tumours reported in either species, though the results were briefly reported and the confidence that can be placed in the reported findings is limited.
Genotoxicity	Non-mutagenic in vitro in bacteria ±S9. Zinc borate 4.1.1 was not mutagenic in vitro in bacteria ±S9. A genotoxic response was seen in mammalian cells in vitro +S9 only.
Reproductive toxicity	
Reproduction target/critical effect	No information on zinc borate submitted. However, in studies investigating reproductive toxicity in mice and rats with boric acid adverse effects were seen on fertility, with male mice more sensitive than females and sterility seen in males at higher dose levels. Investigative studies in rats suggested that boric acid has an inhibitory effect on male spermiation and sperm production due to reductions in testosterone levels.
Lowest relevant reproductive NOEL	1000 ppm in male and female mice (considered equivalent to 40 and 50 mg/kg bw/d in males and females respectively). Based on decreased

	fertility and disruptions in gestational periods and spermatogenesis at higher dose levels.
Developmental toxicity	
Developmental target/critical effect	No information on zinc borate submitted. However, in studies investigating developmental toxicity in mice, rats and rabbits with boric acid, an increase in foetal malformations/litter was seen in mice and rats along with decreased foetal weight in rats in the absence of maternal toxicity, while findings in rabbits were only seen in the presence of marked maternal toxicity.
Lowest relevant developmental NOEL	Not identified in rats, LOEL of 78 mg/kg bw/d. Based on reductions in foetal body weight.
Neurotoxicity	No information on zinc borate submitted.

Acute

- Zinc borate had low acute oral and dermal toxicity and was not a skin irritant or sensitiser but was a slight eye irritant in rabbits. Additionally, read across data from zinc borate 4.1.1 indicated that it had low acute inhalation toxicity.

Repeat dose

- In repeat dose studies, mild anaemia with extramedullary haemopoiesis of the spleen, liver toxicity and glandular stomach lesions were seen in rats administered zinc borate 4.1.1.

Carcinogenicity and genotoxicity

- No tumour findings were reported in a 2-yr rat and dog dietary study with boric acid, though as results were briefly reported the confidence that could be placed in this data was limited.
- Zinc borate was not mutagenic in bacteria with and without metabolic activation. Zinc borate 4.1.1 was not mutagenic in bacteria with and without metabolic activation, though a positive genotoxic response was seen in mammalian cells *in vitro* in the presence of metabolic activation only. This singular positive *in vitro* finding did not provide sufficient evidence to suggest a genotoxic potential *in vivo*.

Reproductive toxicity (boric acid)

- The evaluator concluded from a sub-chronic dietary study in rats (90 d, 120 rats, 10/sex/group) and dogs (40 dogs, 5/sex/group), that boric acid caused severe testicular damage and atrophy at doses of 1750 ppm in male animals. Reduced body weights (linked with general growth suppression) and treatment-related changes in absolute organ weights (liver, spleen, kidneys, adrenals and testes in male rats at 1750 ppm) and relative organ weights (brain thyroid and adrenals in male dogs) were noted. Female rats (at a 1750 ppm dose) were also shown to have reduced absolute body weights absolute liver, spleen, ovaries and adrenal gland weights compared to controls and relative liver weight with increases seen in relative brain and thyroid weights. The evaluator noted:

- That this study, in which the results were not fully reported, was not conducted under good laboratory practice, quality assurance (QA) or Organisation for Economic Co-operation and Development (OECD) guidelines, and therefore had limited regulatory value.
- This limited the overall value of the study even though the highest doses tested were clearly toxic.

· Studies investigating the reproductive toxicity of boric acid in mice (20/group) indicated substantial adverse effects on the reproductive system and fertility, with males being more susceptible than females. From the limited data presented, clear evidence of treatment-related effects on male fertility was noted at doses of 4500 ppm and above, including reductions in sperm content, sperm motility and male gonadal organ weights. Seminal vesicle and prostate weights were reported not to differ between treatment groups, though no results were presented. Histopathology in males receiving 9000 ppm indicated that the germinal epithelium was atrophied and consisted of Sertoli cells and occasional spermatogonia. At 4500 ppm there were fewer immature round germ cells, and fewer elongated spermatids. Multinucleate giant cells were also noted in this group of animals. The evaluator also noted:

- That this study was not carried out under good laboratory practice, QA or OECD guidelines, and was presented as an abstract only.
- Therefore had little regulatory value even though it reported that high levels of boric acid in the male rat are toxic to the reproductive system. Consequently, given the study conditions, a NOEL could be tentatively established at 1000 ppm for male mice.
- The reporting of the results in an abstract format did not allow any type of meaningful analysis of the study to be undertaken and, thus, little confidence could be placed in the reported findings and established NOEL.

· An investigative study in male rats suggested that the observed effects (such as the absence of spermiation) may be the result of boric acid administration reducing basal levels of testosterone, which was clearly noted from d 4 onwards in this study. The evaluator asserted that there was clear evidence in two rodent species of an adverse effect on fertility / spermatogenesis.

Developmental toxicity (boric acid)

· Developmental studies investigating the developmental toxicity potential of boric acid in mice, rats and rabbits were available.

- In rats, the percentages of foetal deformities per litter were significantly higher in the absence of marked maternal toxicity.
- In mice, a decrease in foetal weight was seen in the absence of maternal toxicity with a statistically significant increase in foetal malformations/litter seen at higher dose levels in the presence of maternal toxicity. Foetal weights for both male and female foetuses were statistically significantly decreased at 0.2 and 0.4 per cent compared to

controls. A statistically significant increase in foetal resorptions was seen in the 0.4 per cent dose group compared to controls, but did not result in a statistically significant decrease in the number of live foetuses. A statistically significant increase in foetal malformations per litter was seen in the 0.4 per cent dose group compared to controls. Based on the reported information in the study, the maternal NOEL for boric acid in mice was determined to be 452 mg/kg bw/d, and the foetal NOEL was determined to be 248 mg/kg bw/d.

- In rabbits the most common visceral defect observed was the presence of an interventricular septal defect however developmental findings were seen in the presence of marked maternal toxicity and were considered likely a secondary non-specific consequence of such.

Other information – EU concerns regarding boric acid

- According to the International Uniform Chemical Information Database (IUCLID) published by the European Commission, boric acid in high doses showed significant developmental toxicity and teratogenicity in rabbit, rat, and mouse foetuses as well as cardiovascular defects, skeletal variations, mild kidney lesions. Studies in mice support effects on testes as the underlying cause for reduced male fertility. In August 2008, in the 30th Adaptations of Technical Process to EU directive 67/548/EEC (available at http://ec.europa.eu/enterprise/sectors/chemicals/files/docs_studies/final_report_borates_en.pdf) the European Commission decided to amend its classification as reprotoxic category 2 and to apply the risk phrases R60 (may impair fertility) and R61 (may cause harm to the unborn child).
- The Transitional Annex XV Dossier on boric acid (available at http://echa.europa.eu/doc/trd_substances/boric_acid/ann_xv_trd/trd_austria_boric_acid.pdf) noted that although the available human data were not sufficient to allow judgments about reproductive toxicity, the experimental data from different animal species gave consistent results indicating that boric acid and tetraborates might cause reproductive toxicity in humans. Effects on male fertility had been investigated in detail. A dose related effect on the testis was observed in rats, mice and deer mice, with confirmation from limited studies in dogs.

Applicant's Response to the Evaluation Report

The applicant had not seen a copy of the evaluation prior to consideration by the delegate. At that time, the applicant indicated an intent to provide comments during the public submission period. No comment was received.

February 2012 Pre-meeting Submissions

A single pre-meeting submission was received from XXXXX seeking an exemption from any scheduling of zinc borate when used as a flame retardant in adhesives and sealants. The submission advised that:

- This type of product was used primarily in the construction sector, and that the typical packaging (300 mL cartridge or 600 mL foil sausage) and end use made it unlikely to be ingested.
- Due to the low toxicity and flame retardant properties of zinc borate, it was a good replacement for antimony trioxide, a suspected carcinogen.

Other matters – specificity of any zinc borate entry

Members noted that several variants of zinc borate exist, differing by the zinc/boron ratio and the water content, including:

- $2ZnO \cdot 3B_2O_3 \cdot 3.5H_2O$, CAS number 138265-88-0, (the variant in the OCS evaluation).
- $2ZnO \cdot 3B_2O_3$, CAS number 138265-88-0.
- $4ZnO \cdot B_2O_3 \cdot H2O$, CAS number 149749-62-2, (referred to as zinc borate 4.1.1).
- $4ZnO \cdot 6B_2O_3 \cdot 7H_2O$), CAS number 1332-07-6.
- $2ZnO \cdot 2B_2O_3 \cdot 3H_2O$), CAS number 1332-07-6.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

Read-across data

The Committee noted that the delegate had queried the 'read-across' approach taken by the evaluator in relation to toxicity information on boric acid and sought ACCS's advice as to whether this was an appropriate surrogate. If the Committee decided boric acid was an appropriate surrogate, the delegate also sought it's advice on whether any entry for zinc borate should align with this existing scheduling i.e. Schedule 5, or whether the data supports up scheduling of the existing boric acid entry to Schedule 6.

The Committee discussed whether the evaluator's read-across approach for using toxicity data from boric acid and zinc borate 4.1.1 in consideration of the toxicity of zinc borate was appropriate. It was noted that in general zinc borate, in the presence of stomach acids, hydrolysed fully into boric acid. Toxicity was therefore associated with the availability of boric acid in the gastrointestinal tract. The Committee agreed that the use of boric acid and zinc borate 4.1.1 read-across data was appropriate for the scheduling consideration of zinc borate.

Zinc borate

Members initially discussed whether to schedule zinc borate in line with the existing Schedule 5 entry for boric acid and borax. Members noted that the boric acid read-across data indicated testicular toxicity effects leading to depressed levels of testosterone. A Member asserted that the depressed level of testosterone was subjective and there was no significant evidence to

substantiate this issue. Members, however, generally agreed that the evidence indicated that testicular effects were of valid concern that might warrant control in Schedule 6.

Members also noted the developmental toxicity effects of boric acid in rats, mice and rabbits. It was noted that the developmental toxicity had a clear dose-response effect and although the effect was border line it was still an effect in the absence of marked maternal toxicity. The Committee generally agreed that although developmental toxicity itself was not a significant issue, testicular toxicity was of concern therefore the Committee agreed a schedule 6 entry was appropriate.

Scope of Schedule 6 entry

The Committee noted that as the toxicity studies conducted were based on the agricultural practices, mainly agricultural use patterns, these were not applicable for other uses. It was also noted that both boric acid and borax were scheduled in 1980's and although the toxicity studies were negative and possibly inadequate by today's standards, and the evaluation process was different at that time, therefore this could be the reason for inclusion of boric acid and borax in Schedule 5. Members commented that there were not sufficient data available for the present Committee to determine whether the current Schedule 5 entries of boric acid and borax were appropriate. The Committee therefore decided that the zinc borate entry should be specifically for agricultural use only, therefore excluding all other uses from this schedule entry. The Committee generally agreed that zinc borate, excluding its derivatives, for use as an agricultural chemical warranted a Schedule 6 entry.

The Committee considered a request from the public submission to exempt flame retardants that contain zinc borate from scheduling. It also noted that zinc borate was being used as a flame retardant widely and it was also comparatively lower in toxicity than other flame retardants. As no exposure information was provided, this raised concern regarding exposure to this substance in a domestic setting. Members asserted that as the product would be enclosed, the exposure would be low. It was further noted that other than flame retardants, zinc borate products were being used by various industries and households, such as sealants, therefore exposure to this substance would be frequent and subsequent toxicity effects would be of concern. The Committee decided to list zinc borate for agricultural use only excluding all other uses from the schedule entry.

Members noted there were several variants of zinc borate available and recalled that the precedent for scheduling salts was to be broad unless there were toxicity data specific to a single salt. It was also noted that much of the toxicity data in this case had come from zinc borate 4.1.1 or boric acid. The Committee decided to schedule the general zinc borate form rather than its specific variants.

Boric acid and borax

Members questioned that as scheduling of zinc borate was based on boric acid's toxicity end-points, should listing of zinc borate in Schedule 6 also warrant a Schedule 6 listing for boric acid and borax. Members raised concern that there were several boric acid and borax products

available in the market and asserted that up-scheduling these substances to Schedule 6 from Schedule 5 would have major regulatory impact, such as labelling and licensing.

The Committee noted that more than half of the toxicity studies presented in the evaluation report were conducted before 1990 and that the quality of some of these studies was not up to current standards.

Members noted but did not support alternative resolutions on this matter.

Implementation

The Committee agreed that as there was no product for registration, an early implementation date (i.e. 1 September 2012) was appropriate.

DELEGATE'S CONSIDERATION OF ACCS ADVICE

The delegate concluded that the advice of the ACCS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of no more than six months after the final decision (i.e. 1 September 2012) was appropriate.

The delegate agreed that relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate has decided that a Schedule 6 entry be created for zinc borate for agricultural use with an implementation date of no more than six months after the delegate's final decision (i.e. 1 September 2012).

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to include zinc borate for agricultural use in Schedule 6.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACCS;
- scheduling factors for inclusion in Schedule 6[4]; and

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

· section 52E of the *Therapeutic Goods Act 1989*.

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

The final decision to schedule zinc borate for agricultural use in Schedule 6 included the following reasons:

· developmental and testicular toxicities are the signal effects that drive scheduling consideration of zinc borate and support its inclusion in Schedule 6.
· It was noted that these toxicities were mainly evident from studies where boric acid had been administered to rats, mice and dogs.
· The ACCS advice was that extrapolation of these effects to also include zinc borate was appropriate in the absence of definitive studies on this salt.
· The specific scheduling submission for zinc borate relates to its intended inclusion in pesticide products whose use will be regulated by the Australian Pesticides and Veterinary Medicines Authority (APVMA).
· The APVMA regulatory process will complement the labelling and access controls associated with listing zinc borate in Schedule 6.
· A scheduling cut-off from Schedule 6 was not considered appropriate in the absence of detail on the product formulations and intended uses.
· Restricting the Schedule 6 entry for zinc borate to its uses as an agricultural chemical addresses the request for scheduling exemption of zinc borate when used as a flame retardant in adhesives and sealants. It also differentiates the uses of boric acid and its salts in other schedules of the SUSMP.

SCHEDULE ENTRY

Schedule 6 – New entry

ZINC BORATE (excluding its derivatives) for use as an agricultural chemical.

2. MATTERS INITIALLY REFERRED TO ACMS#5 – FEBRUARY 2012

2.1 PROPOSED CHANGES TO PART 4 OF THE SUSMP (THE SCHEDULES)

2.1.1 ADRENALINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Adrenaline – consideration of a proposal to capture all preparations for injection containing adrenaline at concentrations of 1 per cent or less in Schedule 3 i.e. that the current exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline not apply to preparations for injection. Consideration will also be given to possibly retaining a lower concentration cut-off for such preparations, including a proposal that this cut-off be set at 0.01 per cent or less of adrenaline. Non-injectable preparations containing adrenaline are not being considered.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline be amended to exclude preparations for injection, i.e. preparations for injection containing 1 per cent or less of adrenaline would be Schedule 3, while above 1 per cent would be Schedule 4. The Committee recommended an implementation date of within six months of the delegate's publication of final decision (i.e. 1 September 2012).

BACKGROUND

Adrenaline, a direct acting sympathomimetic, is a powerful cardiac stimulant and has both antihistaminic and bronchodilatory actions.

Adrenaline is used in the emergency treatment of anaphylaxis (acute severe allergic reaction), bronchospasm and/or hypotension. Adrenaline auto-injectors for use in severe acute allergic reactions have been approved in Australia since August 1993. Adrenaline for injection is also used for the management of cardiac arrest.

In January 1955, adrenaline was listed in Schedule 4 with a 1 per cent cut-off to Schedules 2 and 3, depending on use. In May 1956, the Schedule 2 entry was deleted and a general exemption introduced with a cut-off of 0.01 per cent.

In August 1985, the exemption cut-off was raised to 0.02 per cent as it was considered that such a low level was not toxic and did not pose a health risk except in diabetics. No further details were given and there was no record of any subsequent consideration of the exemption cut-off.

In February 1999, it was recommended and subsequently agreed, that New Zealand harmonise with the Australian scheduling of adrenaline.

In February 2010, an application to include adrenaline auto-injectors in Appendix H was not supported. Another application seeking Appendix H listing was referred to the October 2011 ACMS meeting; the delegate's February 2012 final decision reflected the ACMS's recommendation not to support that proposal.

The delegate subsequently decided to refer the scheduling of adrenaline, as a delegate-initiated matter, to the ACMS for advice.

SCHEDULING STATUS

Adrenaline has a Schedule 4 parent entry with a Schedule 3 entry for preparations containing 1 per cent or less of adrenaline and an exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline.

INITIAL SUBMISSIONS

Delegate-initiated consideration

In deciding to initiate a scheduling consideration of adrenaline, the delegate noted that:

- When preparing briefs on the previous proposal to list adrenaline in Appendix H, the Secretariat noted that some adrenaline products on the Australian Register of Therapeutic Goods (ARTG) (specifically, XXXXX 1:10,000 1mg/10mL injection syringe) were listed on the ARTG as being a Schedule 3 medicine.
- 1 mg/10 mL adrenaline equates to 0.01 per cent adrenaline. Preparations containing 0.02 per cent or less of adrenaline are unscheduled.
- A general search of the ARTG for adrenaline products resulted in more than 1000 entries. TGA provided a more refined list of ARTG entries indicating that 51 formulations were supplied in Australia. Many products contained adrenaline as an addition to an anaesthetic.
- XXXXX argued that adrenaline injection products should be Schedule 3 and that it was an inadvertent oversight to not address the application of the existing cut-off (0.02 per cent) when these products were being assessed.
- While this was a rescheduling consideration proposal to increase controls, the concern about regulatory impact was mitigated in this case as the issue involved injection products that were already classed on the ARTG, and have been considered by industry, as being Schedule 3.
  - Members noted that there were two adrenaline injection products on the ARTG for supply in Australia, listed as unscheduled.
- Noted that various types of adrenaline products exist, including ointments with low levels of adrenaline. The delegate confirmed that the issue being put to ACMS for advice was injectable adrenaline preparations only, and that limiting the consideration to these preparations would limit possible unintended regulatory impact.

Cut-off

An examination of a TGA-supplied list of adrenaline products on the ARTG indicated the following for those preparations intended for injection (noting that this data did not always disclose if concentration was straight adrenaline or an adrenaline salt, most commonly adrenaline hydrochloride – 0.01 per cent adrenaline hydrochloride equates to 0.0083 per cent adrenaline):

- There were numerous anaesthesia preparations for injection which contained small amounts of adrenaline (such as: 1:200,000 or 0.0005 per cent; and 1:300,000 or 0.0003 per cent). These appeared to be primarily scheduled through the anaesthetic component, often as Schedule 4.
- There were two 0.01 per cent adrenaline injection preparations which were flagged as not being scheduled. The TGA advised:
  - XXXXX was approved in XXXXX. The PI document listed the lower strength as unscheduled.
  - It appeared that the same happened for XXXXX when originally approved in XXXXX.
  - Prior to writing these entries into the ARTG, staff in the evaluation areas asked the sponsors to verify the provisional record – including the level of scheduling for each pack size.
  - These two entries have always resided in the ARTG with the prescription medicines section being the regulator (despite being unscheduled) as the dose form (injection) met their criteria as outlined in the Therapeutic Goods Regulations 1990.

Product Information (PI) – adrenaline injection for cardiac arrest

Members noted the details from the PI for one 0.01 per cent adrenaline hydrochloride preparation XXXXX for the management of cardiac arrest, which largely represented information for other adrenaline injection products currently listed on the ARTG as unscheduled or Schedule 3.

Other matters – Schedule 4

XXXXX suggested that Members consider whether certain adrenaline presentations, specifically injection ampoules, should be further restricted.

It was argued that such presentations were inherently more concerning than adrenaline auto-injectors. Injection ampoules were not only meant to be injected but were also meant to be drawn up and the dose titrated. Such a presentation would also lend itself to intravenous injection. It was asserted that these use patterns should only occur under medical direction, indicating at least Schedule 3 but that consideration may also need to be given to further restricting to Schedule 4.

February 2012 Pre-meeting Submissions

A single submission was received from XXXXX agreeing with the delegate's proposal. Arguments were not provided.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (d) dosage, formulation, labelling, packaging and presentation.

Members noted that this proposal was largely to bring scheduling in-line with current market practice, also noting that nearly all adrenaline injection products had been marketed as Schedule 3 (or Schedule 4 for some combination preparations) for some time. Members were advised that there would be minimal regulatory impact, including the two unscheduled products currently listed on the ARTG as these are currently being treated as Schedule 3 products. Members also noted that these products were often in ampoule form, requiring the adrenaline solution to be drawn up and the dose titrated. The Committee generally agreed that it would be inappropriate to keep adrenaline for injection unscheduled.

Members noted a suggestion that adrenaline for injection might need to be restricted even further to Schedule 4, with an exemption for auto-injectors to remain Schedule 3. Members were advised that a legitimate need existed for nurses to access some of these products, citing the case of use in immunisation clinics. Members also noted that these products had been marketed in a Schedule 3 like manner for a long time without reports of significant concerns. The Committee agreed that there was sufficient ongoing need for Schedule 3 access, noting the absence of evidence of concerns, to restrict the up scheduling to Schedule 3 rather than Schedule 4.

Members discussed whether there was any need or justification for a low concentration cut-off for adrenaline for injection. The Committee generally agreed that this was unnecessary as low concentration adrenaline products appeared to be combined with a scheduled substance, often a Schedule 4 anaesthetic.

Implementation date

Members noted that up scheduling decisions often warranted extended implementation dates to allow time for reformulation or repackaging. It was noted that in this case, products were already being treated as Schedule 3. Even the two products listed on the ARTG as unscheduled were being supplied and treated in a Schedule 3 like manner. Members agreed that it was likely that any subsequent required regulatory changes would be limited to straight forward labelling approvals which should be achievable within six months of the delegate's publication of the final decision.

Members noted that the implementation date would be included in the delegate's interim decision and that this would allow sponsors to advise if there were any concerns. Members also noted

that, should it transpire that companies were not able to complete re-labelling by the implementation date, a request could be made to jurisdictions for a transitional labelling exemption.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of within six months of the delegate's publication of final decision (i.e. 1 September 2012).

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (d) dosage, formulation, labelling, packaging and presentation.

DELEGATE'S INTERIM DECISION

The delegate decided that the current exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline be amended to exclude preparations for injection, i.e. preparations for injection containing 1 per cent or less of adrenaline would be Schedule 3, while above 1 per cent would be Schedule 4. The delegate also decided an implementation date of within six months of the delegate's publication of final decision (i.e. 1 September 2012).

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline be amended to exclude preparations for injection, i.e. preparations for injection containing 1 per cent or less of adrenaline would be Schedule 3, while above 1 per cent would be Schedule 4.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- the scheduling history of adrenaline;
- public submissions;
- advice from the ACMS; and
- section 52E of the *Therapeutic Goods Act 1989.*

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

The final decision to exclude preparations for injection from the current exemption from scheduling for preparations containing 0.02 per cent or less of adrenaline included the following reason:

· appropriate dosage forms remain available for adrenaline and scheduling will be consistent.

SCHEDULE ENTRY

Schedule 3 – Amendment

ADRENALINE – Amend entry to read:

ADRENALINE in preparations containing 1 per cent or less of adrenaline **except** in preparations containing 0.02 per cent or less of adrenaline unless packed and labelled for injection.

Schedule 4 – Amendment

ADRENALINE – Amend entry to read:

ADRENALINE **except**:

(a) when included in Schedule 3; or

(b) in preparations containing 0.02 per cent or less of adrenaline unless packed and labelled for injection.

2.1.2 CICLOPIROX

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Ciclopirox - seeking advice on a proposal to reschedule ciclopirox from Schedule 3 to Schedule 2 when in preparations containing 8 per cent or less of ciclopirox. Advice was also sought on whether to maintain the Schedule 2 restriction of preparations for dermal use and for application to the nails, or whether this possible broadening of the Schedule 2 entry should be specifically restricted to use in fungal nail infections. Consideration would also be given to amending the Schedule 4 ciclopirox entry to clarify the intent of the June 2006 NDPSC decision to exempt ciclopirox for the treatment of tinea pedis from scheduling.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that ciclopirox in preparations for application to the nail containing 8 per cent or less of ciclopirox be rescheduled from Schedule 3 to Schedule 2. The committee also recommended an editorial amendment of the Schedule 4 entry to clarify that ciclopirox in preparations for the treatment of tinea pedis is exempt from scheduling.

The Committee agreed with an implementation date of within 6 months of the delegate's publication of final decision, i.e. 1 September 2012.

BACKGROUND

Ciclopirox has a broad spectrum synthetic antimycotic agent against dermatophytes, actinomycetes and yeasts as well as antibacterial activity. It is primarily used therapeutically as an antifungal agent.

In February 2002, the National Drugs and Poisons Schedule Committee (NDPSC) agreed to amend the Schedule 3 to Schedule 2 cut-off for ciclopirox dermal preparations from 1 per cent to 2 per cent. In June 2006, the NDPSC agreed to extend this cut-off to include application to the nail.

In June 2006, the NDPSC also agreed to harmonise with New Zealand to exempt from scheduling ciclopirox preparations for the treatment of tinea pedis. While the Schedule 2 and Schedule 3 entries were amended to reflect the exemption, the Schedule 4 entry was inadvertently not amended to reflect the agreed exemption for tinea pedis.

SCHEDULING STATUS

Currently, ciclopirox preparations for dermal use and for application to the nails are Schedule 2 when containing 2 per cent or less of ciclopirox and in Schedule 3 when greater than 2 per cent of ciclopirox. All other preparations are Schedule 4 **except** in preparations for the treatment of tinea pedis, which is exempt from scheduling.

Currently in NZ, the cut off value for Pharmacy only and Restricted medicine is the same as in Australia. It is also available as General Sale when for the treatment for tinea pedis only.

INITIAL SUBMISSIONS

Application

XXXXX referred a rescheduling application which was part of a product registration submission from XXXXX for a new product containing 8 per cent of ciclopirox for use in fungal nail infections. The rescheduling proposal was to include ciclopirox in Schedule 2 when in preparations containing 8 per cent or less of ciclopirox for use in fungal nail infections.

The product registration application was assessed by the TGA's evaluator and the following advice was provided:

- Did not suggest any major safety concerns for 8 per cent ciclopirox nail lacquers for listing in Schedule 2, however, the product appeared to have low efficacy
- Questioned the appropriateness of allowing this product to be purchased by patients without pharmacist advice. Noted that it is effective in a very low percentage of patients, and other,

more effective oral treatments are available on prescription. However, it was noted that a similar situation exists with amorolfine, which is already listed in Schedule 2.

- Given the long duration of use and low efficacy of the proposed product, it was recommended that if the product be rescheduled to Schedule 2, the provision of a Product Information (PI) and of the Consumer Medicine Information (CMI) pack insert be maintained.

The rescheduling application stated the following:

- In addition to ciclopirox being an antimycotic agent, it was also active against a number of gram-positive and gram-negative bacteria. The latter had an advantage over certain azole antimycotics since secondary bacterial infections were commonly found at the site of fungal infections.
- Ciclopirox had been approved as an 8 per cent nail lacquer for the treatment of onychomycosis in France, Germany, Italy, Spain, US, Canada and New Zealand. In Australia, a 1.5 per cent ciclopirox shampoo was approved for the treatment of dandruff, and an 8 per cent nail lacquer was approved in September 2002 but had not been marketed in Australia. [The ciclopirox shampoo preparation was approved as a Prescription Only Medicine (POM) in the UK.]
- The applicant asserted that, like amorolfine (reschedule to Schedule 2 in 2010), ciclopirox met all of the criteria for Schedule 2, as follows:

  - Suitable for self treatment of onychomycosis (an aliment capable of being recognised and monitored by the consumer).
  - Low potential for abuse or inappropriate use.
  - Well characterised incidence of adverse effects or side-effects, and contra-indications.
  - No know interactions with commonly used substances or food.
  - High therapeutic index.
  - Risk of masking a serious disease and /or compromising medical management of a disease is also low.
  - Use of the product does not require ongoing or close medical diagnosis and management.
  - The consumer is able to recognise and self manage the condition, with advice and counselling if necessary.
- Having ciclopirox 8 per cent nail lacquer available as Schedule 2 would allow easy access to the product by consumers who would be able to read the product label and still be able to request advice from pharmacists if necessary.
- Education material would be developed in consultation with the Pharmacy Guild and Pharmaceutical Society of Australia to assist pharmacist and assistants in understanding the condition and how the product should be used.

XXXXX also addressed matters under section 52E of the *Therapeutic Goods Act 1989*, as summarised below:

(a) Risks and benefits

- Fungal infections of the skin and nails of the foot (and to a lesser extent hands) were common, reflecting the contagious nature of the organisms involved. The availability as Schedule 2 would be beneficial for treatment at the onset, stopping the fungal growth spreading to other areas.
- Some consumers were sensitive to discussing this condition with a pharmacist in a public place. In addition, consumers already have unrestricted access to similar antifungals for tinea pedis (e.g. imidazoles) and for the treatment of onychomycosis (e.g. amorolfine) on pharmacies' shelves. [Onychomycosis, also known as "ringworm of the nail" and "tinea unguium", is a fungal infection of the nail.]
- A Periodic Safety Update Report (PSUR) reported a level of 0.02 per cent of spontaneous minor adverse effects in Europe. Further, PSUR discussion is under the toxicity and safety section below.
- The potential adverse effects were easily recognised by consumers and the label of the product would state "if skin irritation occurs, stop treatment and speak to your pharmacist or doctor."
- A comparison of long-term resistance of ciclopirox against fluconazole investigated whether resistance to ciclopirox could be generated. The applicant claimed that the results showed that the presence of sub-inhibitory concentration of ciclopirox (0.6 micrograms /mL) did not change the susceptibilities of *Candida albicans* cultivated for over 6 months. It was further claimed that, in contrast, an increase in the minimal inhibitory concentrations occurred for fluconazole in two months. The applicant stated that, in accordance with the literature, the irreversible binding of ciclopirox to intracellular structures may prevent resistance.
- The risk of masking an underlying serious medical condition through topical treatment of onychomycosis was minor because onychomycosis alone was rarely a symptom of an underlying serious pathology.
- There was a low risk for the consumer to misidentify their conditions as onychomycosis when it is actually e.g. psoriasis, eczematous conditions, senile ischaemia (onychorgryphosis), trauma, and lichen planus. The applicant asserted that these conditions were associated with other symptoms involving the skin and nail that can distinguish them from fungal infections.
- In the unlikely event that onychomycosis was misdiagnosed and ciclopirox nail lacquer was used, there was minimum risk to health either through misuse of the treatment or through lack of treatment of the disorders that could be mistaken for it.

(b) Purposes for which a substance is to be used

- Ciclopirox was used in therapeutic products for treating onychomycosis.
- The only ciclopirox product currently marketed in Australia is a 1.5 per cent ciclopirox topical shampoo.
- In NZ, there were six brands of 8 per cent ciclopirox nail lacquer, which were classified as restricted medicines.

- In the EU, ciclopirox-containing products have been authorised with different forms as follows: 10 mg pessaries, 1 per cent vaginal cream, 0.2 per cent vaginal solution, 1 per cent dermal cream and 1 per cent dermal solution.
- Applications were submitted in late 2011 to down-schedule ciclopirox, currently available as OTC in Hungary and Germany and as Prescription Medicine in the remaining EU countries.
- The estimated sales volume in Europe from 2007 to 2010 for dermal use was XXXXX treatment cycles and XXXXX treatment cycles for the 8 per cent nail lacquer (based on a mean treatment period of 9 months).

(c) Toxicity and Safety

- The low toxicity and safety of ciclopirox was reflected in the current products containing ciclopirox for the treatment of tinea pedis to be available for general sale at any concentration.
- Preclinical data from the European Product Information (PI) for oral dose of ciclopirox 5 mg/kg, reported that a reduced fertility index was observed in rats. There was no evidence for peri- or postnatal toxicity. However, long-term effects on progeny have not been investigated.
- In Australia, four adverse reactions (ARs) have been reported as of February 2011 and were described as 'suspect'. This was in relation to ciclopirox 1. 5 per cent shampoo (the only ciclopirox product marketed in Australia). Three ARs were described as 'application site reaction'. One involved urticaria, hypoaesthesia oral, dyspnoea and pruritus. Another AR involved eye irritation, erythema ocular hyperaemia and pruritus, and could have been linked with the shampoo base.
- The applicant also provided the EU PSUR for the period 2007 to 2010, summarised below:

  Ciclopirox 8 per cent nail lacquer

  - An exposure of about XXXXX patients was estimated with a calculated mean treatment period of 9 months. It was reported that during this period there was XXXXX spontaneous, medically confirmed, reports consisting of XXXXX suspected adverse drug reactions (ADRs) to ciclopirox 8 per cent nail lacquer collected worldwide. XXXXX ADR was regarded as serious and unlisted (digital necrosis, assessed as unlikely to be related to ciclopirox), XXXXX as non serious and unlisted and XXXXX as non serious and listed.
  - Overall, based on all information collected (spontaneous ADRs, clinical studies, case reports), the safety information (as reported in the current company core safety information was asserted to be consistent with the safety profile of ciclopirox.

Ciclopirox olamine

- From 2007 to 2010, the sales volume of products containing ciclopirox olamine for dermal use indicated that XXXXX treatment cycles have been performed.
- No serious adverse events were reported, however XXXXX spontaneous medically confirmed reports consisting of XXXXX suspected ARs collected worldwide. Among the events, XXXXX regarded as serious and unlisted (extra systoles, assessed as unlikely related to ciclopirox olamine 1 per cent dermal cream).

(d) Dosage, formulation, labelling, packaging and presentation

· The dosage form is a XXXXX nail lacquer containing 8 per cent ciclopirox, contained in a bottle.

(e) Potential for misuse/abuse

· The PSUR did not record any misuse or abuse of ciclopirox over a XXXXX period.

(f) Any other matter

Use during pregnancy and lactation

· Although no AEs were reported in relation to pregnancy and lactation in the PSUR, the proposed PI contains the statement "should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus."
· In relation to lactation, the PI states "it is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when XXXXX is administered to a nursing woman".

Pharmacist and Pharmacy assistant training

· The applicant claimed that training material will include:
  - A brochure based on the clinical trials.
  - An interactive computer-based training program.
  - An article in 'Inpharmation' for Self Care pharmacists.
  - In-store training by the applicant's representatives.

Other matters – Dermal use

· The current Schedule 2 entry cut off does not differentiate between dermal and nail applications. While the applicant only asks for the increase from 1 to 8 per cent cut-off to apply to nails, it was suggested that Members may wish to consider whether the information also supports this for dermal use (currently 2 per cent) or to specifically for application to nails (8 per cent), in which case the current limit of up to 2 per cent.

Other matters – Editorial

- Members were advised that, while the Schedule 2 and Schedule 3 entries were amended to reflect the exemption ciclopirox preparations for the treatment of tinea pedis in June 2006, the Schedule 4 entry was inadvertently not amended to reflect the agreed exemption. An option for clarifying this was provided at the meeting.

February 2012 Pre-meeting submissions

XXXXX and XXXXX both supported the applicant's proposal to include ciclopirox in Schedule 2 for preparations for dermal use containing 8 per cent or less of ciclopirox. XXXXX also provided some additional points which are summarised below:

- Topical products were well tolerated with mild adverse effects (AEs) experienced with the use of 1 per cent shampoo and mild to moderate AEs with no serious events reported with the use of 8 per cent nail lacquer.
- As onychomycosis may take several months therapy, and was more common in people with diabetes, it is important to ensure that these patients have access to professional support.
- Schedule 2 was also the most suitable category for substances used for the treatment of dermatitis and dermal fungal infections as it would maintain access to health professional when appropriate, particularly as other skin conditions such as discoid eczema, pityriasis rosea, pityriasis versicolor, psoriasis, granuloma annulare, candidal intertrigo, erythrasma and mechanical intertrigo could present with similar symptoms.
- Pharmacy was familiar with supplying Schedule 2 products for the treatment of dermatitis and fungal infections. Pharmacy assistants were trained to seek pharmacist intervention to assist in case of any concerns or if the patient has any health conditions or is on other medication. Pharmacists were also well placed to refer patients to the GP for nonresponsive or more serious conditions.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risk and benefits and (b) purposes, dosage and formulation.
Members discussed the safety of ciclopirox in a new XXXXX formulation containing 8 per cent of ciclopirox, and generally agreed that it had a good safety profile. Members noted that it was classified as category B3 pregnancy medicine and does not pose a problem if it were to be included in Schedule 2. Members also noted that common adverse events included redness and itchiness around the nail. Members stated that several topical anti-fungal preparations, including amorolfine had been available as Schedule 2 products. Members stated that 1.5 per cent ciclopirox shampoo was approved for the treatment of dandruff and was currently listed in Schedule 2. Members agreed that 8 per cent ciclopirox would be appropriate to be down scheduled to Schedule 2.

Members considered whether the down scheduling should also apply to dermal preparations. As only data for 8 per cent ciclopirox was presented in the application, Members agreed that the

down scheduling of 8 percent ciclopirox to Schedule 2 should apply only for preparations to nail applications, and that dermal preparations should remain in Schedule 3.
The public health benefits of XXXXX ciclopirox preparations available as Schedule 2 were discussed as follows:

- Members noted the applicant's claim that pharmacist involvement was not necessary at point of supply as onychomycosis was an ailment capable of being recognised and monitored by the consumer. Members also noted that the applicant would provide specific training for pharmacists and their staff once 8 per cent ciclopirox was available. Members stated that this type of medicine directed consumers to read the package before purchasing. In addition this product was reasonably expensive, therefore driving consumers to consult with pharmacists before purchase.
- Members contended that clinical efficacy was demonstrated after 48 weeks of treatment with a 27% clinical cure and that advice from a pharmacist was important to assure compliance with treatment time which could be an issue as it required a long treatment period of 6-12 months with daily application to the nails. Members noted that long-term use and non-washing procedures were common traits of any anti-fungal product. A Member reiterated the binding property of ciclopirox to keratin and that such a product could be washed off after 20 minutes.
- Members noted that ciclopirox is an old medicine marketed in Australia since 1970 and has been used for the treatment of onychomycosis for the last 10 to 12 years. Members agreed that having a new XXXXX formulation available on the market is of benefit as the older XXXXX formulations required the consumers to undertake nail preparations before treatment was applied. Members noted that this new formulation contained XXXXX as an excipient, which has affinity to keratin giving an advantage to improve nail permeation. Members agreed that in addition to the new XXXXX formulation being easier to apply it was also as effective as the old anti-fungal products.
- Members were aware that onychomycosis was more common in people with diabetes which may require a more aggressive treatment. However, it was noted that this population would be under regular medical observation.

Members were concerned with the results of low efficacy for ciclopirox 8 per cent and stated that the new formulation should demonstrate efficacy before being included in Schedule 2. Some Members argued that such a low-efficacy product should not be allowed to be down scheduled to Schedule 2. However, Members generally agreed that the issue of efficacy was not a matter for the Committee to consider for (re)scheduling, rather that ciclopirox product had a very safe profile for topical use.

A Member advised that in NZ ciclopirox was classified as a restricted medicine. If the recommendation of Schedule 2 for ciclopirox was to be endorsed, then this down scheduling should be advised to NZ Medicines Classification Committee (MCC) for consideration. Members noted, but did not support, alternative resolutions on this matter.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of within 6 months of the delegate's publication of final decision, i.e. 1 September 2012.
The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risk and benefits and (b) purposes, dosage and formulation.

DELEGATE'S INTERIM DECISION

The delegate has decided that ciclopirox in preparations for application to the nail containing 8 per cent or less of ciclopirox be rescheduled from Schedule 3 to Schedule 2. The delegate has also decided an editorial amendment of the Schedule 4 entry to clarify that ciclopirox in preparations for the treatment of tinea pedis are exempt from scheduling.

The delegate agreed with an implementation date of within 6 months of the delegate's publication of final decision, i.e. 1 September 2012.

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that ciclopirox in preparations for application to the nail containing 8 per cent or less of ciclopirox is rescheduled from Schedule 3 to Schedule 2.

The delegate also decided to amend the Schedule 4 ciclopirox entry to clarify that ciclopirox in preparations for the treatment of tinea pedis is exempt from scheduling.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- public submissions;
- expert advice in regards to the proposed wording of the Schedule 2 entry;
- scheduling factors for inclusion in Schedule 2 and 3[5]; and
- section 52E of the *Therapeutics Goods Act 1989*.

The delegate decided that the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 include (a) risk and benefits and (b) purposes, dosage and formulation.

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

The final decision to reschedule ciclopirox in preparations for application to the nail containing 8 per cent or less of ciclopirox from Schedule 3 to Schedule 2 included the following reason:

- in order to avoid inadvertently exempting products from scheduling, the wording for the Schedule 2 entry should be amended. The proposed wording for the Schedule 2 entry implied that a product for application to the nail containing 8 per cent or less of ciclopirox would be unscheduled if it was indicated for the treatment of tinea pideas. Ciclopirox products for application to the nails are only intended for treatment of tinea unguium.

SCHEDULE ENTRY

Schedule 2 – Amendment

CICLOPIROX – Amend entry to read:

CICLOPIROX:

(a) in preparations for dermal use containing 2 per cent or less of ciclopirox **except** in preparations for tinea pedis; or

(b) in preparations for application to the nails containing 8 per cent or less of ciclopirox.

Schedule 4 – Amendment

CICLOPIROX – Amend entry to read:

CICLOPIROX **except**:

(a) when included in Schedule 2 or 3; or

(b) in preparations for the treatment of tinea pedis.

2.1.3 IBUPROFEN

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Ibuprofen – seeking advice on a proposal to reschedule from Schedule 3 to Schedule 2 ibuprofen divided preparations containing 400 mg or less of ibuprofen per dosage unit. This consideration may include, but is not limited to, restricting the entry to:

- small pack sizes (not more than 25 dosage units);
- a maximum daily dose of 1200 mg or less; and
- for the treatment of adults and children aged 12 years of age and over.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of ibuprofen remained appropriate i.e. Schedule 3 for divided preparations containing 400 mg or less of ibuprofen in a pack of not more than 25, when labelled with a recommended daily dose of 1200 mg or less and not for the treatment of children under 12 years of age.

BACKGROUND

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). It works by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H2 (PGH2). PGH2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A2 (which stimulates platelet aggregation). Ibuprofen is used in the management of mild to moderate pain and inflammation. It is also used to reduce fever.

In February 1973, ibuprofen was first included in Schedule 4. In May 1989, ibuprofen in packs of 24 or less for the relief of dysmenorrhoea or of pain associated with inflammation was rescheduled to Schedule 3.

In May 1995, ibuprofen 200 mg or less in packs of 50 or less when labelled with a recommended daily dose of not more than 1200 mg, was rescheduled from Schedule 3 to Schedule 2. In May and August 1998, the National Drugs and Poisons Schedule Committee (NDPSC) considered, but did not support, a proposal to exempt from scheduling ibuprofen 200 mg or less when in packs of 24 or less.

In October 2002, ibuprofen for external use was exempted from scheduling.
In June 2003, the NDPSC agreed to exempt from scheduling divided preparations containing 200 mg or less of ibuprofen in packs of 25 or less when labelled with a recommended maximum daily dose of 1200 mg ibuprofen and compliant with the mandatory label requirements.

In February 2006, the NDPSC considered a rescheduling proposal from Schedule 4 to Schedule 2 for divided oral doses of ibuprofen 400 mg. The NDPSC agreed to include 400 mg ibuprofen, when in packs of not more than 50 dose units and labelled not for the treatment of children aged less than 12 years, in Schedule 3. Members considered pharmacist involvement at the point-of-sale essential to minimise consumer confusion over the increased strength per dose unit of the proposed product and ensure appropriate use.
In June 2011, the delegate decided to increase the maximum amount of ibuprofen in liquid preparations in Schedule 2 from 4 g to 8 g.

XXXXX submitted an application direct to the Scheduling Secretariat requesting consideration of an amendment to the scheduling of ibuprofen. A delegate has referred this matter to the ACMS for consideration as this issue could benefit from public consultation and advice from the ACMS.

SCHEDULING STATUS

Ibuprofen in divided preparations (as the only therapeutic active substance) is currently:

- unscheduled (200 mg in packs of 25 or less);
- Schedule 2 (200 mg in packs of more than 25, up to and including 100);
- Schedule 3 (400 mg in packs of 50 or less); and
- Schedule 4 (all other divided preparations).

These preparations are also subject to specific container, labelling and indication restrictions depending on the schedule.

INITIAL SUBMISSIONS

Application

XXXXX has requested the rescheduling of ibuprofen from Schedule 3 to Schedule 2 for divided preparations containing 400 mg or less of ibuprofen in a pack of not more than 25, when labelled with a recommended daily dose of 1200 mg or less and not for the treatment of children under 12 years of age.

The main points made by the applicant are summarised below:

- The current dosage recommendations were 2 x 200 mg ibuprofen initially then 1-2 tablets as required. A single 400 mg tablet would be more convenient for short-term self-limiting conditions, particularly for those who required 1200 mg ibuprofen/day for up to 3 days.
- A loading dose was usually required for most pain states, and often only one dose, i.e. 400 mg, was needed for many pain states.
- Over the counter (OTC) ibuprofen 200 mg and 400 mg tablets at a maximum daily dose of 1200 mg have been available worldwide for the treatment of mild to moderate pain.
- Ibuprofen 400 mg met the profile of a medicine suitable for self-selection. It would not cause untoward problems when taken according to the labelling nor would it cause major complications in overdose situations.
- The packaging for ibuprofen 400 mg would clearly differentiate from ibuprofen 200 mg. Required warnings and cautionary statements for ibuprofen will be on the packaging, including that only one tablet or capsule is to be taken at a time.
- In the event that consumers inadvertently take 2 x 400 mg tablets instead of one, and take these for a day or more, this equated to 2.4 g per day which was not considered to produce clinically harmful effects.
- Concluded that there was no public health reason for ibuprofen 400 mg in packs of 25 tablets or less to not be available without pharmacist supervision as evidence had shown that patients took medication only as long as required to control their pain state.

The application also addressed claims against Section 52E of the *Therapeutic Goods Act 1989*, which is summarised under the Evaluation Report section below.

Evaluation Report

The evaluator did not support the rescheduling proposal as the public health case for a change in scheduling from Schedule 3 to Schedule 2 had not been convincingly addressed. The evaluator's main points are summarised below:

- The applicant's argument regarding patient preferences was the only point in favour of a Schedule 2 listing.
- If the 400 mg dose were to replace some use of the 200 mg dose, it would be very likely that some individuals would be taking a higher dose than they require. Noted that in most jurisdictions ibuprofen 400 mg was available OTC 'behind the counter'.
- The applicant claimed that there was a need for a 400 mg dose on the grounds that some people require a dose of 400 mg for optimal analgesia. The evaluator argued that any such need could already be addressed by the ready availability of 2 x 200 mg tablets to achieve the same dose.
- The major public health issue that has arisen in the application was the potential for a person only requiring 200 mg to be forced to take a 400 mg dose because it may be the only product available. Schedule 2 availability of ibuprofen 400 mg would result in a loss of flexibility for consumers.
- While it was likely that there would be no detectable ill effects from the continued use of 400 mg doses, it was always in the public interest to minimise unnecessary use of pharmaceuticals. There may be a subgroup of elderly patients with heart failure or renal dysfunction, for whom the unnecessary use of 400 mg *vs.* 200 mg may cause difficulties.

The evaluators additional assessment against the Scheduling Policy Framework factors for Schedule 2 is summarised below:

- The following applicant claims met the Schedule 2 factors:

    - The use of the medicine at established therapeutic dosage levels was unlikely to produce dependency and the medicine was unlikely to be misused, abused or illicitly used.
    - The risk profile of the medicine was well defined and the risk factors could be identified and managed by a consumer through appropriate packaging and labelling and consultation with a medical practitioner if required.
    - The use of the medicine at established therapeutic dosage levels was not likely to mask the symptoms or delay diagnosis of a serious condition.

However, the evaluator disagreed with the following applicant claims:

- Claim: *The quality use of the medicine could be achieved by labelling, packaging, however access to advice from a pharmacist was available to maximise the safe use of the medicine. The indications for ibuprofen 400 mg were for minor ailments or symptoms that could be*

recognised and were unlikely to be confused by the consumer; therefore suitable for self medication.

- The evaluator contended that given the potential difficulties with dosing arising from the fixed 400mg dose presentation, a requirement for pharmacist advice would maximise the quality use of ibuprofen.

· Claim: *The use of the medicine was substantially safe for short-term treatment and the potential for harm from inappropriate use was low.*

- Evaluator contended that this medicine was suitable for diagnosis and treatment by the consumer, with pharmacist advice, in the management of minor ailments.

· Claim: *400 mg unit dose product should be more readily available (Schedule 2) for the benefit of consumers who require a 400 mg dose for adequate analgesia and preferred to take this dose as a single tablet rather than as two tablets.*

- The evaluator argued that given that a total dose of 400 mg was readily available as 2 x 200 mg tablets (exempt from scheduling), this argument hinged on the convenience of taking a single tablet *vs.* two tablets.
- The evaluator reiterated the significant potential for confusion regarding the dose (since consumers were accustomed to taking 2 tablets of ibuprofen), and a loss of flexibility for consumers who may require 400 mg as an initial dose, but would then be adequately treated by on-going doses of 200 mg.

The evaluator also provided additional specific comments on a number of issues, summarised below:

Packaging and information

· The application referred to the product as XXXXX, however the proposed pack and consumer medicine information (CMI) appeared to be for a product called XXXXX.
· Advised that the wording, including precautions, on the proposed pack was very difficult to read, but it appeared to be for a pack containing 24 unit doses. The words "Do not take more than 1 tablet per dose" appeared on the pack.
· The proposed CMI included appropriate information about the indications for ibuprofen 400 mg.
· Highlighted that the CMI referred to 400 mg "liquid capsules" in addition to tablets, and these would be covered if ibuprofen was down scheduled. Contended that liquid-filled capsules were not capable of being divided making the dose fixed at 400 mg. Stated that the same could apply for tablets; it was not specified whether these were scored for splitting.

Safety

- The statement that a consumer taking two 400 mg tablets three times daily was equivalent to the maximum dose recommended for inflammatory arthritis was correct. The evaluator argued that it did not necessarily follow the risk:benefit balance for an indication such as headache, toothache, backache or period pain to be similar for inflammatory arthritis. The evaluator also argued that higher doses of up to 2400 mg had a greater potential for exacerbation of hypertension or cardiac failure, particularly in elderly patients.

Public health issues

- The applicant should have been arguing a public health benefit arising from the proposed availability instead of presenting only the argument of "burden" of taking two dosage units rather than one.
- The public health arguments against a down scheduling to Schedule 2 were related to safety and flexibility of dosing. Argued that a loss of this flexibility by purchasing a 400 mg unit dose should only occur after a consumer has had a discussion with a pharmacist.

The applicant's claims against Section 52E of the *Therapeutic Goods Act 1989* are summarised as follows, including some comments from the evaluator:

(a) Risks and benefits

- Ibuprofen was possibly more effective than paracetamol for the treatment of pain and fever in adults and in children. The safety profile of ibuprofen in therapeutic doses was favourable and no significant difference between ibuprofen and paracetamol in adverse event incidence was found in a meta-analysis.
- The most common adverse effects (AE) were gastrointestinal (GI) symptoms (dyspepsia, heartburn, nausea, anorexia, epigastric pain and diarrhoea). Serious GI effects, such as upper GI bleeding, were less common with ibuprofen than with other NSAIDs. Other AEs with short-term use of ibuprofen include dizziness, fatigue and headache and hypersensitivity reactions.
- In overdose, ibuprofen was safer than paracetamol.
- Pharmacovigilance data from the former Adverse Drug Reaction Advisory Committee (ADRAC) (replaced by the Advisory Committee on the Safety of Medicines – ACSOM) database indicated that significant AEs were very rare – XXXXX.
- The Periodic Safety Update Report (PSUR) for XXXXX showed that the company received XXXXX AEs for ibuprofen from XXXXX patients. During this period approximately XXXXX packs of solid dose forms and XXXXX packs of liquid dose forms had been sold.
- The applicant claimed that the AEs in children were mild to moderate in severity, predominantly involving skin reactions and gastrointestinal symptoms. The applicant asserted that the overall safety profile was supportive, and the frequency of adverse events was very low.

(b) Purposes

- In Australia the current distribution of ibuprofen 400 mg tablets as Schedule 3 was about XXXXX per year.
- The indications for use of this presentation were similar to that for other ibuprofen-containing products, with usual duration of treatment of 1-3 days.
- The applicant claimed that consumers would only take sufficient medication to control their current pain, and that the packaging would indicate that ibuprofen 400mg should not be taken for more than 3 days without medical advice.

    - The evaluator asserted that this claim did not constitute an argument for the availability of a 400 mg dose in addition to the currently available 200 mg dose preparations.

(c) Toxicity and safety

- The NDPSC had previously accepted that ibuprofen had a lower risk of AE and serious effects after overdose than OTC aspirin or paracetamol. Noted that this was reflected by the NDPSC decision in 2003 to exempt from scheduling products containing ibuprofen in small packs of unit doses of up to 200 mg.
- Noted that ibuprofen had a wide therapeutic index and no potential fatal dose had been defined in humans. Stated that the report of a 15-year-old girl who ingested 100 grams of ibuprofen indicated that, although significant toxicity ensued (including coma, metabolic acidosis and mild thrombocytopenia), there was no renal dysfunction or GI bleeding. The patient recovered within 3 days with supportive management and had no medical sequelae.
- The applicant claimed that in the worst case scenario, if the total contents of a pack containing 25 x 400 mg = 10 grams of ibuprofen were consumed by a child, a medical assessment would be required only if their body weight was less than 50 kg. It was generally accepted that in most cases children did not consume the entire contents of a pack, particularly in a unit dosing presentation.
- Noted the ADRAC data (2005 – 2010):

    - That there were four accidental exposures in children aged 2-3 years old, all of whom had taken solid dosage forms of ibuprofen.
    - There were no deaths in children who had taken ibuprofen, compared with 6 deaths following ingestion of paracetamol.
    - US data confirmed the low incidence of accidental ingestion of ibuprofen and the low frequency of major effects from ingestion of all analgesics. The evaluator commented that, interestingly, this included paracetamol.

- Noted reference in the November 1998 NDPSC minutes to UK National Poisons Information Service data that indicated that in ibuprofen overdose in children, 75-85 per cent of cases remained asymptomatic.

(d) Dosage, formulation, labelling, packaging and presentation

- The applicant claimed that the proposed dose of ibuprofen had been accepted to be appropriate for self-medication by consumers. Also claimed that the best outcome was achieved by an initial dose of 400 mg, followed by either 200 mg or 400 mg at 8 hour intervals, depending on severity of symptoms and adequacy of response.
  - Evaluator's comments*: The issue of lack of flexibility associated with a dosage unit of 400 mg, particularly undivided preparations, was not addressed. Some individual situations may be better managed with a dose of 400 mg than a dose of 200 mg; this could be achieved by taking 2 x 200 mg.*

- The applicant also claimed that it was *quasi* impossible to quantify a comparison between different treatment durations and doses for the treatment of common mild to moderate pain.

  - Evaluator's comment*: The claim was incomprehensible, and did not contribute to the applicant's argument.*

(e) Potential for misuse / abuse

- Reiterated that ibuprofen was not a drug of abuse in any dosing form. Noted that there was no likelihood of diversion for illicit use, and that the hazard associated with the use of this substance, was accidental poisoning. The applicant also claimed that this risk was additionally minimised by the use of blister packaging and appropriate warnings on the label of the product.

Applicant's Response to the Evaluation Report

The applicant did not provide comment on the evaluation report.

February 2012 Pre-meeting Submissions

Three submissions were lodged. XXXXX and XXXXX did not support the proposed rescheduling amendment. XXXXX agreed with a Schedule 2 entry. The arguments from these submissions are summarised below:

XXXXX

- The main issue and concerns were that ibuprofen 400 mg in Schedule 2 may create confusion for consumers and had the potential to increase the incidence of adverse events.
- Where consumers may benefit from a higher dose ibuprofen product, the current arrangement and availability with professional intervention remained appropriate.
- The submission asserted the need of appropriate assessment of potential risks, to optimise the use of the medication for each individual, which would include:

  - review of appropriate use, duration and frequency of ibuprofen use;

- consideration and assessment of possible GI, cardiovascular (CV) or renal-associated risks;
- the possible use of paracetamol in appropriate doses;
- the benefits or need for referral to a medical practitioner; and
- suggestions of non-pharmacological measures (e.g. hot/cold packs, exercise, bandages, weight reduction).

· There were already a range of ibuprofen (and other analgesic) products currently available in Schedule 2 and the proposed amendment seemed to not provide consumers with any real benefits. Ibuprofen was not recommended for first line use for analgesia.
· XXXXX also suggested the need to be aware of ibuprofen being regarded as a contributor to negative health outcomes through the misuse of combination analgesic products.

XXXXX

· There was no demonstrable need for greater access to ibuprofen than could be met by the current scheduling arrangements.
· There are concerns of potential CV risks and GI complications associated with NSAIDs. It had been demonstrated that there may be a dose-dependent increased risk of myocardial infarction with ibuprofen use. XXXXX highlighted that the recommendation is for NSAIDs was to be used for the shortest time possible at the lowest effective dose. Reports indicated that high dose ibuprofen (800 mg three times daily) was associated with an increased risk of vascular events. Ibuprofen could also reduce the antiplatelet activity of low-dose aspirin and potentially reduce or negate its cardioprotective effect.
· XXXXX was concerned that Schedule 2 access to a stronger ibuprofen product posed a public risk. Pharmacist counselling was important as some consumers had a tendency to take more than the recommended dose, particularly with analgesics when pain control was not optimal.
· US surveys showed that 6 to 13 per cent of non-prescription ibuprofen users exceeded the recommended daily dose of 1200 mg and up to 1 per cent reported taking more than 3200 mg daily. This was of concern given that only 200 mg unit dose products were available without prescription in the US.
· XXXXX was also concerned with the risk of consumers inadvertently taking 400 mg units in combination with other ibuprofen products they may be using to treat other conditions.
· In rural/remote areas, there might be no training for retail staff and no access to health professional advice. Rural and remote areas have generally older populations, higher levels of health risk and higher rates of chronic disease, the risks described above would significantly be intensified. This population would not be disadvantaged with the lack of access to a 400 mg product as 200 mg products remained readily available.

XXXXX

- Schedule 2 for 400 mg ibuprofen would be consistent with the 200 mg formulations.
- Also recommended that consideration be given to rescheduling the current unscheduled ibuprofen 200 mg tablets to Schedule 2. Retail stores did not have any system to ensure the appropriateness of the ibuprofen 200 mg products for consumers.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; (c) toxicity; and (d) dosage.

Members agreed that the main argument supporting the proposal was consumer choice i.e. the convenience of using 1 x 400 mg tablet rather than 2 x 200 mg tablets. Members noted the evaluator's conclusion that, apart from this convenience argument, there was no identified public health benefit. Members also noted the evaluator's conclusion that there were some risks from reduced flexibility of dosing and that some consumers could end up taking a higher dose than they required.

Members noted that there were some adverse effects associated with higher doses of ibuprofen. Members also noted that while the 400 mg was available worldwide, in the majority of countries the formulation was restricted to behind the counter (although there were some exceptions, such as the UK, which allowed in front of counter access).

Several Members reiterated the evaluator's concern that it could be difficult to divide the 400 mg single dose if a consumer wished to have a 200 mg dose. Members noted that the 200 mg dose provided more flexible dosing options as it allowed dosing to be readily titrated up or down depending on the consumers need. Members noted that while the 400 mg presentation might reduce pill burden in some circumstances, this was a minor benefit and provided no real grounds for down scheduling.

Members agreed that the arguments tabled in the application were insufficient to support the proposed down scheduling.

Reconsideration of scheduling exemption

Members discussed a request from a public submission that unscheduled ibuprofen 200 mg be up scheduled from exempt to Schedule 2. Members noted that this request had not been included in the delegate's proposal and therefore had not been published for public consultation. Members also noted that the exemption had existed for some time with little concern (noting that codeine preparations combined with ibuprofen, which were associated with reports of misuse, would not qualify for the current scheduling exemption). Members agreed it would be difficult to justify removing the exemption on the tabled evidence.

Members noted but did not support alternative resolutions on this matter.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; (c) toxicity; and (d) dosage.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of ibuprofen remained appropriate i.e. Schedule 3 for divided preparations containing 400 mg or less of ibuprofen in a pack of not more than 25, when labelled with a recommended daily dose of 1200 mg or less and not for the treatment of children under 12 years of age.

SUBMISSIONS ON INTERIM DECISION

No public submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current scheduling of ibuprofen is appropriate i.e. Schedule 3 for divided preparations containing 400 mg or less of ibuprofen in a pack of not more than 25, when labelled with a recommended daily dose of 1200 mg or less and not for the treatment of children under 12 years of age.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- public submissions;
- scheduling factors for inclusion in Schedule 2 and 3[6]; and
- section 52E of the *Therapeutics Goods Act 1989*.

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 and (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The final decision that the current scheduling of ibuprofen is appropriate included the following reasons:

- there is a risk of increased toxicity due to the potential of taking a higher dose than required if scheduling was changed with no additional benefit.

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

· The current usage of available dose forms appears appropriate.

2.1.4 LOPERAMIDE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate sought advice from the ACMS to amend the Schedule 2 entry for loperamide to include undivided preparations. Advice is also sought on potential restrictions on this rescheduling including, but not limited to, preparations containing 0.02 per cent loperamide and also possibly limiting to use in adults and children over 12 years of age.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of loperamide remains appropriate i.e. loperamide undivided preparations in Schedule 4.

BACKGROUND

Loperamide is a synthetic opioid analogue and is used as an adjuvant oral antidiarrhoeal treatment in the management of acute and chronic diarrhoea. It inhibits gut motility and may also reduce gastrointestinal secretions. Loperamide may also be used in the management of colostomies or ileostomies to reduce the volume of discharge.

At the November 1978 National Drugs and Poisons Schedule Committee (NDPSC) meeting, loperamide was included in Schedule 4. Loperamide was down-scheduled to Schedule 3 at the August 1986 meeting. This was further clarified at the November 1986 meeting so that the Schedule 4 entry remained and the Schedule 3 entry specified packs of eight or less dosage units with each dosing unit containing 2 mg of loperamide or less. It was at this meeting that the Committee also decided to include an Appendix F – Part 2 entry which stated that loperamide was not to be taken by children under 12 years, during pregnancy or lactation or beyond 48 hours except on advice from a medical practitioner.

At the November 1996 meeting the loperamide Schedule 3 entry was down-scheduled to Schedule 2. In August 2000, the Committee decided it would harmonize with New Zealand and increase the Schedule 2 pack size limit from eight dosage units to a maximum of 20 dosage units. In June 2009, the Schedule 2 entry was amended to include the word 'divided' in order to further clarify that liquid preparations of loperamide were Schedule 4.

At the June 2011 ACMS meeting the Committee recommended that loperamide in divided preparations for oral use containing not more than 2 mg of loperamide in packs of 8 dosage units or less would be exempt from scheduling. The delegate confirmed this decision and further decided on an implementation date of 1 May 2012.

SCHEDULING STATUS

Loperamide is currently Schedule 4 except when listed in Schedule 2. The schedule 2 listing is for divided preparations for oral use in packs of 20 dosage units of less.

As of 1 May 2012 the scheduling of loperamide will change to reflect the Delegates decision, as mentioned above to include the words "**except** in preparations containing 2 mg or less of loperamide per dosage unit, in a primary pack containing 8 dosage units or less". This change will harmonise with New Zealand.

INITIAL SUBMISSIONS

Application

XXXXX had made an application requesting the amendment of the Schedule 2 entry for loperamide to include undivided preparations for use in adults and children over the age of 12 years. The application noted that a similar proposal was considered by the NDPSC in June 2009. The Committee rejected the proposal on the basis that liquid formulations imply use in paediatrics.

The application agreed with the view put forward by the NDPSC in 2009 regarding antimotility drugs having "no place in the treatment of acute diarrhoea in children". However, the application asserted that this issue was addressed by the mandatory label statement "*Do not give to children under 12 years of age*" as well as through the Product Information (PI).

Further, the application highlighted relevant points in the factors for Schedule 2 medicines as stated in the Scheduling Policy Framework (SPF) that would be addressed by the inclusion of such a label statement. Specifically:

- that the labelling, packaging and/or provision of other information would achieve quality use of medicines;
- the potential harm from inappropriate use was low;
- unlikely to be misused;
- that the risk profile would be managed by a consumer through appropriate packing and labelling and consultation with a medical practitioner if required; and
- that loperamide liquid was unlikely to mask the symptoms or delay the diagnosis of serious conditions as the tablet and capsule formulations were already considered Schedule 2.

The application also noted that the liquid form of loperamide would not be applicable to the SPF factors for Schedule 4, namely factors 3 and 7, as misuse or communal harm would be addressed by labelling and the PI. Misuse and or communal harm would only occur if consumers mistakenly used the product to treat children less than 12 years of age.

The application responded to the issues raised by the NDPSC at the June 2009 meeting, where the inclusion of loperamide liquid in Schedule 2 was rejected, and are summarised as follows:

- Market research suggested a substantial number of adults and children over 12 years would prefer to take a liquid, rather than a tablet or capsule, even more so if they are feeling unwell.
- The risk of paralytic ileus in paediatric populations would be mitigated by the mandatory label statement as well as associated contraindications contained in the PI.
- The identified 'inferences' to children i.e. the previous label statement and inclusion of a dropper had been addressed with the new mandatory label statement and the proposed product being sold without the dropper.
- The sublingual loperamide preparation, referenced during the NDPSC's 2009 decision, appeared to no longer be available on the Australian market. Therefore no alternative existed to the tablet and capsule formulations.
- While liquid formulations are commonly used in children, and it is acknowledged that anti-motility drugs have no place in the treatment of acute diarrhoea in children, the mandatory label statement will alert people that the product is not appropriate for children under the age of 12 years.

The application addressed the following criteria under section 52E:

(a) Risks and benefits of the use of a substance

- The application only addressed the additional risks and benefits relating to the liquid formulation as loperamide in its other dose forms (tablets and capsules) are already included in Schedule 2.
- Many over-the-counter (OTC) products for oral use were available in a variety of dose forms. In Australia, loperamide was only available as tablet and capsules. Market research suggested there was a viable market for a liquid loperamide preparation for use in adults and children over 12 years of age. While the number of people who cannot take a solid dose form was probably low, there was a substantial number who would prefer a liquid preparation and as such a Schedule 2 listing would benefit these people. Products that meet this need were either no longer available, namely Imodium Melts, or had additional actives i.e. Imodium Advanced Chewable Tablets (also containing simethicone 125 mg) which were indicated for a subset of people who also experience "associated gas-related abdominal discomfort".
- The potential risk of giving the liquid preparation to children under 12 years of age was mitigated by the mandatory label statement as well as the PI.

(b) The purposes for which a substance is to be used and the extent of use of a substance

- Loperamide liquid is to be used for the treatment of acute diarrhoea, the same as the current solid dose forms. No further information was provided.
- The submission also noted the current classification of loperamide in other countries.

(c) The toxicity of a substance

· Toxicity and safety data for loperamide for oral use had already been accepted for solid dosage forms in Schedule 2. The only additional issue in relation to a liquid formulation was its contraindication in children under the age of 12. The potential risk to dose children under 12 years of age was also applicable to chewable tablets and sublingual 'melts' which had previously been registered and captured under Schedule 2. The mandatory label statement and PI for liquid preparations would address this risk.

(d) The dosage, formulation, labelling, packaging and presentation of a substance

· XXXXX.
· The *Required Advisory Statements for Medicines Labels* (RASML) would mean the following statements would be included on the label, immediately before the directions:
  - Do not give to children under 12 years of age; and
  - Do not use beyond 48 hours or in pregnancy or lactation except on doctor's advice.

(e) The potential for abuse of a substance

· Loperamide has a low potential for abuse. This had already been accepted through the current Schedule 2 scheduling of solid dose forms. The potential for abuse (or misuse) in persons under 12 years of age was mitigated by the mandatory label statement and the PI.

The application also provided an indicative label, prior to TGA approval.

Evaluation Report

No evaluation report was conducted.

Pre-meeting Submissions

XXXXX submission agreed with the proposal to amend the Schedule 2 entry for loperamide to include undivided preparations.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) were (a) risks and benefits, (b) purposes and extent of use, (d) dosage, formulation, labelling, packaging and presentation, and (e) potential for abuse. Further, the Committee agreed that the applicant had not sufficiently addressed the concerns raised in the 2009 submission.

The Committee noted that the applicant's main argument to include liquid loperamide in Schedule 2 was consumer preference i.e. a liquid preparation would benefit consumers unable to take tablets. Concerns were raised by the Committee that, while reference was made to market research, no data was provided. The validity of the applicants arguments were further questioned

as the Committee noted the current tablets available on the market were quite small. The Committee noted the chewable loperamide tablets which also contained simethicone. It was further stated that while simethicone had dubious efficacy, it had a very good safety profile. It was suggested that a large number of diarrhoea sufferers would benefit from simethicone to treat gas discomfort.

The Committee noted that there was nothing stopping the development of a chewable or dispersible tablet. The Committee noted the table provided by the applicant of loperamide scheduling in other countries did not specify formulation types. It was further noted, in regards to formulation type, that liquids do imply infant use. The Committee argued that the applicant gave too much weight to the label warning statements and the removal of the dropper for dosing. It was noted that there was still potential for use in children. The Committee also noted that liquid preparations, in general, are inherently more dangerous.

XXXXX. The Committee argued that a new formulation type should sit in a higher schedule first to provide awareness and familiarisation to both consumers as well as health professionals. As liquid loperamide preparations had not been previously marketed, there was an increased need to provide awareness. The Committee noted this could be achieved via a Schedule 3 listing. It was further noted that in many cases a liquid preparation was maintained in a higher schedule.

The Committee stated that misuse and harm was not just limited to children and could result in overdose or misuse in adults. Further, members raised concerns regarding use in the elderly. It was noted that this matter was not addressed in the application. The elderly were more likely to take this type of product as they could have difficulty taking tablets and while they may benefit from this product, overdose or misuse would have a significant impact.

The Committee noted that loperamide was a synthetic opioid and as such there was potential for diversion, including IV use. While the pharmacokinetics of loperamide were such that the risk was low, there was still potential to abuse this product due to its opioid structure and liquid formulation. The Committee felt that introducing a narcotic containing product to the marketplace in any form was of concern, but a liquid invited a higher risk of diversion as it makes it easier for someone seeking to abuse this administer it to themselves parenterally.

The Committee noted that loperamide was not first line in the treatment for diarrhoea. It was further noted that loperamide was used to treat side effects of certain medications used in chronic conditions and that a liquid preparation may be beneficial in this population.

However, the Committee argued that the Schedule 2 entry for loperamide was created specifically for traveller's diarrhoea. Any other uses are out of scope for a Schedule 2 listing and would warrant medical intervention and supervision.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported.

The Committee agreed that the relevant matters under section 52E(1) were (a) risks and benefits, (b) purposes and extent of use, (d) dosage, formulation, labelling, packaging and presentation, and (e) potential for abuse.

DELEGATE'S INTERIM DECISION

The delegate decided that the current scheduling of loperamide remains appropriate i.e. loperamide undivided preparations in Schedule 4.

SUBMISSIONS ON INTERIM DECISION

No public submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current scheduling of loperamide remains appropriate i.e. loperamide undivided preparations in Schedule 4.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- public submissions;
- scheduling factors for inclusion in Schedule 2 and 4[7]; and
- section 52E of the *Therapeutics Goods Act 1989*.

The delegate decided that the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 include (a) risk and benefits, (b) purposes, dosage and formulation, (d) the dosage, formulation, labelling, packaging and presentation of a substance and (e) the potential for abuse of a substance.

The final decision that the current scheduling of loperamide remains appropriate included the following reasons:

- increased risks of a liquid preparation in the application outweigh any benefit, especially in children and elderly.
- Inappropriate use in children, which is a potential risk.
- The potential for diversion would be increased with a readily accessible liquid preparation.

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

2.1.5 LORATADINE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Loratadine - seeking advice on a proposal to exempt from scheduling solid dose oral preparations containing loratadine. Advice is specifically sought, but is not limited to, restricting this possible exemption to preparations labelled with a recommended daily dose not exceeding 10 mg of loratadine, in packs containing 5 dosage units or less. Also for consideration is whether to specifically add a maximum length of treatment, i.e. maximum 5 days' treatment.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommends exempting oral preparations containing 10 mg or less of loratadine in packs containing not more than 5 dosage units for the treatment of seasonal allergic rhinitis (SAR). The Committee also recommended an implementation date of within 6 months of the delegate's publication of final decisions (i.e. 1 September 2012). Members noted, but did not support, alternative resolutions on this matter.

BACKGROUND

Loratadine is a non-sedating, long-acting tricyclic antihistamine with selective peripheral H_1-receptor antagonistic activity. Once daily administration of loratadine provides effective treatment of allergic conditions including seasonal allergic rhinitis (SAR).

Loratadine was first included in Schedule 4 at the May 1992 National Drugs and Poisons Schedule Committee (NDPSC) meeting.

In April 1994, the NDPSC rescheduled loratadine tablets to Schedule 3.

In February 1999, the NDPSC considered the rescheduling of loratadine from Schedule 3 to Schedule 2. Also considered recommendations from the Trans Tasman Harmonisation Working Party (TTHWP) in regard to non-sedating antihistamines. The NDPSC agreed that loratadine in preparations for oral use should be rescheduled, and that the restriction to 'only therapeutically active ingredient' should no longer apply. In November 1999, the NDPSC confirmed the down-scheduling of loratadine to Schedule 2.

SCHEDULING STATUS

In Australia, loratadine is currently in Schedule 2 when in preparations for oral use and in Schedule 4 when not listed in Schedule 2.

A decision from the 15 November 2011 NZ Medicines Classification Committee (MCC) meeting, reclassified loratadine to General Sale when in packs for five days supply and when used for SAR.

SUBMISSIONS

Application

XXXXX requested an exemption from scheduling of loratadine 10 mg in packs of 5 tablets or less, i.e. maximum 5 days treatment. The applicant outlined the reasons that loratadine 10 mg tablets in packs of 5 tablets are suitable for exemption from scheduling as follows:

- Allergic rhinitis was readily self-diagnosed and self-treatable by patients.
- Approximately 16 per cent of Australians have allergic rhinitis.
- Loratadine 10 mg, with its once daily dosage, is a safe and effective second-generation antihistamine available internationally since 1988 as either general sale listing (GSL) or over-the-counter (OTC) preparations.
- Loratadine had a rapid onset of action, providing a long duration of action and lack of anticholinergic effects.
- Loratadine had a side effect profile similar to that of placebo and did not potentiate Central Nervous System (CNS) effects of alcohol or diazepam.
- The recent exemption from scheduling of another second-generation antihistamine (fexofenadine) indicated the potential public need for ready access to treatment for their allergic conditions.
- The availability of more than one form of treatment for allergic conditions at grocery or other outlets was desirable to enable patients to make an informed choice about their treatment.

Further, the applicant noted the following:

- A summary of loratadine scheduling history was provided. It was claimed that in May 1997 the NDPSC recommended that all loratadine preparations for oral use should be rescheduled to Schedule 2.
- In February 2011, the NDPSC exempted fexofenadine for SAR treatment from scheduling. Fexofenadine was an orally active non-sedating H_1-receptor antagonist used for the symptomatic relief of allergic conditions, including SAR and chronic urticaria.
- Patients already have an awareness of their allergic conditions (particularly with SAR) and/or knowledge of how to manage these allergies with little help or counselling from a pharmacist or doctor.
- Mentioned that according to the National Asthma Council of Australia:

    - Approximately 16 per cent of Australians have allergic rhinitis.
    - It is most common among young to middle-aged adults.
    - About a quarter of Australians aged 25 to 44 years have allergic rhinitis.
    - Around 8 per cent of Australian children and adolescents have allergic rhinitis.
    - Most people with asthma (up to 80 per cent) have allergic rhinitis.

- Loratadine is a safe and effective non-sedating antihistamine that has been available as a general sale medicine in the US and the UK for a number of years.

[In the UK, loratadine 10 mg is available as Pharmacist Only and is also available as general sales with the following restriction:

- Max strength of 10 mg tablets, max daily dose of 10 mg and max pack of 14 tablets.
- For the symptomatic relief of perennial rhinitis, SAR and idiopathic chronic urticaria in adults and children aged 2 years and over and weighing 30 kg or more.]

The application addressed criteria against Section 52E of the *Therapeutic Goods Act 1989* as summarised below:

(a) Risks and Benefits

- Loratadine belonged to a class of medicines that is regarded as safe and effective.
- Loratadine does not have the potential to cause serious life-threatening cardiotoxicity.
- The availability of safety data on more than 50,000 patients in clinical trials reported that loratadine was not associated with serious adverse events (AEs) nor did it have any potential for abuse (See (**c) Toxicity and Safety** below).
- The availability of small packs of 5 x 10 mg tablets as unscheduled was not expected to increase the potential for misuse or abuse or increase the low incidence of AEs.
- The overall incidence of AEs reported involving > 3000 patients receiving loratadine was up to 23 per cent. Most AEs were rated mild or moderate and the incidence was similar to that seen with placebo.
- Histamine is a neurotransmitter that plays an important part in the control of vigilance during the waking state. Blockade of the neuronal effects of endogenous histamine in the (CNS) leads to the pronounced sedative effects commonly seen with the first generation antihistamines. While not totally devoid of CNS effects, loratadine did not significantly cross the blood-brain barrier and was therefore not associated with this pronounced sedation.
- There have been no reports of clinically significant interactions with drugs such as erythromycin and ketoconazole.
- Loratadine had a wide therapeutic index with no unusual neurological symptoms or signs of toxicity seen in cases of accidental overdose.
- In patients receiving a single dose of 10 mg loratadine, the incidence of drowsiness was no greater than in patients receiving placebo, although drowsiness may become more prominent with higher doses of 20-40 mg loratadine.
- There are other medicines available as unscheduled products, in small packs, which also carry a potential risk of masking more serious conditions, i.e. paracetamol, ibuprofen, aspirin etc. It was not expected that loratadine would carry any greater risk.
- In a retrospective analysis of a comparison with loratadine and fexofenadine, loratadine showed a significant greater relief of symptoms of SAR during the first 3 days of treatment.

It also achieved maximum treatment efficacy earlier after the initiation of therapy than fexofenadine.

- Fexofenadine currently belongs to a Pregnancy Category B2, whereas loratadine belongs to Category B1.
- If SAR was left untreated, the patient's quality of life could be severely affected. This could lead to sleep disturbances, limitations in activity as well as practical and emotional problems. There could be significant lost workdays and school days for patients. It was also stated that people with allergic rhinitis tend not to seek medical advice regarding their treatment.

(b) Purposes

- The applicant stated that loratadine 10 mg tablets have been marketed in more than 100 countries for non-drowsy relief from the symptoms of hay fever (SAR) and allergy relief in adults and children 12 years of age and over. Symptoms included, sneezing, watery, itchy eyes, runny nose and itchy rash.
- In more than 50 countries, loratadine tablets and syrup are either available OTC or general sale. Marketing details for the major countries were listed in the application.
- The applicant claimed that since introduction in Australia in 1993, there have been almost XXXXX loratadine tablets sold XXXXX. About 47 million tablets of generic loratadine have been sold since July 2006.

(c) Toxicity and Safety

- The applicant asserted that the toxicity and safety of loratadine has been well established over more than 20 years in the market, much of which has been as an OTC medicine.
- In overdose situations (in excess of 40-180 mg), there have been reports of somnolence, tachycardia and headache. The applicant claimed that in volunteer studies, single doses of up to 160 mg of loratadine have been administered without any untoward effects.
- Oral LD_{50} values for loratadine were greater than 5000 mg/kg in rats and mice. Doses as high as 10 times the recommended clinical dose showed no effects in mice, rats and monkeys.
- Second-generation antihistamines (terfenadine and astemizole) have been associated with rare but serious adverse cardiac effects including ventricular arrhythmias and cardiac arrest. These AEs occurred through the concentration-dependent blockage of the potassium channels of cardiac cells, causing blockade delays in repolarisation in cardiac conducting cells and the prolongation of QT intervals.
- Animal tissue models suggested that loratadine blocked potassium channels but only at concentrations that were unlikely to be attained clinically.
- In a clinical study, administration of loratadine in single doses up to 160 mg (16 times the maximum daily dosage) was not associated with prolongation of QT intervals.

Use in pregnancy and breastfeeding

- The applicant stated that the labelling of loratadine 10 mg cautions patients to consult their doctor before using the product if they are pregnant, breast feeding or have liver disease.
- Reproduction studies in rats and rabbits using loratadine doses up to 75 to 150 times (respectively) the maximum daily human dosage, dosed as mg/m^2 , have not revealed evidence of harm to the foetus.
- An epidemiological study, published in 2001, suggested an increased incidence of hypospadias in male infants born to women who received loratadine during pregnancy. [***Hypospadias***: A birth defect of the penis involving the urethra]
- A systematic review and meta-analysis provided information about 453,053 male births. Of 2694 male infants born to women using loratadine, 39 (1.4 per cent) had hypospadias. Of 450,413 male infants born to women not using loratadine, 4231 (0.9 per cent) had hypospadias. The results indicated that the use of loratadine during pregnancy does not significantly increase the risk of hypospadias in male off-spring.
- In two small prospective cohort studies that surveyed pregnant women who contacted a teratology information service, use of loratadine during the first trimester of pregnancy was not associated with major congenital anomalies and did not influence the rates of live birth, gestational age at birth or birth weight. It was mentioned, however, that the interpretation of the results was limited by the statistical limitations of the studies. It was explained that, because there were no adequate and controlled studies to date using loratadine in pregnancy, it should be used only when the potential benefits justify the possible risks to the foetus.
- No AEs were seen in breastfed infants whose mothers were receiving loratadine. It was stated, however, that loratadine and desloratadine distributed readily into breast milk. It was recommended that caution should be exercised when loratadine was administered to nursing mothers. The package labelling for loratadine recommended consulting a doctor before use if you were pregnant or breastfeeding.

Renal impairment

- The labelling cautioned against use in the presence of liver disease. Renal impairment had no significant effect on loratadine clearance.

(d) Dosage and formulation

- The applicant stated that loratadine 10 mg tablets are currently marketed in blister packs of 10, 30 and 60 tablets. It was proposed that packs of 5 tablets of loratadine be exempt from scheduling when marked specifically for use in adults and children 12 years and over.
- The approved indications were: For use in the treatment of both seasonal and perennial allergic rhinitis in adults and children 12 years of age or older. Also indicated for the relief of symptoms and signs of chronic urticaria in adults and children 12 years and older.

(e) Potential for abuse

- A literature search had not located any reports of abuse or misuse with products containing loratadine.
- Loratadine did not readily cross the blood-brain barrier and therefore does not interact appreciably with H_1 –receptors within the CNS, reinforcing the unlikeness of loratadine abuse.
- A case of a 16 month old child who ingested up to 13 times the recommended adult dose and another 2 year old that ingested 150 mg loratadine was reported. They showed no neurological symptoms and recovery was uneventful in these unusual cases. No unusual neurological symptoms or signs of toxicity were seen in another three children who ingested between 10-200 mg loratadine.

(f) Other matters

- Non-sedating antihistamines have approximately 79 per cent of the total Australian market, in units, for systemic antihistamines.
- The application did not seek to change the scheduling of the liquid syrup or dosage preparations marketed specifically for children.
- Non-sedating antihistamines (loratadine, fexofenadine and cetirizine) were well-established treatments for SAR, however patients may not always respond to the first antihistamine prescribed.
- Some studies have concluded that loratadine provided significantly better therapeutic response than fexofenadine in patients who failed to respond to initial therapy with the other drug.

Evaluation Report

The evaluator did not support the proposal to exempt loratadine 10 mg from scheduling. The following conclusions were made by the evaluator:

- The applicant may be relying on information submitted for earlier scheduling considerations, the most recent of which was in 1999. It was also contended that the application omitted whether there have been more recent published reports of studies of efficacy or safety of loratadine.
- The applicant's claim that loratadine may be clinically superior to fexofenadine was not backed up with strong evidence.
- Reasonable evidence was provided that cardiac arrhythmias and cardiac death caused by taking loratadine was a very rare event.
- There was also reasonable evidence that loratadine, when taken in pregnancy, was not associated with hypospadias in male infants.
- The application was deficient in a number of regards, which were:
  - Safety issues or concerns were not supported by documentation such as Periodic Safety Update Reports (PSUR) or Australian adverse drug reactions reporting information.

- Some statements about aspects of safety were broad and did not give the basis for the claims.
- Up to date references were not cited and no information had been provided from Australian Poisons Information Centres in regards to misuse and overdose.
- There were inconsistencies in regards to use in renal impairment and by the elderly between the Australian Product Information(PI) and the American Hospital Formulary Service (AHFS) Drug Information monograph referred to in the application.
- No reports of studies exploring possible associations between loratadine and birth defects, other than hypospadias, were provided.
- Proposed labelling and packaging for the unscheduled product had not been submitted.
- The evaluator also argued that the information provided in the application in relation to the May 1997 NDPSC decision was not accurate. The evaluator asserted that the February 1999 NDPSC meeting minutes stated that the NDPSC had rejected a similar application in May 1997. It was further added that the minutes of the NDPSC November 1999 meeting recount the down-scheduling of both fexofenadine and loratadine and then state: "Australian classifications for fexofenadine and loratadine are harmonised in regard to oral preparations. The amendment (Decision No 1999/20-94) is included in Amendment 4 to SUSDP 13."

The evaluator summarised the references included in the application. The following comments were made:

· One of the authors was affiliated to the XXXXX. The evaluator contended that XXXXX provided the funding for the study (efficacy of loratadine vs. fexofenadine) and is a subsidiary of XXXXX. In addition, the paper was silent about the results of the analysis of mean instantaneous Total Severity Symptom Score (TSS) inviting consideration of the possibility that no statistically significant differences were found in the instantaneous scores.
· Stated that one study showed differences in patient and investigator ratings of symptom severity at the end of Phase 2 which favoured loratadine, however, they were not statistically significant.
· The evaluator stated a reference provided a useful tabulation of the most prevalent adverse effects associated with available (in USA) second-generation antihistamines (cetirizine, desloratadine, fexofenadine, loratadine) in large-scale controlled trials.
· In relation to the reference of risk of hypospadias, the evaluator stated that the methodology of the meta-analysis was appropriate. The evaluator also stated that, although the proportion of infants with hypospadias was somewhat higher in the loratadine exposed group (1.4 percent) compared with those not exposed to loratadine (0.9 per cent), the difference was not statistically significant.

The evaluator's specific comments against the applicant's Section 52E are summarised below:

(a) Risks and Benefits:

- The evaluator accepted that loratadine, as a second generation non-sedating antihistamine, was widely regarded as safe and effective for the symptoms and signs of SAR as well as some other allergic manifestations.
- The evaluator made reference to the applicant's claims that the most commonly reported AEs associated with 10 mg loratadine use were headache and drowsiness, and that this incidence was no greater than in placebo group. The evaluator contended that no source for the figure was quoted and that the Australian PI indicated an incidence of headache with loratadine as 12 per cent. The evaluator further contended that the applicant should explain the discrepancy.
- Although the applicant claimed that safety data on more than 50,000 patients showed that loratadine was not associated with serious AE, these data were not available for evaluation.
- The claim "there have been no AE which have required labelling changes in Australia or internationally since product launch" was not supported by any documentation.
- The applicant should advise the ACMS, since the last scheduling submission about loratadine in February 1999, whether:

  - any action had been taken by a Regulatory Authority or by the applicant for safety reasons;
  - the Reference Safety Information (the Company's Core Data Sheet - a corporate document which forms the basis for national product information) or the Australian PI had been changed for a safety reason;
  - internationally the applicant or its affiliated companies were currently undertaking any specific in-depth reviews of any safety issues with loratadine; and
  - details of reports provided to the TGA of all Australian suspected adverse reactions to loratadine since the last scheduling submission.

- Contended that no evidence was provided to support the claim that "The availability of more than one form of treatment for SAR at grocery or other outlets means consumers can make an informed choice about their treatment."

(c) Toxicity and Safety

- The evaluator mentioned that a major concern in the initial life of loratadine was the possibility that it might cause life-threatening or fatal arrhythmias and cardiac arrest as were observed with terfenadine and astemizole. The applicant stated that if acute cardiac events do occur with second-generation antihistamines, they are extremely rare.
- Agreed that loratadine does not prolong the QT interval.
- In the evaluator's opinion, the situation of possible arrhythmic effects of loratadine and fexofenadine was now sufficiently clear and that Schedule 2 for fexofenadine and loratadine

was now appropriate.[Secretariat's note: fexofenadine is now exempt from scheduling when in packs of 5 days supply for treatment of SAR.]

- The application did not include any evaluable references in regards to general safety in pregnancy, for example "Use of an antihistamine medications during early pregnancy and isolated major malformations".
- The results of a study of loratadine use in pregnancy generally were consistent with no association between birth defects and antihistamine use during early pregnancy. However, the evaluator advised to caution women who are pregnant against taking loratadine (or any other antihistamine) except on medical advice.
- The application was silent about use in renal impairment and in the elderly. A study suggested that the half life of loratadine was prolonged in the elderly compared with healthy adults. The evaluator advised that patients with renal impairment receiving loratadine for self medication should consult a clinician before initiating therapy since a different dosage may be recommended, particularly in geriatric patients.
- The application did not include advice to "Consult your doctor if you have renal impairment" or "if you are more than 65 years of age" on the Schedule 2 loratadine packaging. The evaluator contended that there was no reference to dosage adjustment in renal impairment or in elderly patients in the Australian PI.

(d) Dosage, Formulation, labelling, packaging and presentation

- The evaluator objected that the applicant did not supply proposed labelling and packaging for the unscheduled loratadine product.

(e) Potential for Misuse/Abuse

- The application did not provide any details of the literature search strategy to back its claim that "a literature search has not located any reports of abuse or misuse with products containing loratadine".
- Limited details of observations of overdoses in five children (three of whom the ages were not stated) were provided. Noted that no information based on enquiries to the Australian Poisons Centres had been provided.

(f) Any Other Matter that May be Relevant to the Scheduling of a Substance

- Noted the applicant's statement that about 79 per cent of systemic antihistamines in Australia, based on market units, were non-sedating antihistamines.

Applicant's Response to the Evaluation Report

The applicant addressed the following points made by the evaluator:

PSUR

- The latest PSUR, covering a period XXXXX, concluded that the risk/benefit profile of loratadine remained favourable and no safety signal had been identified since XXXXX that

would warrant any changes to the Company Core Dada Sheet. The PI and Consumer Medicines Information (CMI) for loratadine were approved by the TGA on 18 February 2010.

- Since the last scheduling application in February 1999, no action has been taken by any Regulatory Authorities due to safety reasons. The applicant also confirmed that there was no current in depth safety review of loratadine being undertaken by the applicant or its affiliates.

Misuse and overdose

- During the PSUR reporting period XXXXX, there was no medically confirmed reports of drug abuse/misuse identified for loratadine. There was one non-medically confirmed case of a 51-year-old female with intentional drug misuse (20 teaspoons a day of loratadine liquid), with tremors reported.
- In the PSUR, there were XXXXX medically confirmed cases containing information about an overdose with loratadine.
- The applicant asserted that the Australian PI for loratadine indicated that somnolence, tachycardia and headache have been reported with overdoses.

Literature research – Efficacy and Safety

- In response to the evaluator's comment, the applicant stated that a literature search (using EMBASE and MEDLINE) for loratadine was conducted on 20 January 2012 to identify any further efficacy and safety studies in the last 10 years (2002 to 2012).
- One study evaluated early SAR symptom relief through a retrospective analysis of previously published data. Loratadine 10 mg once daily was compared with fexofenadine 60 mg twice daily and placebo over 7 days. The study concluded that loratadine was significantly more effective than placebo for all time points.
- Asserted that a search, using search-terms 'loratadine' AND 'safety', limited to the last 10 years (2002-2012), identified a total of 25 publications and none of these studies reported new safety information.

Renal impairment and Elderly

- The applicant asserted that the pharmacokinetic (PK) profile of loratadine, and its metabolites, demonstrated to be comparable in healthy adult volunteers and in healthy geriatric volunteers. Results from this study supported the approved PI for loratadine, that no dosage adjustment was required for elderly.
- The PSUR XXXXX reported XXXXX medically confirmed cases in elderly patients. A review of the events occurring in elderly patients did not identify any new or significant safety concerns regarding the use of loratadine in this population.
- In patients with chronic renal impairment, both the AUC and peak plasma concentration slightly increased for loratadine and its metabolites. The mean elimination half lives of loratadine and its metabolites were not significantly different from that observed in normal subjects.

- Results from this study supported the approved PI for loratadine that no dosage adjustment was required for patient with renal impairment.
- The slight increase in the AUC and C_{max} observed in patients with renal impairment were not considered clinically relevant, as renal impairment has no significant effect on loratadine clearance.
- With regard to the inconsistencies about use in renal impairment and by the elderly with the AHFS Drug Information reference, it was stated that after discussions with their US Regulatory colleagues, the applicant was advised that a warning statement regarding liver and renal impairment was requested by the US FDA to be placed on XXXXX product labelling. This was based on the effect of sympathomimetic amines (pseudoephedrine) and not the antihistamine (loratadine) because the doses of this fixed combination product could not be individually titrated. The same statement was later added to labelling for consistency between the products labelling in the US.

Associations between loratadine and birth defects

- Reproductive studies in pregnant rats and rabbits showed no evidence of embryotoxic or teratogenic activity at loratadine doses up to 96mg/kg/day.
- Results of two published controlled cohort studies, between loratadine and major malformations of product use in pregnancy, demonstrated that use of loratadine in human pregnancy did not present a major teratogenic risk.
- Asserted that the latest PSUR XXXXX reported XXXXX cases of loratadine exposure during pregnancy and breast feeding, respectively. Stated that a review of the cases of pregnancy exposure did not identify any new safety information that would warrant a change to the PI for loratadine.

Proposed labelling and packaging

- The following label warnings were proposed for the benefits of customers at retail stores: XXXXX

Harmonisation with New Zealand

- NZ MCC had granted a general sale classification for loratadine 10 mg in packs for 5 days' supply.
- The November 2011 MCC minutes stated that the safety, efficacy and abuse potential of loratadine was similar to fexofenadine.

February 2012 Pre-meeting Submissions

XXXXX did not support the proposal to exempt loratadine 10 mg. XXXXX did not support the proposal to exempt loratadine 10 mg for conditions other than SAR.

XXXXX argued that it did not see any benefit to the public in exempting a small pack size of loratadine. Contended that retail stores do not have any mechanism to restrict quantity sales and do not have counselling available for suitable use of this medicine.

XXXXX submission is outline below:

- The submission considered supervision by pharmacy personnel providing advice to be important for antihistamines.
- The recommendation of exempting small packs (5 days supply) of fexofenadine from scheduling, should not be seen as a precedent for other second generation antihistamines.
- Questioned whether any antihistamine was truly non-sedating, and whether public risks associated with its use still exist. The safety margin could be narrow enough to cause a central sedating effect during treatment, which might result from a patient's individual sensitivity, disease-induced sedation, or dosages that were for various reasons relatively larger (weight, poor response, reduced clearance, interactions). There could be a serious public risk for people who are driving or operating dangerous machinery.
- The Australian Defence Force required Defence personnel who conduct specific duties such as flying or operating dangerous machinery to initially undertake a performance assessment to ensure they were not affected by medicines that may affect alertness or concentration.
- The interaction with grapefruit, erythromycin, clarithromycin, ketoconazole, cimetidine and fluoxetine could increase the blood concentration of loratadine, which was a concern.
- XXXXX was also concerned that the risk of cognitive impairment was more likely when people take the medicine sporadically, as tolerance to these effects usually develop with regular use.
- With the lack of quality controls within the supermarket sector, this meant there was no control on the number of packs that could be purchased at any time. The public would see this as a readily available antihistamine which has the potential for doses above the labelled recommendations.
- There was a potential financial impact for consumers who may purchase medicines from the grocery sector that were not suitable for particular conditions, e.g. cold symptoms.

XXXXX pointed out that:

- With the use of loratadine the need for professional intervention may arise, such as:

    - for the provision of current and tailored information and counselling at the time of supply of a product;
    - for the provision of information on ways to optimise therapy and maximise health outcomes;
    - for advice on follow-up when original symptoms have not resolved after a few days;
    - when other causes (e.g. an infection or more acute illness) may be suspected;
    - when reliance (i.e. more than intermittent use) on a medication intended for short-term treatment has been observed or reported; and/or
    - when referral to a medical practitioner was warranted.

- From a patient safety perspective and to ensure optimal use of loratadine for SAR, the submission supported the retention of current scheduling arrangements for loratadine.
- Making loratadine available through outlets which have no opportunity for professional intervention is contrary to the principles of quality use of medicines.
- The inclusion of appropriate warning statements (relevant to the product when exempted from scheduling) through product packaging and labelling would not afford an adequate level of safeguards that the majority of Australian consumers would expect.

XXXXX provided the following comments:

- The submission noted that no reference to a specific indication was included in the gazetted public notice. Loratadine preparations currently sold at pharmacy were indicated for SAR, perennial allergic rhinitis and chronic idiopathic urticaria.
- The exemption of loratadine for indications other than short-term symptomatic relief of SAR was deemed inappropriate based on considerations of diagnosis, purpose, use and need for access.
- The submission stated that the condition of perennial allergic rhinitis required intervention by a healthcare professional to identify substances that trigger the allergic response, confirm a diagnosis of rhinitis and access the presence of risk factors.
- Stated that, in the case of chronic idiopathic urticaria, there was considerable uncertainty around diagnosis and causal factors.
- Also stated that any exemption from scheduling for loratadine, in the treatment of SAR, should be limited to the treatment of adults and children aged 12 years of age and over when sold in small packs containing no more than 5 days supply. This would be consistent with the recommendation made by ACMS for fexofenadine in April 2011.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risk and benefits; (b) purpose; (c) toxicity and safety; and (d) dosage, formulation, package and presentation.

Members noted that the evaluator did not agree with the proposal to exempt loratadine from scheduling. Members generally agreed that loratadine when in pack sizes of 5 days supply specifically for treatment of SAR was appropriate to be exempt from scheduling. In reaching this decision the Members discussed the evaluators concerns including the following:

- In relation to the affiliations of one of the authors to a subsidiary company of the applicant, Members agreed that it was not a major issue as it would be difficult to find private studies for a minor condition such as SAR.
- In relation to inconsistencies between the Australian PI and the US AHFS Drug Information; and between the application and PI. Members stated that the PI had been approved by the TGA and that the discrepancy of PI and US AHFS was a matter for the TGA, rather than the ACMS.

- In relation to the PSUR not being originally provided by the applicant, Members noted the applicant had provided the latest PSUR in their response to the evaluation report, and that it appeared that no new safety data had been reported.
- Members noted the evaluator's concerns that the applicant had not provided any information based on enquiries of Australian Poisons Centres. Members contended that the applicant's annual report from the NSW Poisons Centre provided by the applicant did not address the evaluator's concerns about specific data on exposures to loratadine.
- Members noted and agreed with the evaluator that the applicant had provided sufficient evidence to back up issues on hypospadias and CV events.

Further the Committee addressed the supplementary data received from the applicant in response to the evaluation report. While the data appeared to address the major deficiencies raised by the evaluator, it was noted that the Committee did not have comments from the evaluator regarding the additional data.

Members generally agreed that unscheduled loratadine would benefit those patients who did not respond to fexofenadine. The Committee noted that it had already exempted some presentations of fexofenadine and that it would be agreed appropriate to do to the same for loratadine.

- Members were of the opinion that it was hard to argue that loratadine was less effective than fexofenadine and that it appeared to be safe when supplied in limited pack sizes. Some Members argued there was still a need to prove that loratadine has the same or better efficacy than the current unscheduled fexofenadine.- However, the Committee noted that assessment of efficacy was a matter for the TGA to determine.
- Members noted that the Kaiser et al study that had demonstrated a better onset of action loratadine vs fexofenadine was published by the author in 2008.

Other issues – Sedation

Members noted clinical studies had reported less sedation for loratadine than other 2nd generation antihistamines, particularly cetirizine. Members recognised that public health benefits would be associated with less sedation from loratadine. However, risk of sedation could occur as the side effects include 'sleepiness'.
Members expressed concerns with the use of the term 'non-sedating' and discussed whether a statement such as 'less-sedating' would be more accurate.

Members noted that drowsiness warnings statement was required for cetirizine which had a greater potential for drowsiness / somnolence as an adverse effect than either loratadine or fexofenadine and discussed if such labelling warning statements should apply to loratadine.

Members noted that individuals may respond differently to such medications, for example some patients presented with sedation after administration of loratadine but not with fexofenadine.

Members recalled that an Appendix K entry for fexofenadine had previously been examined, but the Committee had decided this was not required.

Members remained concerned that 2nd generation antihistamines were being promoted as non-sedating and would be better described as less-sedating. The ACMS referred to the delegate the Committee's concerns regarding the terminology in relation to sedation and drowsiness used in the labelling of second generation antihistamines.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of within 6 months of the delegate's publication of final decisions (i.e. 1 September 2012).

The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risk and benefits; (b) purpose; (c) toxicity and safety; and (d) dosage, formulation, package and presentation.

DELEGATE'S INTERIM DECISION

The delegate decided exempting oral preparations containing 10 mg or less of loratadine in packs containing not more than 5 dosage units for the treatment of seasonal allergic rhinitis (SAR).

The delegate decided an implementation date of within 6 months of the delegate's publication of final decisions (i.e. 1 September 2012).

SUBMISSIONS ON INTERIM DECISION

No public submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision to amend the Schedule 2 and Schedule 4 entries for loratadine to exempt solid dose oral preparations containing 10 mg or less of loratadine in packs containing not more than 5 dosage units for the treatment of seasonal allergic rhinitis (SAR).

The delegate decided to vary the interim decision. The term "solid dose" was inadvertently not included in the interim decision, as per the delegate's referral to the ACMS.

The implementation date for this decision is 1 September 2012.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- scheduling factors for inclusion in Schedule 2 and 4[8]; and

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

· section 52E of the *Therapeutic Goods Act 1989*.

The delegate decided that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* include (a) risk and benefits; (b) purpose; (c) toxicity and safety; and (d) dosage, formulation, package and presentation.

The final decision to amend the loratadine listing in both Schedule 2 and Schedule 4 included the following reasons:

· the benefits of accessing the exempt preparations outweighed the risk with the limited pack sizes.
· Improved access was appropriate and consistent with that of fexofenadine.

SCHEDULE ENTRY

Schedule 2 – Amendment

LORATADINE – Amendment to read:

LORATADINE in solid dose preparations for oral use **except** in preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

(a) in a primary pack containing 5 dosage units of less; and

(b) labelled with a recommended daily dose not exceeding 10 mg of loratadine.

Schedule 4 - Amendment

LORATADINE – Amendment to read:

LORATADINE **except**

(a) when included in Schedule 2; or

(b) in solid dose preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when:

(i) in a primary pack containing 5 dosage units or less; and
(ii) labelled with a recommended daily dose not exceeding 10 mg loratadine

2.1.6 PANTOPRAZOLE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Pantoprazole – seeking advice on a proposal to reschedule from Schedule 3 to Schedule 2 oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease, in packs containing not more than 14 days of supply.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current scheduling of pantoprazole remains appropriate i.e. pantoprazole 20 mg, in packs containing no more than 14 tablets (equivalent to 14 day's supply) in Schedule 3.

BACKGROUND

Pantoprazole is a proton pump inhibitor (PPI) that specifically and dose-proportionately inhibits gastric H+/K+ ATPase, the enzyme responsible for gastric acid secretion in the parietal cells of the stomach. Pantoprazole's selectivity is due to the fact that it only exerts its full effect in a strongly acidic environment (pH < 3), remaining mostly inactive at higher pH values.

In February 1995, pantoprazole was first scheduled in Schedule 4.

In October 1999, the Australian Drug Evaluation Committee (ADEC) (now the Advisory Committee on Prescription Medicines) recommended approval of pantoprazole 20 mg for the acute treatment of reflux oesophagitis and the prevention of relapse of moderate to severe reflux oesophagitis in adults. In April 2001, ADEC recommended approval of an extension to these indications to include treatment of heartburn and other symptoms associated with gastro-oesophageal reflux disease (GORD) (symptomatic GORD) and reflux oesophagitis.

In June 2005, 20 mg pantoprazole was down scheduled to Schedule 3 when in oral preparations for the relief of heartburn and other symptoms of GORD in packs containing not more than 14 days supply. A delayed implementation date of 1 May 2008 was set down.
Subsequently, a number of other PPIs have been similarly down scheduled – lansoprazole (15 mg or less), omeprazole (20 mg or less) and rabeprazole (10 mg or less). Another PPI, esomeprazole (the isolated S-enantiomer of omeprazole), remains Schedule 4.

Appendix H

There have been numerous applications for listing both rabeprazole and pantoprazole in Appendix H, which have not been supported.

In June 2011, a delegate published a final decision that did not support an application to list pantoprazole in Appendix H. Points discussed included:

- A Member asserted that GORD required diagnosis by appropriately qualified practitioners (i.e. pharmacists). The Member also stated that, unlike H2 receptor antagonists (H2RAs), there was a risk that pantoprazole could mask symptoms of more serious disorders and advice was required before a treatment was selected. It was asserted that advertising of pantoprazole would transfer the responsibility of diagnosis onto the consumer, which may inappropriately increase pressure on the pharmacist for supply of this product.
- Members noted that PPI efficacy relied on consistent use over a longer period of time. A Member asserted that advertising may inadvertently reinforce inaccurate consumer expectations that PPIs, like some other GORD treatments, may be used as a "quick fix" and would not require adherence to the treatment protocol.

New Zealand (NZ)

In November 2010, NZ's Medicines Classification Committee (MCC) recommended that omeprazole 20 mg be classified as pharmacy-only when in packs of up to 14 dosage units. In November 2011, the MCC, after considering further submissions on this pharmacy-only supply of omeprazole, agreed to increase the allowed pack size from 14 to 28 dosage units (www.medsafe.govt.nz/profs/class/mccMin15Nov2011.htm).

In November 2011, the MCC also recommended that the scheduling and labelling requirements of pantoprazole 20 mg should be the same as omeprazole i.e. pharmacy-only for the short-term symptomatic relief of gastric reflux like symptoms in sufferers aged 18 years and over. Points from the MCC discussion included:

- Overall MCC felt that, because the safety profile of pantoprazole was similar to and arguably better than omeprazole, the scheduling of both should be similar. Evidence was provided that pantoprazole 20 mg a day for 14 days was safe and effective. Overseas approval at the proposed level also supported a reclassification.
- The Periodic Safety Update Report (PSUR) revealed no significant new safety issues since the change in classification in international markets and confirmed the safety profile.
- Discussed the merits of classifying all PPIs to the same classification. The MCC noted that therapeutic group reclassifications could lead to a novel member of the therapeutic group that had a significantly different risk-benefit profile being reclassified without any supporting data.
- MCC were comfortable with a 28 day pack, the same as omeprazole.
  - Members noted that the MCC recommendations were implemented in early February 2012.

XXXXX submitted an application direct to the Scheduling Secretariat requesting consideration of a pantoprazole proposal similar to that discussed by the MCC in November 2011. A delegate has referred this matter to the ACMS for consideration as this issue could benefit from public consultation and advice from the ACMS.

SCHEDULING STATUS

Pantoprazole has a parent entry in Schedule 4 with a Schedule 3 entry for oral preparations containing 20 mg or less of pantoprazole per dosage unit for the relief of heartburn and other symptoms of GORD, in packs containing not more than 14 days' supply. Pantoprazole is also not listed in Appendix H.

INITIAL SUBMISSIONS

Application

XXXXX proposed rescheduling of pantoprazole 20 mg, in packs containing no more than 14 tablets (equivalent to 14 day's supply) from Schedule 3 to Schedule 2. Key applicant's arguments included the following (details of the application are further discussed in the evaluation report section):

- Robust clinical evidence supported the efficacy and placebo-like safety profile of pantoprazole, which had a regulatory status equivalent to Schedule 2 in 33 other countries, including all 27 member countries of the European Union (EU).
- Data supported the suitability of pantoprazole in Schedule 2 and as an appropriate option for the self-management of heartburn, which was extremely common and predominantly self-managed.
- The majority of Australians reporting heartburn and indigestion had no definite explanation for their symptoms and were considered to have non-ulcer (or "functional") dyspepsia, which was not life-threatening and had not been shown to be associated with any increase in morbidity.
- Claimed that within the Australian regulatory environment, it was already accepted that the general public were able to self-diagnose and self-manage heartburn and indigestion without the involvement of a health care practitioner. In particular, it was noted that antacids and the H2RA, ranitidine, were available as unscheduled medicines for this purpose (ranitidine was in Schedule 2 when in packs of 14 dosage units or less with an exemption from scheduling when the dosage units had 150 mg or less of ranitidine). The indications and duration of use of ranitidine and pantoprazole were similar.
- The international consensus was that PPIs were more effective than alternative OTC treatments, including ranitidine, and posed no additional risk. Published guidance for the management of reflux symptoms with OTC PPIs supported these conclusions.
- Rescheduling to Schedule 2 had the potential to provide a number of benefits, including improvement in the quality of care and a more cost effective use of healthcare resources. Schedule 2 access would encourage self care, provide more effective symptom control and result in more rational use of medicines and use of healthcare resources. Rescheduling would also give consumers an alternative choice to antacids and H2RAs, and may encourage consumers to seek advice in the event that the product does not relieve their symptoms.

Evaluation Report

Due to the complexity and size of the application, this was referred for external evaluation. The evaluator supported the applicant's proposal.

The evaluator concluded that there was a reasonable argument for the provision of OTC pantoprazole 20 mg without necessarily involving a pharmacist in every sale. The risk of adverse outcomes appeared very low. Circumstantial evidence supported the argument that this could lead to a more cost-effective use of healthcare resources, as well as better efficacy for consumers using Schedule 2 products for symptoms of heartburn. Key additional reasons for the evaluator's conclusions included:

- Pantoprazole 20 mg has been in Schedule 3 for the past 3 years. Indicated that in making this OTC scheduling decision, the NDPSC had implicitly accepted that both pantoprazole and the indication were suitable for self treatment.
- The application contained a well-supported argument that quality use of medicines for heartburn could be maintained and possibly improved by rescheduling to Schedule 2. This would still allow for provision of pharmacist advice when required by the consumer. This may improve efficient use of healthcare resources.
- PPIs as a group were recognised as being the most efficacious treatment for heartburn and other symptoms of GORD and the greater availability of pantoprazole may result in improved management for the majority of consumers with heartburn.
- Post-marketing surveillance data indicated a low risk of toxicity and a wide therapeutic index, resulting in safety at least as good as ranitidine 150 mg, which was unscheduled.

The evaluator's specific comments and evaluation of claims against Section 52E(1) of the *Therapeutic Goods Act 1989* are summarised below:

- *Efficacy, safety, and regulatory status in Europe*: Controls equivalent to Schedule 2 in Europe, where regulation of medicines was of a high standard and similar to that in Australia, was noted and provided reassurance that rescheduling may be appropriate.
- *NZ regulatory status*: While the application only included a maximum pack size of 14 tablets, consistent with the Schedule 3 entry, the decision made in November 2011 by the NZ MCC was likely to result in future applications to increase pack size to 28 dosage units to maintain trans-Tasman harmony.
- *Re-scheduling benefits*: The applicant argued that PPIs were more effective than the other medicines available for heartburn, and therefore their easier availability would result in better outcomes for patients, less involvement by pharmacists, and less need for consultation of GPs. These were reasonable arguments. A key issue was that consumers whose symptoms do not respond to a PPI would require medical evaluation because their symptoms may be due to a serious pathology. Provision of this information in a highly accessible format would be vital to the safety of the proposed rescheduling.

Section 52E Criteria

(a) Risks and benefits

- The applicant provided reports of several studies of good design supporting the claim that pantoprazole 20 mg daily was more effective and had a more rapid onset of action than H2RAs.
- The safety profile of PPIs as a group was reassuring. For pantoprazole specifically, a total of XXXXX patients had been exposed in safety-relevant trials, with a similar safety profile to that of placebo. Post-marketing surveillance data from an estimated total cumulative exposure of XXXXX patients indicated that approximately XXXXX experienced an adverse event (the provided PSUR indicated no new safety concerns). Most adverse events were minor and transient in nature, and included symptoms such as diarrhoea, nausea and headache. Australian data included only XXXXX case reports of any adverse event associated with pantoprazole; only XXXXX per cent of these were related to the 20 mg dose.
- Drug-drug interactions have been investigated because pantoprazole is a substrate for the cytochrome P450 enzyme system (CYP450). No clinically significant interactions were demonstrated in specific testing with a number of other drugs also metabolized by the same isoforms. Omeprazole has been demonstrated to have inhibitory effects on CYP450 enzymes that result in clinically important interactions, but pantoprazole was regarded as being a less potent inhibitor. There was, however, evidence of a reduction in the bioavailability of some drugs with pH-dependent absorption, including ketoconazole and atazanavir, with concomitant use of PPIs and these combinations were contraindicated.
- At high doses, PPIs were associated with a dose-dependent reduction in protection from hip fracture in patients concurrently taking alendronate. The hazard ratio for low doses of PPIs was no different from that for people not taking PPIs at all.
- Overall, apart from the reduction in bioavailability of ketoconazole and atazanavir, the risk of clinically relevant interactions seemed low. The proposed consumer medicine information (CMI) warned about concurrent use with atazanavir; the evaluator asserted that ketoconazole should also be included in the CMI warnings section.

(b) Purpose and extent of use

- The indications were symptomatic relief of heartburn and other symptoms of GORD. This was similar to that approved in Europe for non-prescription pantoprazole 20 mg ("short-term treatment of reflux symptoms [e.g. heartburn, acid regurgitation] in adults").
- Up to 60 per cent of Australians with heartburn and indigestion have no definite explanation for their symptoms, and were considered to have functional dyspepsia, which was not associated with specific pathology or any increase in morbidity.
- The high prevalence of the condition (up to 25-30 per cent of the adult population) and its considerable impact on patients, health care services and the community as a whole, were all noted and supported by good quality data.
- The application included several references to studies that demonstrated the efficacy of on-demand treatment with PPIs and the appropriate use of OTC PPIs for episodic heartburn.

- Global exposure to OTC pantoprazole was approximately XXXXX defined daily doses per 6 months, or XXXXX treatment courses. In the same period only XXXXX adverse drug reaction reports were submitted (0.004 per cent).

(c) Toxicity and safety

- As discussed under heading '(a) Risks and benefits', there appeared to be no safety concerns relating to self medication with pantoprazole 20 mg, with the appropriate information having been provided to consumers regarding important drug interactions.
- The risk of masking underlying conditions requiring medical attention was argued by the applicant to be the same as for any other OTC products for heartburn. This was a reasonable statement, but depended crucially on appropriate labelling and warnings for the consumer. The proposed CMI contained appropriate wording for this purpose, and advised consumers to seek medical advice if symptoms persist beyond 14 days. The evaluator asserted that it seemed unlikely that significant adverse outcomes would arise if the consultation were to be delayed by 14 days i.e. until day 28 (in line with NZ pharmacy-only pack size).

(d) Dosage, formulation, labelling, packaging and presentation

- XXXXX.
- The proposed labelling included appropriate instructions and cautions, with the exception of any warning about concomitant use of ketoconazole or other drugs with pH-dependent absorption (such as itraconazole and quinolones). It would be reasonable to expect these warnings to be provided in the CMI rather than the label.
- The proposed labelling contained the same warnings as the currently approved Schedule 3 label.

(e) Potential for misuse / abuse

- Not a drug of abuse and there was no likelihood of diversion for illicit use.
- The major hazard associated with the use of this substance, given its low incidence of adverse effects in therapeutic doses, was accidental poisoning. The risk of serious outcomes was very low, given the very wide therapeutic index in animal toxicity studies and the small pack size.

(f) Other matters

- The application compared the efficacy and toxicity of pantoprazole 20 mg with ranitidine.
- 150 mg ranitidine has been available unscheduled for 5 years and audits had demonstrated that consumers were capable of self diagnosis and self management without the involvement of a pharmacist in every sale.
- The applicant also pointed out that neither ranitidine nor pantoprazole interacted with other OTC medicines, so that a drug-drug interaction was unlikely to occur in a patient not under

medical supervision. Overall, the applicant argued that pantoprazole 20 mg and ranitidine 150 mg-300 mg were very similar in benefit and risk and that pantoprazole 20 mg was just as suitable as ranitidine to be included in Schedule 2. This was a reasonable argument.

The evaluator also favourably reviewed the application against the Scheduling Policy Framework factors for Schedule 2. This review largely reiterated the matters addressed above, but did additionally note that the applicant had developed an extensive education program for pharmacists and pharmacy assistants.

Applicant's Response to the Evaluation Report

The applicant agreed with the evaluator's conclusions and recommendation. Key points from the applicant's response included:

- Confirmed that they were only seeking Schedule 2 for packs of no more than 14 days' supply. Asserted that limiting the pack size to no more than 14 days' supply would encourage consumers to seek advice in the event that the product did not relieve their symptoms. Noted that the proposed labelling and CMI supported this message. 14 days' supply was also consistent with other unscheduled and Schedule 2 heartburn relief medications e.g. ranitidine 300 mg.
- Agreed with the evaluator's assessment of the risks and the need for the provision of information in an accessible format.
- Noted that the concern for the potential for hip fractures associated with concurrent therapy with alendronate or interstitial nephritis were dose and duration dependent. Asserted that the risk of these were minimised in OTC dosing and short-term use.
- Noted from the December 2011 TGA Medicines Safety Update bulletin (www.tga.gov.au/pdf/msu-2011-06.pdf) that, while acute interstitial nephritis (AIN) was a class effect of PPIs, the incidence of AIN caused by PPIs was unknown. AIN was also a class effect of non-steroidal anti-inflammatory drugs, many of which were either unscheduled or Schedule 2.
- Agreed that there was potential for reduced absorption of pH-dependent drugs, such as atazanavir and ketoconazole. Agreed with the evaluator's proposal to address this in the warnings section of the CMI.
- Proposed to include a label statement 'Ask your doctor or pharmacist before use if you are taking other medicines regularly', a TGA standard label for PPIs.
- Advised that when TGA was assessing the adequacy of the above statement, the Pharmaceutical Society of Australia (PSA) submitted a request to TGA that the interaction of PPIs with clopidogrel should warrant consideration of a warning statement to seek health professional advice if using blood thinning medicines. In response, the TGA considered that it would be misleading if consumers were only warned about this particular interaction and not to other interactions and may assume that they did not need to check if they were not taking clopidogrel. In line with TGA's conclusion, the applicant proposed to remove the specific warning statement relating to atazanavir and rely instead on the above general label statement.

February 2012 Pre-meeting Submissions

XXXXX (a pharmacist) and XXXXX supported the proposal.

XXXXX did not support the proposal, asserting that PPIs required some form of consultation with the pharmacist to ensure correct and appropriate use before they were sold. XXXXX asserted that while there were some public risks which warranted pantoprazole and other PPIs remaining as Schedule 3, it would be appropriate to allow an Appendix H listing.

Additional details are summarised below:

XXXXX

- Noted that heartburn was already considered to be a condition appropriate for treatment with Schedule 2 and unscheduled medicines, such as antacids and ranitidine.
- Reiterated the applicant's arguments that pantoprazole had a wide therapeutic index and excellent safety profile (equivalent to placebo) with few significant interactions. The time-limited use (up to 14 days), meant that the potential for clinically significant interactions was further reduced. There was virtually no risk of misuse or abuse.
- Regarding the possibility of masking a condition more serious than heartburn, noted that the risk was essentially equivalent to that for ranitidine. This small risk was likely to be lower for Schedule 2 pantoprazole than for currently unscheduled products, as there would be opportunity to consult a pharmacist, either upon direct customer request or via implementation of pharmacy staff protocols.
- In 2009, XXXXX an Australian Pharmacy Audit of the OTC management of heartburn (Bell *et. al.*, 2010, 'An Australian pharmacy audit of the management of heartburn and the role of over-the-counter proton pump inhibitors', *Aust Pharmacist*, vol 29(6), pp 526-528). The audit identified no concerns or impediments regarding consumer ability to self determine the appropriateness of pantoprazole; and this was validated by a subsequent pharmacist review. The audit confirmed that consumer comprehension of the XXXXX packaging was excellent.
- Pharmacists had more than 3 years experience with Schedule 3 pantoprazole. This was sufficient time for pharmacy to become familiar with its use as a non-prescription medication and to determine its appropriate availability. It was now appropriate for pantoprazole to be rescheduled to Schedule 2 to allow consumers easier access to a safe and, in many cases, more effective medication.

XXXXX

- Noted the wide availability of non-prescription medicines for the treatment of heartburn and symptoms of GORD. PPIs were regarded as first line therapy for GORD and were considered to be more effective than H2RAs.
- Argued that pantoprazole met the SPF scheduling factors for Schedule 2. It had a well established safety profile and low risk of misuse, and it was suitable for short term treatment. A number of potential side effects were listed for pantoprazole but most were

mild to moderate in type and/or degree. The most common side effects were largely manageable and other more significant side effects (e.g. increase in risk of hip fracture) were not associated with short term, low dose use.

- Some concern may be raised regarding the possibility of masking more serious conditions; however, the risk of this was low for short term use. Where a consumer may indicate repeated use of pantoprazole or report any alarm symptoms, the pharmacist would be able to initiate a referral for medical attention.
- Had previously supported the inclusion of pantoprazole in Appendix H. Inclusion of pantoprazole in Schedule 2 would result in fewer restrictions on advertising (to consumers), thereby widening options for the conduct of education and training for pharmacy assistants. This was beneficial in the community pharmacy setting, where non-pharmacist staff have a role in assisting with the supply of therapeutic goods and referring the consumer to a pharmacist, when required for certain products and conditions.
- XXXXX guidance document for pharmacists for the provision of pantoprazole as Schedule 3. If pantoprazole was rescheduled to Schedule 2, would advocate continuity and appropriate best practice by drawing out relevant points from the Schedule 3 guidance document for pharmacists.
- XXXXX in partnership with the applicant for the provision of relevant education and dissemination of appropriate information to pharmacists, pharmacy assistants and consumers.

XXXXX

- Referred to a review which advised that PPIs seemed to be associated with increased risk for adverse cardiovascular outcomes, regardless of clopidogrel use for myocardial infarction (Charlot, *et al*, 2010, 'Proton-Pump inhibitors are associated with increased cardiovascular risk independent of clopidogrel use', *Ann Intern Med*., vol 153, pp 378-386).
- There was some concern about an association between chronic PPI use and fractures of the hip or other sites, with the risks increasing with dose and duration of exposure. In 2011, the US FDA concluded that fracture risk with short-term, low dose non-prescription PPI use was unlikely. The US FDA acknowledged that consumers may take the products contrary to the instructions on the label.
- There have been long-standing suspicions that acid-suppressive therapy increased the risk of small intestinal bacterial overgrowth, though it has been uncertain whether this risk was restricted to certain patient groups such as the elderly, those infected with *Helicobacter pylori* or those with irritable bowel syndrome.
- Inhibition of gastric secretion of acid and gastric enzymes could affect the absorption of nutrients such as calcium, iron and vitamin B12. Evidence from large case-control studies suggested an association between current PPI use and community-acquired pneumonia.
- Acknowledging the seriousness of these risks, PPIs have been available for several years as a Schedule 3 medicine without undue adverse health outcomes. Pharmacists supply non-prescription PPIs according to a professional protocol with referral to the GP for more serious issues and identified concerns.
- Although pantoprazole as Schedule 2 would maintain access to pharmacist advice and pharmacy assistants were trained to handle Schedule 2 and Schedule 3 medicines, believed

PPIs should remain available as a Schedule 3 medicine, requiring pharmacist intervention in supply to ensure safe and appropriate use.

- Was concerned with the potential Schedule 2 availability of pantoprazole through licensed non-pharmacy retail outlets in rural/remote areas. In such circumstances, there was no training for any of the retail staff and there was no access to health professional advice. People living in rural and remote areas have generally older populations, higher levels of health risk and higher rates of chronic disease. Although people in rural/remote areas may be disadvantaged to a small extent with regards to access to PPIs for the treatment of oesophageal reflux, other effective treatments such as ranitidine remain readily available.
- It was also anticipated that with the implementation of electronic patient records, consideration would be given in the future to the inclusion of non-prescription medicines on a person's medication history. It would be reasonable to expect that Schedule 3 medicines would be most likely considered in the first instance and believes there would be benefit in recording the incidence and treatment of reflux as part of a person's health records.

Appendix H

- Acknowledged the work to date in developing protocols and training to support the supply of pantoprazole. With this in mind, supported listing of pantoprazole and other PPIs within Appendix H which, in addition to allowing advertising, would allow provision of information to pharmacy assistants to enhance their capacity in responding to direct product requests for these medicines.

EXPERT ADVISORY COMMITTEE DISCUSSION

XXXXX.

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity. Members noted the evaluator's support for the proposal. Several Members agreed that pantoprazole was a safe, efficacious, low risk treatment for a minor ailment recognisable by consumers. A Member also supported the argument put forward by the applicant that pantoprazole was more efficacious than ranitidine and asserting that there would be a public benefit from increased ease of access to pantoprazole which would facilitate self management of this condition.

Members noted that the June 2005 NDPSC minutes, while supportive of a Schedule 3 listing, never stated that pantoprazole was safe for self selection and self treatment. The applicant's argument that the NDPSC had reached this conclusion, although reiterated by the evaluator, was inaccurate; it was the applicant's opinion, rather than a fact, that such a conclusion had been implied when the NDPSC agreed to list pantoprazole in Schedule 3.

Members noted that many of the concerning adverse effects were associated with chronic use. A Member discussed that as GORD was often a chronic ailment, Schedule 2 access could increase the likelihood of repeat, chronic use of pantoprazole. Another Member commented that the 14

days' supply limit would mitigate this risk. Several Members advised the Committee of widespread chronic use of ranitidine and were concerned that consumers might be inclined to use a Schedule 2 pantoprazole product in a similar fashion. A Member commented that the risk of such misuse would be more appropriately addressed through mandatory pharmacist involvement in supply.

A Member also discussed that the chronic use concern could be exacerbated by consumer expectations for immediate relief, often the case for the existing unscheduled H2RAs and ranitidine. While agreeing that pantoprazole was more efficacious, it was argued that the limited acute onset of this efficacy might, without advice from a pharmacist, lead to higher dosing or use of mixed multiple medications.

Several Members further noted reports that there remained some unknowns about pantoprazole – even if they were mostly associated with chronic use. A Member noted that some of these concerns actually appeared to be growing in the literature. Several Members commented that while these unresolved concerns existed, it would be appropriate to mandate the involvement of a pharmacist in the supply of pantoprazole. Another Member agreed that it would seem prudent for the substance to spend more time being supplied as a Schedule 3 medicine while further data is collected and assessed.

Member suggested that the very effectiveness of pantoprazole might also be a reason to retain pantoprazole in Schedule 3. Members noted that retention in Schedule 3 would enhance the likelihood that a pharmacist would detect a patient who was repeatedly accessing pantoprazole, allowing the pharmacist to advise that unresolved GORD symptoms when using pantoprazole were a reason to consult with a GP.

Members noted but did not support alternative resolutions on this matter, including an Appendix H proposal discussed below.

Appendix H

Members discussed a suggestion from a submission that all current Schedule 3 PPIs remain in Schedule 3, but with an Appendix H listing. Members noted that the original application did not propose this and had not provided any new information specific to an Appendix H consideration. Members commented that there was little data that could be used to overturn the previous decisions that a case had not been established for the public benefit / need for advertising.

Members noted that the submission which raised the Appendix H proposal appeared to be under the belief that Appendix H was necessary for education campaigns about PPIs and GORD. A Member reiterated advice from previous considerations that there were legal avenues for education, such as for pharmacy assistants, and that it was specific brand advertising that was restricted. Members noted that there would be little commercial incentive to non-branded education as competitors would also benefit.

Members discussed that it would be difficult to undertake a future Appendix H consideration which did not address all Schedule 3 PPIs at same time. Members noted that there were no precedents for an Appendix H class entry and asserted that the intended focus of Appendix H was advertising of individual substances. Members therefore commented that any future consideration should address a specific PPI or PPIs rather than proposing a generic class entry.

The Committee generally agreed that any future Appendix H consideration, whether for pantoprazole alone or for all the current Schedule 3 PPIs, would need to be the result of a separate application that specifically addressed the public benefit / need for brand advertising.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits; (b) purpose and extent of use; and (c) toxicity.

DELEGATE'S INTERIM DECISION

The delegate agreed that the current scheduling of pantoprazole remains appropriate i.e. pantoprazole 20 mg, in packs containing no more than 14 tablets (equivalent to 14 day's supply) in Schedule 3.

SUBMISSIONS ON INTERIM DECISION

Three submissions were received. One submission will not be considered by the delegate because as a pre-meeting comment was not received. The redacted submissions can be viewed at the following URL: http://www.tga.gov.au/industry/scheduling-submissions.htm

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current scheduling of pantoprazole remains appropriate i.e. pantoprazole 20 mg, in packs containing no more than 14 tablets (equivalent to 14 day's supply) in Schedule 3.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- scheduling factors for Schedule 3[9]; and
- section 52E of the *Therapeutic Goods Act 1989*.

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

The delegate decided that the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 include (a) risk and benefits, (b) purposes, dosage and formulation and (c) the toxicity of a substance.

The final decision that the current scheduling of pantoprazole remains appropriate included the following reasons:

- the information presented does not support the down scheduling of pantoprazole.
- Pharmacist intervention may be required to ensure the quality use of the medicine and to ensure appropriate referral to a medical practitioner occurs if symptons persist.
- There are still concerns regarding the potiential for chronic use in patients expecting immediate relief as well as unresolved concerns raised by ACMS regarding chronic use.

2.1.7 PARACETAMOL

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate sought advice from the ACMS to further restrict the pack size requirements for paracetamol to be exempt from scheduling (currently no more than 25 tablets at no more than 500 mg per tablet).

This proposal arose from the minutes of the 45th meeting of New Zealand's Medicines Classification Committee (MCC), accessible at www.medsafe.govt.nz/profs/class/mccMin12April2011.htm. The MCC had specifically proposed that unscheduled paracetamol packs be restricted to no more than 10 g of total paracetamol (e.g. 20 x 500 mg tablets).

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that Australia harmonise with New Zealand and restrict the exempt pack size requirements for paracetamol to packs containing 10 g or less of paracetamol. The Committee further recommended an implementation date of at least 6 months be set i.e. 1 January 2013 or later.

BACKGROUND

Paracetamol is a non-opioid analgesic. It is a p-aminophenol derivative that has analgesic and antipyretic effects without anti-inflammatory activity.

SCHEDULING STATUS

Paracetamol preparations containing ≤ 500 mg of paracetamol as the only therapeutically active constituent (other than phenylephrine, effervescent agents or guaiphenesin) in packs ≤ 25 are currently exempt from scheduling (when compliant with labelling, packaging and age

restrictions) i.e. 12.5 g of total paracetamol. However, these preparations become Schedule 2 if combined with another therapeutic active such as ibuprofen.

Paracetamol is Schedule 4 when: combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules; in slow release tablets or capsules containing more than 665 mg of paracetamol; in non-slow release tablets or capsules containing more than 500 mg of paracetamol; in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol; or for injection.

INITIAL SUBMISSIONS

Application

At its April 2011 meeting, the NZ Medicines Classification Committee (MCC), received an objection to its intention to harmonise with Australia and increase the pack size of general sale (unscheduled) medicine from 10 g to 12.5 g.

The MCC considered the objection and the additional data package provided. The data supported the MCC's previous conclusion that there was a difference in risk between a 10 g and a 12.5 g pack size of paracetamol. The data also demonstrated that while ingesting 12 g of paracetamol compared with 10 g would not significantly increase the risk of mortality, ingestion of over 12 g increased the risk of harm and the need for intervention. Evidence was also provided that taking the standard dose of paracetamol for an extended period of time, even minimally, can be associated with hepatic injury in some circumstances i.e. when taken with other hepatotoxic substances.

The MCC also stated that an increase to the pack size would contraindicate the spirit of the New Zealand Suicide Prevention Strategy, which specifically encourages the adoption of safer dispensing of medicines (and other lethal chemicals) used in suicide and suicide attempts. The New Zealand Suicide Prevention Action Plan made mention of results seen in the UK which saw, as a result of reducing the pack sizes of paracetamol, a significant reduction in deaths, hospital admissions and liver transplants from paracetamol overdose.

Further, the MCC noted that these UK findings suggest consideration should be given to additional restrictive measures. This was also one of the key areas highlighted in the Action plan i.e. review the feasibility of tightening the regulations of paracetamol to reduce the associated risks.

In conclusion, the MCC decided that harmonizing with Australia i.e. increasing the maximum packet size, would be in direct opposition to the New Zealand Suicide Prevention Strategy and Action Plan. Further, the recommendation was made to Australia to harmonize with New Zealand i.e. from 25 to 20 dosage units.

Evaluation Report

No evaluation report was conducted.

Pre-meeting Submissions

XXXXX

XXXXX submission contended that the current scheduling of paracetamol should remain unchanged. The submission stated that there was no safety-related evidence that the Australian pack size requirements should be changed. Further, that previous reports indicate intentional overdosing with paracetamol reflects jurisdictional peculiarities. The submission noted that the New Zealand Suicide Prevention Action Plan's references to UK findings were from a 2004 study. However a 2011 paper, compiled by several of the same authors as the 2004 paper, investigated the impact of paracetamol pack sizes between the UK and Ireland (with maximum pack sizes of 16 tablets and 12 tablets respectively). The study concluded that overall the differing pack sizes did not appear to result in 'a major difference in the size of overdoses'.

The submission also made references to several other papers. These papers showed that, overall, pack size limitation did not reduce paracetamol related deaths or harm. The submission further suggested that there was no evidence from other jurisdictions that the reduction of paracetamol pack size would have a beneficial long-term impact. Given the evidence provided, the proposed reduction would be unlikely to have any beneficial impact.
The submission noted that the impact would also affect unscheduled combination products. These products had not been implicated in deliberate self-poisonings.

The submission stated that "the Council of Australia Governments (COAG) principles of best practice regulation require any government action to be proportional to the level or risk". The submission then argued that the current Australian scheduling of paracetamol did not pose an increased level of risk over that of New Zealand. Therefore, it would be disproportionate to reduce the maximum pack size from 25 to 20 dosage units.

The submission also addressed the following under section 52E of the *Therapeutics Goods Act 1989*:
(a) Risks and benefits of the use of a substance

- Paracetamol had a long history of safe use in Australia. It had a well documented safety profile. Due to the low risks associated with paracetamol it was unscheduled in certain circumstances. Pack size restrictions were designed to primarily reduce harm associated with deliberate self-poisonings. Studies referred to in the submission show that pack size restrictions had not provided any long term benefit in harm reduction.

(c) The toxicity of a substance

- Paracetamol had a well documented safety profile and poses very low risk to the patient if used according to the label instructions.
- Pack size restrictions were designed to primarily reduce harm associated with deliberate self-poisonings.

(d) The dosage, formulation, labelling, packaging and presentation of a substance

- Paracetamol products exempt from scheduling must include specific label statements and warnings in relation to the maximum dose, the duration of use and actions to take if an overdose is taken or suspected.
- The current pack size of no more than 25 tablets was enough for three days treatment for an adult. Further restricting the pack size would not be expected to have any long term beneficial impact.

(e) The potential for abuse of a substance

- Paracetamol could be used in episodes of deliberate self-poisoning. The submission stated it was unaware of any evidence to suggest that paracetamol was associated with dependence, abuse or illicit use.

XXXXX

XXXXX did not support harmonisation and urges the current scheduling of paracetamol remain unchanged. While the submission acknowledged that consumer safety was paramount, it was believed that there was no evidence-based rationale for change in Australia.

The submission noted that previous TGA reviews on OTC paracetamol had not endorsed reductions or restrictions on pack sizes. Further, the submission noted reviews undertaken in other countries did not support pack size restrictions.

It was also noted that the risk of developing liver injury was extremely low in patients that use paracetamol as per label directions. Moreover, there was no evidence that the current maximum pack size of 25 tablets (12.5 g) poses any public health risks. The submission highlighted that in August 2011 the TGA provided information relating to paracetamol dosing. The TGA was quoted as saying "Labelling and packaging requirements in Australia have proven effective in minimising the risk to either accidental or deliberate overdose with paracetamol."

The submission also made reference to the New Zealand Suicide Prevention Action Plan and the UK data cited therein. In particular, the UK data had been superseded with newer data (as mentioned in the previous submission). The submission also noted that in 2001 the MCC recommended an increased pack size to 25 tablets (2 years after the UK legislation change). In the MCC minutes it was stated that reducing pack sizes would not reduce toxicity in paracetamol overdoses as consumers were able to purchase multiple packs and moreover, seriously suicidal

patients hoarded and stored medicines and as such pack size limitations would not affect the outcome of an overdose in such a situation.

The submission noted jurisdictional peculiarities which exist in New Zealand regarding the availability of paracetamol. The PHARMAC scheme enables contracted suppliers to provide paracetamol in packs of 1000 tablets (100 blister strips of 10). These are then dispensed in a PHARMAC dispensing pack. These packs did not appear to require specific warnings in the same manner required by the manufacturer's packs. The submission stated that 32 per cent of paracetamol tablets dispensed were in the PHARMAC dispensing pack. Thus, 1 in 3 packs in the general population had no warnings of overdose or the potential for liver failure.

However, Australian packs of paracetamol had full labelling regardless of the manner they are available. This situation was unique to New Zealand and therefore should not be reasonable grounds to change the pack size in Australia.

XXXXX

XXXXX supported the proposal, in the interests of public health. The following criteria were addressed under section 52E of the *Therapeutics Goods Act 1989*:

(a) Risks and Benefits of the use of a substance

- If the current pack size of 25 dosage units were to be consumed, either deliberately or accidentally, significant hepatic injury would occur. If a patient survived, it would likely financially burden the publically funded healthcare system. Restricting the pack size to 20 dosage units, at 500 mg per unit, would slightly reduce the risk of hepatic injury and in turn reduce the burden on the public healthcare system.

(c) Toxicity of a substance

- Paracetamol, when used according to label instructions, poses a low risk. Restrictions on pack size are primarily intended to address the risk of self-poisoning. The submission noted that accidental overdose was a significant issue in the USA with the FDA asking manufacturers of prescription paracetamol combination products to limit the dose to 325 mg per dosage unit. The submission stated that there was no data that indicates taking more than 325 mg of paracetamol per dosage unit provides more pain relief. This would also help to further reduce the likelihood of overdose.

(d) The dosage, formulation, labelling, packaging and presentation of a substance

- The submission noted that unscheduled paracetamol products require specific label warnings relating to maximum dose, duration of use and what to do in case of an overdose. The current pack size provided three days treatment for an adult. Given the potential risk for hepatic damage, the pack size should be reduced to not more than 20 tablets.

(e) The potential for abuse of a substance

· No evidence suggests paracetamol was associated with dependence, abuse or illicit use.

XXXXX

XXXXX supported the proposal but felt consideration should be given to re-scheduling the unscheduled formulations to Schedule 2 as non-professional outlets that sell this product do not provide counselling or have any procedures in place to ensure the appropriateness of the product for the consumer.

XXXXX

XXXXX opposed the proposal unless there was sufficient evidence to demonstrate a public benefit. The submission did not support the proposal if it was to solely harmonise with New Zealand. It was also noted that such a change would pose a significant burden on manufacturers of these products. A review of the scheduling and labelling was also recommended for paracetamol products to facilitate pharmacy advice in order to minimise accidental overdose via inadvertent duplication or intentional overdose due to poor pain control.

The submission highlighted concerns regarding the vast array of paracetamol products available both, unscheduled and from within the pharmacy, and the risks for patients to intentionally or inadvertently consume excessive amounts of paracetamol. It was also noted that consumers were previously advised not to exceed eight 500 mg dosage units of paracetamol per day. This warning stated not to exceed 4 g per day. The submission was concerned that limitations with consumer health and numeracy literacy could significantly impact the understanding of this limit and or the unknown consumption of multiple medicines which contain paracetamol.

The submission noted that while there was a risk of people using paracetamol in suicide attempts, the greater risk of accidental or intentional overdose was by those seeking better pain relief. The submission pointed to data that suggests staggered overdose patients were more likely to endure liver and brain problems, require kidney dialysis or breathing assistance and were at greater risk of dying than single overdose patients.

The submission reiterated the US FDAs approach to paracetamol, as noted in another submission. It was further noted, that over half the paracetamol overdoses in the USA are accidental. Contributing factors included treating different conditions or symptoms with multiple paracetamol containing products, unaware that products contain paracetamol, extensive retail availability as well as limited knowledge on associated liver injury. Also, in addition to limiting the dosage unit (to 325 mg) the US FDA had mandated that prescription products include a black box warning for information regarding the risk of severe liver injury and the potential for severe allergic reactions with use. These changes did not apply to non-prescription products.

The submission concluded that the most appropriate solution, without hindering consumer access, would be to limit the scheduling exemption to products which only contain paracetamol

with 500 mg dosage units, assign the minimum restriction for combination products containing paracetamol or single ingredient products with
500 mg to 1000 mg dosage units as Schedule 2, mandate large print warnings on all paracetamol products that state the product contains paracetamol and that excess of the recommended dose can be dangerous.

EXPERT ADVISORY COMMITTEE DISCUSSION

XXXXX.

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutics Goods Act 1989* included (a) risks and benefits; (c) toxicity; (d) dosage, formulation, labelling, packaging and presentation; and (e) the potential for abuse.

The Committee noted the following information:

- paracetamol poisoning is a common form of self poisoning and occurs in 30-40 per 100,000 of the population;
- approximately 8000 patients per year are treated for paracetamol overdose taken as deliberate self-harm and are usually with out suicidal intent;
- the risk of death due to paracetamol overdose was rare (1 in 1000)and that as such it is a relatively poor outcome measure compared to a need for antidote treatment; and
- self-harm is usually impulsive and not the same as deliberate suicidal intent.

The Committee identified a potential problem with the public submissions received. It appeared there was a misinterpretation of the literature as well as the definitions of self harm, overdose and suicide. The Committee noted that overdose was not always suicidal. Self harm was largely impulsive and not the same as deliberate suicidal intent. The public submissions emphasised suicides without referring to hospital admissions due to suspected paracetamol overdose for whatever reason.

The Committee noted that, while this was referred by the MCC, paracetamol scheduling should not be harmonised for harmonisations sake and that it should be considered in relation to the current Australian situation. The Committee did however note the data considered by the MCC as well as the UK and Ireland, as they all took similar action in reducing the pack sizes of paracetamol. It was noted that prior to the changes being made in the UK and Ireland, paracetamol had been available in large quantities in bottles without child resistant closures. Blister packaging had been introduced as part of the changes.

The Committee discussed whether current data showed a link between pack size and the amount of paracetamol consumed in deliberate overdoses. The Committee noted that, in Australia, the median dose taken in an overdose was 12 g, while the mean ingestion was
12.5 g. It was noted that while consumers could purchase multiple packs, the data correlated with the current available pack size, which was an important factor in overdose. The Committee noted

that this agreed with data from 1995 and 2011. The Committee also noted that the TGA review of paracetamol in 2004 did not suggest nor review data in relation to reducing pack size.

On the premise that pack size was linked to the amount of paracetamol consumed in overdose, the Committee discussed whether the current pack size of 12.5 g remained appropriate. The Committee highlighted concerns over hepatotoxicity. The Committee noted that current practice for the treatment of paracetamol overdose required blood levels to be plotted against the time of ingestion in order to determine whether treatment with an antidote was indicated. It was further noted that in cases where too much time had passed or the history of the ingestion was unreliable, 10 g was the conservative threshold for initiation of treatment.

The Committee noted that ingestion of paracetamol above 10 g slightly increased the risk of hepatotoxicity. Further, if overdose treatment does not commence within 8 hours after ingestion there is also a greater risk of hepatotoxicity. Therefore, the Committee stated that it makes sense for the cut off for a pack size to be 10 g. The Committee argued that ideally the pack size should be below 10 g in order to further reduce the potential risk of hepatotoxicity and a suggestion of a maxium pack size of 8 grams was put forward. However, it was noted that the current Australian treatment practices supported a 10 g pack size limit.

The Committee noted that the current pack size of 25 was decided on in the 1970s in order to provide a three day supply. Considering this listing had been in place for a long time, the Committee noted that it may be difficult to justify a change without adequate evidence. It was also questioned as to why this issue had not been considered previously. The issue was raised that clinicians have been concerned with paracetamol overdose for a long time but could only rely on anecdotal evidence as there appeared to be a lack of communication to regulatory bodies. It was further noted that it was easier to measure deaths and admissions to liver units rather than monitor the cases of overdose that were successfully mitigated. The Committee also noted that such reductions would be beneficial in a rural setting as transport times to treatment were crucial.

The Committee noted that by shifting the pack size down, it would lead to a reduction in mean and median ingestion in overdose, and in turn a reduction in deaths. It was noted that a restriction on pack size would not impact those who purchased multiple packs at once. Further, the Committee noted that returning paracetamol to only a pharmacy setting would be unwarranted as consumers were able to purchase paracetamol in packs of 100 as a Schedule 2 medicine.
The Committee noted that amending the paracetamol pack size would also impact unscheduled combination products such as cough and cold medicines. This would cause a significant regulatory and financial impact on industry. If it was decided that, an extended implementation date was warranted.

Members noted but did not support alternative resolutions on this matter.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed to implement this advice. The delegate also agreed that an implementation date of at least 6 months be set i.e. 1 January 2013 or later.

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutics Goods Act 1989* included (a) risks and benefits; (c) toxicity; (d) dosage, formulation, labelling, packaging and presentation; and (e) the potential for abuse.

DELEGATE'S INTERIM DECISION

The delegate agreed that Australia harmonise with New Zealand and restrict the exempt pack size requirements for paracetamol to packs containing 10 g or less of paracetamol. The delegate further agreed an implementation date of at least 6 months be set i.e. 1 January 2013 or later.

SUBMISSIONS ON INTERIM DECISION

Two public submissions were received. The redacted submissions are available at the following URL: http://www.tga.gov.au/industry/scheduling-submissions.htm

DELEGATE'S FINAL DECISION

The delegate has made a final decision to harmonise the Schedule 2 listing for paracetamol with New Zealand and restrict the exempt pack size requirements for paracetamol to packs containing 10 g or less of paracetamol.

The delegate has varied the interim decision. The new implementation date for this decision is 1 September 2013.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- public submissions received on the interim decision;
- scheduling factors for inclusion in Schedule 2[10]; and
- section 52E of the *Therapeutics Goods Act 1989*.

The delegate decided that the relevant matters under section 52E (1) of the Therapeutic Goods Act 1989 include (a) risk and benefits, (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 final decision to harmonise the Schedule 2 listing for paracetamol with New Zealand included the following reasons:

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

- there is increased risk and limited benefit with retaining a 12 g pack size compared with a 10g pack size.
- Clinical advice suggests that a 10 g pack size is an appropriate maximum pack size in view of treatment protocols for overdose.
- Extending the implementation date provides industry with an appropriate timeframe to change packet sizes.

SCHEDULE ENTRY

Schedule 2 - Amendment

PARACETAMOL for therapeutic use **except:**

(a) when included in Schedule 4;

(b) in individually wrapped powders or sachets of granules each containing 1000 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and /or guaiphenesin or when combined with effervescent agents) when:

(i) enclosed in a primary pack that contains not more than 10 such powders or sachets of granules;

(ii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(iii) not labelled for the treatment of children 6 years of age or less; and

(iv) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaiphenesin or when combined with effervescent agents) when:

(i) packed in blister or strip packaging or in a container with a child-resistant closure;

(ii) in a primary pack containing not more than 20 tablets or capsules;

(iii) compliant with the requirements of the Required Advisory Statements for Medicine Labels;

(iv) not labelled for the treatment of children 6 years of age or less; and

(v) not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin.

2.2 PROPOSED CHANGES TO PART 5 OF THE SUSMP (THE APPENDICES)

2.2.1 BOCEPREVIR

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Boceprevir – consideration of inclusion of boceprevir in Appendix L with a requirement for labelling with warning statement 76 "*Do not become pregnant during use or within (Insert number of months as per approved Product Information [2]) months of stopping treatment*".

EXPERT ADVISORY COMMITTEE RECOMMENDATION
The Committee agreed that the scheduling of boceprevir remained appropriate, i.e. not included in Appendix L.

BACKGROUND

Boceprevir is an antiviral drug that inhibits replication of Hepatitis C Virus (HCV) in host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.

Boceprevir is the active ingredient in the product XXXXX, which must be administered in combination with peginterferon alfa and ribavirin. Ribavirin has teratogenic effects and was listed in pregnancy Category X in both the US and Australia.

In February 2012, boceprevir was included in Schedule 4 through a delegate only decision.

At the time the delegate also decided to refer whether boceprevir would require listing in Appendix L to ACMS for advice.

Appendix L

The Scheduling Policy Framework (SPF) sets out that an amendment to Appendix L may be considered following a proposal for a new or existing medicine where:

- specific labelling needs to be applied for safe use of a medicine when dispensed; and
- professional practice standards require specific labelling of the medicine when dispensed.

SCHEDULING STATUS

The implementation date for the February 2012 decision to include boceprevir in Schedule 4 was 1 May 2012.

INITIAL SUBMISSIONS

February 2012 pre-meeting submissions

Three submissions were received, summarised below:

XXXXX

- XXXXX disagreed with the Appendix L proposal.
- Boceprevir would not be administered as a monotherapy in treatment of Hepatitis C because of rapid emergence of resistance. Boceprevir would only be given in combination with ribavirin and peginterferon alpha.
- The boceprevir Product Information (PI) indicated this substance was pregnancy Category B2 "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed and studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage".
- The PI stated that boceprevir on its own did not carry the potential to cause harm to the foetus.

XXXXX

- Boceprevir was to be XXXXX, with recommendations for co-administration with peginterferon alfa and ribavirin (with ribavirin found to be teratogenic and/or embryolethal in nearly all species in which was tested).
- An article was noted regarding other classes of antivirals (NS5A replication complex inhibitors and NS5B polymerase inhibitors) which were in clinical development that may be effective in combination NS3 4A protease inhibitors (e.g. boceprevir) without use of peginterferon and ribavirin.

XXXXX

- The inclusion of boceprevir in Appendix L was supported. No arguments were provided.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (c) toxicity; and (d) dosage, formulation, labelling, packaging and presentation.

Members agreed that, as boceprevir was pregnancy category B2, there was no need for an Appendix L entry. Members noted that it could be expected that consumers would receive very good advice from health professionals when using boceprevir preparations given the nature of the indication.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (c) toxicity; and (d) dosage, formulation, labelling, packaging and presentation.

DELEGATE'S INTERIM DECISION

The delegate decided that the scheduling of boceprevir remained appropriate, i.e. not included in Appendix L.

SUBMISSIONS ON INTERIM DECISION

No submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current scheduling of boceprevir remains appropriate in Schedule 4, i.e. not included in Appendix L.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- scheduling factors for inclusion in Appendix L[11]; and
- section 52E of the *Therapeutics Goods Act 1989*.

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

The final decision that the current scheduling of boceprevir remained appropriate in Schedule 4 included the following reason:

- boceprevir is pregnancy category B2[12]. The concern arises when it is used with ribavirin (pregnancy category X). In view of this, an Appendix L listing is not appropriate for boceprevir.

[11] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm
[12] Definitions of the Australian Pregnancy Categories http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm

2.2.2 TELEPREVIR

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Telaprevir – consideration of inclusion of telaprevir in Appendix L with a requirement for labelling with warning statement 76 "*Do not become pregnant during use or within (Insert number of months as per approved Product Information [2]) months of stopping treatment*".

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee agreed that the scheduling of teleprevir remained appropriate, i.e. not included in Appendix L.

BACKGROUND

Telaprevir is a new medicine that is a potent, reversible, selective, linear peptidomimetic ketoamide inhibitor of the NS3-4A Hepatitis C Virus (HCV) serine protease, an enzyme that is essential for viral replication.

Telaprevir is used with peginterferon alfa-2a (with or without ribavirin) in treatment-naïve and treatment-experienced patients with HCV genotype 1 infection. Ribavirin has teratogenic effects and was listed in pregnancy Category X in both the US and Australia.

In February 2012, teleprevir was included in Schedule 4 through a delegate only decision. At the time the delegate also decided to refer whether teleprevir would require listing in Appendix L to ACMS for advice.

Appendix L

The Scheduling Policy Framework (SPF) sets out that an amendment to Appendix L may be considered following a proposal for a new or existing medicine where:

- specific labelling needs to be applied for safe use of a medicine when dispensed; and
- professional practice standards require specific labelling of the medicine when dispensed.

SCHEDULING STATUS

The implementation date for the February 2012 decision to include telaprevir in Schedule 4 was 1 May 2012.

INITIAL SUBMISSIONS

February 2012 pre-meeting submissions

Three submissions were received, summarised below:

XXXXX

- XXXXX disagreed with the Appendix L proposal.
- Teleprevir would not be administered as a monotherapy in treatment of Hepatitis C because of rapid emergence of resistance. Teleprevir would only be given in combination with ribavirin and peginterferon alpha.
- Telaprevir appeared to qualify for TGA Pregnancy Category B2: "Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed and studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage".
- Stated that telaprevir has shown no teratogenic potential in rats and mice and was not considered a developmental toxicant in these species.
- The combination of telaprevir with peginterferon alfa-2a and ribavirin may be considered Pregnancy Category X based upon the significant teratogenic and/or embryocidal effects that have been demonstrated in all animal species exposed to ribavirin as a component of the combination.
- It was argued that the proposed Appendix L warnings were inappropriate and would misrepresent the safety of teleprevir.

XXXXX

- Teleprevir was to be XXXXX, with recommendations for co-administration with peginterferon alfa and ribavirin (with ribavirin found to be teratogenic and/or embryolethal in nearly all species in which was tested).
- An article was noted regarding other classes of antivirals (NS5A replication complex inhibitors and NS5B polymerase inhibitors) which were in clinical development that may be effective in combination NS3 4A protease inhibitors (e.g. boceprevir) without use of peginterferon and ribavirin.

XXXXX

- The inclusion of teleprevir in Appendix L was supported. No arguments were provided.

EXPERT ADVISORY COMMITTEE DISCUSSION

The Committee agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (c) toxicity; and (d) dosage, formulation, labelling, packaging and presentation.

Members agreed that, as teleprevir was only likely to warrant a B2 pregnancy category, there was no need for an Appendix L entry. Members noted that it could be expected that consumers would receive very good advice from health professionals when using teleprevir preparations given the nature of the indication.

DELEGATE'S CONSIDERATION OF ACMS ADVICE

The delegate concluded that the advice of the ACMS was clear and appropriately supported. The delegate agreed that the relevant matters under section 52E(1) of the *Therapeutic Goods Act 1989* included (c) toxicity; and (d) dosage, formulation, labelling, packaging and presentation.

DELEGATE'S INTERIM DECISION

The delegate agreed that the scheduling of teleprevir remained appropriate, i.e. not included in Appendix L.

SUBMISSIONS ON INTERIM DECISION

One public submission was received. The redacted submission is accessible at http://www.tga.gov.au/industry/scheduling-submissions.htm

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current scheduling of teleprevir remains appropriate in Schedule 4, i.e. not included in Appendix L.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS;
- public submissions;
- scheduling factors for inclusion in Appendix L[13]; and
- section 52E of the *Therapeutics Goods Act 1989*.

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

The final decision that the current scheduling of teleprevir remained appropriate in Schedule 4 included the following reason:

- teleprevir is pregnancy category B2[14]. The concern arises when it is used with ribavirin (pregnancy category X). In view of this, an Appendix L listing is not appropriate for teleprevir.

[13] Scheduling Policy Framework for Medicines and Chemicals http://www.tga.gov.au/industry/scheduling-spf.htm
[14] Definitions of the Australian Pregnancy Categories http://www.tga.gov.au/hp/medicines-pregnancy-categorisation.htm

3. MATTERS INITIALLY REFERRED TO ACMS#4 – OCTOBER 2011

3.1 PROPOSED CHANGES TO PART 2 OF THE SUSMP

3.1.1 SCHEDULE 8 LABELLING REQUIREMENTS

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

Schedule 8 labelling requirements – seeking advice on a proposal to amend Part 2, subparagraph 7(1)(a)(iv) of the SUSMP to allow an appropriate designation under the New Zealand *Misuse of Drugs Regulations 1977* next to the signal word on the signal word line. This possible amendment may allow some common packaging to be used for Schedule 8 products between Australia and New Zealand. Advice is also sought on potential harmonisation of other SUSMP Schedule 8 general labelling requirements between Australia and New Zealand.

EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the current labelling and packaging requirements for Schedule 8 substances remained appropriate.

Members also recommended that the delegate refer the issue of signal heading harmonisation to National Coordinating Committee on Therapeutic Goods (NCCTG).

BACKGROUND

Labelling and availability of controlled substances in New Zealand (NZ) is controlled through the *Misuse of Drugs Act 1975* (MODA). At the June 2003 meeting of the Trans-Tasman Harmonisation Working Party (TTHWP) a common Schedule 8 labelling scheme for Australian and NZ was endorsed.

In June 2003, the National Drugs and Poisons Scheduling Committee (NDPSC) considered the TTHWP decision and agreed to foreshadow an amendment to the SUSMP (then SUSDP) which was intended to achieve partial harmonisation in light of legislative differences between the two countries. The amendment would allow the NZ designation, as specified in NZ's MODA, to be included on the label of Schedule 8 medicines in Australia.

The foreshadowed amendment was considered in October 2003, where it was agreed to omit the letters "NZ" as their inclusion could lead to confusion and would not meet the requirements of the MODA.

In October 2004, the NDPSC considered comments received in relation to the foreshadowed amendment and agreed to proceed with the foreshadowed amendment.

In February 2005, the NDPSC noted that in November 2004, the NCCTG considered options for harmonisation of signal headings. The NDPSC was advised that, in considering these options, NCCTG members noted the following:

- Australia had already made changes to the requirements on signal headings to align with the NZ *Medicines Act 1981*;
- Amending the scheduling standard to allow the NZ designated category for the MODA to be included on the signal heading line would not resolve the need for different signal headings for other medicines containing controlled drugs;
- These options could be seen as contrary to the intent of the then Australian and NZ Treaty to establish a single, bi-national agency to regulate therapeutic products;
- There were policy preferences that labels in Australia and NZ should be uniform; and
- NCCTG preferred the option of NZ reconsidering amending the MODA on order to maximise harmonisation of labels and signal headings. If NZ determined this was not possible, the matter should be referred to the Therapeutic Products Interim Ministerial Council for consideration.

The conclusion from the February 2005 NDPSC consideration therefore was that the then current Schedule 8 signal heading remained appropriate. Members noted that it was likely that NZ would instead be asked (by industry etc) to look at amending the MODA.

In June 2006, the NDPSC noted advice that the labelling of some Schedule 8 products still included the MODA designation on the same line as the words "CONTROLLED DRUG". The NDPSC noted that labelling was not harmonised and felt the presence of MODA labelling on Australian products was not appropriate.

In late June 2011, the Secretary of the Department of Health and Ageing announced the intent to establish a joint Australian NZ agency to regulate medicines, the Australia New Zealand Therapeutic Products Agency (ANZTPA).

XXXXX submitted an application seeking an amendment to Part 2 of the SUSMP to harmonise with NZ's labelling and packaging requirements for Schedule 8 products. This application was submitted direct to the Secretariat in compliance with the requirements for applications of this type. A delegate decided this was a matter warranting advice from the ACMS and referred this to the October 2011 ACMS meeting.

The delegate also requested advice from the Committee and the general public on potential harmonisation of other SUSMP Schedule 8 general labelling requirements between Australia and NZ.

SCHEDULING STATUS

Australia's Schedule 8 labelling requirements are slightly different from requirements in NZ. Australia's Schedule 8 labelling, as per the SUSMP, requires that nothing be added on the line next to the signal wording "CONTROLLED DRUG". The only exception is for a Class label from the Australian Code for the Transport of Dangerous Goods by Road and Rail.

Conversely, under section 25 of the NZ *Misuse of Drugs Regulation 1977*, the signal wording "CONTROL DRUG" must be followed immediately by the appropriate designation (a letter and number code).

Applicant's Submission

XXXXX requested that the labelling requirement in Part 2 Labels and Containers for Schedule 8 preparations be amended to allow harmonisation of labelling and packaging between Australia and NZ.

The applicant made a number of points, as summarised below:

- Noted that one of the aims of the Australia New Zealand Closer Economic Relations Trade Agreement treaty was to eliminate barriers to trade between Australia and NZ. They asserted that the setting up of a joint pharmaceuticals regulatory system, however, was on hold. Members noted the ANZTPA announcement was made after the submission of this application.
- Noted that the SUSMP allows an exemption for Schedule 5 substances, with no apparent negative effects.
- Proposed the inclusion of the following new wording in Part 2, Labels and Containers:

  (iv) if the poison:

  (A) is a Schedule 5 poison, with nothing, other than a Class label as specified in the Australian Code for the Transport of Dangerous Goods by Road and Rail or a statement of the principal hazard of the poison, written on that line; or

  (B) is a Schedule 8 poison, with nothing, other than an appropriate designation as specified in the New Zealand Misuse of Drugs Regulations, written on that line; or

  (C) is not a Schedule 5 poison, or Schedule 8 poison, with nothing, other than a Class label as specified in the Australian Code for the Transport of Dangerous Goods by Road and Rail, written on that line;

- Asserted that the proposed amendment was not expected to change the current use of Schedule 8 substances and would facilitate the use of Australian Schedule 8 substances in NZ and vice versa.
- Indicated that the proposed amendment would improve inventory management and reduce supply problems, particularly for low volume products.
- Stated that the proposed amendment was not expected to substantially reduce the readability of the signal word.

The applicant also provided examples of current Australian and NZ Schedule 8 packages.

October 2011 Pre-meeting Submissions

No pre-meeting submissions were received.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that the relevant matter under Section 52E(1) of the *Therapeutic Goods Act 1989* was (d) the dosage, formulation, labelling, packaging and presentation of a substance.

A Member noted that the issue of harmonisation of Schedule 8 labelling had been considered by the NDPSC during 2003-2006 in the context of the formation of a joint Australian NZ agency to regulate medicines. Members noted that with the 2011 announcement of the formation of ANZTPA, this issue would again be raised.

A Member advised that the current proposed ANZTPA implementation program would start with the Therapeutic Goods Administration (TGA) conducting a business-to-business comparison. This program will also look at legislative changes to form a single agency. The Member stressed that this was envisaged as a long-term project and was unlikely to be examining specific scheduling harmonisation matters for some time. However, the Member also advised that the TGA had also initiated a review of labelling, including packaging requirements.

Members noted that in NZ, labelling was regulated by legislation and there were no current moves to change these requirements.

A Member noted that the applicant's argument that the SUSMP already allows for such an exemption for Schedule 5 products was misleading and asserted that this was a requirement rather than an exemption.

Members questioned to what extent these proposed changes could confuse pharmacists and consumers. A Member suggested that the key consideration was whether these changes to labelling could compromise public safety by making labelling less clear. It was noted that there was a lack of information to gauge the industry response to these changes as no pre-meeting submissions were received. Members noted that the intent of the delegate's proposal had been to facilitate comments from industry on whether there were any other Schedule 8 labelling restrictions imposed by the SUSMP which prevented harmonisation between Australia and NZ.

A Member suggested it was unlikely this proposed change would create any significant concern amongst either industry or consumers and that any concerns could be alleviated by appropriate education. The Member therefore supported the change in principle, but noted that any change should be foreshadowed pending further consultation with peak bodies (such as the Pharmaceutical Society Australia), who may be willing to assist with disseminating information on the change.

Another Member, however, recalled the NDPSC considerations in 2006, where one company had introduced common packaging for a product without seeking approval. This did create confusion amongst pharmacists, who mistook the NZ designation for some unknown scheduling status indicator. A Member suggested that there would need to be significant professional education if this change was approved.

A Member also noted that the current signal heading had been firmly established for 40-50 years. The Member opposed changing such well-established practices for the sake of harmonisation. The Member also raised concerns that such a move may open the floodgates for other information to be included in the signal heading line, which would lessen the already limited effectiveness of signal headings.

Members noted that in NZ, labelling was regulated by legislation and there were no current moves to change these requirements.

Members generally agreed that the proposed changes to the Schedule 8 signal heading requirements were a scheduling policy matter and as such this proposal should not proceed before consideration by the NCCTG.

DELEGATE'S INTERIM DISCUSSION

The delegate concluded that the recommendations of the ACMS were clear and appropriately supported. The delegate agreed with these recommendations.

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

DELEGATE'S INTERIM DECISION

An interim decision was published on 21 December 2012. The delegate decided that the current labelling and packaging requirements for Schedule 8 substances remains appropriate.

The delegate also decided to refer the issue of signal heading harmonisation to the NCCTG.

SUBMISSIONS ON INTERIM DECISION

No public submissions were received.

DELEGATE'S FINAL DECISION

The delegate has made a final decision that the current labelling and packaging requirements for Schedule 8 substances remains appropriate.

The delegate also decided to refer the matter of signal heading harmonisation to the NCCTG.

The delegate considered the following in regards to making a final decision:

- advice and recommendations from the ACMS; and
- section 52E of the *Therapeutics Goods Act 1989*.

The delegate decided that the relevant matters under section 53E(1) of the *Therapeutic Goods Act 1989* include (d) the dosage, formulation, labelling, packaging and presentation of a substance.

The final decision that the current labelling and packaging requirements for Schedule 8 substances remains appropriate included the following reason:

- the request to change the labelling and packing requirements for Schedule 8 substances is a policy issue which needs consideration by the NCCTG. The matter will be referred to NCCTG for consideration.