Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

51st Meeting
16-17 October 2007

TABLE OF CONTENTS

GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
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
BAN	British Approved Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments

CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel
DSEB	Drug Safety and Evaluation Branch
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
FWP	Fluorides Working Party
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
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance

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
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety
ODBT	Office of Devices, Blood and Tissues
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
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
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1. PRELIMINARY MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.1 [ITEM DELETED]

1.7.1.2.1 [ITEM DELETED]

1.7.1.2.2 [ITEM DELETED]

1.7.1.2.3 [ITEM DELETED]

1.7.1.2.4 [ITEM DELETED]

1.7.1.3 COPYRIGHT REFERENCES IN SCHEDULING SUBMISSIONS

PURPOSE

The Committee considered a proposal to include a blanket written authorisation to applicants who submit copies of references as part of a scheduling/ rescheduling applications.

BACKGROUND

The February 2006 NDPSC Meeting agreed to develop a template to facilitate the scheduling/rescheduling process. The June 2006 NDPSC Meeting agreed to foreshadow adoption of a template, posting a draft on the NDPSC website for comment. The October 2006 NDPSC Meeting considered stakeholder feedback and agreed:

- That the template, as amended, provided suitable guidance to industry and would improve the efficiency with which the Committee could consider applications.
- To advise NCCTG of the February 2007 consideration of the proposed template.
- To amend the NDPSC guidelines to allow electronic submission as an alternative to the mandatory submission of 25 hard copies of an application. These amendments were forwarded to NCCTG for consideration.

The February 2007 NDPSC Meeting:

- Noted NCCTG endorsement of the template and amendments to the NDPSC guidelines to allow electronic submissions.
- Agreed to consider finalising the template at the June 2007 NDPCS Meeting, noting that the template would always be open for comments and improvements.

The June 2007 NDPSC Meeting agreed:

- To adopt the draft template for use by applicants making scheduling or rescheduling submissions.

- To refer the issue of copyright on references included in electronic applications to expert Committees such as NDPSC to XXXXX for advice and clarification.

DISCUSSION - SUBMISSIONS

Members recalled the following from the June 2007 NDPSC Meeting regarding the issue of copyright on references submitted to NDPSC:

- A comment noted that the template guidance notes indicated that electronic copies of references should be included with the submission. The comment claimed that this may infringe copyright, asserting that many papers are not permitted to be sent electronically but can be used in hard copy form for 'scientific purposes'.
- Members recalled that following discussion of copyright concerns the February 2007 NDPSC Meeting agreed that it did not appear to be an issue. It was noted that references had always been a component of NDPSC applications (and indeed for the many applications made to regulators such as TGA and APVMA) and did not see that moving from hard-copy to electronic would make any difference. The Committee confirmed that it did not intend to distribute these references.
- Members also noted an information sheet from the Australian Copyright Council's Online Information Centre (http://www.copyright.org.au) regarding the use of copyright material for the services of the Commonwealth or a State. This site advised that the Copyright Act does not provide any guidance on the meaning of "for the services of the Commonwealth or a State". XXXXX
- Members also noted that the copyright issue would be relevant to the various TGA Committees moving to an e-agenda process.

XXXXX. The Secretariat provided the following summary XXXXX:

- Where an applicant cites or relies on a study, journal article, paper or other reference in their application, the NDPSC guidelines and template require applicants to submit copies of these references. It was noted that NDPSC did not intend to make copies of any references received from applicants available to the public.
- XXXXX
- Section 183 of the Copyright Act provides that the doing of acts comprised in the copyright of certain works will not infringe copyright in those works, where the acts are done for the services of the Commonwealth, States or Territories.
- In order for section 183 to apply, the elements of subsection 183(1) must be satisfied. The elements are as follows:
    - there is a literary, dramatic, musical or artistic work in which copyright subsists;
    - an act comprised in the copyright of that work has been done, or is going to be done;

- the act has been done, or is going to be done, for the services of the Commonwealth or State; and
- the act has been done, or is going to be done, by the Commonwealth/ State, or by a person authorised by the Commonwealth/ State.

- XXXXX.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

A Member noted that the XXXXX on copyright could be used to create a reference document for the NDPSC website. The Member asserted that this could provide additional reassurance to applicants who may have copyright concerns. The Committee generally agreed with this proposal.

RESOLUTION 2007/51 – 6

The Committee decided:

- To provide a 'blanket' written authorisation to all applicants who submit copies of references to the NDPSC as part of a scheduling/rescheduling application.
- To amend the NDPSC Guidelines and Template to provide this authorisation.
- To recommend to NCCTG that it endorse this approach.

INTERIM GUIDELINES FOR THE NDPSC – Amendment to Chapter 2.

***PRODUCTION OF THE DOCUMENT* – Amendment to follow the first paragraph after the subsection heading "Bibliographic and Reference Material".**

Where an applicant who copies and submits a reference to the NDPSC for the purposes of making a scheduling/rescheduling application does any act comprised in the copyright of the work under the *Copyright Act 1968* (*Copyright Act*), those acts are taken to be authorised by the Commonwealth under section 183 of the *Copyright Act*.

NDPSC TEMPLATE FOR SCHEDULING/RESCHEDULING APPLICATIONS – Amendment to Part C – Supporting Data

COPIES OF PAPERS REFERENCED – Amendment to follow after the heading.

Where an applicant who copies and submits a reference to the NDPSC for the purposes of making a scheduling/rescheduling application does any act comprised in the copyright of the work under the *Copyright Act 1968* (*Copyright Act*), those acts are taken to be authorised by the Commonwealth under section 183 of the *Copyright Act*.

1.7.1.4 [ITEM DELETED]

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY

1.8.1.1 CADMIUM COMPOUNDS AND CADMIUM SULFIDE

PURPOSE

The Committee considered the scheduling of cadmium compounds (including cadmium sulphide) for human therapeutic use, including a proposal to ban cadmium compounds for human therapeutic use.

BACKGROUND

The February 1970 PSC Meeting agreed to include preparations containing ≤ 2.5% of cadmium sulphide for human therapeutic use in Schedule 5. Members also agreed to a parent entry for all other cadmium compounds in Schedule 6 due to toxicity.

The February 1988 DPSSC Meeting noted that animal studies had shown that cadmium is acutely toxic at low doses and in animal tests cadmium produced embryotoxicity, foetotoxicity and teratogenicity. The Meeting agreed to maintain the Schedule 6 entry and to request that no domestic agvet products be registered.

The August 2000 NDPSC Meeting considered consistency between schedule entries and Appendix I "Uniform Paint Standard". The Committee agreed to an exemption from the Schedule 6 cadmium compounds entry for paints and tinters containing ≤ 0.1% cadmium.

The February 2007 NDPSC Meeting considered the unharmonised status of cadmium sulfide for human therapeutic use and agreed to foreshadow consideration of cadmium compounds, including cadmium sulfide, for human therapeutic use at the June 2007 NDPSC Meeting. The June 2007 NDPSC Meeting considered a proposal to ban human therapeutic uses of cadmium. It was agreed, however, that banning cadmium from human therapeutic use may not have been foreseen as a possible outcome by sponsors and that it was therefore appropriate to defer consideration until the October 2007 NDPSC Meeting to allow an additional opportunity for public comment.

DISCUSSION - SUBMISSIONS

Advice was sought from XXXXX on whether the 1 product containing cadmium [cadmium sulfide in a dentine adhesive] on the ARTG was currently marketed. XXXXX was also invited to comment on whether excluded medical devices not on the ARTG may contain cadmium. Members noted the following from XXXXX comment:

- The one entry identified (the dentine adhesive) as a 'kind of medical device', and potentially covered a range of dentine adhesives. XXXXX

- Excluded devices are devices which the TGA has specifically excluded from the jurisdiction of the *Therapeutic Goods Act 1989* (the Act), declaring them not to be therapeutic goods. As a consequence XXXXX holds no information on these products.
- Exempt medical devices are regulated by the Act, but are exempted from entry on to the ARTG. These devices are detailed in Schedule 4 of the *Therapeutic Goods (Medical Devices) Regulations 2002*. The TGA holds no information which could identify particular device types. Also, because Schedule 4 of these Regulations details categories rather than specific device types, it is not possible to identify clearly if there will be any impact on exempt devices if the NDPSC progresses this matter.
- Additionally, in considering not only salts of the metal, but also cadmium metal, XXXXX advised that cadmium is often used both as a passivation surface for metal structures and in the construction of mechanical bearing surfaces. It is highly unlikely these materials would be incorporated in implanted medical devices, but they may be used in the construction of medical devices (with incidental exposure to the skin of a user or patient). For example, it is conceivable that a custom made medical device such as a leg brace may contain cadmium in a metal alloy form either within the metal used in its construction or in a bearing surface included to allow articulation of the device, or a wheelchair manufacturer may employ cadmium passivation to the frame to protect from corrosion.

Members also recalled the following from their June 2007 consideration:

- A search of Martindale revealed no cadmium therapeutic uses apart from:
  - Cadmium sulfide – used topically in some countries for the treatment of skin and scalp conditions.
  - Cadmium sulfate – used for the treatment of eye irritation.
  - The above cadmium salts had also been used in homoeopathic preparations.
- The Secretariat was unable to locate any other therapeutic uses of cadmium compounds.
- An ARTG search located 1 product containing 0.044% cadmium sulfide (and no products containing cadmium) as an excipient in a medical device - a dentine adhesive. This device appeared to qualify for the Appendix A general exemption for medical and veterinary adhesives, glues and cements. Members noted that medical devices not required to be on the ARTG would not have been located by this search.
- The Micromedex entry for cadmium sulfide provided the following:
  - Cadmium sulfide is a dermatological agent and antiseborrheic.
  - Cadmium sulfide releases toxic hydrogen sulfide upon contact with water or acids.

- Cadmium sulfide is used in photoconductors, dandruff shampoos, pigments and phosphors, electronic components, and in solar cells.

Acute clinical effects:

- No studies were found for acute exposure to cadmium sulfide in humans. It was not acutely toxic in experimental animals (RTECS), and was generally regarded as being less toxic than more soluble cadmium compounds.
- Acute inhalation of cadmium and its salts can cause pulmonary oedema; fatal in approximately 20% of cases. Ingestion of cadmium or its salts produces immediate gastrointestinal distress with pain, nausea, vomiting, diarrhoea, excessive salivation, muscular cramps, signs of CNS depression (such as dizziness, weakness, headache, cardiovascular collapse, and shock), and death.

Chronic clinical effects:

- Cadmium sulfide is relatively inert for causing lung damage in chronic inhalation exposure. Some cases of emphysema have been reported, but only after at least 25 years of exposure. Kidney injury with proteinuria has developed following chronic exposure to cadmium sulfide.
- In a 30-day rat inhalation study, cadmium sulfide was absorbed only one-tenth as much as cadmium chloride or cadmium oxide.
- If cadmium sulfide is being used under conditions where cadmium fumes may be generated, inhalation exposure might cause metal fume fever, a flu-like condition involving fever, chills, sweating, aches and pains, and difficulty breathing. Symptoms of metal fume fever generally appear within hours of exposure and subside within 24 to 48 hours, leaving no permanent effects.
- IARC (2004) listed cadmium sulfide as carcinogenic to humans (rating 1). In animal studies, cadmium sulfide was carcinogenic in rats. It is relatively insoluble; tumours developed at the site of injection. Cadmium sulfide caused broken chromosomes in cultured human cells and also caused in vitro transformation of hamster cells.
- Cadmium caused birth defects in several species of laboratory animals and was embryotoxic and fetotoxic. There was some evidence that cadmium may be a human reproductive hazard. There had been isolated cases of impotence and microscopic changes in the testes of men working with cadmium.
- It was also noted that sulfide is traditionally spelled ‘sulphide’ in British english, but IUPAC has adopted the spelling "sulfide", as has the Royal Society of Chemistry Nomenclature Committee.

- The Committee generally agreed that there were strong concerns about allowing any cadmium compound for therapeutic use, especially given its propensity to bioaccumulate. A Member proposed that there should therefore be no exemption and that a Schedule 4 entry be considered.

- Other Members indicated that a Schedule 4 entry did not sufficiently restrict cadmium from use in human therapeutics, and instead proposed an Appendix C listing based on concern about cumulative renal effects. A Member noted that there may also be a need to amend the various exemptions in Appendix A so as not to apply to those human therapeutics containing cadmium. An alternative suggestion was to reflect the 1988 request to APVMA (that no domestic agvet products containing cadmium be registered) and write to TGA requesting that no cadmium containing human therapeutic be registered.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee generally agreed that the following matters under 52E(1) were particularly relevant to this consideration:

- (a) – the toxicity and safety of cadmium (especially concerns with bioaccumulative effects);
- (c) – the potential hazards associated with cadmium (especially reproductive hazards in humans);
- (d) – extent and patterns of use (given that there is little, if any, human therapeutic use); and
- (f) – need for access (given the seemingly limited therapeutic uses).

The Committee generally agreed that there appeared to be no real need for access to cadmium for human therapeutic use, and that no stakeholders had come forward opposing the foreshadowed rescheduling.

A Member noted that a rescheduling to Schedule 4 any human therapeutic use would have to go through an evaluation process where ADEC would have to review the risk/benefit profile. Additionally, in arguing for Schedule 4 rather than an Appendix C listing, a Member noted that if a legitimate therapeutic use was to emerge then Schedule 4 could still allow access. Another Member argued that the health risk from cadmium warranted a ban, and any future possible use could be addressed through a rescheduling application with appropriate supporting evidence.

Members noted that it did not appear possible to obtain a full picture of potential use in devices.

RESOLUTION 2007/51 - 8

The Committee decided:

- To create a new cadmium compounds Schedule 4 entry for human therapeutic use.
- To delete cadmium sulphide for human therapeutic use from Schedule 5.

- To amend the Schedule 6 cadmium compounds entry to exclude human therapeutic use.

Schedule 4 – New Entry

CADMIUM COMPOUNDS for human therapeutic use.

Schedule 5 – Amendment

CADMIUM SULPHIDE – Delete entry.

Schedule 6 – Amendment

CADMIUM COMPOUNDS – Amend entry to read:

CADMIUM COMPOUNDS **except**:

(a) for human therapeutic use; or

(b) in paints or tinters containing 0.1 per cent or less of cadmium calculated on the non-volatile content of the paint or tinter.

1.8.2 FLUORIDES WORKING PARTY

PURPOSE

The Committee noted progress by the Fluorides Working Party (FWP).

BACKGROUND

The February 2007 NDPSC Meeting noted some issues regarding cut-offs in the current fluoride entries including the Schedule 3 cut-off (particularly for non-cleaning of teeth use patterns), and a possible inconsistency with the Schedule 2 cut-offs for mouth wash type products. The Members therefore agreed to foreshadow consideration of fluorides scheduling at the June 2007 NDPSC Meeting.

The June 2007 NDPSC Meeting considered a number of submissions on the scheduling of fluorides and agreed that the best way to progress this issue was to establish a working group (the Fluorides Working Party – FWP) to look at remodelling the scheduling framework for fluoride, with an emphasis on clarity and consistency. The FWP was composed of XXXXX. The Committee agreed to defer consideration while the FWP undertook its review.

DISCUSSION - SUBMISSIONS

The FWP had agreed that the following terms of reference reflect the June 2007 NDPSC Meetings intent and mandate for the FWP. The FWP was:

- To look at remodelling the scheduling framework for fluoride, with an emphasis on clarity and consistency (such as a scheduling cascade).
- To consider the consistency of the cut-offs, and whether these represent universal risks, or risks that sufficiently vary for some use patterns (age, use, formulation etc) as to warrant alternative cut-offs.
- To consider the proposal that professional dental products would be adequately controlled through the regulator and professional practice so as to not warrant scheduling.
- To progress this issue in a timely manner and to supply progress reports to NDPSC Meetings.
- To supply a final set of recommendation(s) to the NDPSC addressing the above issues.

The FWP had considered a number of issues as detailed below, thereby progressing consideration of fluorides scheduling.

Evaluation Report

An evaluator was tasked with providing an overview of the toxicology of fluoride, together with an examination and evaluation of the following documents:

- XXXXX submission to the June 2007 NDPSC Meeting.
- An EU SCCP opinion (2005) "The safety of fluorine compounds in oral hygiene products for children under the age of 6 years".

The FWP particularly noted the following points from the evaluator's report:

- The issues of concern in relation to human exposure to fluoride are acute toxicity in children and adults and fluorosis in children and adolescents. The acute lethal dose of fluoride for man is about 70 mg/kg, although a toxic dose is considered to be 5 mg/kg. The ADI for fluoride in children 1 to 3 years of age, in relation to the incidence of dental fluorosis, is 0.7 mg.
- Fluoride ion is rapidly absorbed from the alimentary tract, but not from the oral cavity, reaching peak plasma levels within 30 minutes. About 50% of the dose lodges in the skeletal tissues and 50% is excreted in the urine. The elimination of fluoride from the plasma is biphasic with the half life of the second exponential phase from 2 to 9 hours. Fluoride bound to bone is mobilisable with bone growth and remodelling. For fluoride to adversely affect skeletal development in humans, it is estimated that the level of intake needs to be from 20 to 80 mg/day for 10 to 20 years.

- An excessive exposure of the enamel organ to fluoride during tooth development can adversely affect the ameloblasts and give rise to defective enamel in the subsequently erupting teeth, leading to lesions of fluorosis.
- It has become recognised in more recent times that the main protective effect exerted by fluoride on teeth post eruption is a topical effect rather than a systemic effect and that this is how fluoridated tooth paste, mouth washes and drinking water work. The fluoride ions present in the fluids in the oral cavity perfuse into the enamel and exchange with hydroxyl groups on enamel apatite to form fluorapatite and this is more resistant to the erosive effects of low pH generated by microbial metabolism at the tooth surface. This then is the basis for the development of daily and/or weekly mouth washes containing fluoride – to maintain adequate fluoride levels in saliva and plaque fluids.
- The mineralization of enamel is a dynamic process. Acids generated by caries bacteria metabolising carbohydrates tend to break down the apatite, while calcium and phosphorus derived from saliva tend to reverse the process. Recently, a new product has been developed which can promote this mineralization process, called casein-phospho-peptide-amorphous calcium phosphate (CPP-ACP), known as "tooth mousse". Tooth surface lesions of fluorosis, once believed to be permanent and untreatable, can now be reversed by the use of this product.
- In the original proposals for the scheduling of fluoride, the systemic effects of oral sodium fluoride as 2.2 mg tablets, was considered, and this daily dose was placed in Schedule 2. Since the subsequent recognition that the beneficial effects of fluoride on teeth was due to topical exposure, the use of sodium fluoride tablets for daily oral use is really no longer necessary, and the practice also probably exacerbates the possibility of fluorosis.
- In Australia, over 80% of the population is exposed to fluoride in the drinking water at around 1 mg/L. Queensland towns deriving their water supplies from the Great Artesian Basin already had adequate exposure to fluoride, but most coastal cities, such as Brisbane, are still without fluoridation of their drinking water. The presence of fluoride in water supplies leads to the "halo" effect, that is, fluoride becomes widely dispersed into the human environment, particularly in foods and beverages.
- There are situations in which the remineralisation of enamel needs to be more actively promoted and the use of products containing levels above 1000 ppm may be used, but with appropriate professional advice. Mouth washes and gels containing fluoride ion at around 5000 ppm are bacteriocidal for caries bacteria. At this stage the possibility of toxic effects has to be considered should such products be ingested or swallowed. The dose of fluoride ion for toxic effects in humans is generally considered to be about 5 mg/kg. This means that for a 70 kg human the ingestion of 350 mg of fluoride would be enough for a toxic effect. Ingested sodium fluoride is converted in the stomach to hydrofluoric acid which is highly irritant.
- Fluoride has been subjected to a large amount of genotoxicity testing. The results so far do not confirm fluoride as unequivocably non-mutagenic because responses

overall have been mixed. However, the apparent absence of teratogenicity and carcinogenicity support a conclusion of non-genotoxicity for fluoride ion.

The EC Scientific Committee on Consumer Products – Opinion (2005).

- This statement followed a submission that the "maximum permitted concentration of 1500 mg/kg fluorine does not pose a safety concern when used by children under the age of 6 years". This is qualified by the statement to the effect that toothpaste was the sole source of fluoride and that the child use only a pea sized amount on the tooth brush and that brushing is supervised.
- It was noted that there is an overlap between beneficial effects of topical fluoride in relation to caries reduction and the incidence of fluorosis associated with the effects of all exposure sources.
- It was pointed out that the risk of fluorosis occurs from 20 months to 5 years during the development in the jaw of the most visible teeth. There is minimal risk associated with ingestion of toothpaste up to the age of 2 years. Meta analyses had shown that the daily use of fluoride toothpaste is effective in preventing caries in the permanent teeth of children and adolescents and that this is a dose-dependent effect. It is claimed that there is no evidence to support the use of low fluoride toothpaste as being inhibitory of caries – in fact the opposite seemed to be true. This is not the view of expert opinion in Australia.
- In an attempt to calculate the amount of fluoride orally ingested by a child cleaning his/her teeth, the presumption was made that a child would have, say, 0.3 g of tooth paste on the brush, of which he/she would swallow 40%. If the fluoride concentration was 1.5 mg/g then the amount of fluoride on the tooth brush would be 0.45 mg. If 40% was ingested then the amount of fluoride swallowed would be 0.18 mg. If the teeth were brushed twice daily, the fluoride intake per day would be 0.36 mg from toothpaste. The allowable daily intake of fluoride for such a child (1 to 3 years of age) is given as no more than 0.7 mg if fluorosis is to be avoided. This is the argument advanced by XXXXX in support of the use of toothpaste containing 1500 mg/kg of fluoride for general sale.
- In a footnote to the SCCP statement it is noted that other sources of fluoride for such a child could also be possible, namely from fluoridated water consumption and diet. If the ADI for fluoride in these children is more than adequately supplied by "other sources", particularly in situations of water supply fluoridated at 1 mg/L, then the ADI for fluoride is already exceeded before any toothpaste is used at all. Therefore, in the risk assessment recommendation for the use of 1500 mg/kg of fluoride in toothpaste, calculated by XXXXX, there was no consideration given to the so called "other sources of fluoride".
- As the XXXXX submission noted, early US data indicated that even at fluoridation levels at 1 mg/L in domestic water supplies, up to 2% of the population can have dental fluorosis. In fact, in a more recent meta analysis of a systematic review of water fluoridation (McDonagh et al (2000) BMJ 321, 855-859), it was reported that

fluoridation at 1 mg/L can give rise to an average of 12.5% incidence of fluorosis of "aesthetic concern", while fluorosis, in general, had an incidence of 48%.

Current Scheduling Issues for Fluorides

- Fluoride for human use is exempt from scheduling in preparations containing 15 mg/kg, since no form of adverse effect is likely to ensue following oral consumption at this exposure level.
- In Schedule 2, provision is made for oral preparations for ingestion containing ≤ 2.2 mg sodium fluoride/unit (i.e. 1mg fluoride/unit). The use of oral supplementation with fluoride in this form is no longer relevant since the contribution of systemic fluoride for the prevention of caries is now considered to be minimal. For protection of teeth from caries, topical application of fluoride is required even in infants and could begin as soon as the teeth erupt if drinking water is fluoridated. If oral administration of fluoride supplements is thought to be necessary, they should be in the form of lozenges, rather than tablets, as the former provide for topical exposure of the teeth, while the latter do not. The dental profession in Australia, however, does not currently support the use of such supplements. Given the existence of water fluoridation and the inclusion of fluoride, universally, in toothpaste, an oral fluoride supplement of 1mg per unit is too high. In addition, as noted above, if concentration in plasma peaks too high, then the enamel organ of developing teeth will be adversely affected (the basis for subsequent dental fluorosis). As set out in the 1992 review by Paul Riordan "*Fluoride Supplements in Caries Prevention*", the oral dose of a fluoride supplement should be no more than 0.5 mg fluoride and as little as 0.25 mg per unit in infants. If more than this dose is considered to be required, then 0.25 mg or 0.5 mg should be given twice per day, once in the morning and once in the evening, so as not to cause an inordinately high plasma fluoride peak.
- The second element of the Schedule 2 entry is in relation to the topical use of fluorides. Here the principal issue is potential for toxicity. As pointed out above, the acute oral toxic dose is considered to be 5 mg/kg bw, which for a 70 kg adult gives an oral toxic dose of 350 mg fluoride. For a 20 kg infant the toxic dose would be 100 mg. A few years ago, the schedule entry was redrafted to include preparations containing up to 2.5% of fluoride (25000 mg/L). In the form of a mouth wash, such a preparation if swallowed, would deliver a toxic dose in 14 mL for an adult and 4 mL for a small child. This figure of 2.5% fluoride is clearly too high. A child's single swallow should not deliver a toxic dose of fluoride.
- In Schedule 2(b), a number of exceptions to a general proposition, not so far proposed in principle, are listed. Among these is an exemption from the Schedule of dentrifices, such as toothpaste, containing ≤ 1000 mg/kg fluoride, and a further two exceptions for mouth washes etc containing ≤ 220 mg/kg fluoride, so long as the pack size contains ≤ 120 mg of fluoride and has a child resistant closure.
- Schedule 3 provides that dental hygiene products may contain more than 1000 mg/kg or /L but does not set any limits. According to the dental profession guideline for high strength fluoride dental hygiene products that should be available for home use,

tooth pastes may contain up to 5500 mg/kg. These are recommended for individuals who are at high risk for caries.

- Dental hygiene products containing fluoride at levels in excess of 5500 mg/kg should only be available for dental professionals for use in dental surgeries. These products include fluoride gels, foams and varnishes. They contain from 9000 to 22,600 mg/kg.

The evaluator also identified an article setting out the current and proposed *use patterns of fluoride use in Australia* – "The use of Fluorides in Australia: Guidelines" (Australian Dental Journal (2006) **51** (2), *195-199*), which was provided to the FWP.

Matrix

A Member suggested at the June 2007 NDPSC Meeting that a matrix approach be used for this issue, starting with the acute toxicity of fluoride to a child to define pack size limits for a scheduling cascade.

Consequently, the data from the evaluation report, together with the data from the June 2007 NDPSC Meeting, and data mined from previous NDPSC minutes, were used to provide entries in a number of tables/matrices. These tables reflected the issues that underpinned the development of the existing schedule entries for human use – risk (acute versus long term exposure), age and use pattern.

FWP considerations

The above information was distributed by the Secretariat to the FWP for consideration. The FWP subsequently agreed to hold a teleconference on 8 October 2007 to discuss and progress this issue. The following summarises the teleconference discussion:

- The recommendations from the consultancy report were reviewed.
- A Member queried the extent of fluoridation in the EU and in Australia. Of particular interest was the intention of XXXXX with regards to fluoridated water. It was agreed that XXXXX would be approached regarding this question. The October 2008 NDPSC Meeting was advised that the question of fluoridation in XXXXX was unlikely to be resolved in the near future.
- It was noted that in Australia the general population would usually get fluoride from other sources. A Member queried whether the modern trend to bottled drinking water would be a mitigating factor.
- Members revisited the issues relating to dental whitener use versus cleaning. The Members agreed that the acute toxicological and fluorosis risks were better captured through the descriptors "supplements", "liquids" and "non-liquids" rather than the current use pattern descriptors – dental hygiene, whitening or bleaching.

  Supplements

  - Members noted that the article referenced in the consultancy report above recommended that "fluoride supplements in the form of drops or tablets to be

chewed and/or swallowed, should not be used". The FWP therefore agreed that one supplements option was that all preparations for ingestion become Schedule 4 (except in preparations containing ≤ 15 mg/kg fluoride ion) i.e. delete the current Schedule 2 (a).

- A Member asserted that access in remote rural areas could be one reason to hesitate over moving all supplements to Schedule 4.
- Members also noted that the consultancy report recommended that the current Schedule 4 to Schedule 2 cut-off of ≤ 1 mg fluoride ion (2.2 mg sodium fluoride) was too high and should be reduced to ≤ 0.5 mg fluoride ion in preparations for ingestion. The FWP agreed that this was another option for consideration at the February 2008 NDPSC Meeting.

Non-liquids

- The FWP agreed that "non-liquids for topical use" will adequately capture the various presentations, both now and in the future, which would be of concern.

Schedule 2

- A Member reiterated that the EU maximum cut-off was 1500 ppm fluoride ion, but noted that this also required mandatory labelling to the effect of "Do not swallow" and "Do not use in children under the age of 6 years". It was noted that in setting the 1500 ppm cut-off the EU did not take into account other sources of fluoride e.g. fluoridated drinking water.
- The FWP agreed that an option for non-liquid Scheduling would be to increase the current pastes, powders and gels exemption cut-off from 1000 ppm to 1500 ppm, with the above mandatory labelling for products > 1000 ppm and ≤ 1500 ppm fluoride ion. It was noted that use of reverse scheduling would require a duplication of entries (therapeutic and non-therapeutic). [A Member subsequently proposed, at the October 2007 NDPSC Meeting, that all toothpastes > 1000 ppm fluoride ion should require the above mandatory labels (whether >1000 and < 1500 ppm is unscheduled –proposal 3c; or Schedule 2 – proposal 3d). The Committee agreed that this was another option that should be considered in February 2008. Another Member noted that a reason for a > 1000 ppm and ≤ 1500 ppm category in Schedule 2 could be legitimate use for a child, in which case the labelling would not be appropriate.]
- The FWP also agreed that an alternative option for consideration at the February 2008 NDPSC Meeting would be the across the board 1000 ppm cut-off as recommended in the consultancy report i.e. there would be no Schedule 2 non-liquids for topical use.

Schedule 3 and Schedule 4

- The FWP agreed that the consultancy report's proposed Schedule 4 to Schedule 3 cut-off of 5500 mg/kg for topical use was an appropriate option for consideration in February 2008.

Liquids

- The FWP agreed that "liquids for topical use" will adequately capture the various presentations, both now and in the future, which would be of concern.

Schedule 2

- The FWP noted the consultancy reports recommendation to reduce the 2.5% topical use cut-off to 1000 ppm. The Committee agreed that this was an option for consideration. A Member noted that the current 2.5% may have existed due to use by dental professionals of high strength fluoride liquids (discussed below).
- The FWP also noted the consultancy reports recommendation that the pack size for the presently exempt 220 mg/L products should have a total fluoride content of 100 mg rather than 120 mg (noting that for a 20 kg child a toxic dose of fluoride would be 100 mg). The FWP agreed that this was another option for consideration in February 2008. [The October 2007 NDPSC Meeting was advised that the move from 120 mg to 100 mg for total fluoride content may have a large impact on current products]

Schedule 3 and Schedule 4

- The FWP agreed that the consultancy report's proposed Schedule 4 to Schedule 3 cut-off of 5500 mg/kg for topical use was an appropriate option for consideration in February 2008.
  [A Member subsequently proposed, at the October 2007 NDPSC Meeting, that all products > 1000 ppm fluoride ion should require the mandatory labels from the current reverse scheduling condition in Schedule 2. The Committee agreed that this was another option that should be considered in February 2008.]

Professional use

- The FWP noted the consultancy report's recommendation to create an Appendix A exemption for dental devices for supply to dental professionals.
- A Member queried what difference it would make to a dentist whether a product was scheduled or not, given that scheduled substances were already in use by dentists. Another Member indicated that there would be labelling and supply issues, and that there would be the question of use by dental professionals who were not dentists (i.e. recognised dental auxiliaries such as dental hygienists).
- There was also a question as to why an exemption should be limited to dental devices, and who would determine what was, or was not, a dental device.

- The FWP agreed that the option for consideration at February 2008 should be consideration of a specific exemption from the fluoride schedule entries when for use by a dental professional, rather than a broad Appendix A listing.

- XXXXX

- Additionally, it was agreed that the February 2008 pre-meeting notice should detail the above proposals to allow appropriate public consultation.
  [The October 2008 NDPSC Meeting subsequently agreed with providing a detailed February 2008 pre-meeting notice for this issue, noting that this would allow the FWP to add additional options following the October 2008 NDPSC Meeting which otherwise could not be provided to stakeholders for comment.]

-

- The following table summarises the various FWP proposals (and the additional proposals from the October 2007 NDPSC Meeting) for the February 2008 NDPSC consideration:

	UNSCHEDULED	S2	S3	S4
General-**Proposal 1**	• ≤ 15 mg/kg • Supply to dental professionals			
Oral supplements				
• **Proposal 2a**	General	Nil	Nil	Parent entry
• **Proposal 2b**	General	≤ 0.5 mg	Nil	Parent entry
Non-liquid				
• **Proposal 3a**	≤ 1000mg/kg	Nil	≤ 5500 mg/kg	Parent entry
• **Proposal 3b**	• 1000 < fluoride ≤ 1500 mg/kg when labelled – "Do not swallow"; & "Do not use in children 6 years of age or less" • ≤ 1000 mg/kg	>1000 and ≤ 1500 mg/kg not labelled.	≤5500 mg/kg	Parent entry
• **Proposal 3c**	As above		Vary above - be conditional on labelling	Parent entry
• **Proposal 3d**	≤ 1000 mg/kg	1000 < fluoride ≤ 1500 mg/kg when labelled – "Do not swallow"; & "Do not use in children 6 years of age or less"	As above	Parent entry
Liquid				

• **Proposal 4a**	≤ 220 mg/kg & ≤ 120 mg total fluoride with CRC and labelled – "Do not swallow"; & "Do not use in children 6 years of age or less"	≤ 1000 mg/kg with CRC	≤ 5500 mg/kg	Parent entry
• **Proposal 4b**	Vary above - total fluoride ion reduced to ≤ 100 mg	≤ 1000mg/kg with CRC	≤ 5500 mg/kg	Parent entry
• **Proposal 4c**	One of the above	Vary above - conditional on labelling	Vary above - conditional on labelling	Parent entry

Additionally, while the Committee generally agreed with the FWP's proposal that the risks were better captured through the descriptors "supplements", "liquids" and "non-liquids" rather than the current use pattern descriptors, several Members requested that some examples be include in the Minutes to add clarity. Some examples are:

Supplements

- Dietary fluoride supplements are usually oral tablets or droplets.

Liquids

- Includes mouth rinses, varnish.

Non-liquids

- Includes toothpaste, gels, foams, and mousse.

RESOLUTION 2007/51 - 9

The Committee noted progress by the Fluorides Working Party.

2. PROPOSED CHANGES/ADDITIONS TO PARTS 1 TO 3 AND PART 5 OF THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

2.1 SUSDP, PART 1

2.1.1 STERIOISOMER EXEMPTION – LEVOMETHORPHAN AND LEVORPHANOL

PURPOSE

The Committee considered a proposal to move the stereoisomers exemption from Part 1.(2)(e) of the SUSDP to the specific schedule entries for these substances.

BACKGROUND

Levorphanol is a potent synthetic mu-agonist opioid that exerts its action at receptors in the periventricular and periaqueductal grey matter in the brain and spinal cord, thus altering transmission and perception of pain. It produces morphine-like analgesia. It is a phenanthrene derivative which is used in the management of moderate to severe pain and for premedication. The analgesic effect usually begins about 10 to 60 minutes after oral doses and lasts up to about 8 hours. It is included in Schedule I of the *United Nations Single Convention on Narcotic Drugs*.

An extensive search was unable to turn up any scheduling history for levorphanol apart from a brief reference to it in the February 2003 Minutes in relation to a dextromethorphan consideration.

Levomethorphan is the l-stereoisomer of methorphan and shows many similarities to the opiates, including the potential for addiction. The d-stereoisomer, dextromethorphan, does not have the same painkilling component and has a much lower addiction potential. Members noted that levomethorphan is also the methyl ether of levorphanol. An extensive Medline search did not reveal any evidence of a clinical use for this substance and, further, it is not listed in the Martindale and is included in Schedule I of the United Nations Single Convention on Narcotic Drugs.

An extensive search was unable to turn up any scheduling history for levomethorphan apart from a brief reference to it in the February 2003 Minutes in relation to a dextromethorphan consideration.

Part 1 – 'Interpretation' currently advises that:

1. (2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes:

    (e) except where the substance is levomethorphan or levorphanol, every stereoisomer of the substance and every salt of such a stereoisomer; and

No discussion was located as to why the exceptions for levomethorphan and levorphanol were set out in 1.(2)(e) rather than in the specific Schedule entries for these compounds. While no discussion was located as to why these compounds were excepted, it is likely to relate to the pronounced differences in the biological activity of the enantiomers.

The June 2007 NDPSC Meeting agreed that the exception to Part 1.(2)(e) for levomethorphan or levorphanol would be better expressed by including the contrary intention in the schedule entry. Members therefore agreed to foreshadow amendments to the levomethorphan and levorphanol entries, with a consequential amendment to Part 1.(2)(e).

DISCUSSION - SUBMISSIONS

The Committee recalled the following foreshadowed amendments to the levorphanol and levomethorphan entries from the June 2007 Meeting:

Schedule 8 – Amendment

LEVORPHANOL – Amend entry to read:

LEVORPHANOL (excluding its stereoisomers).

Schedule 9 – Amendment

LEVOMETHORPHAN – Amend entry to read:

LEVOMETHORPHAN (excluding its stereoisomers).

DISCUSSION – ADDITIONAL INFORMATION RELEVANT UNDER 52E

The Committee noted that there were considerable differences in the dextro- and levo-isomers of these two substances. The Committee agreed that, due to these differences in pharmacological activity, individual schedule entries for these substances were warranted.

The Committee also noted that the references to these substances would need to be deleted from Part 1 of the SUSDP.

RESOLUTION 2007/51 - 11

The Committee decided to amend the scheduling of levorphanol and levomethorphan to include an exemption for their stereoisomers.

Part 1 – Interpretation – Amendment

Amend paragraph **1.**(2)(e) to read:

1. (2) Unless the contrary intention appears a reference to a substance in a schedule or an appendix to this Standard includes:

(e) every stereoisomer of the substance and every salt of such a stereoisomer; and

Schedule 8 – Amendment

LEVORPHANOL – Amend entry to read:

LEVORPHANOL (excluding its stereoisomers).

Schedule 9 – Amendment

LEVOMETHORPHAN – Amend entry to read:

LEVOMETHORPHAN (excluding its stereoisomers).

2.1.2 INTERPRETATION OF AEROSOL CONCENTRATION IN THE SUSDP

The Committee noted the inclusion of the interpretation of aerosol concentration in the SUSDP as a standing item on the agenda to remind the Committee that the implementation date for part of the June 2007 Decision (to Part 2 Paragraph 8.(2)), regarding a specific labelling requirement for aerosols to express concentration as mass of the poison per stated mass of the preparation, was 1 January 2009.

2.1.3 INTERPRETATION OF EXTERNAL

PURPOSE

The Committee considered the interpretation of “external” with regards to nasal sprays for systemic effect.

BACKGROUND

No previous consideration of the SUSDP interpretation of external with regards to nasal sprays for systemic effect was located.

DISCUSSION - SUBMISSIONS

A possible inconsistency between the SUSDP definitions for internal and external use has been brought forward by XXXXX. XXXXX specific query was whether a nasal spray that administers a poison for systemic effect is internal or external. XXXXX noted that application to the nose is included in the external definition whereas use for systemic effect would be captured under internal use.

XXXXX was advised by the Secretariat that this issue would be brought to the attention of the Committee. It was proposed that the Committee consider amending the definition of external to insert (except when intended for systemic effect) immediately after "in the eyes, ears or nose”. The systemic effect exception could not be generally applied to all of the external definition as applications to unbroken skin (a body surface) for systemic effect do not fall within the current internal use definition.

The Committee noted that this issue was not included in the October 2007 NDPSC pre-meeting gazette notice.

A Member noted that this was a question between site of treatment and route of administration. Another Member asserted that any unintended impact of the proposal could be addressed through pre-meeting comments for the February 2008 NDPSC Meeting, noting the current situation would capture any affected product in both the internal and external definitions.

RESOLUTION 2007/51 – 12

The Committee decided to foreshadow an amendment to the SUSDP interpretation of external by inserting “except when intended for systemic effect” immediately after "in the eyes, ears or nose”.

FORESHADOWED DECISION (for consideration at the February 2008 Meeting)

Part 1 – Interpretation – Amendment

“External” – Amend entry to read:

“External” in relation to the use of a poison means application in the ears, eyes or nose (except when intended for systemic effect) or to a body surface other than in the mouth, rectum, vagina, urethra or other body orifice.

2.2 SUSDP, PART 2

No items.

2.3 SUSDP, PART 3

2.3.1 SCHEDULE 5/SCHEDULE 6 STORAGE STATEMENTS

PURPOSE

The Committee considered progress on the drafting of the *Code of Practice for National Retail Storage of Schedule 5 and Schedule 6 Products* (the draft Code).

BACKGROUND

The June 2005 NDPSC Meeting agreed with a STANZHA recommendation to include a new paragraph in Part 3 of the SUSDP relating to the retail storage of Schedule 5 and Schedule 6 poisons to enhance national consistency.

The October 2005 NDPSC Meeting set aside the decision of the June 2005 NDPSC Meeting based on post-meeting comment and to allow further consultation with stakeholders. S5 and S6 storage statements was discussed by the NDPSC at its meetings in February, June and October 2006.

The February 2007 NDPSC Meeting was briefed on the progress of the working group. The Committee agreed that the working group would continue developing the draft guidelines in consultation with industry; States/Territories and industry be encouraged to move forward on this issue; legal advice be sought as to whether the Committee could adopt such a "code"; and the matter be included on the agenda for the June 2007 NDPSC Meeting.

The June 2007 NDPSC Meeting agreed that States and Territories would provide comment to XXXXX before 31 July 2007 on the draft S5 and S6 storage guidelines; and that XXXXX would provide the October 2007 NDPSC Meeting with a report of the jurisdictional comment and draft guidelines for consideration of proceeding to wider consultation through the Committee's standard pre-meeting public consultation process.

DISCUSSION

XXXXX informed the Meeting that the two States XXXXX illustrated the most and least restrictive in jurisdictional control for storage requirements for S5 and S6 substances. Queensland legislates for ≥1.2m or with a CRC, whereas Victoria has no legislation. The working group is looking at the wide ranging spectrum of retailers from the corner store through to the warehouse stores like XXXXX.

XXXXX tabled the draft Code, informing the Meeting that State and Territories had provided feedback, in which four key points had been raised.

- Concern that inference of first dot point on draft Code went beyond the concept of KOOROC (keep out of reach of children) and was therefore more restrictive.
- Whether supervised storage areas, such as direct line of sight staffed service counters, would with certainty minimise access by children.
- Concern over specific emphasis only on ingestion and 'serious' consequences. What mechanisms were there for incident reporting and follow-up of breaches?
- Concern with reference to granular or reduced flow presentation packages – it was not clear as to what was intended, and therefore it was suggested that granular be removed in the consultation draft, noting there may be some other formulation types suggested by industry.
- The working group had looked at many examples of presentation of Schedule 5 and Schedule 6 products addressing different toxicological concerns and was reassured by these examples of possible presentations and packaging options available to the market, e.g. S5 trigger, S6 trigger and barrier (shrink wrap), vast majority of S6 products have CRC packaging and S5 powders in canisters that are sealed or tamper proof.

XXXXX sought the Committee's guidance on other options, not more restrictions, to avoid placing S7 label "Keep out of reach of children" on S5 and S6 products.

XXXXX put forward that there needed to be a de-emphasis in the draft Code that no public access is mandatory.

Other issues that had been raised included incident reporting, staff training, signage and increased lighting in aisles, but it was agreed that the Code should be focused on the specific issue of retail storage of S5 and S6 products.

The Meeting agreed to a number of changes to the draft Code, including a preamble that the Code is a hierarchy of control and that each dot point option is equal in their effectiveness. However, with regard to incident reporting, the Committee agreed that this was more about good business practice and a workplace issue within the retail outlet which would be included in the retailer's standards and codes of practice.

The Meeting agreed that:

- XXXXX incorporate changes to the draft Code,
- the final draft Code be included in the Record of Reasons,
- the final draft Code be published for public consultation on the NDPSC webpage,
- the Secretariat would write to industry associations informing them of the public consultation, with XXXXX to provide the Secretariat with a suitable contact list,
- the consultation period would be late March 2008 to allow the working group to consider public comment and incorporate changes into the draft Code, and
- the working group to report back to the June 2008 NDPSC Meeting.

RESOLUTION 2007/51 - 13

The Committee decided to make the amended final draft Code available for broad public consultation in time for consideration at the June 2008 NDPSC Meeting.

draft Code of Practice for National Retail Storage of Schedule 5 and Schedule 6 Products

Preamble

The purpose of scheduling is to classify chemicals into groups that require similar regulatory controls over their access and availability.

Chemicals are not classified on the basis of a universal scale of toxicity or hazard. Although these are very important factors to be considered, scheduling decisions also take into account many other criteria such as the purpose of use, safety in use and labelling and packaging mechanisms to mitigate any safety concerns.

The Schedules have been developed over a long period of time and ancillary compliance obligations such as retail storage requirements have also been initiated around Australia.

The *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP) sets out the decisions of the National Drugs and Poisons Schedule Committee regarding the national scheduling of chemicals. It also includes, where necessary, model provisions about packaging and labelling and recommendations about any other relevant controls.

Objective

The objective of this document is to provide guidance to manufacturers and retailers on achieving a consistent safety standard for the storage of Schedule 5 and Schedule 6 products in a retail setting that is commensurate with the risk of accidental ingestion by a child.

This Code of Practice provides for an equivalent safety outcome as intended by State and Territory regulations whilst allowing for national consistency in retail storage that meets the expectations of consumers, regulators and other stakeholders, and is commercially feasible.

Scope

The scope of this document is limited to Schedule 5 and Schedule 6 products when packaged and displayed for retail sale in packs of 5 litre and/or 5 kg or less.

Such Schedule 5 products are labelled **CAUTION** and **Keep out of Reach of Children**. The SUSDP summarizes this schedule to include products with a low potential for harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.[1]

Risk Management Considerations

The following risk management considerations have been taken into account in the development of this document:

- the ease and/or likelihood of children with sufficient time and motivation to gain access to the product and/or its contents and accidentally ingest a sufficient quantity which could result in serious injury and/or permanent damage;
- in limiting the likelihood of such ingestion through barriers to a child readily or delay to opening the product, the Code should also serve to provide limited general

[1] Introduction and classification from the SUSDP.

exposure to the contents (and potentially improve the products' integrity in the transport and storage prior to retail sale); and

- Schedule 6 products will generally present a higher risk if accidentally ingested compared to Schedule 5 products.

Guidance

Flexible retail storage is possible where the product's storage and/or nature and/or packaging limits the likelihood of accidental ingestion by a child through providing a barrier and/or delay to opening the product as per the risk management consideration set out above.

A retailer, when displaying Schedule 5 and/or Schedule 6 products for sale, where the public has access, should ensure that:

- the area is directly supervised or within the direct line of sight of a manned service counter; or
- products are stored at least 1.2 metres above the floor; or
- the product is presented with a child resistant closure and/or packaging[2;] or
- the product packaging/presentation limits or delays access.

Examples of presentation and/or barrier packaging features to achieve this are set out below. This list is not intended to be exhaustive and does not preclude product and/or packaging innovations that aim to achieve the same outcome.

- Composite packs e.g. an outer box that contains multiple product packs, or
- Blister or strip packaging, or
- Heat sealed or glued clam shell packaging, or
- Sealed cartons, or
- Aerosol packs, or
- Non-access packaging presentations e.g. bait stations, or
- Shrink wrapped containers and/or closure, or
- Liquid preparations that are presented as a dab on or roller, or
- Powder and/or solid that are in containers that are foil and/or paper wrapped and/or sealed, or
- Products that use tamper evident packaging including
    - Film wrappers
    - Bubble packs
    - Heat shring bands or wrappers

[2] Please note that if scheduling requires a CRC, then this is mandatory.

- Pouches, sachets and form fill seal packs
- Container mouth inner seals
- Tape seals
- Breakable caps
- Tear away caps
- Sealed metal tubes
- Sealed plastic/laminate tubes

OR

- Schedule 5 liquid or gel preparations (other than above) that are:
  - trigger packs, or
  - very viscous, or
  - presented with a small orifice or restricted flow insert
- Schedule 5 powder and/or solid preparations (other than above) that are
  - presented as shaker packs, or
  - reduced flow formulations, or
  - presented in a pack with a small orifice
- Schedule 6 liquid or gel preparations (other than above) that are
  - trigger packs and presented with another barrier feature to limit access/exposure, or
  - very viscous and presented with another barrier feature to limit access, or
  - presented in a pack with a small orifice with another barrier feature to limit access, or
  - presented with a restricted flow insert
- Schedule 6 powders and/or solid preparations (other than above) that are
  - presented as shaker packs and presented with another barrier feature to limit access, or
  - reduced flow formulations and presented with another barrier feature to limit access, or
  - presented in a pack with a small orifice with another barrier feature to limit access.

2.4 SUSDP, PART 5

2.4.1 LEAD IN PAINTS & INKS AND THE UNIFORM PAINT STANDARD (APPENDIX I)

PURPOSE

The Committee considered a proposal to:

- amend the Uniform Paint Standard (Appendix I) of the SUSDP with regards to controls on lead in paint; and
- capture inks containing lead in Appendix C.

BACKGROUND

The February 2004 NDPSC Meeting considered a request for advice and support from XXXXX on the viability of an initiative to reduce lead in decorative and industrial coatings including inks. XXXXX was proposing that legislative changes be implemented to ban the use of lead in decorative and industrial coatings including ink. XXXXX were seeking advice on how the required legislative controls for lead reduction could be achieved for manufacturing industrial paints and inks. The Committee agreed to endorse XXXXX initiative of reducing lead exposure in industrial paints and recommended that the matter be referred to NOHSC (now known as the Australian Safety and Compensation Council – ASCC) as the agency with responsibility for occupational health and safety including the development of standards for the safe use of lead in the workplace.

Following the February 2007 NDPSC meeting, NICNAS published a Priority Existing Chemical (PEC) assessment report "Lead in Industrial Surface Coatings and Inks" (http://www.nicnas.gov.au/Publications/CAR/PEC/PEC29.asp). The report recommended:

(1) that ASCC consider including the declared lead compounds for use in industrial surface coatings and inks and mixtures containing lead compounds, used as or for use in industrial surface coatings and inks, in Schedule 2 (or its successor) of the NOHSC *National Model Regulations for the control of Workplace Hazardous Substances* effective 1 January 2010. Consistent with the NOHSC National Model Regulations employers should ensure that these substances are not used for the purpose specified in the schedule.

(2) that the NDPSC consider:

  (a) Including lead compounds for use in inks in Appendix C of the SUSDP;

  (b) Reviewing the Uniform Paint Standard of the SUSDP in relation to the declared lead compounds for surface coatings.

DISCUSSION - SUBMISSIONS

A late submission was received from XXXXX regarding a proposal for changes to Appendix I, the Uniform Paint Standard, with regards to controls on lead in paint. The Chair considered XXXXX argument and agreed to allow this issue to be tabled at the October 2007 Meeting, noting that this was not to set a precedent for other applications received after the NDPSC deadline for submissions.

The Committee was advised that XXXXX sought scheduling consideration prior to finalisation of the NICNAS PEC report. While XXXXX may have had concerns that the

consultation process for the draft NICNAS PEC report could have resulted in changes to the reports key recommendations, the report was finalised with only minor changes.

In the submission, XXXXX advised that:

- XXXXX was endeavouring, through an amendment of the Australian Inventory for Chemical Substances (AICS), to obtain a legislative underpinning for the elimination of lead from those remaining areas in which it is still used in paint. Reference was made to communications with XXXXX in XXXXX.
- At the time of XXXXX submission, XXXXX asserted that this process was under threat from third parties and XXXXX therefore proposed an urgent amendment to Appendix I. The proposal was that the existing Clause 3 be deleted and substituted by the following:

"3. a) A person shall not, from 31 March 2008, manufacture, sell, supply or use a Third Schedule Paint or Ink other than as provided in clauses b and c below.

b) A person may up until 31 December 2008, but not thereafter, manufacture a Third Schedule Paint for use as an automotive refinish or collision repair paint, or for use in the repair or maintenance of commercial vehicles and equipment or components of such vehicles and equipment, or for use on any aircraft of any type or size, whether in the manufacture, repair or refurbishing of such aircraft.

c) A person may up until 31 December 2009, but not thereafter, sell, supply or use an automotive refinish or collision repair paint or a paint for use in the repair or maintenance of commercial vehicles and equipment, or for use on components of such vehicles and equipment, or for use on any aircraft of any type or size, whether in the manufacture, repair or refurbishing of such aircraft."

- XXXXX indicated that the basis for this application was:
  - The continued use of lead in these products constitutes a health hazard in the handling, transport and storage of the lead as a raw material.
  - A similar health hazard is experienced in the manufacture of the respective coatings.
  - Health and environmental risks occur in the degradation of the products at the end of their life cycles.
  - The technology exists for manufacture of lead free products though sometimes at a greater cost and with some loss of colour density in reds and yellows.
  - Lead free products, in the categories not already covered by the existing restrictions, are being made overseas.
- XXXXX requested that this application be treated as urgent as:

- Many Australian paint manufacturers have already committed a considerable amount of time and money in reformulating their products to exclude lead.
- In the absence of a suitable legislative underpinning for this initiative there will be nothing to stop the importation of lead containing paints, in the categories concerned. The importation of such products will therefore continue to grow and very likely increase.
- The proposed SUSDP amendment and its adoption by States and Territories is very much in the best interests of public health and of Australia in general.

Members also considered the XXXXX correspondence to NICNAS referred to above. This initiated the NICNAS review of lead in industrial surface coatings. XXXXX proposal to NICNAS was to place lead paint and coatings into several categories of controls as follows:

Category One

- Auto refinish car collision repair.
- Commercial vehicle and component builders, refurbishers and repairers.
- Aviation (heavy, general & light aviation) builders, refurbishers and repairers.

Timing

- End of December 2008: Cease manufacture and importation of all lead based paints and coatings used in Category One.
- End of December 2009: Cease distribution, sale and end use of all lead based paints and coatings used in Category One.

Category Two

- All other remaining paint and coating types and end use applications (e.g. paints for automotive original equipment- car builders, industrial coatings, aerosol coatings, protective coatings, packaging coatings etc.) and inks.

Timing

- End of March 2007: Cease manufacture and importation of all lead based paints and coatings used in Category Two.
- End of March 2008: Cease distribution, sale and end use of all lead based paints & coatings used in Category Two.

XXXXX advised that the above time frames were needed to ensure that local manufacturers, some of whom had in excess 400 tints to re-formulate, were not prejudiced by importers able to switch to lead free products in a much shorter time-frame. Other reasons relate to equipment modification in spray shops, staff training etc.

Members noted the following details from the NICNAS PEC report:

- The use of lead compounds in industrial surface coatings and inks was not supported by NICNAS.
- AICS will be annotated to restrict the use of the declared lead compounds in industrial surface coatings and inks in a two stage process beginning in April 2008.
- Lead compounds were not essential in industrial surface coatings and inks and a number of substitutes were available. Use of these substitutes in formulation of industrial surface coatings and inks and use of surface coatings and inks that do not contain lead will avoid the risks associated with the formulation and use of industrial surface coatings and inks that contain lead compounds.
- There were no voluntary controls implemented by the paint/surface coatings and inks industries regarding lead-based compounds. A number of companies however have phased out or are currently phasing out the use of lead compounds in their products. XXXXX have embarked on a phase out of all lead compounds in industrial surface coatings and inks over about the next three years.
- Public exposure to lead from industrial surface coatings will occur from renovation of buildings which have been painted with lead based paints. Exposure is also possible from inappropriate use of surface coatings intended for industrial use. Lead has not been a component of domestic surface coatings since the mid 1970s. Inks containing lead compounds are currently not sold for consumer use.

Members noted the following considerations from the February 2004 NDPSC consideration of lead in paint:

- The Committee noted that the XXXXX proposal to reduce lead in paint would have benefit from a public health perspective. Members discussed that articles imported into Australia may contain lead paint, as these are not covered under NICNAS legislative controls. The importation of lead painted products into Australia may be increasing public health risk.
- Members also noted that, while the amount of lead in paint (but not inks) available commercially is controlled under Appendix I, control of lead in paint for industrial uses in the workplace falls under the jurisdiction of NOHSC (now ASCC).

The Committee also considered the following overseas regulation of lead compounds in surface coatings and inks both for consumer and industrial use from the NICNAS PEC report:

- The US *Ban of Lead-Containing Paint and Products Bearing Lead-Containing Paint* from the *Consumer Product Safety Act* is applied to all products manufactured after February 27, 1978. It bans the commercial sale of paints and surface coatings to consumers that contain lead in excess of 0.06 percent of the total non-volatile content of the paint or the weight of the dried paint film. Industrial uses remain permissible provided there is a warning label.

- The UK has banned the general sale of lead paint that consists of lead carbonate and sulphate pigments (white lead). There is an exception to this rule for the restoration or maintenance of historic and heritage buildings. Other than this exception, lead-based paints containing lead sulphate or carbonate cannot be supplied in the UK for any purpose, whether it be residential, commercial or industrial.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee agreed that the toxicity and safety of lead (52E(1)(a)), its risks and benefits (52E(1)(b)), the potential hazards (52E(1)(c)) as well as the need for access and its toxicity compared with other substances available for a similar purpose (52E(1)(f)) were relevant with regard to this proposal.

Members noted, with regard to the NICNAS PEC report's recommendations that, as Recommendation 1 covered all industrial use of lead in inks and surface coatings, Recommendation 2b would not be necessary as domestic use was already controlled (through the S6 lead compounds entry and Appendix I) while industrial use would be controlled by ASCC. However, Recommendation 2a would still be relevant in banning any potential domestic use of lead in inks. The Committee generally agreed that banning domestic use of lead in ink was justified to protect public health and safety, but noted that there was a possibility of unintended consequences given the breadth of the printing industry. The Committee therefore decided to foreshadow an Appendix C entry for lead in inks to allow additional time for stakeholders to comment. The Committee also noted that the general exemption in Appendix A for "PRINTING INKS or INK ADDITIVES" would also need to be amended so as to no longer apply to inks containing lead.

A member noted the availability of substitutes (i.e. lead-free paints and inks) and the Committee generally agreed this meant it would not be difficult to phase out the use of lead in paints or inks. A member noted the matching of colours may be a problem in restoration. It was also noted that paint being legitimately used in industry may leak into domestic use. It was recognised that residual stocks of lead paint continue to exist in the hands of the public, and that this remains an issue of concern for enforcement.

Additionally, a member asserted, and the Committee agreed, that as industrial use of paint fell within the ASCC's jurisdiction, the various references to industrial use in the current Appendix I were in need of review. XXXXX

The Committee generally agreed that ASCC should be encouraged to consider the NICNAS recommendations and give consideration to similarly controlling the use of lead in industry which the Committee has already achieved for domestic use.

RESOLUTION 2007/51 - 14

The Committee confirmed that the Chair should write to ASCC encouraging them to consider the recommendations of the NICNAS report as soon as practicable given the high priority that the NDPSC has placed on removing lead from domestic settings.

The Committee decided to foreshadow inclusion of lead compounds in inks in Appendix C with a consequential amendment to the Appendix A entry for "PRINTING INKS or INK ADDITIVES" for the February 2008 NDPSC meeting.

The Committee also agreed to foreshadow a review of the Uniform Paint Standard (Appendix I) for the February 2008 NDPSC meeting.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

No items.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 4-AMINOPYRIDINE AND METALLIC PHOSPHIDE (INCLUDING ZINC PHOSPHIDE)

PURPOSE

The Committee considered the scheduling of 4-aminopyridine and metallic phosphides (including zinc phosphide), deferred from the June 2007 NDPSC Meeting.

BACKGROUND

4-Aminopyridine

The November 1968 PSC Meeting considered a pest bird control product (grain impregnated with 4-aminopyridine hydrochloride) and agreed to include 4-aminopyridine in Schedule 7, noting an acute oral LD_{50} of 32.5 mg/kg for rats.

The November 1987 DPSSC Meeting noted veterinary use of 4-aminopyridines for the reversal of xylazine induced anaesthesia in cattle. The Committee concluded that Schedule 7 was inappropriate for this use and agreed to list 4-aminopyridine in Schedule 4 for therapeutic use with an Appendix D listing that "this drug should be available only for the treatment of animals" (and retained Schedule 7 for all other uses).

The February 1995 NDPSC Meeting agreed to remove 4-aminopyridine from Appendix D as there was no need to specify animal use in the Schedule 4 entry because product use pattern was a professional matter which was subject to other controls.

The May 1995 NDPSC Meeting considered a review of Appendix J, and agreed to include 4-aminopyridine in this appendix (except when included in Schedule 4).

Phosphides, metallic

Metallic phosphides will produce phosphine gas in the presence of acid or water.

Prior to August 1994, metallic phosphides were included in Schedule 6. The Appendix E entry for metallic phosphides had been amended at the November 1992 DPSSC Meeting due to concerns for the safety of hospital and ambulance personnel treating patients who had ingested metallic phosphide tablets and were exhaling phosphine gas.

The August 1994 NDPSC Meeting agreed to a proposal to include metallic phosphides in Schedule 7 and Appendix J. Inclusion in Appendix J was confirmed following a review of this appendix at the May 1995 NDPSC Meeting.

Draft Appendix J report

At the October 2006 NDPSC Meeting, XXXXX provided a copy of a draft report 'Project to address inconsistencies between substances listed in Appendix J of the SUSDP and products declared as Restricted Chemical Products'. The Committee noted the following from the draft report's conclusion:

- Extrapolated acute toxicity of XXXXX was commensurate with a Schedule 6 poisons schedule. The report recommended that NDPSC consider including grain based products containing ≤ 25 g/kg zinc phosphide in Schedule 6.
- The extrapolated acute toxicity of 4-aminopyridine in XXXXX was commensurate with a Schedule 6 poisons schedule. The report suggested that the NDPSC consider including grain based products containing ≤ 5 g/kg 4-aminopyridine in Schedule 6.

The Committee agreed to foreshadow consideration of 4-aminopyridine and zinc phosphide at the February 2007 NDPSC Meeting. The February 2007 NDPSC Meeting was advised that 4-aminopyridine and zinc phosphide were inadvertently omitted from the pre-meeting Gazette Notice. Noting that the XXXXX report was soon to be released for public comment Members agreed to foreshadow the following decisions regarding 4-aminopyridine and zinc phosphide for consideration at the June 2007 NDPSC Meeting:

Schedule 6 – New Entries

4-AMINOPYRIDINE in preparations containing 0.05 per cent or less of 4-aminopyridine.

PHOSPHIDES, METALLIC when included in preparations containing 2.5 per cent or less of metallic phosphides.

Schedule 7 - Amendments

4-AMINOPYRIDINE **except** when included in Schedule 4 or Schedule 6.

PHOSPHIDES, METALLIC **except** when included in Schedule 6.

The June 2007 NDPSC Meeting deferred consideration of the above proposal until the October 2007 NDPSC Meeting to allow time for XXXXX to make a final decision on the

Restricted Chemical Product (RCP) status of 4-aminopyridine and metallic phosphine products. The Members also agreed to consider an editorial issue regarding the nomenclature of 4-aminopyridine at that Meeting – cross referencing fampridine (the INN) in the SUSDP index.

DISCUSSION - SUBMISSIONS

XXXXX advised that the RCP status of 4-aminopyridine and metallic phosphides had not be finalised prior to the October 2007 NDPSC Meeting.

Members also recalled from the June 2007 NDPSC Meeting that a Member noted that the rINN for 4-aminopyridine was fampridine. The June 2007 NDPSC Meeting agreed that this should be considered as an editorial issue at the October 2007 NDPSC Meeting.

Members noted that an ARTG search located no human therapeutic products for fampridine or 4-aminopyridine.

The Committee generally agreed that this issue could not be progressed until the issue of RCP status had been resolved, noting that this may not occur for some time yet.

RESOLUTION 2007/51 - 15

The Committee decided to defer consideration of the proposed scheduling changes for 4-aminopyridine and metallic phosphides. The Committee also decided that the INN fampridine be cross-referenced to 4-aminopyridine in the SUSDP 23 index.

SUSDP 23 Index – New Entry

FAMPRIDINE
see 4-aminopyridine

4.2 FORMALDEHYDE AND PARAFORMALDEHYDE

PURPOSE

The Committee considered the scheduling of formaldehyde and paraformaldehyde for all use patterns including human therapeutic use, cosmetic use and non-cosmetic domestic use.

BACKGROUND

Formaldehyde is a colourless gas with a pungent, irritating odour produced commercially by the catalytic oxidation of methanol. In Australia formaldehyde (and paraformaldehyde) is mainly used in the manufacture of formaldehyde-based resins, which are 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 a wide range of personal care and consumer products. The concentrations of formaldehyde in these products range from 40% (in embalming and film processing solutions) to < 0.2% (in the majority of cosmetics and consumer products).

The August 1991 DPSSC Meeting considered a review of the toxicology of formaldehyde and agreed that Schedule 6 remained appropriate for formaldehyde (with an exception for preparations containing ≤ 5%).

The November 1999 NDPSC Meeting noted that formaldehyde and paraformaldehyde, for most practical purposes, are the same compound. Paraformaldehyde consists of short chain polymers of 8-100 units of formaldehyde and readily dissociates to form gaseous formaldehyde when heated or dissolved in water. Members therefore agreed to create entries for paraformaldehyde mirroring the formaldehyde entries.

The February 2000 NDPSC Meeting considered a harmonisation proposal to include formaldehyde and paraformaldehyde in Schedule 2 for human therapeutic use except in preparations containing ≤ 5% formaldehyde/paraformaldehyde. The May 2000 NDPSC Meeting agreed to this proposal, although the ≤ 5% formaldehyde/ paraformaldehyde exception was varied to ≤ 5% formaldehyde for both the formaldehyde and paraformaldehyde entries.

The June 2007 NDPSC Meeting considered the scheduling of formaldehyde and paraformaldehyde, including recommendations from a National Industrial Chemicals Notification and Assessment Scheme (NICNAS) formaldehyde Priority Existing Chemical (PEC) Assessment Report. The Committee agreed to foreshadow consideration at the October 2007 NDPSC Meeting of the scheduling of formaldehyde and paraformaldehyde, to allow a broadening to all use patterns (include human therapeutic use and non-cosmetic domestic use) rather than that stipulated in the NICNAS PEC report (cosmetic use). The following draft wording was included in the Record of Reasons to encourage stakeholder comments (stakeholders were advised that the October 2007 NDPSC consideration would not be limited in any way to these drafts):

Schedule 2 – Draft Amendment

† FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.

Schedule 6 – Draft Amendment

† FORMALDEHYDE (excluding its derivatives) **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or less of free formaldehyde;

(d) in all other non-aerosol cosmetic preparations containing 0.2 per cent or less of free formaldehyde; or

(e) in all other non-cosmetic preparations containing 0.2 per cent or less of free formaldehyde.

Appendix C – Draft New Entry

FORMALDEHYDE in aerosols for cosmetic use.

DISCUSSION - SUBMISSIONS

The June 2007 NDPSC Meeting requested an ARTG search for products containing formaldehyde > 0.2% and ≤ 5%. A list of current products containing formaldehyde was provided. None of these products had formaldehyde as anything other than as an excipient. In summary:

- 27 products in total (3 had no concentration data).
- 23 appeared to have ≤ 0.04% formaldehyde.
- 1, a hospital disinfectant, had 0.2% formaldehyde.

Members recalled the following from the June 2007 Meeting:

The NICNAS PEC Report:

- Formaldehyde was declared a PEC in March 2002 in response to occupational and public health concerns, including sensitisation potential and carcinogenicity. There had been substantial public consultation process in relation to this report.

Recommendations

- Recommendation 15 – that NDPSC consider amending the current scheduling for formaldehyde and paraformaldehyde taking note of the following:

  1) the need to consider more restrictive categories given its potency of causing skin sensitisation and its classification for the workplace as a Category 2 carcinogen;

2) the need for more protective cut-off values for cosmetics and personal care products containing formaldehyde. The EU cut-off values were highlighted as representing a potential best practice model and have the following restrictions:

- Formaldehyde and paraformaldehyde (as a preservative) for cosmetic use:
  - free formaldehyde at 0.2% or less in all cosmetic preparations [except oral hygiene preparations, nail hardeners and aerosol dispensers (sprays)];
  - free formaldehyde at 0.1% or less in oral hygiene preparations;
  - free formaldehyde at 5% or less in nail hardeners; and
  - use of formaldehyde and paraformaldehyde in aerosol dispensers (sprays) is prohibited.

Health effects

- The critical health effects of formaldehyde for risk characterisation were sensory irritation, skin sensitisation and carcinogenicity. Formaldehyde is readily absorbed by all exposure routes. When inhaled, it reacts rapidly at the site of contact and is quickly metabolised in the respiratory tissue.
- Following acute exposure via inhalation, dermal and oral routes, formaldehyde was moderately toxic in animals. Humans experience sensory irritation (eye, nose and respiratory tract irritation) at levels in air ≥ 0.5 ppm.
- Evidence clearly indicates that formaldehyde solution is a skin irritant and a strong skin sensitiser. However, the available human and animal data indicate gaseous formaldehyde was unlikely to induce respiratory sensitisation. Limited evidence indicates that formaldehyde may elicit a respiratory response in some very sensitive individuals with bronchial hyperactivity, probably through irritation of the airways.
- No systemic toxicity was observed following repeated exposure to formaldehyde in animals and humans. Effects at the site of contact show clear dose-related histological changes (cytotoxicity and hyperplasia). An inhalation NOAEL of 1 ppm and an oral NOAEL of 15 mg/kg bw/day were identified for histopathological changes to the nasal tract and the fore- and glandular stomach in the rat, respectively.
- Formaldehyde was clearly genotoxic *in vitro*, and may be genotoxic at the site of contact *in vivo*. Overall, formaldehyde was considered to have weak genotoxic potential.
- The possible relationship between formaldehyde exposure and cancer has been studied extensively in experimental animals and humans. There was clear evidence of nasal squamous cell carcinomas from inhalation studies in the rat, but not in the mouse and hamster. Although several epidemiological studies of occupational exposure to formaldehyde have indicated an increased risk of nasopharyngeal cancers, the data are not consistent. The postulated mode of action for nasal tumours in rats was biologically plausible and considered likely to be relevant to humans.

- There were also concerns of an increased risk for formaldehyde-induced myeloid leukaemia, however, the data was not considered sufficient to establish a causal association. There was no postulated mode of action to support such an effect.
- Based on the available nasopharyngeal cancer data, formaldehyde should be regarded as if it may be carcinogenic to humans following inhalation exposure. Formaldehyde meets the NOHSC Criteria for a Category 2 carcinogen (R49, may cause cancer by inhalation). Other classifications that remain applicable are: toxic by inhalation, in contact with skin and if swallowed (R23/24/25), causes burns (R34), and may cause sensitisation by skin contact (R43).
- Based on animal and limited epidemiology data, formaldehyde was unlikely to cause reproductive and developmental effects at exposures relevant to humans.
- The best available LOEL for non-cancer effects in humans is 0.5 ppm for sensory irritation.

Public exposure and health risks

- The general population may come into skin contact with formaldehyde solutions due to its use in a wide range of cosmetics and consumer products. Because formaldehyde solutions 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.
- Formaldehyde functions as a drying agent, surfactant or preservative in cosmetics and consumer products, such as homecare products and household cleaning products. The following table lists reported products containing formaldehyde.

Cosmetics and personal care products	Shampoos and conditioners Shower gels Liquid hand soaps Cream cleansers Skin moisturiser Toothpastes Nail hardeners
Household cleaning products	Sink detergent Toilet cleaner Stainless steel cleaner Glass cleaner Leather cleaner Laundry liquid cleaners/sprays Surface liquid cleaners Floor cleaner Rinse aid Carpet cleaners Dishwashing liquids
Homecare products	Fabric conditioners/softeners

	Fabric wash Wool wash

- Skin contact is the principal route of direct exposure, but exposure can also occur via eyes, mucous membranes, and respiratory epithelium. Small amounts of aqueous formaldehyde were also likely to be ingested during use of oral hygiene products. Therefore, although at low concentrations, direct exposure to formaldehyde was expected to be widespread and repeated with total exposure varying greatly, depending on the formulation and product type, route of exposure, individual habits and practices.
- Because of high reactivity with biological macromolecules and rapid metabolism, formaldehyde exposure via the skin and inhalation is unlikely to cause systemic toxicity. The main concern for cosmetic and consumer exposure remains at site of contact. Although concentrations of formaldehyde in these products are generally low, the direct exposure via cosmetic and consumer products is expected to be widespread and repeated.
- The majority of cosmetic products used in Australia contain < 0.2% free formaldehyde. However, some products, such as nail hardener, contain up to 1% formaldehyde. Other reported products containing > 0.2% formaldehyde include concentrated fabric softener (0.3%), concentrated detergent (0.3%) and concentrated dishwashing liquids (0.6%).
- Overseas publications report the formaldehyde content of some cosmetics as high as 4.5% (in nail hardeners) and concentrations in dry skin lotions, crème rinses and bubble bath oil are in the range of 0.4% to 0.6%.
- There was no Australian standard limiting the amount of formaldehyde allowed in cosmetic products. The Australian cosmetics industry follows international practice based on the Cosmetic Ingredient Review (CIR) reports for formaldehyde (CIR Expert Panel, 1984) and formaldehyde donor products, such as DMDM Hydantoin (CIR Expert Panel, 1988). These reports concluded that the concentration of free formaldehyde should not exceed 0.2% and aerosolised cosmetic products containing formaldehyde should not be used. These reports have been reviewed recently and no changes have been made (CIR, 2003; CTFA, 2003).
- In the EU, Annex VI (List of preservatives which cosmetic products may contain) of the Cosmetics Directive 76/768/EC (EC, 1999) requires:
    - That all finished products containing formaldehyde (or substances listed in the Annex which release formaldehyde) must be labelled with the warning ‘Contains formaldehyde’ where formaldehyde in the finished product exceeds 0.05%.
    - The maximum authorised concentration of free formaldehyde and paraformaldehyde is 0.2% in cosmetic products, except for oral hygiene products where the maximum concentration of free formaldehyde is 0.1%. Use of formaldehyde and paraformaldehyde in aerosol dispensers (sprays) are prohibited.

- Formaldehyde is also listed in Annex III of Cosmetics Directive 76/768/EC (a list of preservatives which cosmetic products must not contain except subject to the restrictions and conditions laid down due to toxicological concerns), which limits the maximum authorised concentration in nail hardeners to 5%.
- The Annex also states that nail hardeners with > 0.05% formaldehyde as a preservative must carry the warning statement of 'Protect cuticles with grease or oil. Contains formaldehyde'.
- In Canada, formaldehyde is acceptable for use in non-aerosol cosmetics provided that it does not exceed 0.2%. In addition, the recommended limit for formaldehyde concentration in cosmetics is less than 0.3% except for nail hardeners, for which a maximum concentration of 5% is recommended.

XXXXX **recommendation at the June 2007 Meeting**:

- XXXXX commented on the scheduling of non-cosmetic domestic products which were not addressed in the PEC report's recommendations. XXXXX:
    - Advised that a more conservative cut-off than the current 5% (in the Schedule 6 formaldehyde/paraformaldehyde entries) should be applied to non-cosmetic domestic products. It was noted that there was no information in the NICNAS PEC report on overseas restrictions applying to non-cosmetic domestic products.
    - Recommended that the general cut-off be reduced from 5% to 0.2% as:
        - Formaldehyde is a potent skin sensitiser. No threshold had been identified for this sensitisation. (Members noted that the PEC report indicated that the best available LOEL for non-cancer effects in humans was 0.5 ppm for sensory irritation.)
        - There should be consistency between the cut-off for cosmetics and that for other domestic products. (A Member noted that the exposure pattern for the risk of skin sensitisation may differ between cosmetics and other domestic products.)
        - The current level of formaldehyde in most such products was already ≤ 0.2%. (A Member noted that the PEC report indicated a number of products contained > 0.2% formaldehyde such as concentrated fabric softener (0.3%), concentrated detergent (0.3%) and concentrated dishwashing liquids (0.6%)).

June 2007 pre-meeting comment:

- For industry the PEC report lowered the threshold for industrial products with trace formaldehyde from 0.2% to 0.1% to become Hazardous substances. Many companies don't know they have this trace level present and many have worked hard to keep their level < 0.2% so their product would not be classified as Hazardous - Sensitiser. It would be very hard to be below 0.1% free formaldehyde.
- Queried whether such trace levels of formaldehyde (0.1-0.2%) really present a cancer inhalation hazard, noting that the PEC report seems to decide this is so.

- Queried, for domestic products, such a cancer inhalation risk at the 0.1-0.2% levels, asserting that there was probably not a risk at <1% free formaldehyde. Asserted that there was no need to advise of cancer inhalation risk at <1% free formaldehyde in domestic products. Members noted that no evidence was supplied in support of this assertion. The comment did not address the sensitisation or irritation risks.

Members discussion:

- In discussing whether to proceed with a scheduling decision at the June 2007 NDPSC Meeting the Committee:
  - Noted that it appeared that the cosmetics industry was already complying with a code which mirrored the current EU limits, so there would be little impact on this group.
  - Noted a Members opinion that the issue driving lower cut-offs for scheduling should be skin sensitisation as the data regarding the carcinogenicity risk was not strong.
  - Noted that the PEC report used "free formaldehyde" when stipulating cut-off concentrations, while the current scheduling of paraformaldehyde and formaldehyde refer to "formaldehyde". A Member proposed, and Committee agreed, that any scheduling decision should adopt use of "free formaldehyde" as this more clearly reflects the risk being addressed by scheduling.
  - Noted advice indicating anecdotal evidence of non-cosmetic product manufacturers having concerns about their ability to reduce free formaldehyde levels to ≤ 0.2%.
  - Noted that formaldehyde may be used in human medicines at levels below the current 5% cut-off yet > 0.2%. A Member asserted that if the sensitisation risk at > 0.2% was of concern for cosmetics, then perhaps medicines with this concentration should be retained in Schedule 2 instead of exempted.
- The Committee generally agreed that dropping the exemption cut-off from 5% to 0.2% for non-cosmetic domestic use products could have a large regulatory impact, as could a similar move for medicines in Schedule 2.
- The Committee therefore agreed to foreshadow consideration at the October 2007 NDPSC Meeting to allow time to obtain information about formaldehyde in medicines, and for stakeholders to comment – particularly should there be impact on a non-cosmetic domestic use that the Committee had overlooked.

October 2007 pre-meeting comments

A pre-meeting comment was submitted by XXXXX raising particular concern over the possibility of a prohibition on formaldehyde in 'cosmetic aerosols'. Members noted:

- The concern related to the likelihood of an extremely small trace presence of formaldehyde in some aerosols as a result of the degradation of other material e.g. dihydroxyacetone (DHA), the ingredient in self tanning sprays.
- Some DHA degradation to formaldehyde is technically unavoidable. The major DHA supplier advised that this is unlikely to exceed 2.5 ppm, assuming a maximum content of 50 ppm formaldehyde in DHA and a 5 % concentration of DHA in a formulation. (XXXXX were advised that 50 ppm is a specification limit on the Australian specification for DHA and are assured that the product is always within this limit).
- XXXXX noted that similar prohibitions on formaldehyde in cosmetic aerosols exist in several other countries and yet DHA-based self tanning sprays are also common in those countries. Accordingly, it would appear that some form of words has been found in those countries to ensure that such minor and inevitable traces present are not impacted.

A pre-meeting comment was also submitted by XXXXX contending that the proposed scheduling for cosmetic aerosols is more stringent than the current EU requirement and this will have an impact on products currently on the market. Members noted:

- XXXXX, in principle, supported the proposal to implement the EU cut-off values as representing a potential best practice model. The concern is that the proposed method of implementing these cut-off values into scheduling has a different effect when compared to the EU requirements. The current EU requirement prohibits the addition of formaldehyde to aerosol sprays whereas the proposed scheduling prohibits the presence of formaldehyde in aerosols for cosmetic use.
- Under the EU Cosmetic Directive Annex iv, there are two separate sections that refer to formaldehyde:
    - Preamble (Paragraph 5) – All finished products containing formaldehyde or substances in this Annex and which release formaldehyde must be labelled with the warning ‘contains formaldehyde’ where the concentration of formaldehyde in the finished product exceeds 0.05%.
    - Table Part 1 (List of preservatives allowed):

Substance	Maximum authorised concentration	Limitations and requirements
Formaldehyde paraformaldehyde	0.2% (except for products for oral hygiene) 0.1% for oral hygiene products Expressed as free formaldehyde	Prohibited in aerosol dispensers (sprays)

- As the cosmetics industry appears to be complying with the requirements of the current EU limits, XXXXX contend that these limits should be modified to ensure that the way in which they are applied in Australia has a similar result to how they are applied in the EU.

- Scheduling should therefore be phrased in such a way that it reflects the EU requirements around the addition of free formaldehyde rather than the current wording that refers to the presence of formaldehyde in products.
- The Appendix C entry would have particular impact on certain products that do not have free formaldehyde added but do have low levels of formaldehyde formed in the product. These products are available in an aerosol format but this is not a spray – in XXXXX particular instance, this is a foam product.
- One of the major health effects of concern is the inhalation effects of formaldehyde, therefore aerosolised particles of formaldehyde from cosmetic products are an area subject to severe limitations. A foam product has a different effect and this has been recognised in the limitations imposed in EU.
  [Members agreed that the EU specification "aerosol (sprays)" was inadvertently overlooked when drafting possible wording for the June 2007 NDPSC Minutes.]
- This product is available in the EU and it is not directly impacted by the EU Cosmetic Directive requirements for formaldehyde:
  - Free formaldehyde is not directly added to the product;
  - It is in the format of an aerosol but it is not a spray; and
  - It is well under the set limits for labelling 'contains formaldehyde'.
- XXXXX therefore proposed that rather than be included under Appendix C, aerosol cosmetic products containing 0.05% or less of free formaldehyde should be considered to be included under Schedule 6.

A pre-meeting comment was received from XXXXX. XXXXX raised the following matters for the Committee's consideration:

Mousse or foam products in pressurised containers

- XXXXX noted XXXXX pre-meeting comment above, and in particular the discussion on its foam product and the current EU controls.
- XXXXX suggested that the physical form of material dispensed from the pressurised container is important in any consideration of exposure. A foam or mousse presents a different inhalation risk to an aerosol mist that is intentionally dispersed in the air as the product's mode of application. From this perspective it would be useful to follow the EU description and describe specific limitations in the context of: "Formaldehyde in aerosol dispensers (sprays) for cosmetic use". This would provide increased clarity to the intention of the limitation.

DHA in self tanning spray products

- XXXXX noted the XXXXX pre-meeting submission on this topic above.
- As the presence of low levels of formaldehyde in products based on DHA is technically unavoidable, if provision cannot be made to accommodate what are

effectively trace levels then these products will no longer be available in the marketplace.

- XXXXX asserted that possible solutions could be:
  - adopt the EU terminology "aerosol dispensers (sprays)" to differentiate from other pressurised container presentations such as mousses and foams; and
  - provide a general exclusion; or
  - provide a targeted remedy to address the specifics of DHA in self tanning products.

Non-cosmetic preparations

- XXXXX believed that the most significant burden from the marked change in the Schedule 6 threshold (5% to the proposed 0.2%) would be the ability of small-medium enterprises to reformulate.

XXXXX also submitted comment further to the recommendations presented at the June 2007 NDPSC Meeting. Members noted:

- The XXXXX comment covered the following use patterns:
  - Cosmetics (the use pattern covered by the NICNAS PEC Report).
  - Non cosmetic consumer products (raised at the June 2007 NDPSC Meeting).
  - Use in textiles such as blankets and clothing (not previously raised as an issue).

Cosmetics

- XXXXX reiterated the risks and use pattern concentrations set out in the PEC report and reiterated that the EU cut-off values represented a potential best practice model.
- Further to the general recommendation "consideration of scheduling" in the PEC report, XXXXX had submitted the following detailed recommendations for cosmetic use:
  - Cosmetic products at above the relevant cut-offs should be listed in Appendix C. This would be consistent with the international regulatory activity and with the principle that potent skin sensitisers should not be deliberately applied to skin. This action would be expected to have little impact compared with the use of these cut-offs in Schedule 6. In addition, nail hardener preparations containing above 0.2% should be listed in Schedule 6.
  - The use of labelling requirements for cosmetic products equivalent to those in use in the EU was also proposed i.e. a new warning statement 'Contains formaldehyde' and, for nail hardeners only (in addition to existing formaldehyde safety directions) include a new safety direction 'Protect cuticles with grease or oil'.

Non cosmetic consumer products

- XXXXX noted that there is less scope for deliberate application of the non-cosmetic domestic products to skin, and for those such as dishwashing liquid for which skin exposure is likely, a dilution step will commonly take place.
- Such products would be classified as workplace sensitisers at concentrations greater than 0.2% formaldehyde, and accordingly would meet the requirement of Schedule 6.
- XXXXX proposed that the cut-off for non-cosmetic domestic products in Schedule 6 be reduced to 0.2%, consistent with the workplace cut-off for formaldehyde as a sensitiser.
- Additionally, such products should also bear a new warning statement 'Contains formaldehyde'.

Use in textiles such as blankets and clothing

- XXXXX noted recent concern about the release of formaldehyde from textile products, particularly blankets and clothing. Several recent but undocumented case reports from Australia and New Zealand appear to support the risks of both sensitisation and sensory irritation due to release of formaldehyde from these sources. XXXXX provided a reference (Carlson RM, Smith MC, Nedorost ST (2004) "Diagnosis and Treatment of Dermatitis Due to Formaldehyde Resins in Clothing" Dermatitis, 15(4), 169-175) detailing a study of formaldehyde sensitisation from clothing sources.
- Formaldehyde is not deliberately added to textiles, but rather is released from fabric treatments such as anti-crease treatments that use formaldehyde based resins. Dye fixation systems and pigment printing may also use such resins. These resins in uncured form contain methylol groups which may readily hydrolyse to release formaldehyde.
- The Australian Competition and Consumer Commission (ACCC) have adopted interim maximum residue benchmarks for formaldehyde. These are 30 ppm for infant garments, 75 ppm for garments which contact the skin and 300 ppm for other garments or fabrics.
- The risk of exposure in the NICNAS PEC Report did not cover risks arising from local exposure following formaldehyde release from textiles.
- Standard methods for determining formaldehyde content in textiles do not address the content of free formaldehyde. They range between methods which measure free and readily hydrolysable formaldehyde (e.g. ISO 14184-1: Textiles - Determination of formaldehyde - Part 1: Free and hydrolysed formaldehyde (water extraction method)) to those which measure total available formaldehyde. XXXXX provided a reference which discusses current methodologies (Priha E (1995) "Are Textile Formaldehyde Regulations Reasonable? Experiences from the Finnish Textile and Clothing Industries" Regulatory Toxicology and Pharmacology 22 243-249).
- The standard methods do not give an indication of the rate of release of the hydrolysable or available formaldehyde, and therefore cannot be used to determine

the free gaseous formaldehyde at a particular instant to relate directly to health based standards. In addition, determination of concentrations of formaldehyde in textiles that would have a sensitising effect is difficult as the available evidence does not allow this to be converted to a dose or concentration of formaldehyde at the skin.

- XXXXX provided a document (OECD (2005) "*Environmental Requirements and Market Access*" Chapter 1: Limits on Formaldehyde in Textiles; ISBN Number: 9264013741) which noted that a number of countries have established limits for formaldehyde content in textiles, but the basis of setting the limits is not clear. No documentation is available for any of these to link them directly to a health-based concentration cut-off, although the intent of each of the limits appears to be protection of human health.
- A model group of standards may be those applied in the EU. Two major Standards are in use, the EU Eco-label system which has limits of 30 ppm for infant clothing and clothing in contact with skin, and 300 ppm for other textiles (ISO 14184-1), and Oeko-Tex Standard 100, which has limits of "not detectable" (15-20 ppm) for infant clothing, 75 ppm for clothing in contact with skin, and 300 ppm for other textiles (Japanese Law method). The initial Eco-label requirements also specified 75 ppm for non-infant clothing in contact with skin.
- An article reviewing scientific literature indicated that reactions to formaldehyde in textiles as measured by a method similar to ISO 14184-1 would commonly not occur at levels less than 500 ppm, although levels of 30 ppm may lead to reactions in some sensitive individuals (Scheman AJ, Carroll PA, Brown KH, Osburn AH (1998) "Formaldehyde-related textile allergy: an update" Contact Dermatitis, 38, 332-336).
- XXXXX concluded that, given that health based limits cannot be set for free formaldehyde in textiles and that the analytical method available estimates free and some hydrolysed formaldehyde, issues to be considered are:
    - Setting a scheduling cut-off for formaldehyde in textiles to provide protection from health effects.
    - Restriction of "free and partly hydrolysable formaldehyde" (based on measurement standards such as ISO 14184-1) rather than free formaldehyde itself.
- XXXXX recommended that NDPSC adopt a level of 30 ppm for infants clothing, 75 ppm for non-infant clothing that is likely to be in contact with skin, and 300 ppm for other textiles. The SUSDP entry should specify that analysis be conducted according to ISO 14184-1. XXXXX considered that the properties of formaldehyde are such that textiles with above these levels of formaldehyde should be listed in Schedule 6.
- Labelling with the signal word and "Contains formaldehyde. Wash before using" was also recommended.

Members noted an August 2007 ACCC statement on this issue stating that it had begun testing a range of clothing for significant residual formaldehyde following heightened public concerns. The statement indicated that:

- There was currently no evidence that clothing in the Australian market contained unacceptably high levels of formaldehyde. However, over recent months there had been two recalls of blankets which had residual amounts of formaldehyde which may cause short term skin or respiratory irritation for some individuals.
- More recently, New Zealand media reports indicated that tests of some children's and adult clothing resulted in formaldehyde levels that were excessive when compared with limits set in regulations or guidelines in several countries.
- Formaldehyde is often used in the production process for clothing and other textiles. However, formaldehyde is both soluble in water and volatile and very little, if any, residual formaldehyde should remain in final textile products.
- The ACCC was working with the Department of Health and Ageing and seeking other expert advice on an appropriate maximum level for formaldehyde in clothing and textiles. XXXXX
- In the interim, the ACCC will use the EU benchmark for the applicable maximum residue limits for formaldehyde.

XXXXX was asked to comment on its recommendation for specific scheduling controls on textiles when controls are already being enforced through the ACCC (through administration of the *Trade Practices Act 1974*). XXXXX verbally advised that the scheduling recommendation was to allow a specific labelling requirement to be enforced for textiles failing the EU benchmark, as XXXXX believed that this would be more efficiently achieved through scheduling than by ACCC controls.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The following matters under 52E(1) were particularly relevant to this consideration – (a) toxicity and safety; (b) risks and benefits; (c) potential hazards; (d) extent and patterns of use; and (h) purposes for which a substance is to be used.

A Member noted that in nail hardener products formaldehyde is an active, whereas other products contain formaldehyde as a preservative or as a residue. A Member asserted that most nail hardeners had < 1% formaldehyde and suggested a lower nail hardener cut-off. However, the Committee was advised that there were some nail hardener products with higher levels of formaldehyde, and that the proposed 5% cut-off remained appropriate.

A Member noted that for non-cosmetic use products a move to a lower exclusion cut-off will not necessarily require reformulation for affected products. That is to say that they would still be allowed to supply these products, as long as they were compliant with the Schedule 6 labelling and packaging requirements.

The Committee noted that while the cosmetic industry may already comply with the proposed changes, this was unlikely to be the case for many non-cosmetic domestic products and there may be need to consider a delayed implementation date on any scheduling change. The Committee generally agreed that this could be considered at the

February 2008 NDPSC Meeting, should post-meeting comment be received justifying such a move. The Committee also agreed that relevant comments which might not normally be considered as valid post-meeting comment may in this case be tabled at the February 2008 NDPSC Meeting.

RESOLUTION 2007/51 - 16

The Committee decided:

- To lower the Schedule 2 and 6 general exemption cut-offs from 5% to 0.2%. Additionally, a preparation containing > 0.05% free formaldehyde would only qualify for the Schedule 6 exemption (i.e. between 0.05 and 0.2%) when compliant with a reverse schedule label "contains formaldehyde".
- To specifically exclude ≤ 0.1% oral hygiene products (whether therapeutic or non-therapeutic) from Schedule 2 and 6.
- To include nail hardener cosmetics containing between 0.2% and 5% free formaldehyde in Schedule 6. Additionally, a nail hardener preparation containing > 0.05% free formaldehyde would only qualify for the Schedule 6 exemption (i.e. between 0.05 and 0.2%) when compliant with a reverse schedule label "protect cuticles with grease or oil".
- To ban formaldehyde or paraformaldehyde for the following uses through inclusion in Appendix C:
    - Oral hygiene products > 0.1%.
    - Aerosol sprays for cosmetic use (with an exemption for trace levels of free formaldehyde below 0.005%). This does not include other possible aerosol presentations such as foams or mousses.
    - Nail hardener cosmetic preparations ≥ 5% free formaldehyde.
    - All other cosmetics (including non spray aerosols such as foams etc) except in preparations containing ≤ 0.2%. Additionally, a preparation containing > 0.05% free formaldehyde would only qualify for the exemption (i.e. between 0.05 and 0.2%) when compliant with a reverse schedule label "contains formaldehyde".
- To include a new warning statement "contains formaldehyde" in Appendix F Part 1 and to apply this to formaldehyde in Appendix F part 3.
- To include a new safety direction "protect cuticles with grease or oil" in Appendix F Part 2 and to apply this to formaldehyde when used in nail hardener cosmetics in Appendix F part 3.

Textiles

The Committee agreed that, as ACCC was still establishing its regulations for formaldehyde levels in textiles, it was not appropriate to consider scheduling at this time.

Schedule 2 – Amendments

FORMALDEHYDE – Amend entry to read:

† FORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.

PARAFORMALDEHYDE – Amend entry to read:

† PARAFORMALDEHYDE (excluding its derivatives) for human therapeutic use **except**:

(a) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde; or

(b) in other preparations containing 0.2 per cent or less of free formaldehyde.

Schedule 6 – Amendments

FORMALDEHYDE – Amend entry to read:

† FORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

PROTECT CUTICLES WITH GREASE OR OIL; or

(d) in all other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE.

PARAFORMALDEHYDE – Amend entry to read:

† PARAFORMALDEHYDE (excluding its derivatives) in preparations containing 0.05 per cent or more of free formaldehyde **except**:

(a) for human therapeutic use;

(b) in oral hygiene preparations containing 0.1 per cent or less of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

PROTECT CUTICLES WITH GREASE OR OIL; or

(d) in all other preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE.

Appendix C – New Entries

FORMALDEHYDE (excluding its derivatives):

(a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

(b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

(d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE.

PARAFORMALDEHYDE (excluding its derivatives):

(a) in oral hygiene preparations containing more than 0.1 per cent of free formaldehyde;

(b) in aerosol sprays for cosmetic use containing 0.005 per cent or more of free formaldehyde;

(c) in nail hardener cosmetic preparations containing 5 per cent or more of free formaldehyde; or

(d) in all other cosmetic preparations containing 0.05 per cent or more of free formaldehyde **except** in preparations containing 0.2 per cent or less of free formaldehyde when labelled with the warning statement:

CONTAINS FORMALDEHYDE.

Appendix F – Part 1 – New Entry

WARNING STATEMENTS

106. Contains formaldehyde.

Appendix F – Part 2 – New Entry

SAFETY DIRECTIONS – GENERAL

36. Protect cuticles with grease or oil.

Appendix F – Part 3 – Amendment

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**

Formaldehyde – Amend entry to read:

Formaldehyde .....

(a) in nail hardener cosmetics. 106 1,4,8,36

(b) in other preparations.....106 1,4,8

5. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS.

5.1 SUSDP, PART 4

5.1.1 MONENSIN

PURPOSE

The Committee considered the scheduling of monensin including a proposal to broaden the Schedule 6 entry to capture stockfeed supplements, blocks and licks containing ≤ 0.75% monensin.

BACKGROUND

Monensin (the INN) is an ionophore polyether antibiotic produced by *Streptomyces cinnamonensis*. The ionophores are crown polyethers that act by binding and then facilitating cation transport across the cell membrane of gram positive bacteria, overwhelming the ATP dependent cation pumps leading to osmotic cell disruption and death. The ionophores are widely used both as preventative medication (as ionophores tend to reduce the incidence of lactic acidosis, bloat, and ketosis through their effects on rumen fermentation) and as growth promotants in poultry, cattle, sheep, pigs and goats. Ionophores also control the protozoan that causes coccidiosis.

The ionophore class includes:

- Lasalocid – Schedule 6 except animal feeds with ≤ 100 mg/kg antibiotic substances.
- Maduramicin – Schedule 7, with a Schedule 5 cut-off for animal feed premixes ≤ 1% antibiotic substances, and an exception for animal feeds ≤ 5 mg/kg antibiotic substances.
- Monensin – Schedule 6 for animal feed premixes ≤ 12.5 % antibiotic substances, Schedule 5 for intraruminal implants for cattle ≤ 35 g monensin, and Schedule 4 for all other uses with an exception for animal feeds ≤ 360 mg/kg antibiotic substances.
- Narasin – Schedule 6 for animal feed premixes ≤ 12.5 % narasin and Schedule 4 for all other uses with an exception for animal feeds ≤ 100 mg/kg antibiotic substances.
- Salinomycin – Schedule 6 for animal feed premixes ≤ 12 % antibiotic substances and Schedule 4 for all other uses with an exception for animal feeds ≤ 60 mg/kg antibiotic substances.
- Semduramicin – Schedule 6 in animal feed premixes for coccidiosis with ≤ 5 % antibiotic substances and Schedule 7 for all other uses with an exception for animal feeds ≤ 25 mg/kg antibiotic substances.

Monensin products are registered mainly as feed additives for:

- growth promotion in cattle;
- improved feed efficiency in feedlot cattle;
- increased milk production in dairy cattle;
- reduction in severity of non-clinical ketosis in lactating dairy cattle;
- prevention of coccidiosis in cattle, goats and poultry; and

- bloat reduction in pasture feed cattle (capsule).

The Committee first examined monensin in November 1971 when it was included in Schedule 4 with an exemption for animal feeds containing 120 ppm (33 mg/kg) or less of monensin. A Schedule 6 entry for use as an animal feed pre-mix was recommended in February 1982. The Schedule 6 entry was then revised in November 1986 by specifying growth promotion and coccidiosis prevention, and to include intraruminal implants. In February 1990, the Schedule 4 cut-off for animal feeds was raised to 360 mg/kg while consideration of monensin, as part of a wider review of oral Schedule 5 and Schedule 6 veterinary substance undertaken in February 1996, resulted in the intraruminal implant being down scheduled to Schedule 5. The February 2002 meeting amended the Schedule 6 entry in line with other animal feed premixes containing antibiotics to give the current wording.

DISCUSSION - SUBMISSIONS

A submission was received from XXXXX requesting a rescheduling of monensin in stockfeed supplements, blocks and licks from the Schedule 4 parent entry to Schedule 6. The following wording was proposed for the Schedule 6 entry:

MONENSIN:

(a) in animal feed premixes containing 12.5 per cent or less of antibiotic substances; or

(b) in stockfeed supplements, blocks and licks containing 0.75 per cent (7.5 g/kg) or less of antibiotic substances.

Members noted the following from the XXXXX submission:

- APVMA-registered premix products contain monensin at concentrations ranging from 100 to 900 mg/kg. These are traditionally incorporated into complete rations or supplementary feeds (which are consumed at lower rates) for cattle, goats and poultry. The maximum individual-animal dose for cattle of 450 mg/head/day of monensin is currently approved by the APVMA for increased milk production, as an aid in reducing the severity of non-clinical ketosis and as an aid in the control of bloat in dairy cattle.
- Newer types of animal nutrition preparations such as liquid supplements, loose licks, molasses blocks and micromixes often have medications such as monensin incorporated at the feed mill or on farm. Due to the current wording of the SUSDP, unless it fits the definition of an "animal feed" containing ≤ 360 mg/kg of monensin, or a "premix" containing ≤ 12.5% monensin, a supplement medicated with monensin using a Schedule 6 product defaults to Schedule 4.
- It was asserted that this situation meant that an APVMA-approved Schedule 6 monensin premix may be legally purchased, blended with standard nutritional

ingredients in accordance with the approved use pattern, and end up being a Schedule 4 preparation. It was asserted that this was an illogical situation.

- XXXXX asserted that the current situation probably arose through oversights due to limitations in the scope of the definitions and terms currently described in the SUSDP listings for monensin. XXXXX proposed that any toxicological risk associated with monensin medication of feedstuffs is related more to the concentration of the active ingredient than to the form of delivery, and there is no justification for nutritional preparations defined as "premixes" to be classified as Schedule 6, while "supplements", regardless of the monensin concentration, are included in Schedule 4 due to the lack of a specific entry.
- No additional data was provided with this submission as extensive information regarding the human health risks associated with monensin use in animals had been reviewed by the NDPSC on previous occasions, noting that the monensin concentration of 0.75% proposed as the maximum for stock food supplements, blocks and licks is 17 times lower than the level allowable in animal feed premixes under Schedule 6.

The XXXXX submission made detailed claims against the 52E(1) criteria which are summarised below:

(a) Toxicity and safety of the substance:

- It was asserted that the toxicity and safety of monensin had been previously assessed by OCS. As this proposal involved the addition of supplements with lower concentrations of monensin than those currently included in Schedule 6, no further assessment of the toxicological aspects of monensin was considered necessary.
- Known toxicological endpoints for monensin include:

  <u>Single exposure</u>

  - Oral (monensin sodium, rat) median lethal dose 34 mg/kg, incoordination, reduced activity, skeletal muscle weakness, diarrhoea, decreased weight gain.
  - Skin (monensin sodium 24% mixture, rabbit) 500 mg/kg, no deaths or toxicity.
  - Inhalation (monensin sodium 24% mixture, rat) 370 mg/m3 for 1 hour, no deaths.
  - Skin contact (monensin sodium 24% mixture, rabbit), slight irritant.
  - Eye contact (monensin sodium 24% mixture, rabbit), corrosive but permanent damage prevented by immediate rinsing.

  <u>Repeat exposure</u>

  - Heart effects (degenerative and reparative tissue changes, electrocardiogram changes, congestive heart failure), muscle effects (skeletal muscle changes, elevated blood enzymes of muscle origin).

- Decreased body weight gains, increased kidney, heart, thyroid, adrenal, prostate, testes, liver and spleen weights.
- Reproduction. No effects identified in animal studies.
- Sensitisation. Guinea pig, not a contact sensitiser.
- Mutagenicity. Not mutagenic in bacterial cells.

(b) Risks and benefits associated with the use of monensin:

- The risks/benefits according to the currently approved use patterns have been assessed by OCS, EAGAR and the APVMA. It was asserted that as the proposal does not involve any change to the use patterns, no further risk/benefit assessment is necessary.
- Proposed that while feeds, supplements and premixes may take various forms ranging from powders and loose mixes to liquids and blocks, all are blended with similar nutritional ingredients and the toxicological risk associated with monensin medication of feedstuffs is related more to the concentration of the active ingredient than to the form of delivery. All types of monensin-medicated feeds and premixes containing up to 12.5% monensin may be handled and/or mixed by feed millers as well as by end users on-farm and therefore exposure patterns and toxicological risks for Schedule 6 and unscheduled feedstuffs only vary due to the different monensin concentrations. There is no additional risk associated with monensin in preparations defined as "supplements" (including blocks and licks), compared to premixes containing the same concentration of monensin.

(c) Potential hazards associated with the use of monensin:

- Potential hazards associated with the currently approved use patterns were previously assessed. Potential hazards associated with the proposed entry would be significantly less than those previously assessed when establishing the current SUSDP listings for monensin (since the supplements would be at lower concentrations of monensin than the premixes). No further assessment of potential hazards is considered necessary for this submission.

(d) Extent and patterns of use of monensin and (e) Dosage and formulation:

- Monensin is currently registered for administration to poultry, goats and cattle in a number of formulations including premixes and intra-ruminal implants.
- The current APVMA-approved directions for use do not limit the form of supplement that monensin premixes may be incorporated into, however the label instructions for supplements state, “Do not feed a supplement containing greater than 360 mg monensin/kg supplement”. It was asserted that this statement was included on the label to prevent the inadvertent mixing of supplements that could be considered Schedule 4 animal feeds, using the Schedule 6 premix product.
- XXXXX considered the supplement statement to be ambiguous and inconsistent with current medication and feeding practices which may require the daily dose of

monensin (up to 450 mg/head) to be provided in a supplement consumed at a rate as low as 60-200 g/head/day. XXXXX

(f) Need for access to monesin:

- XXXXX asserted that this criterion was not relevant to their submission. The need for access had been evaluated previously and access was unchanged by this proposal.

(g) Potential for misuse/abuse of monensin:

- XXXXX asserted that this criterion was not relevant. Stockfeed supplements are formulated using the same nutritional ingredients as premixes and feed rations. Therefore the use of a Schedule 6 premix (containing up to 12.5% monensin) to make a stockfeed supplement, block or lick containing a maximum of 0.75% monensin would be associated with a corresponding reduction in the potential for deliberate or accidental misuse or abuse.

(h) Purpose for which monensin is to be used:

- Referred to discussion for 1.(d) above.

Additional matters:

- No known additional matters were considered to be relevant to this submission.

Members noted the following from the November 2001 NDPSC consideration of monensin:

- It was noted that ionophores were included in the scope of the JETACAR report. However, it had been suggested that ionophores should be excluded from the JETACAR definition of antibiotics, as these compounds were not currently used in human medicine or related to any currently used human therapeutic agents. Additionally, it was highlighted that existing scientific and technical knowledge supported the conclusion that the ionophores are unlikely to contribute to the development of antibacterial resistance to important antibiotics used in human or veterinary medicine.
- The Committee agreed that as there were no public health or animal welfare concerns, the Schedule 6 entry for monensin be amended in line with the Schedule 6 wording for other antibiotics used in animal feed pre-mixes (bacitracin, bambermycin, salinomycin, semduramycin).

The general issue of the scheduling of ionophores was discussed at the June 2002 NDPSC Meeting. Members noted that:

- The Committee considered the EAGAR risk assessment on the polyether ionophores in relation to the Commonwealth Government response to Recommendation 6 of the JETACAR Report. Members noted from the EAGAR assessment that:
    - Gram positive bacteria were usually sensitive to the ionophores while gram negative bacteria were naturally resistant. While resistance may develop in gram

positive strains the mechanism by which this occurs and is maintained remains to be elucidated.

- There are currently no registered human therapeutic uses for the ionophores as antibiotics, however a number of uses including as antibiotics are being investigated. There are no related agents registered for human therapeutic use however a number were listed for antimicrobial use in animals.
  [Members were advised that a search of the ARTG for each of the scheduled ionophores failed to locate any registered human therapeutic products containing an ionophore]
- No cross-resistance has been recorded in humans however, various members of the class exhibit cross-resistance in animals.
- The use pattern, particularly low doses for extended periods of time, was conducive to development of resistance however, there was no evidence of this occurring.

- Members were reminded that the Committee had reviewed the Schedule 5 and 6 scheduling of all the ionophores in the early 1990's.
- The Committee noted the EAGAR recommendation that: "At the present time the risk to public health from antibiotic resistance arising from the use of the polyether ionophores is low. EAGAR therefore recommends that there is no need, on the grounds of antimicrobial resistance, to change the scheduling of all ionophores to Schedule 4."
- The Committee agreed that there was no need to alter the current scheduling of the polyether ionophores on the basis of antibiotic resistance.

Members noted that the Secretariat sought advice from XXXXX concerning whether EAGAR had revisited the ionophores resistance issue since producing the risk assessment. XXXXX confirmed that the 2002 risk assessment was the last EAGAR consideration of either monensin or ionophores.

The Committee also noted a review published subsequent to the EAGAR risk assessment "Ionophore resistance of ruminal bacteria and its potential impact on human health" (J.B. Russell, A.J. Houlihan FEMS Microbiology Reviews 66 27 (2003) 65-74). Members particularly noted:

- Beef cattle in feedlots are routinely fed ionophores, and these compounds increase feed efficiency by as much as 10%.
- Some groups have argued that ionophore resistance poses the same public health threat as conventional antibiotics, but humans are not given ionophores to combat bacterial infection.
- Ionophores are highly lipophilic polyethers that accumulate in cell membranes and catalyze rapid ion movement. When sensitive bacteria counteract futile ion flux with membrane ATPases and transporters, they are eventually de-energized. Aerobic

bacteria and mammalian enzymes can degrade ionophores, but these pathways are oxygen-dependent and not functional in anaerobic environments like the rumen or lower GI tract. Gram-positive ruminal bacteria are in many cases more sensitive to ionophores than Gram-negative species, but this model of resistance is not always clear-cut. Some Gram-negative ruminal bacteria are initially ionophore-sensitive, and even Gram-positive bacteria can adapt.

- Ionophore resistance appears to be mediated by extracellular polysaccharides (glycocalyx) that exclude ionophores from the cell membrane. Because cattle not receiving ionophores have large populations of resistant bacteria, it appears that this trait is due to a physiological selection rather than a mutation per se. Genes responsible for ionophore resistance in ruminal bacteria have not been identified, but there is little evidence that ionophore resistance can be spread from one bacterium to another. Given these observations, use of ionophores in animal feed is not likely to have a significant impact on the transfer of antibiotic resistance from animals to man.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

A Member noted that monensin was highly toxic to horses. The Committee agreed that this was a registration issue. The Committee also noted that it was very unlikely that monensin would be used in humans.

XXXXX Member advised that using the original definitions could lead to inadvertent non-compliance in certain forms of animal feed, and that capture of such products in Schedule 4 was never the intent of the Committe.

RESOLUTION 2007/51 - 17

The Committee decided to amend the monensin Schedule 6 entry to also capture stockfeed supplements, blocks and licks containing $\leq 0.75\%$ antibiotic substances.

Schedule 6 – Amendment

MONENSIN – Amend entry to read:

MONENSIN:

(a) in animal feed premixes containing 12.5 per cent or less of antibiotic substances; or

(b) in stockfeed supplements, blocks or licks containing 0.75 per cent or less of antibiotic substances.

5.2 SUSDP, PART 5

No items.

6. MATTERS REFERRED BY THE AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY.

6.1 METRIBUZIN

PURPOSE

The Committee considered the scheduling of metribuzin.

BACKGROUND

Metribuzin is a triazine herbicide which was first recommended for inclusion in Schedule 5 in July 1972. At that time the acute oral LD_{50} in male rats was determined to be 2200 mg/kg.

Metribuzin (CAS: 21087-64-9) is the common name. The chemical name is 4-amino-6-tert-butyl-3-methylthio-1,2,4-triazin-5-(4H)-on.

DISCUSSION - SUBMISSIONS

XXXXX has prepared an evaluation report on an APVMA application by XXXXX to extend the use of a XXXXX formulation (XXXXX g/kg metribuzin) to XXXXX This herbicide is currently registered for selective weed control in asparagus, barley, chickpeas, faba beans, lentils, lupins, peas, pigeon peas, potatoes, soybeans, tomatoes, vetch, wheat and white lupins.

Members noted the following from the evaluation report:

- The product XXXXX contains XXXXX % metribuzin and is currently in Schedule 5. Based on acute oral toxicity to the rat and the guinea pig, this classification may not be appropriate. The toxicity of metribuzin had been assessed by XXXXX previously (in 1982, 1988, 1990, 1992 and 1995).
- In previous XXXXX evaluations metribuzin had an acute oral LD_{50} of 1140-1986 mg/kg bw in female and 1090-1937 mg/kg bw in male rats, and an LD_{50} of 274 mg/kg bw in female and 198 mg/kg bw in male guinea pigs. In the present report, an LD_{50} of XXXXX was reported for metribuzin.
- Metribuzin was of low acute dermal toxicity in XXXXX and low inhalation toxicity in XXXXX. Metribuzin did not irritate the skin or eyes of XXXXX or cause skin sensitisation in XXXXX.
- XXXXX
- Metribuzin was not genotoxic in XXXXX
- No evidence of carcinogenic potential was observed in the longer term studies. Metribuzin was not teratogenic.

- XXXXX
- It was concluded that the principal route of exposure would be the dermal route. XXXXX
- XXXXX
- Metribuzin is listed on the Australian Safety and Compensation Council (ASCC) Hazardous Substances Information System (HSIS) Database (ASCC, 2005) with the classification Xn (Harmful) and the following risk phrase for concentrations greater than or equal to 25%: Harmful if swallowed.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

52E(1)(a), the toxicity and safety of the substance, was particularly relevant to this consideration.

Members noted that low LD_{50}s had been seen numerous times in the past, but the scheduling implications of this had not been picked up. Reasons for this remained unclear. A Member noted that the XXXXX effects also support the need for controls through a Schedule 6 listing.

Members were advised that XXXXX did not have the opportunity to respond to the evaluation report due to a procedural issue. The Committee therefore agreed that for procedural fairness any decision would need to be foreshadowed for consideration at the February 2008 NDPSC Meeting.

A Member noted that metribuzin was an old, established substance so there would be generics etc that may also be impacted by a new scheduling decision. XXXXX Foreshadowing would provide a further opportunity for such stakeholders to comment.

RESOLUTION 2007/51 - 18

The Committee decided to foreshadow consideration of rescheduling metribuzin to Schedule 6 at the February 2008 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the February 2008 Meeting)

Schedule 5 – Amendment

METRIBUZIN – delete entry.

Schedule 6 – New Entry

METRIBUZIN.

6.2 DIDECYLDIMETHYLAMMONIUM CHLORIDE AND DIDECYLDIMETHYLAMMONIUM CARBONATE

This item was withdrawn by XXXXX prior to the Meeting.

6.3 FLUBENDIAMIDE

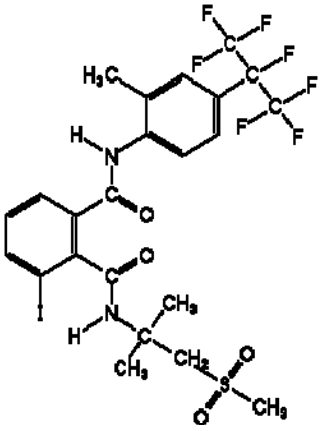
PURPOSE

The Committee considered the scheduling of flubendiamide.

BACKGROUND

Flubendiamide belongs to the phthalic acid diamide chemical class, a ryanodine receptor agonist, which activates ryanodine-sensitive intracellular calcium release channels in insect neurons. Flubendiamide shares its mode of action with chlorantraniliprole, another diamide insecticide. The release of calcium causes muscle contraction, resulting in the death of the insect. This mode of action has been shown to be highly specific to insect ryanodine receptors and not to affect mammalian ryanodine receptors.

Flubendiamide is the ISO approved common name. The IUPAC chemical name is 3-iodo-N′-(2-mesyl-1,1-dimethylethyl)-N-{4-[1,2,2,2-tetrafluoro-1-(trifluoromethyl)ethyl]-o-tolyl}phthalamide. The chemical structure is:



DISCUSSION - SUBMISSIONS

XXXXX has evaluated an application from XXXXX seeking registration for a new insecticidal active constituent, flubendiamide, and for XXXXX products containing flubendiamide XXXXX. Members noted the following from the XXXXX report:

- XXXXX recommended that, based on the toxicity profile, in particular the slight eye irritation, the NDPSC may consider placing flubendiamide and the XXXXX products

in Schedule 5. [Members noted that the XXXXX products – XXXXX flubendiamide – were also slight eye irritants]

- Studies were well conducted and conformed with current test guidelines and protocols. The scientific and regulatory quality of the toxicology database was high and was considered sufficient to clearly define the toxicity of flubendiamide.
- XXXXX
- Flubendiamide was moderately well absorbed orally, but due to biliary excretion was mostly excreted in the faeces. Flubendiamide is lipophilic; XXXXX studies indicate some potential for accumulation in fat tissue. XXXXX
- Flubendiamide has low acute oral XXXXX and dermal XXXXX toxicity in XXXXX. It is not a skin irritant in XXXXX or a skin sensitiser in XXXXX at the doses tested. However, it is a slight eye irritant in XXXXX.
- Based on XXXXX it is expected the acute inhalational toxicity of flubendiamide will be low.
- Flubendiamide was found to have similar effects in short-term and long-term repeat dose studies, often at relatively low doses. XXXXX.
- XXXXX Flubendiamide and its derivatives were not found to be genotoxic.
- XXXXX
- Public exposure during use of the products is considered unlikely. XXXXX
- The OCS report also recommended that the following safety directions appear on the labels of XXXXX products, taking into consideration the potential toxicological hazard, use pattern and likelihood of handler exposure:
    - May irritate the eyes
    - Avoid contact with eyes
    - Wash hands after use
- XXXXX
- There is no evidence from the toxicity of the products that would support an exemption from the requirements of scheduling for lower concentrations of flubendiamide.

XXXXX

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee agreed that the toxicity profile generally aligned with the Schedule 5 criteria (i.e. low acute toxicity, slight eye irritant). A Member asserted that the possibility of bioaccumulation was another reason that a Schedule 5 listing would be appropriate.

Given the toxicity profile and the intended patterns of use, it was agreed that 52E(1) (b) risks and benefits, (c) potential hazards and (h) purpose for which it is to be used, were relevant matters for the Committee to consider.

A Member noted the extended half life of flubendiamide in the field could lead to possible human exposure.

A Member also noted the inability to measure inhalation toxicity for flubendiamide, but asserted that this was expected to be low given the formulation of the product.

The Committee generally agreed that no low level cut-off could be set.

RESOLUTION 2007/51 - 19

The Committee decided to include a new entry in Schedule 5 for flubendiamide.

Schedule 5 – New entry

FLUBENDIAMIDE.

6.4 PROSULFOCARB

PURPOSE

The Committee considered the scheduling of prosulfocarb.

BACKGROUND

Prosulfocarb is an S-benzyl thiocarbamate herbicide, which is absorbed by the leaves and roots of weeds and acts by inhibiting lipid synthesis in the meristematic region. It is intended for use as a pre-emergence and early post-emergence herbicide to control a wide range of grass and broad-leaved weeds in winter wheat, winter barley and rye.

The Committee decided to include prosulfocarb in Schedule 6 at the June 2006 NDPSC meeting.

DISCUSSION - SUBMISSIONS

XXXXX had prepared an evaluation report on an application to APVMA by XXXXX to amend the scheduling of prosulfocarb XXXXX

The XXXXX report:

- Concluded that the proposed use of XXXXX according to label directions will not be an undue health hazard to humans according to the criteria stipulated in Section 14 (5)(e) of the Ag/Vet Code Act of 1994;

- XXXXX
- Recommended that the NDPSC, based on the toxicological profile of XXXXX, may wish to consider amending the entry for prosulfocarb to read:

Schedule 5

PROSULFOCARB in preparations containing 80% or less of prosulfocarb.

Schedule 6

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

Members noted the following from the XXXXX evaluation report:

- The data package provided in the submission comprised XXXXX acute toxicology studies conducted with a formulation XXXXX. The acute toxicology studies had been conducted in accordance with the contemporary test guidelines and were considered adequate for the assessment of the toxicology profile of XXXXX, and the establishment of Safety Directions for XXXXX.
- Prosulfocarb has low acute oral toxicity XXXXX. It has low acute dermal toxicity in XXXXX and low acute inhalation toxicity in XXXXX. It is not a skin and eye irritant in XXXXX. It was not a skin sensitiser in XXXXX but it was considered to be a potential skin sensitiser in XXXXX.
- XXXXX. Prosulfocarb is not genotoxic or carcinogenic. Neurotoxicity studies in XXXXX showed possible minor cholinergic effects, including cholinesterase inhibition, but only at high dose levels XXXXX. An *in vitro* study conducted using XXXXX confirmed that prosulfocarb may have only little inhibitory effect on acetylcholinesterase in XXXXX.
- XXXXX
- An acute inhalational toxicity study was not conducted with XXXXX. However, XXXXX had submitted information on acute inhalation toxicity data from related studies. Based on this information and on the acute inhalation toxicity data of non-active constituents, XXXXX is likely to have low inhalation toxicity.
- XXXXX.
- XXXXX. The main routes of exposure to the product/spray will be dermal and inhalation. XXXXX.
- The report stated that acceptable margins of exposure were achieved when exposure was mitigated by wearing appropriate PPE. Based on the re-entry assessment, a re-entry statement was not considered necessary.

The Committee also noted the following from the June 2006 consideration of prosulfocarb:

- The XXXXX evaluation report concluded that the toxicological profile of prosulfocarb was consistent with its inclusion in Schedule 6. Given its intended use and potential to induce acute neurotoxicity at low doses XXXXX suggested that the NDPSC might consider a cut-off for prosulfocarb at 20 per cent to Schedule 5 noting that any skin sensitising potential of prosulfocarb can be adequately covered through appropriate safety directions on the product label.
- XXXXX

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

Members discussed the reliability of the XXXXX test and its use as the only test for sensitization provided with the application. A member asserted that previous considerations regarding sensitization for other substances have been made with only the XXXXX test. The member felt therefore that it may be inconsistent to reject the application on these grounds alone. The Committee had concerns that there was a positive XXXXX test at XXXXX prosulfocarb from previous considerations, whereas this data set included a negative result for a XXXXX test at XXXXX prosulfocarb. This caused some members to question the validity of the XXXXX test.

While there is no mandated test for skin sensitivity, the comment was made that for both animal welfare reasons and lower incidence of false negative results, an LLNA test is preferred over a XXXXX test for skin sensitization with regard to APVMA assessments.

A member noted the long retention period which may pose a risk. Given that this issue relates to worker safety exposure rather than public exposure, the Committee agreed this was not relevant to scheduling, as the risk could be dealt with through product registration.

A member raised the XXXXX data, as it had formed the basis for the XXXXX recommendation in June 2006 of a cut-off at 20 per cent. The Committee's concerns regarding this remained as no new data addressing XXXXX had been presented with this application.

In addition to the sensitization concern, the Committee noted that 80% was very high for a cut-off, given the variability of LD_{50}s.

In summary, the main concern was that while the data package had a negative XXXXX test at 80%, the Committee also had data before it that there was a positive XXXXX at 10%. It was recognised that the sensitization results were probably not enough on their own to sway the Committee's decision, but the XXXXX concerns together with reservations against extrapolation of data for setting cut-offs, left the Committee to conclude that the current scheduling was appropriate.

RESOLUTION 2007/51 - 20

The Committee decided that the current scheduling of prosulfocarb remained appropriate.

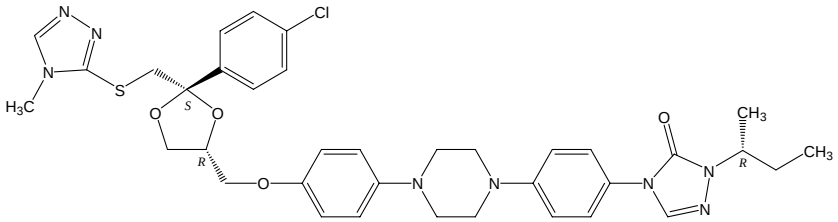
6.5 MITRATAPIDE

PURPOSE

The Committee considered the scheduling of mitratapide.

BACKGROUND

Mitratapide is the approved common name and INN for the chemical [2S-[2α,4α(S∗)]]-4[4-[4-[2-(4-chlorophenyl)-2-[[4-methyl-4H-1,2,3-triazol-3-yl)thio]methyl]-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one. The structure is:



The microsomal triglyceride transfer protein (MTP), which is located within the lumen of the endoplasmic reticulum (ER) in hepatocytes and absorptive enterocytes, plays a pivotal role in the assembly and secretion of triglyceride-rich, apolipoprotein B (apoB)-containing lipoproteins (VLDL and chylomicrons) from the liver and intestine. It also catalyses the transport of triglycerides, cholesteryl esters, and phospholipids between membranes. Although the exact role of MTP in the assembly of apoB-containing lipoproteins is still under investigation, MTP is proposed to transport lipids from the ER membrane to the growing apoB polypeptide chain in the ER lumen, thereby allowing proper translocation and folding of apoB to occur.

Mitratapide is a potent inhibitor of MTP. Dietary lipids are absorbed into the enterocytes where formation of VLDL and chylomicrons is blocked through inhibition of MTP. Because of the high turn-over rate, these enterocytes are rapidly sloughed into the lumen of the intestine and shed with faeces.

DISCUSSION - SUBMISSIONS

XXXXX has evaluated a toxicology data package submitted by XXXXX to support an APVMA application seeking the approval of a new XXXXX substance, mitratapide, XXXXX. In addition to the toxicology data package, an expert report on the toxicology of mitratapide prepared by an independent evaluator was also assessed.

The evaluation report:

- Advised that, as XXXXX was to be used only as XXXXX in non-food producing animals, the establishment of an ADI or ARfD was not considered necessary.
- Recommended to APVMA that there were no objections on human health grounds to the approval of mitratapide XXXXX.
- Recommended that, based on the toxicology profile and intended use as XXXXX requiring professional veterinary diagnosis and management and its proposed presentation as a XXXXX solution in glass bottles with child-resistant screw caps, the NDPSC consider including mitratapide in Schedule 4.

Members noted the following from the evaluation report:

- Most of the studies submitted were conducted in the late 1990's and comply with GLP standards. The toxicology data package was limited but adequate for the characterisation of the toxicity of mitratapide.
- XXXXX
- Mitratapide has low acute oral toxicity in XXXXX. Dermal and inhalational studies were not considered necessary given the low oral toxicity, the proposed scheduling in Schedule 4, and the presentation and packaging of the product. The product is a slight skin and eye irritant in XXXXX but not a skin sensitiser in XXXXX.
- The effects of repeated oral administration of mitratapide to laboratory animals included lipid accumulation/vacuolation within epithelial cells of the small intestine, the jejunum and perilobular and centrilobular hepatocytes of the liver, but a NOEL could not be established. Mitratapide does not accumulate in fat. XXXXX.
- XXXXX
- Although little information is available for this class of compound, there are currently no structural alerts relating to MTP inhibitors in terms of their carcinogenic potential. In addition, XXXXX mutagenicity studies showed that mitratapide is unlikely to be genotoxic in vivo. Mitratapide is not a teratogen but any effects on fertility are not known.
- Further pharmacological investigations have shown that mitratapide has no effect on cytochrome P450-dependent reactions, cortisol levels and renin activity at therapeutic concentrations. XXXXX.
- XXXXX
- Users of XXXXX may be dermally exposed to it through accidental contamination due to breakages or spills and such exposure is likely to be acute in nature. Since exposure is expected only as a result of accidents or spillages, a repeat-dose NOEL is not appropriate for the risk assessment.
- XXXXX
- It is possible that children could drink XXXXX because the flavouring agent is XXXXX. A calculation of risk for a child drinking XXXXX ml of XXXXX (50 mg

of mitratapide) for several days XXXXX gave a Margin of Exposure (MOE) of XXXXX. Because the MOE is less than XXXXX, child-resistant packaging is recommended for XXXXX.

- XXXXX

- The toxicology data and other information on the active constituent, and the use pattern of the product considered in this assessment indicate that the proposed use would not be an undue health hazard to the public according to the criteria stipulated in Section 14 (5)(e) of the *Ag/Vet Code Act of 1994*.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee generally agreed that mitratapide was a veterinary therapeutic agent requiring professional management. There was also general agreement that there was potentially a risk of diversion for human use. A Member also raised concerns about the lack of data on human dermal absorption.

The Committee also agreed that the packaging issues identified in the evaluation report were a product specific matter for the regulator and did not require action through scheduling.

It was felt that the toxicity of this substance, the patterns of use and the potential for abuse required that it be made a Schedule 4 substance.

RESOLUTION 2007/51 - 21

The Committee decided to include a new entry in Schedule 4 for mitratapide.

Schedule 4 – New entry

MITRATAPIDE.

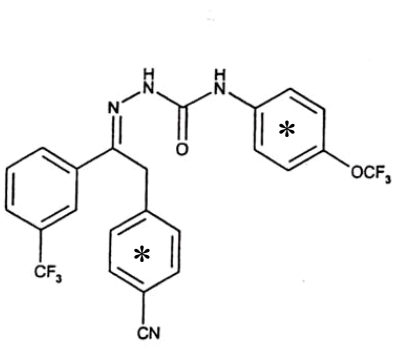
6.6 METAFLUMIZONE

PURPOSE

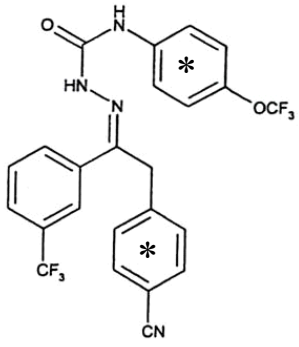
The Committee considered the scheduling of metaflumizone.

BACKGROUND

Metaflumizone is the ISO approved common name for the racemic mix comprising of the E (*cis*-) and Z (*trans*-) isomers of the chemical (EZ)-2′-[2-(4-cyanophenyl)-1-(α,α,α-trifluoro-m-tolyl)ethylidene]-4-(trifluoromethoxy)carbanilohydrazide (CAS 139968-49-3). The racemic mixture in technical grade metaflumizone is E:Z in the ratio of ~92:8. The structure of the 2 isomers is:



BAS 320 I (E-isomer)



BAS 320 I (Z-isomer)

The June 2006 NDPSC Meeting was advised that while metaflumizone had been included in the pre-meeting Gazette Notice the item had been withdrawn.

DISCUSSION – SUBMISSIONS

XXXXX prepared an evaluation report on an APVMA application by XXXXX seeking the approval of a new active, metaflumizone. XXXXX also sought registration for XXXXX for the treatment of XXXXX. Members were advised that:

- In June 2007, XXXXX forwarded new data relating to the risk assessment for the XXXXX metaflumizone XXXXX. XXXXX and XXXXX agreed that, notwithstanding the new data, the active constituent metaflumizone should be referred for scheduling consideration as soon as possible.
- The draft report was therefore referred to the NDPSC for consideration at the October 2007 NDPSC Meeting.
  [Members noted Secretariat advice that this referral was not received in time to be included in the NDPSC pre-meeting gazette notice. The Chair agreed with XXXXX proposal to publish an additional pre-meeting gazette notice for metaflumizone given the XXXXX and XXXXX concerns over the extended period that had already elapsed with the assessment of metaflumizone. It was agreed that this was not to set a precedent and that the publication of additional pre-meeting gazette notices remained an unfavoured recourse that should be avoided where possible.]

The draft report concluded that:

- On the basis of its overall low toxicity profile and its accumulative and persistent nature, the approval of metaflumizone is supported subject to the following conditions:
  - the active metaflumizone is only for use in non-food producing animals or on non-food producing plants; and
  - the active metaflumizone is only suitable for those use patterns where there is no human exposure to the product containing metaflumizone or to its residues; and

- any application for a product containing the active metaflumizone and proposing a new use pattern would require an occupational health and safety assessment for each new product application and use pattern.

- XXXXX
- Whilst noting that the acute toxicity of metaflumizone was low, on the basis of the slight eye irritation in rabbits and its tendency to accumulate in body fat, the NDPSC may wish to consider placing it in Schedule 5.

The Committee noted the following from the draft report:

- The metaflumizone toxicological database was complete and all of the submitted studies were well conducted and performed in accordance with contemporary test guidelines. All submitted studies were considered adequate and were relied upon to enable the recommendations to be made.

XXXXX

- Metaflumizone displayed low acute oral XXXXX, dermal XXXXX and inhalational toxicity XXXXX. It was non-irritant to the skin and a slight irritant to the eyes of XXXXX, but not a skin sensitiser in XXXXX.
- XXXXX However metaflumizone was not found to be a developmental toxicant.
- There was no evidence of any teratogenic effects. XXXXX. A battery of genotoxicity tests indicated that metaflumizone was not likely to be a genotoxic agent in vivo. Similarly, there was no indication of any neurotoxicity.
- Metaflumizone has poor water solubility with a tendency to partition in the fat by virtue of its lipophilic property XXXXX.
- XXXXX
- Independent expert advice was sought from the XXXXX. The XXXXX members:
    - expressed concerns that post-application exposure to the compound was unacceptably high for children, pet groomers and kennel workers when exposure was estimated using data from XXXXX;
    - supported the approval of the active constituent metaflumizone, with the addition of cautionary warnings on its potential to persist and accumulate;
    - agreed that given its accumulative nature and persistence, future assessment of products that contain metaflumizone must be assessed on a case-by-case basis according to their use pattern;
- XXXXX

A pre-meeting comment was received from XXXXX. XXXXX advised (with regard to section 52E(1)(d) – the extent and patterns of use) that there are plans for XXXXX.

A pre-meeting comment from XXXXX noted that metaflumizone had originally been gazetted for consideration at the June 2007 NDPSC Meeting together with amitraz, but was withdrawn. Comment was supplied on the presumption that amitraz may also be under consideration at this meeting. Members noted that this was not relevant to the current consideration.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee generally agreed that the toxicity of metaflumizone was very low, with only slight eye irritation being of any note. However, Members noted that metaflumizone was very lipid soluble and could bioaccumulate.

A Member asserted that 52E(1)(d) (extent and pattern of use) and (h) (purpose of use) was particularly relevant to this consideration as use pattern had a direct bearing on the human bioaccumulation risk arising from XXXXX treated with metaflumizone XXXXX.

The Committee generally agreed the low toxicity together with the bioaccumulation potential, constituted a risk that could be adequately addressed through a Schedule 5 listing and the product registration process.

RESOLUTION 2007/51 - 22

The Committee decided to include a new entry in Schedule 5 for metaflumizone.

Schedule 5 – New entry

METAFLUMIZONE.

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS)

7.1 CASTOR OIL, MONOMALEATE

PURPOSE

The Committee considered the scheduling of monomaleate castor oil.

BACKGROUND

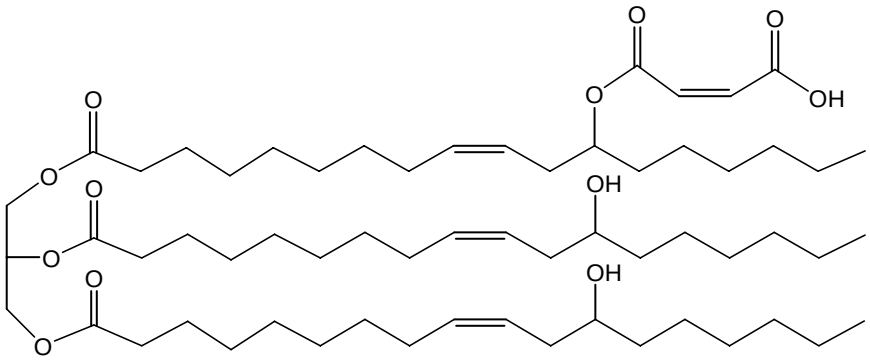
Monomaleate castor oil is formed through a reaction of maleic anhydride with one of the castor oil hydroxy groups (this functional group is not present in all oils in the mixture that makes up castor oil).

Castor oil is a vegetable oil obtained from the castor bean. Ninety percent of fatty acids in castor oil are ricinoleic acid. Ricinoleic acid, a monounsaturated, 18-carbon fatty acid, has a hydroxyl functional group at the twelfth carbon, an uncommon property for a

biological fatty acid. This functional group causes ricinoleic acid (and castor oil) to be unusually polar, and also allows chemical derivitization that is not practical with other biological oils. Castor oil also contains 3-4% of both oleic and linoleic acids.

Castor oil and its derivatives have applications in the manufacturing of soaps, lubricants, hydraulic and brake fluids, paints, dyes, coatings, inks, cold resistant plastics, waxes and polishes, nylon, pharmaceuticals and perfumes. The poison ricin is made from the by products in the manufacture of castor oil.

The diagram below is a representative structure, showing the major ricinoleate chain and the monoester. Some di-and tri-esters would also be present.



Castor oil, monomaleate is the common chemical name. Another synonym is ceraphyl MTE 9 which is analogous to the marketing name ceraphyl RMT.

DISCUSSION - SUBMISSIONS

The Committee was advised that a new industrial chemical (castor oil, monomaleate) was assessed under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). An initial assessment report was submitted for scheduling consideration but was withdrawn pending submission and assessment of a local lymph node assay study report. This study had been received and assessed. NICNAS concluded that this additional data did not change the original conclusion that castor oil monomaleate represented a hazard for skin sensitisation and that NDPSC should still consider monomaleate castor oil for scheduling. Members noted that no specific schedule or schedules were recommended in the report.

Members noted the following from the assessment report:

- XXXXX

Full public report

- The monomaleate castor oil was intended to be used as a skin conditioning aid in rinse-off personal care products.

Toxicology

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral	low toxicity LD_{50} >5000 mg/kg bw
Rabbit, acute dermal	low toxicity LD_{50} > 2000 mg/kg bw
Rabbit, skin irritation	slightly irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – 2 adjuvant tests	evidence of sensitisation
Guinea pig, skin sensitisation – non-adjuvant test	evidence of sensitisation
Repeated Insult Patch Test	no evidence of irritation/sensitisation
Rat, repeat dose oral gavage toxicity – 28 days	NOAEL > 1000 mg/kg bw/day
Phototoxic/photoallergic potential in humans	no evidence of phototoxic or photoallergic potential
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – chromosome aberrations in vitro cultured human peripheral blood lymphocytes	non genotoxic

- Significant skin sensitisation potential was demonstrated in animal testing, but was not seen in a human repeated insult patch testing.
- Extensive repeated dermal exposure to the notified chemical at up to 1% may occur during use of consumer personal care products. The duration of exposure will generally be short because the products are washed from the skin; however a proportion of the notified chemical may be deposited on the skin during the washing-off process.
- The predicted systemic exposure to monomaleate castor oil is estimated to be 41.6 µg/kg bw/day. Based on the NOAEL of 1000 mg/kg bw/day in a 28-day repeated dose study in rats, the margin of safety is > 24,000.
- Based on the positive results in three animal tests, it is considered that skin sensitisation in humans cannot be ruled out. The risk of sensitisation is likely to increase with increasing concentration of monomaleate castor oil in consumer personal products. However a quantitative risk assessment cannot be carried for sensitisation on the basis of available studies. Taking into account that a challenge concentration of 5% was positive in animals, it is considered that use above 1% in wash-off personal products may lead to adverse effects in humans. The risk may be increased if the chemical was to be used in leave-on products. The risk could be better estimated if a local lymph node assay (LLNA) was available for the notified chemical (see below).
- The undiluted monomaleate castor oil showed slight dermal and ocular irritation characteristics in animal tests indicating a risk of irritation during the recommended use of the products containing it. The risk of dermal and ocular irritation during the recommended use would be significantly reduced by the dilution of monomaleate castor oil in the products and their wash off nature. In addition, cumulative irritation studies with self perceived sensitive skin human volunteers indicate that wash-off products containing the notified substance at concentration <1% do not cause dermal irritation.

Toxicokinetics

- No information was supplied on the absorption, distribution, metabolism or excretion of monomaleate castor oil. Diarrhoea noted in acute oral and dermal studies in rats may be indicative of metabolism to castor oil. Dermal absorption is expected to be reduced by the relatively high molecular weight (~1000).

Hazard

- Based on the available data, monomaleate castor oil is classified as a hazardous substance. The following risk and safety phrase applies to the neat chemical – R43: May cause sensitisation by skin contact.
- The classification using the Globally Harmonised System for the Classification and Labelling of Chemicals (GHS) is:

	Hazard category	***Hazard statement***
Skin sensitisation	1	May cause allergic skin reaction

Conclusion

- There is low concern for use of monomaleate castor oil at < 1% in wash off personal care products.

Recommendations

- The NDPSC should consider the notified chemical for listing in the SUSDP.
- When the notified chemical is added to the Australian Inventory of Chemical Substances (AICS), it should be annotated with the following condition of use: "For use only in wash-off personal care formulations containing < 1% notified chemical".

Members also noted that the additional local lymph node assay study report to the NICNAS report found evidence of induction of a lymphocyte proliferative response indicative of skin sensitisation to monomaleate castor oil.

Members noted the following points from two pre-meeting comments:

XXXXX

- Asserted that monomaleate castor oil should not be included in Appendix C as the controls imposed by the *Industrial Chemicals (Notification and Assessment) Act 1989* through the NICNAS enablement and AICS listing were adequate.
- It was noted that the monomaleate castor oil AICS entry was annotated with the following: This chemical may only be used in wash off personal care formulations at concentrations less than 1%.
- If monomaleate castor oil were used in a formulation which did not meet the above compulsory conditions, the supply of the product would constitute the introduction of a "new industrial chemical".

- It was asserted that inclusion in Appendix C would be an unnecessary duplicated regulatory control and would imply that the inclusion of the ingredient on the AICS and the conditions for use placed upon this ingredient are inadequate.
- If the NDPSC decided that the controls imposed by the AICS were not adequate and thus monomaleate castor oil needed to be included in Appendix C, requested an opportunity to submit further information regarding the proposed cut-off concentration at a later meeting.
- XXXXX

XXXXX

- Noted both the NICNAS controls discussed above and that the NICNAS Assessment Report did not appear to make specific recommendations with regard to the labelling of consumer products with a concentration of less than 1% but provided a reference to NDPSC that it "should consider the notified chemical for listing on the SUSDP."
- Sought clarification with regard to the following:

The nature and extent of controls – NICNAS / NDPSC

- The conditions of the NICNAS approval limit the introduction quantity to no more than 1 tonne of the substance per year. Conditions are also placed on the use of the substance. The NICNAS Secondary Notification requirements included reporting requirements for additional toxicology data, adverse reaction reports and other information. It was not clear to XXXXX whether the NICNAS and scheduling regulatory interventions are duplicative or complementary? XXXXX would welcome NDPSC discussion and advice in this regard.

  The Committee noted that scheduling and controls through NICNAS were complementary.

Consequences of an Appendix C entry

- The NICNAS assessment report makes additional recommendations with regard to occupational health and safety and makes recommendations to the NOHSC Chemical Standards Sub-Committee with regard to hazard classification and risk-phrases for concentrations greater than 1%.
- XXXXX understands that inclusion in Appendix C may also have an impact on the substance for any industrial purposes and would welcome NDPSC consideration and advice in this regard.

Potential for regulatory consideration complexity

- Given the range of conditions and requirements both through NICNAS and separately through scheduling there would appear strong disincentive for any current or potential introducer or manufacturer of a substance to consider any secondary notification which may entail further product development – both in terms of timelines and complexity of dealing with separate agencies.

The Committee noted that scheduling and controls through NICNAS were complementary.

In addition, XXXXX provided some late additional comments specific to the scheduling of monomaleate castor oil. Members noted:

- NICNAS's intent in the recommendations of the assessment report, and specifically in the AICS annotation, was to allow cosmetic use when <1% in wash-off products without scheduling. The assessment did not cover non-cosmetic use of the chemical, as it was not proposed for this use.
- On the basis of the above, the XXXXX preference would be that the chemical be scheduled for cosmetic use only, in Schedule 5 or 6, with an exemption from scheduling for use in wash-off products at <1%. An entry in Appendix C was not needed.
- XXXXX asserted that a warning statement under Appendix F - Part 3 was warranted for the scheduled products. The Committee, however, generally agreed that an Appendix F warning statement was not necessary.
- XXXXX also asserted that if the company had not been advised that the chemical was being considered for scheduling, then it would be desirable to do this. Member's noted that XXXXX was subsequently advised of the NDPSC consultation process and was satisfied that XXXXX concern on this point had been addressed.
- XXXXX subsequently provided verbal advice that non-cosmetic use was not covered in the NICNAS new chemicals assessment and would therefore be subject to a Secondary Notification process. As such XXXXX had no recommendation on the scheduling of non-cosmetic use.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee generally agreed that monomaleate castor oil was a moderate to strong sensitiser, and as such use in cosmetic applications, where skin contact is likely, would warrant control through inclusion in Schedule 6. One Member noted that there were no other significant parameters which met the criteria for Schedule 6 but the Committee felt that a positive result in multiple animal sensitiser tests compelled the Committee to make this substance Schedule 6. However, Members also noted that a human patch test at ≤ 1% had given negative results. The Committee therefore agreed that wash-off cosmetic preparations at ≤ 1% could be exempt from scheduling.

RESOLUTION 2007/51 - 23

The Committee decided to include a new entry in Schedule 6 for monomaleate castor oil when for cosmetic use with an exemption for ≤ 1% monomaleate castor oil for cosmetic use in wash-off products.

Schedule 6 – New entry

CASTOR OIL, MONOMALEATE (excluding its salts and derivatives) in preparations for cosmetic use **except** in wash-off preparations containing 1 per cent or less of castor oil, monomaleate.

7.2 METHYLNORBORNYLPYRIDINE

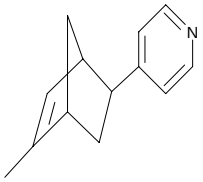
PURPOSE

The Committee considered the scheduling of methylnorbornylpyridine, including its methyl substitution isomers (at 1, 4, 5 or 6 positions of the norbornene ring).

BACKGROUND

The reaction of 4-ethenyl-pyridine with 3a,4,7,7a- tetrahydrodimethyl-4,7-methano-1H-indene results a mix of product isomers, mainly 5- and 6-methylnorbornylpyridine (5-MNBP and 6 MNBP), together with lesser quantities of the methyl substitution isomers (at 1 or 4 positions of the norbornene ring). The product isomer mix is referred to as MNBP in the following discussion, while individual isomers are identified by a methyl positional number.

The major methyl substitution isomers included those at the 1, 4, 5 and 6 positions of the norbornene ring. The October pre-meeting gazette notice referenced the 5-MNBP through the chemical naming "pyridine, 4-(5-methylbicyclo[2.2.1] hept-5-en-2-yl)" but incorrectly assigned this naming to the 4-MNBP isomer. The structure of 5-MNBP, is:



MNBP is found as a component of a fragrance oil.

DISCUSSION - SUBMISSIONS

The Committee noted that a report "Pyridine, 4-ethenyl-, reaction products with 3a, 4,7,7a - tetrahydrodimethyl - 4,7 - methano - 1H-indene"' from an assessment under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS), was submitted for scheduling consideration. The report recommended:

- NDPSC should consider the notified chemical [the MNBP isomer mix] for scheduling.
- Products containing the notified chemical and available to the public must carry safety directions and warning statements on the label consistent with the following:

- May cause allergy.
- Keep out of reach of children.

[Members noted that while written as "must" this was actually a labelling recommendation. The 'Keep out of reach of children' statement was already mandated for scheduled substances.]

Members noted the following from the report:

- MNBP will be imported as a component of a fragrance oil. The typical concentration of MNBP present in this mixture would be 4% (but may be up to 40%).
- The fragrance oil containing MNBP will be used in cosmetic and household products. The typical range of MNBP in these products is 0.01 to 10%, detailed in Table 1 below (this may not be an exhaustive list).
- Table 1 (Margin of exposure (MOE) data discussed latter)

Product Type	% of Fragrance (typical)	% MNBP (maximum)	% MNBP to give a MOE of 100
Cosmetics/Personal care products			
Leave-on			
Body lotions	0.4	0.16	≤0.05
Creams	0.3	0.12	≤0.2
Sun creams/lotions	0.4	0.16	NA
Hairsprays	0.5	0.20	≤0.2
Deodorant sprays	1.0	0.40	≤0.03
Wash-off			
Shampoos	0.5	0.20	≤3.8
Bath products	2.0	0.80	≤10*
Shower gels	1.2	0.48	≤0.6
Soap bars	1.5	0.60	≤0.6
Fragrance			
Air fresheners (sprays)	5.0	2.00	NA
Toilet waters	8.0	0.50	≤0.4
Household products			
Dishwashing liquid	0.2	0.08	≤10*
Fabric washing liquid	0.8	0.32	≤1.4
Surface cleansers	0.6	0.24	≤1.1

* 10% was the maximum concentration in the consumer products.

[Members noted that the NICNAS report did not cover therapeutic products including the majority of sunscreens. A search by the Secretariat for various synonyms of MNBP was unable to locate any use in current ARTG listed products.]

- Public exposure will be widespread and will result through the use of consumer products containing 0.01-10% MNBP. The main route of exposure is expected to be dermal, although ocular exposure to splashes is possible and inhalation exposure could occur when using spray products such as perfumes or spray cleaning products.
- Based on data regarding exposure to a range of products in Europe, public exposure (dermal and inhalation) to MNBP is estimated to be 0.06 to 61 mg/kg bw/day, assuming a bodyweight of 60kg; a 100% dermal absorption factor; a concentration of 0.01% to 10%; and product usage that was similar in Australia to Europe. This was likely to be an overestimate.
- It is possible that the cosmetic/personal care product categories include baby care products. Comparing with adults, it was expected that children's systemic exposure would be higher due to the physiological features of young children. In addition, since products containing MNBP are stored and used in a domestic environment, there are possibilities of accidental ingestion, especially by young children.
- Toxicological investigations summary:

Endpoint and Result	*Assessment Conclusion*
Rat, acute oral toxicity (LD_{50} = 1400 mg/kg bw)	harmful
Rat, acute dermal toxicity (LD_{50} = 1300 mg/kg bw)	harmful
Rabbit, skin irritation	moderately irritating
Rabbit, eye irritation	slightly irritating
Guinea pig, skin sensitisation – Buehler test	evidence of sensitisation
Human repeated insult patch test	no evidence of skin irritation and sensitisation
Rat, repeat dose oral toxicity – 28 days	NOAEL = 5 mg/kg/day
Genotoxicity – bacterial reverse mutation	non mutagenic
Genotoxicity – in vivo (Mammalian Erythrocyte Micronucleus Test)	non genotoxic

- MNBP was moderately irritating to the skin (very slight to well-defined erythema with very slight or slight oedema) and eye (scatter or diffuse corneal opacity, iridial inflammation and conjunctival irritation) in rabbits. The severity of the skin and eye irritation does not meet the criteria for hazard classification.
- A Buehler guinea pig sensitisation assay indicated that MNBP (at 1%) was a skin sensitiser. However, a human patch test in 56 human subjects using 0.5% solution of MNBP showed negative results.
- A 28-day repeated oral study found a number of treatment-related changes in haematology and clinical chemistry parameters in the high dose group (200 mg/kg/day). Significant and dose-related increase in liver weight with corresponding macroscopic changes (enlargement of the liver) and microscopic changes (hepatocyte enlargement) were found in all high dose and some of the mid dose rats. Higher adjusted kidney weight and microscopic changes in kidney (increased incidence and

frequency of eosinophilic droplets in cortical tubular epithelium in male rats at mid and high doses, an increased incidence and degree of golden-brown pigment in the proximal tubular epithelium in male rat of all treated doses, and basophilic tubules in rats at high dose) were also found. However, the kidney changes are sex and species specific and considered not relevant to humans. The NOAEL is established as 5 mg/kg bw/day in both male and female based on the liver changes.

- Based on the 5 mg/kg bw/day NOAEL, margin of exposure (MOE) for a number of likely consumer product categories were calculated, including the concentrations that could yield a MOE of 100 for the listed products in table 1 above. MOEs ≥ 100 are considered acceptable to account for intra- and inter-species differences.
- The MOE data indicates that the risk of systemic effects is acceptable when using consumer products containing <0.01% MNBP, but not for concentration of 10% (except bath products and dishwashing liquid). With the typical maximum concentrations, the risk of systemic effects is acceptable in the majority of the products listed, except body lotions, deodorant sprays and toilet waters. To yield a MOE of > 100, the concentration of MNBP in these three product categories must be at ≤0.05%, ≤0.03%, and ≤0.4%, respectively. The MOE for soap bars is borderline (MOE=94) and is considered acceptable, as it is a wash-off type product so less skin absorption is expected. The risk of systemic effects for air fresheners and sunscreens cannot be quantified because of lack of exposure estimation data. Due to the nature of incidental exposure to air fresheners, the risk is not expected to be high for using this type of product.
- The above risk estimations were based on the systemic exposure estimation from using one single product listed. Therefore, the risk is likely to be higher for individuals using more than one product at the same time. Based on the concentrations calculated for yielding a MOE of 100, restrictions on the concentrations of different consumer product will be recommended to ensure safe use of the product by the public.
- Due to lack of exposure estimation data, the risks to babies from use of baby care products containing MNBP cannot be quantified, but is expected to be greater than adults because of the expected higher systemic exposure.
- Although MNBP was harmful by ingestion, the risk of toxic effects from accidental ingestion of products containing MNBP is considered to be low due to the low typical concentrations in products.
- The risk of skin sensitisation to the general public exists from use of the products containing high concentration of MNBP, especially for the leave-on type of products, such as body lotions. Appropriate consumer protections will be recommended to minimise the risk. However, the risk should be limited as the typical maximum concentrations of MNBP are low in the majority of the product listed. The risk would also be reduced by use of appropriate warning and safety directions on the label.

Hazard classification

- Based on the available data MNBP is classified as hazardous under the NOHSC Approved Criteria for Classifying Hazardous Substances. The classification and labelling details are:
  - R21/22 Harmful in contact with skin and if swallowed
  - R43 May cause sensitisation by skin contact
- As a comparison only, the classification of MNBP using GHS is:

	Hazard category	Hazard statement
Acute oral toxicity	4	Harmful if swallowed
Acute dermal toxicity	4	Harmful in contact with skin
Skin sensitisation	1	May cause an allergic skin reaction
Environment		
Acute	1	Very toxic to aquatic life
Chronic	1	Very toxic to aquatic life with long lasting effects

- There is concern to public health when there is use of certain consumer products that contain high concentrations of MNBP.
- The report recommended that MNBP should only be used:
  - in leave-on type of cosmetics/personal care products containing ≤0.2%, except body lotion (≤0.05%) and deodorant sprays (≤0.03%);
  - in wash-off type of cosmetics/personal care products containing ≤0.6%; and
  - in fragrance type of cosmetics/personal care products containing ≤0.4%.
- The above conditions were recommended to be applied when MNBP was added to the Australian Inventory of Chemical Substances (AICS).

A late comment from XXXXX advised that:

- Methylnorbornylpyridine, including the methyl substitution isomers (at the 1, 4 or 6 positions of the norbornene ring), was an acceptable description of the assessed reaction products.
- Based on the risk assessment, Schedule 6 would be the appropriate parent entry schedule.
- XXXXX prefers the use of the word “spray” rather than “aerosol”.
- A labelling requirement should be applied to both cosmetic / personal care products and household use patterns.
- No AICS notification was included for household products, but secondary notification is required if the level in such products is > 1%.

A pre-meeting comment was received from XXXXX. Members particularly noted the following XXXXX points:

- Notes that the introducer made a limited small volume notification to NICNAS on the basis that MNBP is intended to be imported only as component of fragrance oil. This notification category limits the introduction to 1 tonne or less of the substance per year.
- The following conditions are specified on the AICS:
    - This chemical is approved for use only in leave-on type of cosmetics/personal care products containing no greater than 0.2% notified chemical, except body lotion (no greater than 0.05%) and deodorant sprays (no greater than 0.03%).
    - This chemical is approved for use only in wash-off type of cosmetics/personal care products containing no greater than 0.6% notified chemical.
    - This chemical is approved for use only in fragrance type of cosmetics/personal care products containing no greater than 0.4% notified chemical.
- MNBP is deemed to be a new industrial chemical under the definition given in section 5 of the *Industrial Chemicals (Notification and Assessment) Act 1989* if the proposed use does not meet the above condition.
- Sought clarification with regard to the following:

The nature and extent of controls – NICNAS / NDPSC

- The conditions of the NICNAS approval limit the introduction quantity to no more than 1 tonne of the substance per year. Conditions are also placed on the use of the substance. The NICNAS Secondary Notification requirements include reporting requirements for additional toxicology data, adverse reaction reports and other information. It is not clear to XXXXX whether the NICNAS and Scheduling regulatory interventions are duplicative or complementary? XXXXX would welcome NDPSC discussion and advice in this regard.

  The Committee noted that scheduling and controls through NICNAS were complementary.

Potential for regulatory consideration complexity

- Given the range of conditions and requirements both through NICNAS and separately through Scheduling there would appear strong disincentive for any current or potential introducer or manufacturer of a substance to consider any secondary notification which may entail further product development – both in terms of timelines and complexity of dealing with separate agencies.

  The Committee noted that scheduling and controls through NICNAS were complementary.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members considered the issue of multiple exposure through various products, noting that NICNAS had addressed this by specific listings through AICS. A Member suggest that such an approach, based on MOEs, was not suitable for scheduling and instead suggested a parent entry with a single cut-off, to be applied to all domestic use patterns including cosmetics.

The Committee generally agreed that the sensitivity and acute toxicity data for MNBP was commensurate with a Schedule 6 parent entry. A Member noted that the positive XXXXX test indicating moderate sensitivity at 1% should set the maximum upper limit of any exemption from a Schedule 6 listing. A Member also thought it worth mentioning that the near identical dermal and oral toxicology data was indicative of a high dermal absorption.

Another Member noted that there currently appeared to be insufficient data to allow the Committee to set a Schedule 6 to Schedule 5 cut-off, and that there was some concern about relying on an extrapolation of data, particularly as the sensitisation risk may not be linear.

It was noted that there was no evidence of skin irritation or sensitisation in the human repeated insult patch test at a concentration of 0.5%.

RESOLUTION 2007/51 - 24

The Committee decided to include methylnorbornylpyridine in Schedule 6 with a cut-off to exempt of 0.5% and an Appendix F warning statement 59 – MAY CAUSE ALLERGY.

Schedule 6 – New entry

METHYLNORBORNYLPYRIDINE **except** in preparations containing 0.5 per cent or less methylnorbornylpyridine.

Appendix F – New entry

POISON	**WARNING STATEMENTS**	**SAFETY DIRECTIONS**
Methylnorbornylpyridine	59	

– *Include on February 2008 agenda if Allan Seawright advises to do so.*

8. OTHER MATTERS FOR CONSIDERATION

No items.

9. INFORMATION ITEMS (AG/VET, INDUSTRIAL & DOMESTIC CHEMICALS)

9.1 CHEMICALS AND PLASTICS REGULATION

PURPOSE

The Committee noted action being taken by the Productivity Commission regarding the regulation of chemicals and plastics in Australia.

DISCUSSION-SUBMISSIONS

The October 2007 NDPSC Meeting noted the Productivity Commission's circular No.ChemPlasC1 of 1 August 2007, which announced that they will be undertaking a research study on the current arrangements for the regulation of chemicals and plastics in Australia, with a report to be provided in 12 months.

- The Commission is to identify measures that could be introduced to achieve a streamlined and harmonised system of national chemicals and plastics regulation and any alternatives to regulation.
- The Commission will have discussions with a range of interested parties to identify issues and relevant sources of information.
- Anyone can participate in the study by lodging written submissions before mid October 2007 and by participating in other forums. Submissions are sought from interested parties, with individuals and representative s of companies, agencies and organisations invited to register their interest in the study.
- Timetable:

Release of issues paper	5 September 2007
Initial submissions due	mid October 2007
Release of draft report	early March 2008
Submissions on draft report due	mid April 2008
Completion of final report	27 July 2009

- The Commission will release a draft report for public comment prior to submitting its final report.

The Meeting was informed that this item had been referred to the NCCTG for its information.

RESOLUTION 2007/51 - 25

The Committee noted that the Productivity Commission is undertaking a research study on the current arrangements for the regulation of chemicals and plastics in Australia. The Committee also noted the Issues Paper released in September 2007.

9.2 WHAT IS A DERIVATIVE?

PURPOSE

The Committee considered comment regarding the February 2007 NDPSC decision to amend the SUSDP's "Principles of Scheduling" to clarify the intent of the Committee in using derivative in the context of a schedule entry.

BACKGROUND

The February 2007 NDPSC Meeting agreed to amend the SUSDP's "Principles of Scheduling – Reading the Schedules" to include the following paragraph to clarify the intent of the Committee in using the term 'derivative' in the context of a schedule entry:

- It is important to note that a substance is not classed as a derivative on the basis of a single, prescriptive set of criteria. Classification of a substance as a derivative of a Scheduled poison relies on a balanced consideration of factors to decide if a substance has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison. However, a substance is only considered a derivative of a Scheduled poison if it is not individually listed elsewhere in the Schedules, or captured by a more restrictive group or class entry. Additionally, some entries specifically exclude derivatives. Once a substance is determined to be a derivative of a Scheduled poison, the same scheduling requirements as the Scheduled poison, including limits on access, supply and availability, will apply.

DISCUSSION - SUBMISSIONS

XXXXX sought clarification from the Committee over the above statement on derivatives. In particular:

- In XXXXX it was noted that this statement may have a wider effect for substances such as hexafluorotitanic acid, hexafluorozirconic acid and hexafluorohafnic acid. These are compared directly to the currently scheduled hexafluorosilicic acid and are "expected to have very similar toxicological properties" due to their structure and release of hydrofluoric acid. Given this it was asserted that these may therefore become Schedule 7 poisons based on "a substance has a similar nature (e.g. structurally, pharmacologically, toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison".
- Asserted that another example possibly covered by this statement is DMDM Hydantoin in a 55% solution, which has about 17% available formaldehyde, and about 1-2% free formaldehyde. XXXXX queried on what basis should a 55% DMDM Hydantoin solution be classified?

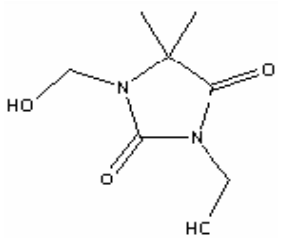
Members noted the following:

Metallic hexafluoroacids

- Each of the 4 hexafluoro metal acids (titanium, zirconium, tin and silicon) had a different metal centre complexed to 6 fluoride ligands and, despite their similar activity in reacting to produce hydrofluoric acid, it would be reasonable to consider that the titanium, zirconium, and tin compounds are not derivatives of hexafluorosilicic acid (scheduled as hydrosilicofluoric acid). The situation may have differed had the question arisen for two versions of hexafluorosilicic acid where one of the fluorides had been substituted for another halide.
- Metallic hexafluoroacids can, however, be generally regarded as sources of hydrofluoric acid (usually through hydrolysis in neutral or basic pH). The Schedule 5, 6 and 7 entries for hydrofluoric acid explicity exclude "its salts and derivatives" but do capture "admixtures that generate hydrofluoric acid". Hexafluorotitanic acid, hexafluorozirconic acid and hexafluorohafnic acid would only be scheduled should they form part of an admixture that will generate hydrofluoric acid.

DMDM hydantoin

- DMDM hydantoin refers to the chemical 1,3-bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione (structure below) which is a preservative that works by releasing formaldehyde into the product. DMDM hydantoin is used in shampoos and cosmetics to prevent moulds, mildews, and bacterial spoilage. The Schedule 2 and 6 entries for formaldehyde (and paraformaldehyde) explicitly exclude "its derivatives". DMDM hydantoin would not be scheduled, however, any formaldehyde generated in a preparation would be subject to scheduling.



Conclusion

- Both examples are of substances that could be readily converted (either physically or chemically) to a scheduled poison. However, in both cases the schedule entries (formaldehyde and hydrofluoric acid) specifically indicate that derivatives were excluded.
- The metallic hexafluoroacids could possibly be scheduled should they form part of an admixture that will generate hydrofluoric acid.
- Should formaldehyde or hydrofluoric acid be present in a preparation then scheduling would apply, regardless of the source (including from precurors).

RESOLUTION 2007/51 - 26

The Committee confirmed that the current advice under the SUSDP's "Principles of Scheduling – Reading the Schedules" reflected the intent of the Committee in using the term 'derivative' in the context of a schedule entry.

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCZ)

10.1 PARACETAMOL AND PHENYLEPHRINE

PURPOSE

The Committee considered post-Meeting comments about the decision made on the scheduling of paracetamol and phenylephrine.

BACKGROUND

The June 2007 NDPSC Meeting considered the scheduling of paracetamol when combined with phenylephrine with a view to exempting a paracetamol/ phenylephrine combination from the requirements of scheduling. The Committee considered all the information put before it and decided that the safety profile of these substances was such that allowing a fixed combination to be exempt from scheduling was reasonable. Furthermore, the Committee also felt that there was sufficient Australian market experience to support this down scheduling decision.

The Schedule wording agreed to by the Committee to allow the exemption was as follows:

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 (<u>other than phenylephrine</u> or when combined with effervescent agents) when:

(i) enclosed in a primary pack that contains not more than 12 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; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine 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 25 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.

DISCUSSION - SUBMISSIONS

The Committee recalled the following from the June 2007 Meeting:

- The Committee was concerned about the possible lack of efficacy of phenylephrine at a 10mg dose and this leading to increased dosing with the product, which, in turn may lead to the potential for paracetamol toxicity. The Committee agreed to pass their concerns about the efficacy of phenylephrine 10mg to the Medicines Evaluation Committee (MEC). XXXXX.
- The Committee felt that it had been presented with sound data about the lack of side effects and drug interactions that were previously thought to occur with phenylephrine and noted that the only interaction of significance was with monoamine oxidase inhibitors (MAOIs).

A post-Meeting comment was received from XXXXX outlining XXXXX concerns about the Committee's decision and asking them to reconsider it. The Committee noted the following:

- XXXXX believed that the appropriate schedule for a paracetamol/ phenylephrine combination was Schedule 2 if the product contained 500 mg or less paracetamol and 5 mg or less of phenylephrine. XXXXX stated that doses over this should be included in Schedule 3 in order to allow appropriate counselling and cautioning.

- XXXXX noted that the bioavailability of phenylephrine when taken orally is 38% and that its half-life is approximately 2.5 hours. XXXXX stated that this could be a potential reason for the lack of efficacy seen with lower doses. It was also stated that the lack of efficacy at lower doses may lead the patient to increase the dose and that this behaviour posed a risk if the phenylephrine was in a combination with paracetamol, given the toxic effects of paracetamol overdose.
- XXXXX believed that the risk of paracetamol toxicity would be countered by keeping the combination in Schedule 2 as this would allow consumers access to advice from staff who would be able to caution them against combining the product with other paracetamol containing ones. Staff would also be able to refer patients to the pharmacist if the patient was on other medication or expressed concerns about the product. XXXXX made passing reference to a number of coronial inquests which recommended the public be educated about the risks of paracetamol toxicity and also stated that XXXXX believed that relying on warning information written on packets was insufficient. XXXXX also noted that it was possible to buy multiple packs of paracetamol containing medications at a supermarket and stated that this would not be possible in a pharmacy setting.
- XXXXX stated that it would be erroneous to suggest that the use pattern of a combination paracetamol/ phenylephrine cold and flu product (used for a number of consecutive days) would reflect that of a single active paracetamol product used for acute pain.
- XXXXX also stated that there was a potential for interactions and, thus, an increased risk of adverse events with phenylephrine and paracetamol and other medications. It was asserted that substances which induce hepatic microsomal enzymes (eg, alcohol, barbiturates, anticonvulsants) may increase the hepatotoxicity of paracetamol. Vasodilators, other sympathomimetics, beta-blockers, methyl-dopa and MAOIs were all mentioned as potentially having adverse interactions with phenylephrine.

The Committee noted that, while this submission had raised some matters which were relevant to S52E, there was no information provided that the Committee had not already considered when making its decision at the June 2007 Meeting.

The Committee noted that the RASML does not mandate a maximum daily dose for OTC paracetamol. The Martindale stated a maximum daily dose of 4 grams per day for adults via all routes of administration.

A minor editorial variation to the June 2007 Decision (2007/ 50 -14) is set out under item 21.2 of this Meeting.

RESOLUTION 2007/51 – 27

The Committee confirmed its June 2007 NDPSC decision (2007/50-14), noting the minor editorial variation set out under item 21.2 of this Meeting.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETING

11.1 PANTOPRAZOLE

The Committee noted the inclusion of pantoprazole as a standing item on the agenda to remind the Committee that the implementation date for the June 2005 Decision, to include an entry in Schedule 3 for pantoprazole, was 1 May 2008.

11.2 FRACTIONATED AND RECOMBINANT BLOOD PRODUCTS

PURPOSE

The Committee considered the scheduling of fractionated and recombinant blood products including consideration of a possible Appendix A exemption.

BACKGROUND

In the past the Committee had considered that adequate control exists at Commonwealth and State/ Territory level, and, thus, has had a standing policy not to schedule blood products. The Committee considered the recommendations arising from the Review of the Australian Blood Banking and Plasma Product Sector at the February 2005 Meeting and was satisfied that appropriate regulatory mechanisms were in place to warrant the exemption of blood products from scheduling requirements and agreed to foreshadow the inclusion of blood products in Appendix A of the SUSDP.

XXXXX provided advice in May 2005 stating that it would be illogical to exempt product derived from blood and not equivalent recombinant products, especially considering some are only available as recombinant products (eg Factor VIIa). XXXXX stated that historically, CSL manufactured most plasma derived products and this was distributed by the Australian Red Cross Blood Service (ARCBS) but also noted that foreign produced product was becoming more readily available. XXXXX also noted that plasma-derived products are intended for the treatment of serious disease and as such require medical supervision and, therefore, should not be exempt from scheduling.

At the June 2005 Meeting, the Committee concluded that hospitals and health services had policies and guidelines in place to ensure best practise in the supply and use of whole blood products and these controls obviate the need for scheduling controls. Furthermore, the Committee felt it was inappropriate and impractical for a pharmacist to dispense such a product, particularly in an emergency setting. However, the Committee was conscious of the shift in supply arrangements of plasma derived product, including foreign-manufactured and recombinant product. Thus the Committee agreed to include an entry in Appendix A of the SUSDP for whole blood and blood components (effective 1 January 2006) but to foreshadow the consideration of the scheduling of plasma fractionated and comparable recombinant product at the October 2005 Meeting.

At the October 2005 Meeting, the Committee agreed that, before a decision could be made to include fractionated plasma and comparable recombinant products in Appendix A, input should be sought from the National Blood Authority's Jurisdictional Blood Committee (JBC) on the possible ramifications of scheduling such products. It was agreed to consider this input, along with other public submissions, at the February 2006 Meeting.

At the February 2006 Meeting, the Committee agreed that advice should also be sought from XXXXX as to how scheduling of fractionated plasma and recombinant blood products might fit into current control frameworks. As a starting point, XXXXX would be provided with the list of products that had been supplied to the Committee by XXXXX. XXXXX could then provide advice on the regulatory arrangements that exist for distribution and supply of each of the products on the list. Each product could then be assessed for inclusion in or exclusion from the SUSDP (via Appendix A).

The June 2006 Meeting of the NDPSC considered a request received from XXXXX that a 12 month consultation period on the possible scheduling of blood products be conducted by XXXXX to allow the blood sector adequate time to raise and discuss all concerns and issues. The Committee also considered provisional advice from XXXXX in which it agreed in principle to exempting fractionated product & recombinant product, should mechanisms ensuring appropriate oversight of transport, storage and traceability be in place. Given the request from XXXXX and the obvious need for wider stakeholder consultation, the Committee agreed to defer this item to allow time for XXXXX to establish a working party and carry out a consultation process involving all relevant stakeholders.

DISCUSSION - SUBMISSIONS

A report was received from the JBC following the conclusion of their stakeholder consultation period. The JBC provided the following information:

- After consideration of all stakeholder input, the JBC was of the opinion that fractionated and recombinant blood products should be granted an Appendix A exemption. This opinion was formed on the basis that there were already adequate controls in place and that scheduling may place superfluous restrictions on supply, thus potentially compromising patient care. The JBC also felt that scheduling these substances would add no value to the current system.
- The JBC stated that any improvements related to the supply of these products would be best occurring through improvements to operational policy. JBC noted that, in order to facilitate this, they were undertaking a number of measures including development of a national blood prescription form and authorising systems for products in short supply as well as improving data registers.

XXXXX

The Committee noted that the points that the JBC raised over patterns of use and supply of these substances fall under S52E (1)(d) and S52E (1)(f) of the Act respectively (i.e., the extent and patterns of use and the need for access to a substance). The Committee felt that the JBC seemed to consider that the patterns of use and need for access was such that scheduling would be an unwarranted burden and that public health and safety was adequately protected by the current supply and documentation mechanisms in place for these products. Members also noted that the JBC had proposed some improvements to operational policy that would improve supply of these substances.

All stakeholders who had previously supplied comment on this matter were informed of the JBC advice and invited to provide further submissions considering this outcome.

XXXXX provided a pre-Meeting submission in which XXXXX supported the proposal and initiatives being undertaken by the JBC. XXXXX agreed that formalising the supply chain along prescription medicines lines, excluding the need for scheduling, would not impede delivery of these substances. XXXXX also felt that this formal model may improve the management and oversight of usage of such products.

XXXXX provided a pre-Meeting submission in which XXXXX stated that XXXXX endorsed XXXXX January 2006 submission to the Committee and, thus, supported the JBCs' position on this matter.

The XXXXX provided a pre-Meeting comment in which XXXXX stated that XXXXX maintained XXXXX position of 25 January 2006. XXXXX position on the matter in January 2006 was that XXXXX did not seem necessary to schedule blood products given the processes in place. In addition it noted that there may be unintended consequences for and delays in supply if such products were scheduled.

A pre-Meeting submission was provided by XXXXX in which XXXXX stated that scheduling of fractionated and recombinant blood products would not be beneficial to patients and may result in significant inconvenience and compromise of supply of such substances. The following points were made:

- The potential scheduling of recombinant factors posed a barrier to timely access to the substances as well as increasing the challenges of patients receiving effective home treatment.
- Patients with severe/ moderately severe disease generally require multiple infusions 2 – 3 times per week. Most of these patients are educated by their healthcare professional in how to treat themselves so as they are able to do this in their home setting and many of them are enrolled in programs which supply the product directly to the patient. These programs have been shown to have a positive impact on patients' quality of life and treatment compliance.
- If these substances became scheduled, it would be most likely that such programs would end and, consequently, there would be a significant impact on a patients' ability to effectively manage their condition at home. This would mean that patients,

especially those in rural areas, would have to make considerable changes to their current treatment procedures. This would be of particular concern in the rural setting where a patient may have a major bleed and the local pharmacy have insufficient stock to treat the patient.

- XXXXX also noted that pharmacists, in general, are unfamiliar with these products and may also not have sufficient refrigerated storage space for them.

Members further discussed XXXXX concerns that scheduling of these substances would remove the ability to supply them directly to the patients where circumstances require (i.e., patients in regional and remote areas). The Committee felt that scheduling may stop this and, thus, adversely effect patient care. (This relates to S52E (1)(f), the need for access to a substance.)

A pre-Meeting submission was received from the XXXXX which stated that XXXXX supported the JBC's recommendations and agreed with JBC's opinion that adequate controls are already in place for these substances.

Members noted that all of the patient and practitioner groups, i.e., key stakeholders on the ground, agreed with the JBC's recommendation. It was further noted that some of these submissions stated that pharmacists did not have the relevant expertise to supply such substances. A Member noted that, with regards to supply of these products if they were made S4, there was no requirement specifically for a pharmacist to be involved in their supply but rather that they must be prescribed by a medical practitioner. (S52E (1)(f) the need for access to a substance.)

The Committee discussed that the majority stakeholders had supported an exemption from scheduling for recombinant blood products and had provided information describing the current supply mechanisms as well as future developments which served to reassure the Committee that there was little risk from leaving these substances unscheduled. (S52E (1)(d) extent and patterns of use of a substance.) The Committee further noted comments that the scheduling of these products may actually be disadvantageous in terms of patients receiving the products in a timely fashion and the products were currently being managed by the staff with the most expertise (i.e., blood bank staff.)

A number of stakeholders who had provided submissions to previous considerations did not provide a response to the Secretariat's invitation to comment further on this issue.

XXXXX**:** XXXXX comments to the June 2005 consideration were as follows:

- XXXXX regulates products derived from human plasma such as coagulation factors, immunoglobulins and albumin.
- As the Committee had previously exempted medicines containing recombinant Factor VIII from scheduling, the foreshadowed definition would pose a problem due to the following reasons:

- There were many other recombinant versions of naturally occurring human proteins that are produced by recombinant DNA technology and are not plasma-derived products such as filgrastim, ancestim, interferon and erythropoietins which would not be desirable to be exempted from scheduling.
- If the Committee's intention was to exempt only those products which are derived from human blood, this would mean that recombinant products would not be exempted as it would seem illogical to exempt one Factor VIII product and not another Factor VIII product solely on the basis of the method of manufacture used. In addition, Factor VIIa is only available in Australia as a recombinant product.
- It would be undesirable for plasma-derived products to be unscheduled as these should only be used under the supervision of a medical practitioner. Previously, most plasma-derived products were being manufactured from Australian blood by CSL and distributed free of charge by the Australian Red Cross Blood Service. In recent years however, a number of foreign products have been registered in Australia (eg. immunoglobulins, recombinant coagulation factors) which are commercially available direct from sponsor companies, as with any registered pharmaceuticals and the number of these foreign blood products on the Australian market is likely to increase in the future.

- Given the above reasons, the foreshadowed (at June 2005) Appendix A entry viz, "blood products for use in clinical and hospital setting except when separately specified in the Schedules", was not appropriate.
- XXXXX was of the view that all plasma-derived products should be made subject to scheduling as these are intended for the treatment of serious diseases, require supervision by a medical practitioner and are not universally subject to Commonwealth/State controls that would obviate the need for scheduling.

XXXXX**:** In XXXXX submission to the February 2006 NDPSC Meeting, XXXXX attached its September 2005 submission made on behalf of XXXXX. The following points were made in favour of an exemption for fractionated blood products:

- Currently, it is staff within hospital blood banks and not pharmacy staff that hold the required skills to manage such product.
- Access to such products is required 24 hours a day, 7 days a week. There is concern that access via pharmacy may therefore compromise patient care.
- As rapid access to such product is essential, broader distribution through pharmacies may result in more stock expiring. Given that such product is sourced from plasma of blood donors, replacement of such product is difficult.
- XXXXX provides a gate-keeper role for product that is in short supply and requests for such products are reviewed by a medical officer. Such a safety net would not exist if these products were supplied via pharmacies.

- Blood component products and plasma-derived product are usually supplied simultaneously and this is both simple and cost effective. Scheduling plasma-derived products would require development of new ordering systems.
- Scheduling plasma-derived products would not add value to the health system and may indeed lead to deterioration in optimal patient care.

XXXXX**:** made a submission to the February 2006 Meeting which raised the following points:

- It did not seem necessary to schedule these products given that there are appropriate mechanisms in place for the oversight and management of the national blood supply, including the supply of blood products and comparable recombinants by XXXXX.
- There appeared to be a very low level of relative risk as many of the products are for treatment of specific conditions like haemophilia which are managed by specialist doctors and nurses in hospital settings or through haemophilia treatment centres (HTC). Scheduling of these products may adversely impact on patients who have been treated for many years through home therapy programs managed by the HTC. No cases of inappropriate distribution to the public have been reported to XXXXX.
- Hospital blood banks have extensive expertise with inventory of blood products including traceability and appropriate use. Any change to the current system (i.e. a scheduling change) which could result in delays in or restrictions on providing product to patients could impact adversely on their care, potentially leading to increased patient morbidity and mortality. Furthermore, broadening distribution networks via pharmacies may result in increased costs.
- The gate-keeper role managed by the ARCBS ensures that use of short-supply product is closely scrutinised and they often order both blood components and plasma-derived product for the same delivery. This system ensures simplicity in the context of ordering and efficiency in the context of logistics.
- There should be a consistent approach to scheduling/exemption of fractionated plasma products and comparable recombinant products. It was highlighted that "IMMUNOGLOBULINS for human parenteral use except where separately specified in these Schedules" is currently listed in Schedule 4 of the SUSDP. While in contrast to the immunoglobulin products, haemostasis plasma products eg Factors XVIII, IX etc or albumin are not listed in Schedule 4.
- Given the move to the Australia New Zealand Therapeutic Products Agency, there may be value in exploring the New Zealand arrangements for the scheduling and distribution of these products, noting that the scheduling of some of these products in New Zealand is supported by a broader licensing program that allows products to be distributed in a manner comparable to that currently in place in Australia.
- Concern that, other than consultation with XXXXX and XXXXX, there was a view that consultation with the wider Australian Blood Sector had been inadequate. Stakeholders also consider that there has been no opportunity to examine the potential

impact of scheduling changes or to identify other means of improving governance arrangements.

XXXXX**:** provided a pre-Meeting submission to the June 2006 Meeting where the following points were made:

- A consistent approach should be taken for exemption/scheduling of blood products, regardless of their method of manufacture. That is to say, recombinant product should be treated the same as plasma-derived product.
- A consistent approach is needed to be adopted for all plasma products. XXXXX noted that immunoglobulins are currently listed as S4 but no other plasma derived or recombinant product is scheduled.
- XXXXX also suggested, given the complexity of the situation, that a 12 month consultation period involving key stakeholders be initiated.
- XXXXX felt that, as all these products are sterile injectables and fully evaluated by TGA prior to marketing, a case-by-case approach is not appropriate but these products should all be treated the same.

The Committee discussed XXXXX concerns and felt that the TGA evaluation of such substances only gave reassurance about their safety and efficacy but that this was not relevant to issues of supply, i.e., that evaluation gave an assurance on toxicity and safety but did not relate the need for access to a substance. (52E (1)(a), toxicity and safety and (f), the need for access to a substance.)

DISCUSSION – ADDITIONAL MATTERS RELEVANT UNDER 52E

In discussing the submission from the JBC concerns were raised XXXXX from XXXXX. The XXXXX Member stated that XXXXX main concern was that substances such as erythropoietin (EPO) and other performance enhancing substances would be captured by the potential exemption and thus become open to further abuse. (52E (1)(d), extent/ patterns of use and (g), abuse potential.) Members agreed that the wording of a potential exemption would have to be crafted in order to avoid inadvertently capturing substances such as this, interferons and haemopoietic growth factors.

The concerns that XXXXX raised were for the most part in relation to the supply of intravenous immunoglobulin (IVIg).

XXXXX did not completely agree with XXXXX statement that there were already adequate controls in place with no adverse events having been reported under the current arrangements, given that proper reporting mechanisms are not in place. XXXXX stated that intravenous immunoglobulin products are supplied to patients on the basis of guidelines which are not rigid. XXXXX also stated that, although new guidelines on supply have been developed, they felt that these were even less rigid than the current ones. XXXXX felt that current supply arrangements through ARCBs may lead to

anomalies in substance distribution and, in turn, may lead to patients being unnecessarily switched across product types. (52E (1)(d), extent and patterns of use.)

XXXXX also felt that the restrictions placed on supply by scheduling may be justifiable as it would ensure that there was a more accountable allocation of substances and, thus, the patients who had great need for such substances would be better assured of obtaining them. The Committee noted these concerns but agreed that the consensus view of the JBC was that scheduling of these substances was not warranted. (52E (1)(d), extent and patterns of use.)

A Member raised concern that an Appendix A exemption for these substances would not fit with other listings contained in this appendix, given that Appendix A is for specific substances exempted in specific circumstances. The Committee, however, agreed that a number of other entries in Appendix A, e.g. parenteral nutrition preparations, were in keeping with the exemption that would be granted for these products.

RESOLUTION 2007/51 - 28

The Committee decided to include fractionated blood products and equivalent recombinant products in Appendix A to allow the exemption of such products from the requirements of scheduling. The Committee also decided to request that the Drafting Advisory Panel (DAP), in consultation with appropriate stakeholders, draft the wording of the new Appendix A entry and that the wording ensure that recombinant versions of other naturally occurring human proteins such as filgrastim, ancestim, interferon and erythropoietins are not inadvertently exempted.

APPENDIX A – New entry

HUMAN BLOOD PRODUCTS including:

(a) whole blood;

(b) blood components including red cells, white cells, platelets and plasma (including cryoprecipitate); and

(c) the following plasma-derived therapeutic proteins and their equivalent recombinant alternatives:

(i) albumin;

(ii) anticoagulation complex;

(iii) clotting factors;

(iv) fibrinogen;

(v) protein C;

(vi) prothrombin complex concentrate (PCC); and

(vii) thrombin.

APPENDIX A – Amendment

WHOLE BLOOD AND BLOOD COMPONENTS – Delete entry.

12. PROPOSED CHANGES/ADDITIONS TO THE STANDARD FOR THE UNIFORM SCHEDULING OF DRUGS AND POISONS

12.1 SUSDP, PART 4

12.1.1 HYOSCINE BUTYLBROMIDE

PURPOSE

The Committee considered the scheduling of hyoscine butylbromide including a proposal to increase the Schedule 2 pack size restriction.

BACKGROUND

Hyoscine butylbromide is a quaternary ammonium derivative of hyoscine. It acts as an anticholinergic agent and due to quaternisation of the compound it has ganglion-blocking activity. Hyoscine butylbromide reduces the tone and peristalsis of smooth muscle in hollow organs with parasymphathetic innervation. Hyoscine butylbromide 10 mg tablets are currently approved in Australia for the treatment of spasms of the GI tract at the recommended oral dose for adults and children over 6 years of 20 mg, four times daily (maximum of 10 tablets per day).

Hyoscine butylbromide was first included in Schedule 4 (S4) at the February 1967 Meeting of the Committee. The Schedule 4 entry for hyoscine butylbromide was deleted and a new S4 entry for hyoscine, which captured hyoscine butylbromide, was included at the November 1988 Meeting, but no reason for this decision was minuted.

The November 1993 DPSSC Meeting rejected an application to reschedule hyoscine butylbromide from S4 to Schedule 3 (S3) on the basis that it had received advice from a professional body that there was no place for the substance in the treatment of irritable bowel syndrome. At the April 1994 DPSSC Meeting, the Committee considered information relating to the rescheduling of hyoscine butylbromide from S4 to S3. At this Meeting, the Committee agreed to finalise an ongoing review of solanaceous alkaloids and to also conduct a review of the scheduling of them.

The August 1994 NDPSC Meeting considered a large amount of information relating to the safety and efficacy of hyoscine butylbromide and were satisfied with its safety profile. However, the Committee considered that a comprehensive review still needed to

be undertaken and requested that all relevant information be obtained from other sponsors of the substance. The November 1994 NDPSC Meeting reviewed this information and agreed that hyoscine butylbromide should be included in S3 with dose and pack size restrictions.

At the May 1998 NDPSC Meeting, the Committee considered a submission to reschedule hyoscine butylbromide to Schedule 2 (S2), however, due to concerns about mandatory pharmacist advice being required, the Committee decided that the Schedule 3 classification remained appropriate. The August 1998 Meeting reconsidered this decision with new evidence presented by XXXXX. The Committee felt that this new evidence addressed its concerns about access and use without pharmacist advice and agreed to include hyoscine butylbromide in S2.

A proposal to increase the S2 dose and pack size limits was considered at the June 2002 NDPSC Meeting. The Committee agreed to amend the S2 entry on the basis of a long history of safe use and there being no significant safety concerns with the substance at the current S2 dose and pack size.

DISCUSSION - SUBMISSIONS

Applicant's submission

XXXXX submitted an application outlining the case for amending the scheduling of hyoscine butylbromide by:

(i) Increasing the pack size restriction from 200 mg to 500 mg for the Schedule 2 entry; and

(ii) The removal of the single active substance restriction from the Schedule 2 entry.

The following points were considered by the Committee with regards to the submission:

- Hyoscine butylbromide had a long history of safe use in Australia and worldwide. A Clinical expert statement XXXXX provided by the applicant (outlined below) stated that XXXXX;
- The initial inclusion of the restriction on pack size was at the applicant's suggestion. It was not a requirement of the NDPSC at that time. The NDPSC minutes did not mention why the "only therapeutically active substance" restriction was included in the Schedule 3 entry in 1994 and no proposal to remove or change the restrictions has been considered by the NDPSC in the period for which minutes are available;
- The risks associated with hyoscine butylbromide were less than those associated with other anticholinergics because it does not cross the blood-brain barrier easily, is poorly absorbed from the gastrointestinal tract and has a very short half life. It only rarely causes the CNS side effects (such as blurred vision, palpitation and dry mouth) associated with hyoscine;

- Hyoscine butylbromide was at least as safe as other forms of hyoscine and the other non-prescription anticholinergics to which less restrictive scheduling requirements apply regarding both pack size and use in combination;
    - Other Schedule 2 anticholinergics include *Atropa belladonna*, atropine (excluding atropine methonitrate), *Datura spp, Datura stramonium (stramonium), Datura tatula (stramonium), Duboisia leichhardtii, Duboisia myoporoides*, hyoscine (excluding hyoscine butylbromine), hyoscyamine and *Hyoscyamus niger*. In each case the relevant entry states that the substance is included in Schedule 2 "for oral use in divided preparations containing 0.3 mg or less of total solanaceous alkaloids per dosage unit when labelled with a maximum recommended daily dose of 1.2 mg or less total solanaceous alkaloids." No pack size restriction applies to any of these substance entries, and there is no restriction on combinations. New Zealand includes corresponding entries for each of these substances in its 'Pharmacy-Only' classification;
    - The applicant named hyoscine hydrobromide as a comparison to hyoscine butylbromide with regards to safety, noting that hyoscine hydrobromide, unlike hyoscine butylbromide, is readily absorbed through the gastrointestinal tract after oral dosage. It crosses the blood-brain barrier and has been stated to cross the placenta;
    - The applicant concluded that hyoscine butylbromine should have the same scheduling status as the other related anticholinergics and has noted that the NDPSC has acknowledged the comparative safety of hyoscine butylbromine on several occasions;
- The applicant noted that the Adverse Drug Reaction Advisory Committee (ADRAC) advised the Trans-Tasman Harmonisation Working Party in 2005 that they held 120 case reports for hyoscine butylbromine, of which 16 specified the oral route of administration. The Working Party's advice to NDPSC (endorsed at the NDPSC February 2005 meeting) was that, having regard to the established safety in use of products containing hyoscine butylbromide over an extensive period of time and in the interests of harmonisation, that the New Zealand Ministry of Health reconsider harmonisation of scheduling with the SUSDP;
- The applicant recognised that a possible argument for retaining the current pack size limitation could be a concern that long term use of oral hyoscine butylbromine could mask another more serious illness for which medical attention should be sought. A similar concern had been expressed in minutes of the NDPSC and XXXXX, in relation to inappropriate long-term use, related to anticholinergics in general, not just hyoscine butylbromide. The applicant stated that these concerns could be addressed effectively by appropriate label warning statements (already on the XXXXX label). The applicant also believed that this type of statement should be mandatory. "these should apply equally to all anticholinergic substances";

- The sponsors of both S2 hyoscine butylbromide products registered for supply in Australia already include warning statements on their labels;
- The current pack size limitation was not an effective means by which to achieve the desired outcome because:
    - The consumer was at liberty to buy multiple packs at a time, or to buy additional packs at frequent intervals;
    - There was no information required through RASML, on the label, to indicate that the product should not be used for more than a few days at a time without a doctor's advice;
- Currently the New Zealand 'Restricted' entry for hyoscine butylbromide allows for combinations. Removal of the restriction on hyoscine butylbromide combinations in Schedule 2 would be consistent with the current New Zealand 'Restricted' entry for hyoscine butylbromide;
- The applicant was aware that any new combinations would need to go through the TGA for registration. As it will still be Schedule 2, a pharmacist would still be available for advice on the product;
- The applicant claimed that allowing the development of new OTC combinations of medicines containing hyoscine butylbromide would be a benefit to the consumer;
- An increase in the pack size limitation on hyoscine butylbromide from 200mg to 500mg would benefit consumers by reducing the unit cost of XXXXX and, given the product has a shelf life of 36 months, it could be safely used on more than one occasion over this period of time. Increasing the pack size limitation would align the substance with other similar agents.

XXXXX provided a Clinical Expert Statement / Safety assessment based on XXXXX - sponsored GCP-conforming, controlled clinical studies on XXXXX. The studies themselves were not provided, only a summary was provided. The experts' findings are as follows:

- Currently XXXXX is an OTC product in 16 countries world-wide;
- XXXXX;
- The report included summarised data and results of clinical studies. The Committee noted that page numbers of the studies were given but the studies themselves were not provided. In a double-blind, randomized, placebo-controlled clinical study, 51 patients were treated with a 60 mg (20 mg t.i.d) orally per day for 7 days; 52 patients received placebo tablets. In a structured interview, patients were asked specifically for anticholinergic side effects. There was no difference in the frequencies of these side effects reported. The total number of adverse events was even lower in the XXXXX group. In another double-blind, randomized, placebo-controlled clinical study, 53 patients were treated with a 60 mg (20 mg t.i.d) orally per day for 3 days; 45 patients received placebo tablets. The author reported one ADR for a XXXXX patient

(dryness of mouth). Again, no difference between ADR for XXXXX and placebo could be detected after enteral administration;

- XXXXX;
- In the majority of cases where XXXXX had been administered with suicidal intention, an overdose had been taken. None of those cases had a fatal outcome. The highest single dose was 70 tablets of XXXXX. The events in this case were "only" nausea and vomiting and the patient had completely recovered. The author stated this might illustrate that XXXXX bears no serious risk concerning overdose. The Committee noted that reference was made to Appendices but data was not provided with the report;
- The author claimed that the XXXXX (not provided) stated the potential interactions between XXXXX and other drugs: "the anticholinergic effect of tricyclic antidepressants, antihistamines, quinidine, amantadine and disopyramide may be intensified by XXXXX. Concomitant treatment with dopamine antagonists such as metoclopramide may result in diminution of the effects of both drugs on the gastrointestinal tract. The tachycardic effects of beta-adrenergic agents may be enhanced by XXXXX";
- The experts stated that no public health concern can be seen with the product when administered at the recommended dosages in the approved indications. XXXXX had a favourable benefit-risk profile, especially when considering the patient exposure.

NDPSC evaluation report

The NDPSC evaluation report is outlined below:

- The evaluator recognised that hyoscine butylbromide had a previously identified favourable adverse event profile compared to other non-prescription anticholinergics available in Australia and NZ including hyoscine hydrobromide which is more readily absorbed through the GI tract and crosses the blood-brain barrier and placenta. Also noted is hyoscine butylbromide's low abuse potential and low potential for harm from inappropriate use;
- The evaluator's main concern with increasing the pack size as S2 for up to six days of treatment was that under S2 there may be no pharmacist or medical intervention (notwithstanding appropriate medical labelling) in patients with abdominal cramping. This could lead to a greater duration of masking of the onset of a more serious gastrointestinal disease such as bowel obstruction, renal calculi etc. in addition to previously identified concerns of cardiac arrhythmias and glaucoma and urinary retention. Furthermore, these symptoms could initially be relieved by this agent (potentially delaying necessary medical attention). Having larger pack sizes may send the message to consumers that treatment for up to six days is acceptably safe without professional advice;

- The evaluator was not satisfied that the ADRs provided by the applicant gave enough information about adverse events according to the duration of treatment, i.e. it is not clear from the data provided whether longer duration of treatment results in a greater incidence of adverse events;
- The evaluator recommended the request for an increase in pack size be rejected due to unknown safety profile over six days of treatment and risk of masking serious gastrointestinal disease causing similar symptoms;
- The evaluator recommended that a warning label stating that "this product should not be used for more than two to three days without medical advice" would be more adequate than the applicant's suggestion of "should symptoms persist, please consult your doctor";
- The evaluator recommended the request for use of hyoscine butylbromide in combination be rejected due to there being no currently registered combination products and thus safety of individual formulations is currently unknown. The evaluator added that this should be a matter of safety and efficacy assessment by the TGA prior to registration, on a product-by-product basis.

Pre-meeting response from applicant

The applicant provided a pre-Meeting response to the evaluator's report and the following points were made:

- The applicant considered the recommendations made by the evaluator to be unfair and inconsistent with the current SUSDP allowances for other OTC anticholinergics, and when compared with other products which may have the same potential risk of masking serious gastrointestinal disease;
- The applicant claimed that existing pack size limitation and single active substance restriction were arbitrary;
- XXXXX;
- In response to the evaluator's claim that safety has not been established over 6 days, the applicant stated that the safety analysis provided with the original submission covered pack sizes of both 20 and 100 tablets (2.5 to 12.5 days supply) and did not appear to indicate significant safety issues caused by duration of treatment;
- XXXXX;
- XXXXX tablets with pack sizes offering 5 days of treatment or more with an OTC status were available in Germany, Netherlands, Switzerland, Spain, Canada and South Africa. Worldwide, the overall number of suspected adverse reactions was less than 0.001 per 1,000 treatment episodes (based on the assumption of an average treatment cycle of 3 days);
- The existing packaging had warnings to ensure the product was used for short term treatment and the applicant agreed with the evaluators recommendation to strengthen

the OTC product labelling of its hyoscine butylbromide product for any pack sizes providing more than 3 days of treatment;

- The applicant reiterated that the risk of masking serious GI disease is a potential issue for all S2 anticholinergic substances having similar indications as hyoscine butylbromide. They also restated that there was no pack size limitation in the existing S2 anticholinergics (eg hyoscine hydrobromide) which enables the products (eg XXXXX) to be currently sold in a pack of 50 (providing 6.25 to 16.67 days supply) without any specific warning statements on their product labels to advise patients against inappropriate long-term use;
- The applicant made the recommendation that the RASML be amended to include the label warning statement *"do not use for more than three days at a time except with doctor's advice"* for all products containing hyoscine butylbromide or any other S2 anticholinergic substances having similar indications that provide more than 3 days of treatment per pack;
- The applicant disagreed with the statement made in the evaluation report that "by having larger pack sizes a potentially misleading message the consumer may receive is that treatment for up to six days is acceptably safe without professional advice". It was stated that the current pack advises consumers to consult their doctor if symptoms persist and that statement is to be strengthened for the larger pack sizes (see above);
- The applicant mentioned the June 2007 NDPSC decision to exempt ranitidine from scheduling *"when in divided preparations for oral use containing 150 mg or less of ranitidine per dosage unit in the manufacturer's original pack containing not more than 14 dosage units"* (7 days supply). Ranitidine has a potential for masking serious GI diseases such as carcinoma, yet the Committee allowed the product to be available to consumers without the need for professional intervention;
- XXXXX also noted that the Committee allowed medications with pack sizes well beyond their recommended duration of treatment to be sold within pharmacies, eg ibuprofen (100 dosage units, providing over 16 days of treatment) and paracetamol (no restriction). These substances have the same potential to mask serious diseases if used inappropriately long term without medical advice yet in these cases a warning label has been considered adequate;
- The applicant reminded the Committee that the larger pack sizes of hyoscine butylbromide would still be a "Pharmacy Medicine" and thus, there is still the opportunity for supervision and advice from the pharmacist;
- The applicant referred to ADRAC reports (not provided by the applicant) which they said showed that although XXXXX had been available on prescription in large pack sizes for over 50 years and small packs OTC for over 10 years, there were few ADRs and no indication of problems with masking of serious GI diseases. The ADRAC database (not provided by Sponsor) showed 54 cases where XXXXX was the sole suspected drug including 12 (minor) GI reactions. There was one report of paralytic

ileus with intestinal perforation where both XXXXX and XXXXX were suspected drugs;

- The applicant referred to XXXXX tablets (a product containing hyoscine hydrobromide, atropine sulfate and hyoscamine sulfate for the same indications as XXXXX). It had been marketed in Australia as a 50 pack (ie. 6.25 – 16.67 days supply) for at least 10 years as S2 medicine. As mentioned in the original application, hyoscine butylbromide had a better safety profile than hyoscine hydrobromide because of its lower bioavailability and short half-life;
- The applicant addressed the evaluator's point regarding previously identified concerns of cardiac arrhythmias and glaucoma and urinary retention. The applicant claimed that these are concerns with any anticholinergic, and are rarely associated with hyoscine butylbromide in the tablet form (no data provided);
- The applicant recognised that the basis for the evaluator's decision was the lack of currently registered products containing hyoscine butylbromide combinations and therefore lack of safety information regarding such combinations. It was the belief of the applicant that because there are no restrictions on combinations with the other anticholinergics in S2, there should be no restrictions on hyoscine butylbromide;
- The applicant agreed with the evaluator that combinations of other OTC substances with hyoscine butylbromide "should be a matter of safety and efficacy assessment by the TGA prior to registration, on a product-by-product basis". XXXXX added that the issues of combinations and the safety of individual formulations are a matter for the TGA, and not poisons scheduling, in this instance.

Pre-Meeting submissions

A submission was received from XXXXX supporting an increase in the pack size limitation of hyoscine butylbromide in Schedule 2. In this submission, it was asked that the following be considered:

- XXXXX currently distribute a 20-tablet pack of 10 mg tablets under the XXXXX brand;
- While the product was expressly marketed for treatment of short term stomach discomfort which clearly should be self limiting or would require review by a doctor, the dosage restriction was really too small to allow the consumer to establish treatment and assess response before visiting a doctor. Most consumers will need one to two days to assess whether relief has been achieved and the condition has cleared or whether a visit to the doctor is warranted. Obtaining a doctors appointment may well take another day or so thus the consumer is placed in the position of needing to purchase another pack of product to maintain symptomatic relief.
- Raising the maximum pack content to 400 mg would effectively deliver the consumer a more effective and logical treatment modality.

A submission was received from XXXXX expressing the view that the present pack size limitation of hyoscine butylbromide under Schedule 2 was appropriate, but that the advice of the Medicines Evaluation Committee should be sought.

- The point was made that given the anticholinergic effect of hyoscine and that greater than short term treatment may disguise more serious medical conditions; treatment for more than 2-3 days without medical direction is to be avoided.

A submission was received from XXXXX with the opinion that the current scheduling of hyoscine butylbromide was appropriate and the submission to increase the pack size restriction should not be approved. The following points were made:

- Despite this medicine having been used for many years, use has been based on anecdotal rather than clinical evidence derived from well controlled studies;
- Painful abdominal conditions that last more than three days should be reviewed by a health professional;
- Anticholinergic medicines carry a high risk of adverse effects and also have the potential to worsen several disease states such as heart disease, Inflammatory Bowel Disease and prostatic hypertrophy;
- XXXXX argued that to doubling the pack size of hyoscine butylbromide would encourage consumers to self-treat conditions for longer than is appropriate and discourage appropriate diagnosis and the use of more effective treatments.

Information received from XXXXX revealed the following:

- There are no currently registered products which contain hyoscine butylbromide in combination.
- XXXXX

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

It was agreed that toxicity and safety (52E(1)(a)), the risks and benefits associated with the use of hyoscine butylbromide (52E(1)(b)), the extent and pattern of use (52E(1)(d)), the dosage and formulation (52E(1)(e)) and the need for access (52E(1)(f)) were all relevant matters in considering the scheduling of hyoscine butylbromide.

The safety profile of hyoscine butylbromide taken over six days was unknown. This, along with the fact that it may mask more serious conditions, was a major concern for the Committee relating to safety. The Committee rejected outright the extrapolation the applicant made on XXXXX in their pre-meeting response.

The Committee noted the applicant's claim that both South Africa and Canada have a 5 day OTC pack available. Given that neither of these countries have ADR reporting similar to Australia, this point gave the Committee little assurance on safety of a larger pack size.

A Committee Member maintained that there are other substances intended for treatment of acute conditions which are in larger pack sizes. From this, it was argued that pack size should not be limited by scheduling. Further, the Member argued that it should be up to the registration process to determine whether two Schedule 2 products should be combined, not the NDPSC. The Committee did not agree with either of these points.

It was noted that the applicant had presented no data to justify the removal of the single active requirement from the Schedule 2 entry. The Committee agreed that such data would need to address the matters set down in S52E, as it is these matters which the Committee must take into account. Given that the NDPSC made a deliberate decision to make hyoscine butylbromide Schedule 2 only as a single active, it should not be amended until data is presented warranting such an amendment.

The Committee agreed with the evaluator and applicant in recommending to RASML to include a warning label on all anticholinergic products, including hyoscine butylbromide.

RESOLUTION 2007/51 - 29

The Committee decided that the current scheduling of hyoscine butylbromide remained appropriate.

12.1.2 DICLOFENAC

PURPOSE

The Committee considered the scheduling of diclofenac, including a proposal to increase the Schedule 2 pack size restriction.

BACKGROUND

Diclofenac, a phenylacetic acid derivative, is a nonsteroidal anti-inflammatory drug (NSAID). Diclofenac exhibits pronounced anti-inflammatory, analgesic and anti-pyretic properties by inhibiting prostaglandin synthesis through inhibition of cyclo-oxygenase-1 (COX-1) and COX-2. It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions including musculoskeletal and joint disorders.

Diclofenac was included in S4 in March 1981. The NDPSC then agreed to reschedule diclofenac 25 mg or less in packs of 30 or less for oral use to S3 in August 1999 as recommended by the TTHWP and listed it in Appendix H of the SUSDP in August 2001.

The June 2004 NDSPC meeting considered an application to reschedule diclofenac from S3 to S2 in divided preparations for oral use containing 12.5 mg or less per dosage unit in packs of 30 or less. XXXXX. The dosage recommendation was an initial dose of two x 12.5 mg tablets and continued with one or two tablets every four to six hours if needed with a maximum dose of six tablets in a 24-hour period. However, the NDPSC did not agree with the proposal as members were not convinced that rescheduling diclofenac 12.5

mg to S2 was appropriate at the time in the absence of an evaluation for OTC registration and in the absence of local post-marketing experience with the 12.5 mg oral dose formulation in Australia to establish the safety, efficacy and use pattern for the indications sought for the product.

Subsequently, the applicant provided a post-Meeting comment for consideration at the October 2004 meeting in response to the outcome of the June 2004 meeting for diclofenac 12.5 mg. However, as the submission was received after the publication of the pre-October 2004 meeting gazette notice, the October 2004 NDPSC meeting could not consider the submission without appropriate public consultation. The Committee also indicated that it was open for the applicant to submit a new application at a future Meeting. Furthermore, the NDPSC was informed that XXXXX.

The February 2005 NDPSC Meeting considered a new submission to reschedule diclofenac 12.5 mg from S3 to S2. Although the Committee was advised that XXXXX, it agreed to include in S2 diclofenac in preparations containing 12.5 mg or less per dose in packs containing not more than 20 tablets or capsules. The Committee was convinced that the available data including results of clinical trials and post-marketing safety data supported an acceptable safety profile of diclofenac 12.5 mg at a daily dose of up to 75 mg consistent with the criteria for S2 medicines. Members also agreed that this decision would harmonise the scheduling of diclofenac 12.5 mg with New Zealand.

DISCUSSION - SUBMISSIONS

Applicant's submission

XXXXX submitted an application outlining the case for amending the scheduling of diclofenac by increasing the pack size restriction from 20 dosage units to 40 dosage units for the Schedule 2 entry.

In summary, the submission asserted that:

- XXXXX. Diclofenac is not able to compete with this due to the Schedule 2 pack size restriction.
- The safety and efficacy of XXXXX for use within its approved indications has previously been reviewed by the NDPSC when it decided to include diclofenac in Schedule 2 in 2005. It was noted that the decision made by the NDPSC limited the pack size to 20 units as this was in line with the MCC scheduling of the substance.
- The 20 tablet pack size (which was in line with worldwide pack sizes) was requested by the applicant in XXXXX submission to the MCC, thus this was not a restriction imposed by the MCC as such. The applicant stated that XXXXX had no reason to believe that a larger pack size would not have been granted if requested.
- A summary of post-marketing safety XXXXX with diclofenac was given highlighting the long use and large number of patients (over 1 billion) treated with diclofenac

worldwide. The applicant noted that most of this data related to prescription products but stated that it could be extrapolated to the lower dose products.

- The applicant noted the comments made by the Committee at the October 2006 Meeting regarding the safety of diclofenac and stated that XXXXX had submitted a comment on this article to the TGA. The applicant believed that the JAMA article (Cardiovascular Risk and Inhibition of Cyclooxgenase – A systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2) gave an incomplete picture of the safety of the substance and also overstated the potential for cardiovascular risk with diclofenac. The applicant further stated that this data was even less relevant to the XXXXX preparation which has a dosage limit of 75mg/ day.
- The applicant provided current ADRAC information on the incidence of ADRs reported with diclofenac sodium. Since it became available in the 1980s, 64 ADR reports (totalling 201 reactions) have been received by ADRAC for diclofenac potassium. The most commonly reported reactions were dyspnoea, dizziness, pruritis and rash.
- The applicant made note of the Schedule 2 dose limits for other analgesics. The applicant noted that ibuprofen 200mg had a limit of 100 units and that both paracetamol and aspirin have no dose limit applied to their respective entries. The applicant stated that, given this, the NDPSC clearly regarded larger pack sizes of analgesics to be appropriate in a pharmacy setting. It was also stated that, given the demonstrated equivalent safety and efficacy, as well as a long history of usage, of diclofenac to these other substances it would seem appropriate to allow for the requested increase in pack size. The applicant further noted that if this increase were granted it would still be well below the maximum pack sizes allowed for other analgesics.
- The applicant included copies of the current product packaging and labelling for XXXXX.

NDPSC evaluation report

The NDPSC evaluation report stated that it was the evaluator's view that a decision about whether to approve the request for an increased pack size required the Committee's judgement as to whether consumers would continue to observe the dosage instructions. The evaluator stated that the answer could not be obtained from available clinical information. The evaluation report made the following points:

- The NDPSC had previously evaluated safety data from double-blind, randomised, controlled clinical trials for the 75mg daily dose when it agreed to include diclofenac at 12.5mg in Schedule 2 of the SUSDP. The sponsor relied on this data (submitted in 2004) and there was no new clinical data presented in the current submission which directly related to the request for a change in pack size to 40 dosage units.

- The evaluator stated that they looked for information in the submission that may have been directly related to the proposed increase in pack size, such as whether there were implications if a consumer took the maximum daily dose until the pack was finished (7 days), from a consumer taking double the recommended dose (150mg) until all tablets were used (3 days) or whether there were any implications for overdose. The evaluator acknowledged that these differences in safety may be small but noted that the applicant had not provided any information on them.
- The evaluator obtained two previous evaluations done on behalf of the NDPSC as well as XXXXX. The evaluator noted that the safety data from all of the clinical trials showed that the most frequent side effects were gastrointestinal. However, it was also noted that none of the studies compared the differences in safety and efficacy between use of 75mg/ day for 3 and 7 days or the differences between 75mg and 150mg when used for a 3 day period.
- The evaluator noted that the PSUR provided was for all strengths and forms of diclofenac and there were no separate analyses conducted for diclofenac potassium 12.5mg. The evaluator also noted that of the 64 reports to ADRAC about diclofenac potassium, 58 referred to XXXXX, which was available as 50mg (S4), 25mg (S3) and 12.5mg (S2). The evaluator stated that, as no analysis of this data had been provided, the applicant's claim that most of these ADRs occurred with the prescription product was not able to be substantiated. The evaluator observed that the tabulated ADR data provided contained two reports of fatal reactions to diclofenac potassium, one involving severe gastrointestinal (GI) reactions and one involving anaphylaxis and that the most common ADRs were dyspnoea (12), dizziness (9) and anaphylaxis (6).
- The evaluator discussed in detail the information contained in the PSUR about cardiovascular risk. The evaluator stated that the all the published meta-analyses mentioned (bar one) lack detailed information about dose and duration, but that it was likely, given that most of the studies were conducted in arthritis patients, that they reflect doses of > 100mg/ day diclofenac taken for extended periods. The evaluator stated that the one study that did look at lower doses showed that the risk seemed to be smaller with these. The evaluator also stated that only one of the three major clinical trials mentioned in the PSUR was helpful to this evaluation due to use of concomitant medications or lack of data about comparator substances.
- XXXXX

Pre-meeting response from the applicant

The applicant provided a pre-Meeting response to the evaluator's report and the following points were made:

- With regard to the evaluator's comment that the Committee would have to judge whether consumers will observe dosage instructions on an increased pack size, the applicant stated that the increased pack size would merely allow consumers more flexibility and convenience by providing enough medication to treat two episodes of acute pain. The applicant also stated that customers were used to larger pack sizes of

analgesics and there was no reason to believe that consumers would treat larger pack sizes of diclofenac any differently to those of ibuprofen or paracetamol.

- The applicant addressed the concerns raised about abuse and misuse of diclofenac in the larger pack sizes. It was stated that the dosage regimen had not changed from 75mg for a few days and that, even if used at double the daily dose (150 mg), it was still within recommended doses for long-term treatment of a chronic ailment. It was further stated that, although the risk of adverse events seemed to be dose and duration-dependant, increasing the pack size to 40 tablets should not increase the risk any more than for the 100 tablet packs of ibuprofen or aspirin. To support this, the applicant referred to data submitted to the June 2004 NDPSC Meeting showing that short and long-term use of diclofenac was comparable to ibuprofen.
- The applicant noted the evaluator's concerns about possible overdose with the increased pack size. The applicant stated that cases of overdose were rare for diclofenac potassium and that detailed information regarding this was also submitted in the June 2004 application to the Committee. In summary, the applicant noted that this information stated that; NSAID overdose resulting in significant morbidity and mortality was rare, diclofenac was not known to be toxic in overdose, in acute or chronic overdose diclofenac compares favourably with other NSAIDs, no signs or symptoms of toxicity were observed in patients who ingested 2 – 4g of diclofenac and that the risk of overdose was further reduced with diclofenac potassium as even at 150 mg/day this was still within the recommended doses for long-term, chronic use.
- The applicant noted that it had provided the evaluator and NDPSC Secretariat with all the correspondence between it and the TGA relating to the review of NSAIDs, and stated that the available data on the use of low-dose diclofenac for short-term treatment did not suggest an increase in CV risk.
- The applicant noted that the current product labelling reflected the requirements of the RASML and provided more information than was required by the RASML. The applicant stated that any further changes to the RASML would be reflected in the product labelling if it was not already contained on it.
- Information was provided about the maximum registered pack sizes in other countries. It was noted that the product is available OTC in 55 countries and the maximum registered pack size is generally 20 tablets (reflecting the original global registration strategy.) It was noted, however, that larger pack sizes have since been registered in some countries including Denmark (40), the Netherlands (40) and Germany (30).
- The applicant agreed with the evaluator that it could not be concluded from the ADRAC data that most of the ADR reports for diclofenac potassium were for prescription medicine products. The applicant stated that this conclusion was drawn by an external consultant on the basis of the information submitted by the applicant to ADRAC. It was also noted that the individual case reports were often incomplete and did not allow for a clear picture to be drawn.

- The applicant stated that it took a conservative approach to ensure patient safety and that any proposed changes to scheduling were assessed against a stringent set of criteria. It also noted that it followed strict post-market surveillance procedures and that any serious or significant health concerns were reported to the TGA.

Pre-Meeting submissions

XXXXX provided a pre-Meeting submission which stated that, given the Schedule 3 entry accommodates the more realistic strength and quantity, there seemed little need to amend the Schedule 2 entry. XXXXX also stated that XXXXX was concerned about the trend to reduce controls on the more potent NSAIDs, especially given the increasing concern over GI and CV adverse events.

XXXXX provided a pre-Meeting submission in which XXXXX concurred with the submission made by the XXXXX. XXXXX also made known XXXXX concern regarding the increased potential for the 'triple whammy' effect to occur with larger amounts of NSAIDs being available to the public. XXXXX referred to the August 2003 ADRAC Bulletin article warning about the dangers of the 'triple whammy' in patients using concomitant ACE inhibitors, diuretics and NSAIDs. The Committee had recently, at its October 2006 Meeting, considered advice from ADRAC on the 'triple whammy' effect.

XXXXX provided a pre-Meeting submission in which XXXXX supported the increase in pack size for diclofenac due to its long history of safe use justifying a pack size comparable with other NSAIDs in Schedule 2.

A pre-Meeting comment was received from XXXXX which stated that the application for an increase in pack size should not be approved. The following points were made:

- The current S2 pack size allowed 3 days of regular treatment and if the patients' pain persisted for longer than this, then it would be appropriate for them to seek advice from a healthcare practitioner rather than continue self-treatment. Persistent pain was a warning sign which should be investigated by a healthcare practitioner and increasing the pack size would delay patients receiving appropriate diagnosis and management of their condition.
- Non-selective NSAIDs carry a high risk of severe adverse events including asthma and renal failure caused by the 'triple whammy' effect. These NSAIDs may also cause gastrointestinal and cardiovascular problems. These risks were especially high in the elderly.

XXXXX provided a pre-Meeting comment which requested that the Committee ensure any decision it made was to be consistent with the entries for other Schedule 2 NSAIDs.

DISCUSSION – ADDITIONAL RELEVANT MATTERS UNDER 52E

The Committee agreed that the most relevant provisions of S52E for this consideration were (1) (a) toxicity and safety, (b) risks and benefits, (c) potential hazards and (d) extent and patterns of use.

Members discussed concerns regarding data showing that CV risk was emerging with short-term use of NSAIDs and this relates to 52E (1)(b), risks and benefits. The Committee noted that it was established that long-term use had more risks than short-term use. Members were concerned that the sponsor had presented no new safety data for the more prolonged use that the proposed pack size may encourage. The potential hazards (52E (1)(c)) in regards to CV risk, as well as the extent and patterns of use (52E (1)(d)), given that longer term use has increased risk, were relevant to this concern.

A Member stated that a larger pack size did not necessarily correspond with a longer pattern of use and that labelling would be sufficient to deal with this concern. However, the Committee agreed that there was an assumption on the part of consumers that the availability of a 7 day pack size as an S2 medicine meant that it was safe to take the product continuously for a 7 day period. The Committee expressed concern that the sponsor had not submitted any data to show that the safety profile of the proposed larger pack size was the same as the current S2 pack size i.e., that there had been no data provided showing the safety of 7 day use compared to 3 day use. The Committee felt that this data would be particularly relevant considering the emerging data for acute risk with NSAIDs.

The point was made that the side effect profile for ibuprofen is slightly different to other NSAIDs. Further, the fact that all other NSAIDs have pack size limits relates to 52E (1)(f), the need for access to diclofenac, taking into account its toxicity compared with other substances available for a similar purpose. The Committee also noted that to increase the S2 pack size to 7 days supply would make the S2 and S3 entries near identical.

The Committee agreed that the safety profile for acute risk was still emerging and that it is not yet established as to whether there was lower risk with the 7 day treatment.

RESOLUTION 2007/51 - 30

The Committee decided that the current scheduling of diclofenac remained appropriate.

12.1.3 PARACETAMOL AND MORPHINE

PURPOSE

The Committee considered the scheduling of morphine when in combination with paracetamol, including a proposal to include the combination in Schedule 3.

BACKGROUND

Opioid analgesics include the opium alkaloids morphine and codeine and their derivatives as well as synthetic substances with agonist, partial agonist, or mixed agonist and antagonist activity at opioid receptors. The term opiate analgesic refers only to those opioids derived from opium, or their semisynthetic congeners. Most opioids are used as analgesics, and morphine is the standard against which all other opioid analgesics are compared. Opioids such as codeine or dextropropoxyphene are used in the treatment of less severe pain, and are often combined with non-opioid analgesics such as aspirin, other NSAIDs, or paracetamol. More potent opioids such as morphine are used in severe acute and chronic pain, including cancer pain.

At the November 1971 Meeting, the Committee agreed to delete all entries other than the S8 entry for morphine as this would help to reduce the incidence of misuse and diversion of morphine containing products. This decision was confirmed at the July 1972 Meeting of the Committee.

At the October 2006 NDPSC Meeting, the Committee considered a submission from XXXXX requesting that paracetamol in combination with either morphine 3 mg, oxycodone 2 mg or hydromorphone 0.5 mg be rescheduled to Schedule 3 and to also consider re-scheduling fixed dose analgesics containing paracetamol in combination with either morphine 7.5 mg/ 10 mg/ 20 mg, oxycodone 5 mg/ 7.5 mg/ 10 mg or hydromorphone 1 mg/ 2 mg/ 4 mg to Schedule 4. After consideration of all the evidence presented to it, the Committee agreed that, due to the lack of evidence provided about both the safety and efficacy of the substances in slow metabolisers of codeine and due to concerns regarding the abuse potential of the medications, the current scheduling of these substances remained appropriate. In reaching this conclusion the Committee also took into account the fact that the NDPSC guidelines require that S3 substances have a low abuse potential and that substances which present a substantial risk of abuse, dependence or misuse must be included in S8.

DISCUSSION - SUBMISSIONS

Applicant's submission

XXXXX submitted an application outlining the case for the down scheduling of:

(i) Paracetamol compounded with morphine 3 mg, which is equianalgesic to 15 mg of codeine phosphate, packed in blister or strip packaging or in a child-resistant closure containing 8 dosage units to Schedule 3; and

(ii) Paracetamol compounded with morphine 6 mg in packages containing 12 or more dosage units to Schedule 4.

(iii) The applicant requested that if the Schedule 3 submission was not granted, this also be considered for Schedule 4.

The applicant put forward the argument that the clinical use of paracetamol and opioid analgesia was well established and that the application involved neither new therapeutic agents nor novel indications. The applicant also stated that studies have shown that the use of opioids to treat acute pain rarely leads to addiction, but no data was provided from specific studies. In summary, the submission contained the following sections:

- Background was given on the prevalence in the community of poor metabolisers of codeine. The applicant stated that approximately 10% of the Caucasian population and 20% of the Asian population cannot convert codeine to morphine as they lack the enzyme Cytochrome P450 2D6 (i.e., they are poor metabolisers). The applicant also stated that this lack of enzyme may be caused by other medications blocking its activity. The applicant noted that codeine's analgesic effect is due to its conversion to morphine and quote a handbook from the Royal Children's Hospital in Melbourne (Royal Children's Hospital**.** *Paediatric Handbook.* Melbourne: Blackwell Publishing, 2003. p. Chapter 3; Pain Management) which states that codeine is a "complicated and unreliable" method of giving morphine. The applicant also made reference to "ultra-rapid metabolisers" posing problems with codeine dosing.
- The applicant stated that by approving a paracetamol 500 mg/ codeine 15 mg combination as a Schedule 3 preparation, the Committee had acknowledged the public health benefit of timely availability of low-dose opioid OTC compound analgesics for mild to moderate acute pain. The applicant stated that their proposed product would be equi-analgesic to the abovementioned codeine product. The applicant stated, however, that poor metabolisers do not have access to this type of analgesia which the Committee has acknowledged is of public health benefit. The applicant made reference to Human Rights legislation and the indirect discrimination that not allowing a morphine/ paracetamol combination in Schedule 3 imposed on poor metabolisers.
- Reference was made to the *UN Single Convention on Narcotic Drugs* (the 'Single Convention') and it was noted that low dose morphine containing compounds were included in Schedule III, which means they are exempt from the restrictions that apply to pure opioids. The applicant' noted that Schedule III substances were not required to have a prescription for supply and that the Single Convention called for signatory countries to provide both adequate control over and access to analgesics. The applicant stated that their proposed product met the requirement of Schedule III of the Single Convention.
- The applicant discussed the lengthy availability of morphine OTC in the United Kingdom, both as an analgesic and as an anti-diarrhoeal. The applicant stated that, despite this, there was no evidence of significant abuse of these substances whereas it is a known fact that people do abuse OTC codeine.
- The applicant addressed the issues of safety and efficacy of the proposed combination. It was stated that the use of paracetamol in combination with morphine was the clinical standard (*Acute Pain Management: Scientific Evidence*) endorsed by the NH&MRC and that this was based on accumulated evidence and clinical experience with morphine over a long period of time. The applicant also referenced

the WHO analgesic ladder which recommended the addition of opioids to paracetamol. The applicant stated that the doses of morphine in the proposed combinations have been shown to be efficacious in post-surgical pain studies (*Acetaminophen as an adjunct to morphine by patient-controlled analgesia in the management of acute postoperative pain.* 2, 1998, Anesthesia & Analgesia, Vol. 87, pp. 368-372) and noted that, while the product would not be suitable for all patients, it would provide a public health benefit to a large number of patients, especially those who were poor metabolisers of codeine.

- The addiction potential of the combination was addressed. The applicant stated that, when used to treat acute pain, the risk of addiction is less than 1:1000 (however no reference was given for this statement), which was a low risk and, thus, use of the product was unlikely to induce addiction. The applicant further stated that there were studies which demonstrated that the propensity to opioid abuse in the community was low and that jurisdictions with a different (easier) availability of opioids have a similar rate of abuse to Australia. The applicant agreed with a comment made at the October 2006 Meeting that there was a problem with codeine abuse and stated that the amount of morphine available in the proposed product would be much lower than that in prescription products. Therefore, in order to abuse the product, the patient would have to buy a large number of packages through different pharmacies at a significant cost. The applicant also noted that the patient would be exposing themselves to a large amount of paracetamol.
- A cost (risk) versus benefit analysis was explored. The benefits put forward were parity for slow metabolisers, more consistent analgesia for ultra rapid metabolisers, less reliance on codeine (which, it was stated, some clinicians find to be an inefficient analgesic) as well as providing alternative analgesics to NSAIDs. The costs included accidental poisoning, deliberate poisoning, medicinal misadventure and the risk of diversion and each of these were discussed in some detail in the submission.
- The EU Directive for Fixed Combination Medicinal Products was referred to and the application was addressed using the framework of the directive. The applicant maintained that there was an enormous amount of clinical experience accumulated that demonstrated the safety and efficacy of the paracetamol/ opiate combinations.
- The provisions of s52E of the Act were listed and arguments for each provision were put forward. The applicant also addressed the guidelines for including a substance in Schedule 3 and Schedule 4.
- The applicant also provided a response to a number of issues raised in the public submissions and by Members in the October 2006 Record of Reasons.

NDPSC evaluation report

The NDPSC evaluation report recommended that the proposal could not be assessed for rescheduling to S3 or S4 without detailed data on the efficacy, bioequivalence,

pharmacokinetics and safety of the actual formulations proposed. The following points were highlighted in the report:

- Approximately 10% of Australians and 1% of Asians are CYP2D6 deficient and, thus, obtain little or no pain relief from codeine as it is not able to be metabolised to morphine. Ultrarapid metabolisers make up approximately <1% of the population. However, there is no easily accessible, simple test to identify these individuals and, further, most health professionals were not familiar with the complicated details of the disorder. The evaluator stated that the effect of some medications which inhibit CYP2D6 would vary in extent between individuals, would be difficult to estimate and would resolve when the inhibitory medication was ceased. The evaluator noted that there was only one case report of an ultra-rapid metaboliser who became unconscious due to morphine toxicity. The evaluator stated that this was an unusual case as the morphine would usually be eliminated by CYP450 3A4 enzyme as well, but that the patient was on medications which inhibited this enzyme family. The evaluator stated that they had been unable to find any cases of codeine toxicity without such a confounder.
- The evaluator stated that most of the data quoted with regards to the use, safety and efficacy of morphine in combination with paracetamol was related to chronic or post-operative pain, not short-term, acute pain (which the applicant wish to be the indication for their product). The evaluator also stated that the application failed to acknowledge the many differences between prescribing the same medications together as separate formulations and using a fixed-dose combination of them. A fixed-dose combination may have many disadvantages including different pharmacokinetics and pharmacodynamics between and of the components, dose adjustment of an individual component causing unnecessary dose increase in the other and additive toxicity. It was noted that *The Australian Regulatory Guidelines for OTC Medicines* (ARGOM) has very strict guidelines for the evaluation and approval of fixed-dose combination products, including the provision of studies on the pharmacokinetics, safety and efficacy of the fixed-dose combination product, not the two substances used separately. The evaluator noted that the two substances have different pharmacokinetic profiles, with morphine oral absorption being very variable and, thus, requiring careful titration. It was also noted that tolerance to morphine occurs commonly but this does not occur with paracetamol and that this may cause problems with dose adjustment.
- The evaluator addressed the Schedule 3 criteria, namely that a medicine should have low potential for abuse, low potential for harm from inappropriate use and a low incidence of adverse reactions for which medical intervention is required. The evaluator stated that it appeared impossible for any formulation of morphine to fulfil these criteria and expressed concern that patients may take this product for chronic as well as acute pain states.
- It was also noted that the Schedule 4 criterion of ‘low to moderate abuse potential’ seemed to rule out the inclusion of morphine in that Schedule. The evaluator expressed concern that it would be possible for patients to obtain large doses of

morphine through visiting a number of pharmacies or 'doctor shopping' for prescriptions once the public became aware that the combination was available.

- The evaluator felt that there had not yet been demonstrated a large enough social benefit to outweigh the potential for harm of this combination as there was no way to easily identify and, thus, selectively target, poor metabolisers. The evaluator also noted that there were a wide range of other analgesics available OTC and stated that it must be considered that the increased availability of morphine may lead to ram-raids to obtain the substance for illicit diversion (such as had occurred with pseudoephedrine).
- It was stated that none of the UK OTC products mentioned by the applicant were relevant to the consideration as two did not contain morphine and the third contained it only in a very low concentration.

Pre-meeting response from the applicant

The applicant provided a pre-Meeting response to the evaluator's report and the following points were made:

- The applicant stated that XXXXX had provided a large amount of clinical data to the Committee, through reference to the NHMRC document *"Acute Pain management: Scientific Evidence"*. XXXXX also noted that they had included information from ADRAC demonstrating that there were no significant interactions (this may be an error, and the sponsors may have meant ADRs). The applicant requested that the Committee put forward a drug combination that had a greater incidence of use than paracetamol and morphine. The applicant stated that there was evidence supporting their nominated ratio of paracetamol to morphine, that there was a large variability in the dose requirements for morphine and noted that they had referenced material relating to the range of morphine requirements. The applicant stated that the reason the doses of morphine were chosen was because they were equi-analgesic to the Schedule 3 and 4 availability of codeine. The Committee noted that the issue the evaluator highlighted was not the use of paracetamol and morphine concomitantly, rather the use of them in a fixed dose combination, given that they have very different pharmacokinetic profiles.
- It was stated that a fixed dose combination in Schedule 3 and 4 was justified as the NDPSC had recognised the benefit of having access to codeine fixed dose combination products in lower schedules and, therefore, already justified access to morphine/ paracetamol combinations through the scheduling of these codeine combination products. It was also reiterated that the UN Treaty allowed an exemption for morphine in a fixed-dose combination. It was stated that while, in the ideal world it would be best that such medications were used and titrated individually, this could not be achieved in the real world. The applicant requested that the Committee record their rationale for allowing codeine fixed-dose combinations but not morphine containing ones.

- The applicant stated that reaction from their colleagues to the evaluators' suggestion that a clinical trial be conducted to evaluate safety and efficacy of the proposed combination was that it would not be ethically possible to run such a study when such a combination is universally accepted. They also noted the evaluator suggested possibly using intravenous patient controlled analgesia (PCA) morphine in order to get around certain of the ethics issues related to using paracetamol alone. However, the applicant stated that they had already described such trials using PCA morphine and paracetamol. The applicant also stated that in order for them to identify any previously unidentified ADRs in such a study it would have to be powered to randomise billions of patients. The applicant also rejected the evaluator's suggestion that pharmacokinetic and pharmacodynamic studies were required to look at the differences between poor metabolisers and (PMs) and extensive metabolisers (EMs) as, they stated, it was a known fact that PMs did not get pain relief from codeine but they did from morphine.
- The applicant refuted the evaluators claim than <1% of the population were ultrarapid metabolisers (UMs) and that there was only one case report of problems with codeine. It was again stated that up to 25% of the population of the Horn of Africa were UMs (no reference is given for this data). The applicant referred to two other fatal case reports of (a child and a neonate who were) ultrarapid metabolisers of codeine. The applicant stated that, for UMs of codeine, blood levels of morphine can be 10 times higher and, thus, it could be expected that they would experience an increase in non-fatal ADRs as well.
- With regard to the PMs, the applicant stated that the evaluator was still indulging in indirect racial discrimination by suggesting that Caucasians were more likely to be PMs than Asians. The applicant noted the evaluator referenced a study which stated there was no good evidence that people of Chinese origin obtained less pain relief from codeine. However, the applicant stated that this was a small study where analgesia was not an outcome. The applicant also expressed strong concerns about the evaluators position that patients taking CYP2D6 inhibiting substances stopping their medications would ensure that CYP2D6 function returned to normal. The applicant stated that it seemed the evaluator was suggesting patients on these medications go off them in order to obtain pain relief and that it would be clinically negligent for a doctor to prescribe such a patient codeine.
- The applicant also refuted the evaluators' statement that many health professionals were unaware of the issues with poor and ultrarapid metabolisers of codeine. They stated that all major textbooks and guidelines recognise the condition and again referred to the Royal Children's Hospital document mentioned in their application, noting the document stated the clinical consensus was that codeine was difficult to use and not consistently metabolised.
- The applicant again asserted that the rate of addiction to opiates is one in thousands and that this was referenced in their initial submission. They also stated that this had not been shown to be reduced with codeine. They also made reference to the evaluator's comment that patients were likely to use an S3 or S4 morphine

combination to treat chronic pain. The applicant asked why, if this was a better combination, this should not be the case and stated that the evaluator seemed to be saying that it was alright to use codeine (which is converted to morphine) for chronic pain, but not morphine itself. It was also noted that the proposed indication for the product was acute pain. The applicant also refuted the evaluator's statement that most of the studies presented on safety and efficacy were conducted in chronic and post-operative pain states, not acute. The applicant stated that post-operative pain is an acute pain state.

- The applicant stated that XXXXX were troubled by the evaluators' concerns over the appropriateness of a paracetamol/ morphine combination in Schedule 3, particularly the statement that it would be impossible for any formulation of morphine to meet the Schedule 3 criteria. The applicant noted that the provisions of the UN Treaty allowed for morphine to be sold in a lower schedule when combined with another active substance and scheduling in other countries reflected this. The applicant also stated that there was little concern about the public becoming aware of the combination product being available, as this has not led to a problem in the UK where the public was aware of such a combination. The applicant also refuted the evaluator's claim that patients would be able to 'doctor shop' or go to a number of other pharmacies to obtain large supplies of morphine. The applicant reiterated their statements from their application, particularly noting that up to 500 pharmacies would have to be visited in order to obtain the same amount of morphine as is in one pack of maximum quantity, highest quality morphine.
- The applicant made particular note of the evaluator's comment about 'ram raids' and stated that it was unlikely thieves would be tempted by such combination low-dose product when single-active, higher dose products were available in the same pharmacy.
- The applicant also stated that the evaluators' conclusions about the OTC products in the UK were incorrect, with all of them containing morphine at similar levels to the proposed product.

The Committee noted that the applicant submitted a further pre-Meeting response containing more information, after the deadline had passed. As the guidelines state, a pre-Meeting response must not introduce any new data that was not referred to in the original submission.

Pre-Meeting submissions

XXXXX provided a pre-Meeting submission in which XXXXX stated that there should be no change to the scheduling arrangements for morphine. The following points were made:

- Although there was no current morphine/ paracetamol combination available, there were many other combinations of paracetamol and opioid agents.

- Direct comparison of codeine and morphine activity is difficult, but it appears that codeine is about 1/10th as active as morphine. It was also noted that these two substances have different receptor affinities. Codeine has unpredictable and uncertain effects and its therapeutic benefit in combination with paracetamol was uncertain as were its benefit as a single agent. It was also noted that between 7 and 10% of the population are unable to metabolise codeine. XXXXX stated that, given this and morphine's superior analgesic effect, it would seem like the proposed combination was logical.
- XXXXX recalled the change to morphine scheduling (all preparations to S8) in the 1970s and the fact that, before this, any sale of the S2 preparation Chlorodyne BPC had to be recorded due to abuse of the product. It was noted that opiate abuse is still widespread.
- It was stated that, despite the logic of the proposed combination, there were public health concerns surrounding it. XXXXX believed that the S3 or S4 availability of the combination would create an immediate risk of and invitation to abuse. It was also stated that a person intent on obtaining a significant dose of morphine, whether it be for analgesia or abuse would run the risk of paracetamol poisoning if they took a dose above that recommended. XXXXX also stated concerns that the morphine may be extracted from the tablet.
- XXXXX noted that XXXXX had given evidence in coronal inquests into deaths from iatrogenic use of morphine and stated that if controls were lowered greater morbidity and mortality would be expected.
- XXXXX stated that XXXXX believed the best course of action would be to leave the scheduling of morphine unchanged, then it would be a matter for the TGA, on the advice of ADEC, to determine whether such a combination be available as an S8 product.

XXXXX provided a pre-Meeting submission in which XXXXX stated that XXXXX agreed with all the points the XXXXX raised. Further, XXXXX emphasised the potential, in large hospital or assisted care settings, of inadvertent paracetamol overdose with this product through the administration of it concomitantly with other paracetamol containing products which may be recorded on a different part of the medication chart.

A pre-Meeting submission was made by XXXXX This submission did not address the criteria of S52E, rather it posed 41 separate questions to the Committee which XXXXX asked that the Committee answer as XXXXX felt that there was significant public benefit to knowing the Committee's position on them. It was noted that these questions largely reflect the issues raised in the applicant's submission.

XXXXX submitted a pre-Meeting comment in which XXXXX addressed issues relating to the proven safety and efficacy of paracetamol and morphine. The following points were made:

- The Acute Post-Operative Pain project (APOP – funded by the National Prescribing Service) guidelines endorse the use of paracetamol and morphine as a safe and effective treatment in a number of clinical situations. These guidelines did not specify a maximum dose of morphine with paracetamol, therefore, XXXXX stated, all doses of morphine, within the clinically accepted range (up to 48 mg), were safe and effective to use with paracetamol.
- Morphine was safe and effective to use in all CYP2D6 metaboliser states.
- The safety of paracetamol and morphine in combined use had been established through extensive worldwide use of the combination and there were no significant interactions between the two substances. Therefore, there was no need for any further clinical trials to establish safety for this combination.
- Dose requirements for morphine vary greatly in the population; however there was an accepted continuum for effective doses. While individual doses (eg 44 mg, 45 mg, etc) within this continuum had not been tested in large clinical trials, they were accepted as being safe and effective for some patients with some conditions.
- XXXXX therefore believed that there was no further need to investigate the safety and efficacy of the paracetamol/ morphine combination as these had been established and, further, were recognised by APOP.

XXXXX provided a pre-Meeting submission in which XXXXX stated that that XXXXX strongly believed that Schedule 8 was the most appropriate schedule for all forms of morphine. The following points were made:

- Morphine is a powerful and highly addictive substance which has a high abuse potential. Reference was made to a Victorian Drugs and Crime Inquiry (*Inquiry into the misuse/abuse of benzodiazepines and other forms of pharmaceutical drugs in Victoria; Parliament of Victoria, Drugs and Crime Prevention Committee, August 2006*) which noted that, when misused, opiate analgesics result in not only physical and medical problems, but also cause serious legal and social problems for the individual and community in general.
- XXXXX stated that even with the current Schedule 8 category and associated State and Territory requirements, doctors and pharmacists still come across drug-seeking patients requesting access to morphine for personal use or to on-sell. It was asserted that the current S8 listing keeps this behaviour to a minimum by monitoring prescribing and dispensing of this substance. It was also stated that this monitoring allows the identification and ability to offer treatment to opiate-addicted patients.
- XXXXX stated that this monitoring would not be possible if morphine were included in Schedule 3 or 4. XXXXX drew parallels with pseudoephedrine pharmacist and "doctor shopping" showing that illicit diversion can be effectively organised and executed. XXXXX further noted a study (*White J, Taverner D: Drug-seeking behaviour;* Australian Prescriber 1997*; 20: 68-70*) which stated that patients who are addicted to a substance will usually show some form of drug-seeking behaviour.

- XXXXX stated that XXXXX was also concerned about the risk of diversion if this combination was made more freely available. Again, parallels were drawn to pseudoephedrine diversion and particular mention was made of the programs which have been put in place to help minimise this (including XXXXX Pseudo-Watch). XXXXX stated that the separation of morphine from paracetamol was an easy two-step process which may be undertaken using ingredients obtained from a hardware store. XXXXX had commissioned and provided a report on this process (detailed later). XXXXX stated that a significant amount of morphine could be extracted from a relatively small number of combination tablets and, given the higher purity of this morphine compared to street heroin, a single packet could yield the equivalent of a 100 mg bag of street heroin.
- Concern was also raised that, if the proposed combination was promoted as a potent analgesic, patients may find the relatively low S3/ S4 dose not as efficacious as they expected. This may lead to patients increasing the dose which may then lead to tolerance and further dosage increases. XXXXX also noted that this may lead to paracetamol toxicity and overdose, which was potentially life-threatening and that this could be of particular concern in an opiate-addicted patient who had no other access to opiates at the time.

An expert report outlining the chemistry of separating morphine from morphine/ paracetamol products and comparing this to other morphine containing products was provided by XXXXX. The report made the following points:

- A list of currently available morphine preparations was given, including combination products, noting that in Australia all morphine containing preparations are currently S8 due to their addiction and abuse potential.
- It was noted that for the morphine and chloroform tincture and the morphine and kaolin mixture (available in the UK), the formulations were sufficiently complex enough to make extracting the morphine from them a formidable task.
- The procedure for separating the morphine from the paracetamol in the combination tablet was outlined, with the expert noting that the task was simple and could be done with an acid readily available from a hardware store. It was noted that paracetamol at the pH stated was insoluble in water while morphine was readily soluble.
- The expert stated that, depending on the skill of the ‘chemist’ a significant amount of morphine would become available from a small number of tablets. The expert stated that with a 66% recovery rate, 10 mg of morphine would be available from 5 tablets.
- The expert stated, that given the ease of separation, there was considerable risk of diversion with the proposed combination product and, thus, that morphine should remain in Schedule 8.

A late pre-Meeting submission was received from XXXXX stating that the proposed combination (assumed to be the same as the October 2006 proposal) did not meet the

requirements for a Schedule 3 medicine. The Committee chose to consider this submission and noted the following:

- XXXXX recalled the October 2006 Record of Reasons, noting that approximately 10% of the population were slow metabolisers of codeine and of this population the number of those requiring opioid analgesia for short term use would be limited. XXXXX stated that, given this and the fact that morphine was a serious drug of dependence, such patients would be better served by visiting their GP to obtain the medicine rather than potentially exposing the broader population to an unnecessary drug of dependence. XXXXX asserted that this would also allow for the management of any potential paracetamol toxicity issues.
- XXXXX stated that the potential for harm through abuse, misuse or diversion and the societal costs associated with this outweighed any potential benefit to the public from having this combination available in Schedule 3.
- XXXXX also questioned the potential size and viability of the target market for the combination, reiterating their risk/ benefit statements.
- A statement from the October 2006 NDPSC evaluation report was recalled, questioning whether there was any evidence that slow codeine metabolisers who receive other opiates have improved analgesia without any compromise in safety. XXXXX asked that, if the Committee felt that this had now been answered, they consider pack size, labelling, advertising requirements, multi-pharmacy purchases, the likelihood of abuse/ misuse/ diversion and accidental overdose with this combination.

Members discussed the applicants point about the proposed combination being allowed under Schedule III of the UN Single Convention. Members noted that for such combinations to be in Schedule III of the Single Convention, they must be "preparations of… morphine containing not more than 0.2 per cent of morphine calculated as anhydrous morphine base and compounded with one or more other ingredients in such a way that the drug cannot be recovered by readily applicable means or in a yield which would constitute a risk to public health." Members discussed this, particularly noting that since a percentage rather than a quantity was specified, it may be that the Single Convention refers to only liquid preparations. The Committee did not conclude this was the case but rather pondered if it were.

That said, Members further discussed this requirement which set out that any combinations must not contain more than 0.2 per cent of morphine calculated as anhydrous morphine base should it refer to solid dosage forms. Members observed that, under this requirement, each capsule or tablet of the combination product would need to have a total weight of 1.5 g in the case of the 3 mg morphine preparation and a total weight of 3 g in the case of the 6 mg preparation, noting that even with 500 mg of paracetamol in each tablet, there would still have to be between 1- 2.5 g of excipients included. A Member stated that current paracetamol tablets weigh around 630-650 mg and that this would be close to the upper limit of a tablet size consumers could easily

swallow. Members agreed that it would therefore be very difficult to produce 3 mg and 6 mg morphine tablets which were compliant with this requirement.

The requirement in Schedule III of the Single Convention that obliged the combination to be compounded in such a way that the drug could not be recovered by readily applicable means or in a yield which would constitute a risk to public health was discussed by Members. In particular Members recalled the submission by XXXXX which detailed how the morphine may be separated out of the proposed combination via a simple two step acid/ base chemical reaction which could be conducted with ingredients readily available from a hardware store.

Members discussed the potential for illicit diversion of OTC morphine products. Members noted the evaluators' comments that this would be a likely outcome of the substance being more readily available and noted the applicants' contention that this was unlikely as much higher quantities of morphine were already available in pharmacies. However, the Committee felt that it would be much easier to illegally obtain morphine if it were at the front of the shop in a Schedule 3 area or in the Schedule 4 dispensary than when kept in the locked Schedule 8 safe.

The Committee also considered the evaluator's comment that people wishing to abuse morphine could suggest to doctors or pharmacists (including multiple doctors/ pharmacists) that they were a person without sufficient Cytochrome P450 2D6 to metabolise codeine and therefore required morphine instead. The Committee noted that, as far as it was aware, there was currently no easy means for a GP or, even more so, a pharmacist to ascertain whether a patient was a poor metaboliser and that this could lead to easy access for people who wished to abuse the substance.

The Committee noted that XXXXX had concerns about the rescheduling of a paracetamol/ morphine combination. XXXXX felt that while a proposal to down schedule combination products containing paracetamol and morphine could be seen by some to be analogous to the current OTC and Schedule 4 availability of combination products containing paracetamol and codeine, XXXXX was concerned about the potential for increased abuse of morphine if morphine-containing products were made available OTC.

Members debated the applicant's contention that approximately 4 million (i.e., 1 in 5) patients are poor metabolisers. Members noted and discussed the comment by XXXXX that, even if this were the case, only a small number of these patients would require treatment for pain, thus the number of patients potentially affected was likely much smaller than that quoted. Members also agreed that not all of the 4 million patients quoted would be adults and therefore, for non-adult patients, morphine would not be appropriate. Members also noted that there were a large number of alternatives to codeine, including NSAIDs, tramadol and dextropropoxyphene, already available at the S3 and S4 level. Members further discussed that the applicants had provided no data on the safety, toxicity and efficacy of their proposed combination compared to those alternatives currently available on the market. This relates to S52E (1)(f), the need for access to a substance,

taking into account its toxicity compared with other substances available for a similar purpose.

The applicant's suggestion that that people wishing to abuse morphine were unlikely to choose their suggested combination when they could already doctor shop for pure morphine preparations was considered. The Committee felt that, even if this were true, as was pointed out by XXXXX, because morphine was currently in Schedule 8 there was the ability to track its provision to such people and, thus, there existed the ability to potentially help these people with their addiction. The Committee noted that this would be lost by rescheduling the substance to anything less restrictive than Schedule 8.

The Committee discussed the morphine containing OTC substances which the applicants noted were available in the UK and NZ and observed that these all appear to be mixtures (not solid dose forms) which contain 0.2% or less of morphine. The Committee considered the applicants' statement that there was no evidence of abuse of these products, noting that no evidence was provided to substantiate this claim. The submission by XXXXX which detailed previous incidences of the abuse (in the 1970s) of oral liquids containing morphine (eg Chlorodyne PBC) before they were made S8 was recalled by the Committee. The Committee also noted a statement issued (on 1 August 2007) by the Royal Pharmaceutical Society of Great Britain which discussed products which may be misused and which specifically mentioned both Gee's Linctus and Kaolin and Morphine Mixture.

The Committee noted that there was established clinical evidence supporting use of a paracetamol/ morphine combination in both chronic and post-operative pain, however it also discussed the lack of data provided by the applicants on the use of XXXXX specific fixed combination in the proposed indication (i.e., short-term acute pain that would be expected to be treated by consumers buying such a combination from a pharmacist.)

The Committee noted that there was a section in the current *Australian Analgesic Therapeutic Guidelines* which describes a number of pharmacokinetic and pharmacodynamic disadvantages with the currently available fixed dose analgesic combinations. Members also discussed the pharmacokinetic profiles of both paracetamol and morphine, noting the significant differences between the two. Members felt that these differences were considerable enough to exclude these two substances being combined in a fixed dose combination.

DISCUSSION – ADDITIONAL MATTERS RELEVANT UNDER 52E

The Committee agreed that the main provisions under S52E which applied to the consideration of this submission were (1)(f) and (1)(g) (need for access and abuse potential).

Members considered data supplied by XXXXX which showed that diversion of prescribed opiates is already documented as a significant problem in Australia, this related, of course, to S52E (1)(g), the potential for abuse. The data in the submission also

showed that the formulation of the opiate did not exclude its use as an injectable by addicts and noted that oral formulations had been extensively used for injection, occasionally with significant adverse consequences. The Members also discussed the findings in the study that, notwithstanding the significant morbidity and mortality suffered by the addicts themselves, the diversion of prescribed opiates had cost implications for the Commonwealth PBS scheme, Medicare, the police, hospitals and the community as a whole. The Committee agreed that including morphine in a schedule other than Schedule 8 would increase the amount available for diversion.

The Committee discussed the current National Drug Strategy which states its aim as "to improve health, social and economic outcomes by preventing the uptake of harmful drug use and reducing the harmful effects of licit and illicit drugs in Australian society." Members felt that rescheduling morphine to lower schedules would be at odds with this stated aim of the Federal Government and, as such, is contrary to the protection of public health, which relates to S52E (1)(i), any matters considered necessary to protect public health.

Notwithstanding the provisions set down by the Single Convention, Members discussed the NCCTG guidelines for the classification of Schedule 4 and 8 medicines. Members agreed that it would be difficult to argue that morphine did not have a high potential for addiction and, therefore, under the guidelines, could only be included in Schedule 8, as Schedule 4 medicines should have a 'low to moderate' abuse potential. This consideration related to S52E (2), guidelines of the NCCTG which are notified to the Committee.

The Committee discussed whether, if such morphine combinations were to be placed in Schedule 4, access to them would change, as a visit to a doctor would still be required to access the medication. The Committee noted that the applicant provided some anecdotal information from the Galbally Review which indicated some perceived legislative barriers to appropriate Schedule 8 access used to exist. However Members felt that, for a legitimate patient with pain who would benefit from morphine, the current Schedule 8 status would not preclude a doctor from prescribing this drug if they considered it therapeutically suitable for the patient. The Committee felt that the need for legitimate access to morphine must be balanced against its high potential for abuse. This was particularly relevant to S52E (1)(f), need for access.

Members noted that morphine is currently available in many strengths and a number of different immediate and slow release formulations at Schedule 8 and can easily be prescribed in conjunction with paracetamol if the medical practitioner so desires. Members agreed that the currently available single ingredient products allowed for considerably more flexibility in dosing than would be available from a fixed combination product of paracetamol and morphine as proposed by the applicants. This fact relates to S52E (1)(e), the dosage and formulation of a substance.

RESOLUTION 2007/51 - 31

The Committee decided that the current scheduling of morphine remained appropriate.

12.1.4 PIPER METHYSTICUM (KAVA)

PURPOSE

The Committee considered the scheduling of *Piper methysticum* with a view to potentially foreshadowing an amendment to the Schedule 4 entry.

BACKGROUND

Kava is the rhizome of *Piper methysticum*, a member of the pepper family indigenous to islands of the South Pacific. It contains pyrones including kawain, methysticin and yangonin. Kava has been used in the South Pacific to produce an intoxicating beverage used for recreational purposes and during convalescence. It is reported to have sedative, skeletal muscle relaxant, and anaesthetic properties.

At the October 2003 NDPSC Meeting, the Committee noted a safety evaluation report prepared by the XXXXX on kava containing medicines, which made recommendations on the regulation of kava as an ingredient in Listed Medicines. Due to the potential risk of liver toxicity from use of non-aqueous extracts of kava plants at high doses, the Committee considered there was a need to restrict the use of alcohol/ acetone extracts of kava, including those for bulk supply to health care practitioners for use in extemporaneous compounding. In addition, it was agreed that a schedule entry to minimise the risk, without affecting the current usage of listed complementary products, should be considered by the Committee following a review of products on the ARTG.

The February 2004 NDPSC Meeting was advised that the Complementary Medicines Evaluation Committee (CMEC) Recommendation 41.3 regarding the listing and registration of kava had been included in Schedule 4 of the *Therapeutic Goods Regulations 1990* (TG Regulations). This recommendation only allowed specified concentrations of aqueous kava extracts in Listed medicines and required that all other kava products be cancelled from the ARTG. The Committee noted that the available information suggested that whole or peeled kava rhizomes and their aqueous preparations containing 250 mg or less of kavalactones were acceptable for use in exempt medicines while medical advice was necessary for safe use of other kava preparations due to toxicity. On this basis, the Committee agreed to foreshadow the inclusion of kava in Schedule 4 of the SUSDP with exemptions consistent with those specified in the TG Regulations.

The June 2004 NDPSC Meeting, on the grounds of public health and safety, agreed to include kava in Schedule 4 of the SUSDP, as well as adopt the exemptions specified in the TG Regulations. Post-meeting comments were received and considered at the October 2004 NDPSC Meeting. The Committee confirmed the decision from the June 2004 Meeting and agreed that, given the toxicity concerns on kava and in the absence of evidence to demonstrate the safety of products containing kava other than those forms recommended by CMEC as suitable for use in Listed medicines, it would be appropriate

to allow the supply of such products to the public only under the advice of a medical professional.

At the June 2005 NDPSC the Committee deferred consideration of minor editorial changes and errata, including an amendment to the Schedule 4 entry for kava to resolve a possible ambiguity, to the October 2005 NDPSC Meeting to allow time to seek comment from the NDPSC's Drafting Advisory Panel (DAP). Following the meeting the Secretariat noted that the kava amendment was a scheduling change rather than an editorial change and therefore included kava in the pre-meeting gazette notice.

The Committee considered public submissions on this issue at the October 2005 Meeting and confirmed that all parts of the Schedule 4 exemption for oral use for kava required the mandatory warning statement. The Committee agreed that the only exception to this should be for preparations containing less than 25 mg kavalactones per dose and agreed to amend the SUSDP Schedule 4 entry for kava to clarify this ambiguity.

DISCUSSION - SUBMISSIONS

XXXXX provided a submission requesting that the Schedule 4 entry for kava be amended to remove the exemption for dried whole or peeled rhizome in preparations for oral use. This request was part of the Australian Government's efforts to reduce the abuse of the substance in some indigenous communities. The following points, relevant to the matters which the Committee must take into account under Section 52E(1) of the *Therapeutic Goods Act 1989*, were made:

- As of 26 June 2007 the Australian Government had banned the commercial importation of kava except for medical or scientific purposes. This follows Council of Australian Governments (COAG) discussions on 14 July 2006 in which COAG agreed to provide additional support (including implementing and enforcing supply controls) for indigenous communities attempting to limit access to substances of abuse.
- It was felt that the raw form of kava was an abusable substance and the current exemption for it from the requirements of scheduling opened a pathway for diversion to illicit uses.
- With regards to the risks and benefits of the use of the substance, it was stated that, when used in a traditional manner, kava had a sedative/ relaxing effect. However, when used excessively (240 – 440 g/ week or more), health problems including skin rash, abnormal liver function, lymphocytopenia, decreased body mass and malnutrition (as a result of apathy) could occur. Kava toxicity and withdrawal may also cause *grand mal* seizures and occurrences of sudden cardiac death had been reported. It was also stated that there had been reports (Clough, A & Warin, J 2004, 'Kava Use in Aboriginal People in Arnhem Land. Monitoring the Impacts', *Of Substance*, vol 2, no. 3, pp. 24-25.) of the general apathy from overuse resulting in the neglect of children's welfare and decreased participation in work.

- The potential hazards associated with the use of kava were dose-dependant and 'traditional' use had not been reported to cause any serious health effects. High or excessive use may result in both adverse health and social hazards (Food Standards Australia New Zealand 2004, *Kava A Human Health Risk Assessment*, Technical Report Series No. 30, Food Standards Australia; Clough, AR, Currie, BJ, Yunupingu, MW, & Conigraves, KM 2006, 'Action is Required to Reduce Kava Supply in Arnhem Land…Again!', *MJA*, vol 184, no 2, pp. 91-92; Clough, A, 2003 'Enough! Or too much. What is 'excessive' kava use in Arnhem Land?', *Drug and Alcohol Review*, vol 22, pp 43-51.)
- The traditional pattern of use of kava was by Pacific Islander communities as a ceremonial or celebratory drink which is consumed in a group setting.
- In the early 1980s, when kava was first introduced into indigenous communities, imports to one community were estimated to be 24 kg/month. It was stated that, due to changes in regulations and formalisation of supply networks in the 1990s, this increased to an estimated 124 kg/month in the same community. 2005 figures put total sales of kava in the Northern Territory at 26 tonnes, up from 3.4 tonnes in 2002. It was further asserted that this increase in access had increased the abuse potential of the substance, with average consumption increasing from 145 g/week in 1989 – 1990 to 370g/week in 1990 – 1991.
- It was stated that, due to its use as an alternative to alcohol, some of this use of kava by the indigenous community has not been in the traditional Pacific Islander manner. XXXXX stated that raw forms of kava being imported for medical use were currently able to be freely supplied with only labelling requirements being imposed. XXXXX further stated that this leads to a very real possibility that kava imported for such uses may be diverted for illegitimate use/ abuse and, thus, that it was not appropriate to maintain the exemption from scheduling. XXXXX felt that the removal of this exemption would provide a safeguard against diversion and abuse and, therefore, improve health impacts associated with this substance. It was stated that, in recognition of the cultural significance of kava to Pacific Islanders, the 2 kg personal import exemption, in place since 1997 under Regulation 5, Subsection 3 of the *Customs (Prohibited Import) Regulations 1956*, would be maintained.
- It was noted that this change to scheduling would also ensure that supply of any other form could only occur via registered medical practitioners [It was noted that under XXXXX proposal, there would still be an exemption from scheduling for tablets, capsules or teabags and certain topical and dermal preparations] and that any suppliers of raw material for listed/ registered products be licensed under State and Territory legislation. XXXXX stated that it was unlikely that the tablet, capsule or teabags currently listed on the ARTG would be abused and, thus, the scheduling for these should not be altered.
- As additional information, XXXXX provided a brief outline of the COAG discussion and decision on this matter.

XXXXX provided a submission outlining a different suggested amendment to the Schedule 4 entry than that proposed by XXXXX. The following points were made:

- The Schedule 4 entry for *Piper methysticum* needs to be amended to limit avenues for illicit diversion while still allowing *bona fide* medicinal forms of the substance to be available to practitioners.
- One way of ensuring this would be to amend the schedule entry to make reference to only those substances included on the Australian Register of Therapeutic Goods (ARTG). This would allow traceability of raw materials coming into Australia via a manufacturing audit trail while still allowing practitioners access to all forms of kava included on the ARTG. It was noted that this would allow practitioners, who currently use raw forms of kava, access to powdered forms if manufactured under GMP compliance and included on the ARTG.
- It was noted that an unintended consequence of XXXXX proposed wording would be to allow solvent derived kava extracts to be used in Listed products. Previously it had been determined that, on safety grounds, the only forms of kava suitable for Listed medicines were aqueous extracts and suspensions.
- XXXXX suggested alternate wording for the Schedule 4 entry.

The Committee agreed that the matter most relevant to the scheduling of kava was under S52E (1)(g) of the *Therapeutic Goods Act 1989* which relates to the potential for abuse of a substance.

Members discussed the potential wording of the Schedule 4 entry supplied by the OCM. Members agreed to refer this to DAP.

DISCUSSION – ADDITIONAL INFORMATION RELEVANT UNDER 52E

The Committee noted that the Department of Health and Ageing was working with Food Standards Australia New Zealand (FASNZ) to remove kava from the permitted foods list. This entailed the Kava Code of Management Plan proposing that kava revert back to being classified as a prohibited botanical, which would mean that it could not be cultivated in Australia. This is relevant under S52E (1)(g) and (i) the potential for abuse as well as other matters needed to protect public health.

RESOLUTION 2007/51 - 32

The Committee decided to foreshadow an amendment to the Schedule 4 entry for *Piper methysticum* (kava). The wording of the entry was referred to DAP and finalised out-of-session.

FORESHADOWED DECISION (for consideration at the February 2008 meeting)

Schedule 4 – Amendment

PIPER METHYSTICUM – Amend entry to read:

PIPER METHYSTICUM (Kava) in preparations for human use **except** when included on the Australian Register of Therapeutic Goods in preparations:

(a) for oral use when present in tablet, capsule or teabag form that is labelled with a recommended maximum daily dose of 250 mg or less of kavalactones, and;

(i) the tablet or capsule form contains 125 mg or less of kavalactones per tablet or capsule; or

(ii) the amount of dried whole or peeled rhizome in the teabag does not exceed 3 g;

and, where containing more than 25 mg of kavalactones per dose, compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(b) in topical preparations for use on the rectum, vagina or throat containing dried whole or peeled rhizome or containing aqueous dispersions or aqueous extracts of whole of peeled rhizome; or

(c) in dermal preparations.

12.2 SUSDP, PART 5

No items.

13. MATTERS REFERRED BY REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 MIGLUSTAT

PURPOSE

The Committee considered the new chemical entity miglustat for scheduling.

BACKGROUND

Miglustat is an N-alkylated imino sugar, a synthetic analogue of D-glucose. It actively reduces substrate production as an inhibitor of the enzyme glucosylceramide synthase,

which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycosphingolipids.

XXXXX

Miglustat had been granted an orphan designation and was registered in the USA, XXXXX and the European Union for the oral treatment of patients with mild to moderate Type 1 Gaucher disease for whom enzyme replacement therapy (ERT) is unsuitable, or for maintenance therapy of patients with Type 1 Gaucher disease stabilised on enzyme replacement therapy.

Gaucher disease is an inherited lysosomal storage disorder resulting from a deficiency of the enzyme, β-glucocerebrosidase. Accumulation of the substrate causes multi-system effects including severe anaemia, thrombocytopenia, hepatosplenomegaly, osteonecrosis, osteopenia and fracture. The disease is Type 1 (non-neuropathic) in 90% of cases.

The current standard treatment is imiglucerase rch (Cerezyme) to replace the deficient enzyme and requires administration up to 3 times weekly by intravenous infusion. It is approved for all degrees of disease severity.

XXXXX

DISCUSSION - SUBMISSIONS

XXXXX

The Committee noted that under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, even though it was not on the Australian Register of Therapeutic Goods (ARGT). These avenues include personal importation, the Special Access Scheme (SAS) and clinical trials.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee agreed that the toxicity and safety of miglustat (52E(1)(a)) as well as the purpose for which it is to be used (52E(1)(h)) were relevant to consideration of scheduling.

The Committee recognised that Gaucher disease is a rare disease and difficult to study. XXXXX. The Committee decided that there would be a need for professional oversight with the use of miglustat and therefore a Schedule 4 entry for miglustat would be appropriate.

RESOLUTION 2007/51 - 33

The Committee decided to include miglustat in Schedule 4 of the SUSDP.

Schedule 4 – New entry

MIGLUSTAT.

13.1.2 AGOMELATINE

PURPOSE

The Committee considered the new chemical entity agomelatine for scheduling.

BACKGROUND

Agomelatine is a melatonin agonist and a serotonin receptor antagonist.

XXXXX

DISCUSSION - SUBMISSIONS

XXXXX

Under the therapeutic goods legislation, there are a number of avenues whereby a drug can be accessed, even though it is not on the Australian Register of Therapeutic Goods. These avenues include personal importation, the Special Access Scheme and clinical trials. With this in mind, the Committee decided it was appropriate to schedule agomelatine even though no marketed product is approved for use in Australia.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee agreed that the toxicity and safety of agomelatine (52E(1)(a)), its risks and benefits (52E(1)(b)), its potential hazards (52E(1)(c)), and the purpose for which agomelatine is intended to be used (52E(1)(h)) were all relevant to consideration of scheduling.

The Committee decided that medical supervision was required with agomelatine and therefore Schedule 4 was considered appropriate.

It was decided by the Committee that not enough data was presently available for inclusion of agomelatine in Appendix D or K and that Schedule 4 should be enough at this stage.

RESOLUTION 2007/51 - 34

The Committee decided that agomelatine be included in Schedule 4 of the SUSDP.

Schedule 4 – New entry

AGOMELATINE.

13.1.3 ZONISAMIDE

PURPOSE

The Committee considered the new chemical entity zonisamide for scheduling.

BACKGROUND

Zonisamide is an anticonvulsant approved for use in Japan, USA and Europe as adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

The ADEC considered a submission from XXXXX to register XXXXX, containing the new chemical entity, zonisamide. This submission was approved subject to finalisation of the Product Information to the satisfaction of the TGA.

- *Proposed indication:*

Adjunctive therapy in the treatment of adult patients with partial seizures, with or without secondary generalisation.

- *Proposed dosage:*

XXXXX *must be added to existing therapy and the dose should be titrated on the basis of clinical effect. Initial daily dose 50 mg in two divided doses. After one week the dose may be increased to 100 mg daily and thereafter the dose may be increased at weekly intervals, in increments of up to 100 mg. Use of two weekly intervals should be considered for patients with renal or hepatic impairment and patients not receiving CYP3A4-inducing agents.*

DISCUSSION - SUBMISSIONS

XXXXX

The Committee considered the following from the approved Australian Product Information (PI) for XXXXX:

- "The most common adverse reactions in controlled adjunctive-therapy studies were somnolence, dizziness and anorexia".
- "*Cognitive adverse events:* Some patients may experience drowsiness or difficulty with concentration, particularly early in treatment or after a dose increase. Patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machinery."

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

The Committee agreed that both the toxicity and safety of zonisamide (52E(1)(a)), as well as the purpose for which it is to be used (52E(1)(h)) were relevant to scheduling considerations.

The Committee noted the two-fold increase in CNS effects (somnolence, dizziness and sedation) between the active and placebo listed in clinical trials in the PI and agreed that inclusion in Appendix K was required.

The Committee decided that medical supervision was required with zonisamide and therefore inclusion in Schedule 4 would be appropriate.

RESOLUTION 2007/51 – 35

The Committee decided to include zonisamide in Schedule 4 and Appendix K of the SUSDP.

Schedule 4 – New entry

ZONISAMIDE.

APPENDIX K – New entry

Zonisamide

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

13.2.1 [ITEM DELETED]

13.2.2 [ITEM DELETED]

13.2.3 [ITEM DELETED]

13.2.4 [ITEM DELETED]

13.2.5 HUMAN PAPILLOMAVIRUS VACCINE (HPV)

PURPOSE

The Committee noted ADEC consideration of the new medicine human papillomavirus vaccine (HPV).

DISCUSSION-SUBMISSIONS

The October 2007 NDPSC Meeting noted the Minutes of the June 2006 ADEC Meeting XXXXX:

- XXXXX

The October 2007 NDPSC Meeting also noted the Minutes of the March 2007 ADEC Meeting XXXXX:

- XXXXX

The October 2007 NDPSC Meeting noted the following during discussion:

Micromedex

- HPV is a non-infectious, subunit, viral vaccine for use in the immunization against infection caused by HPV;
- a clear association exists between HPV infection and the subsequent development of cervical cancer so the ability to immunize patients against HPV infection has the potential of preventing hundred of thousands of cervical cancer cases worldwide every year;
- HPV is indicated for the prevention of cervical cancer, genital warts, cervical intraepithelial neoplasia, cervical adenocarcinoma in situ, vulvar intraepithelial neoplasia and vaginal intraepithelial neoplasia in women 9-26 years of age; and
- there are more than 40 types of HPV which infect the genital track, with HPV types 16 and 18 responsible for about 80% of cervical cancers.

Scheduling History

In New Zealand, "vaccines" is listed as a prescription medicine.

Australia includes vaccines in Schedule 4 either by virtue of the Schedule 4 generic 'vaccines' entry or in individual entries.

Uniform Poisons Schedule – May 1971 contains the earliest record of scheduling found in available records **Schedule 4** VACCINES, sera, toxoids, and antigens for human parenteral use.
August 1986 DPSC Meeting **Appendix D – delete entry** **VACCINES**, sera, toxoids, antitoxins and antigens other than live virus vaccines except for human parenteral use
November 1988 DPSC Meeting **Schedule 4– amend entry:** VACCINES for human therapeutic use. Schedule 4 – new entries SERA for human therapeutic use. TOXOIDS for human therapeutic use. ANTIGENS for human therapeutic use.
November 1990 DPSC Meeting Decided that oral vaccines should be given individual entries, but to retain the S4 entry for vaccines

for human therapeutic use because it covered both oral and parenteral forms and could be applied to homoeopathic vaccines. **Schedule 4 – delete entry** SERA for human therapeutic use. **Schedule 4 – amend entry** ANTIGENS for human parenteral use. VACCINES for human therapeutic use **except** when separately specified in this Schedule. **Schedule 4 – new entries** ANTISERA (immunosera) for human parenteral use. IMMUNOGLOBULINS for human parenteral use. TYPHOID VACCINES. POLIOMYELITIS VACCINES.
February 2000 NDPSC Meeting Oral vaccines such as typhoid and polio were listed separately in Schedule 4 and Part 1. Had previously included such oral vaccines under the S4 generic entry for vaccines to discourage their marketing in Australia. Because the generic entry covered all vaccines, the NDPSC Secretariat did not keep records of specific registered oral products
May 2000 NDPSC Meeting That in Australia, all oral vaccines were included in S4 either by virtue of the generic vaccines or individual vaccine entries;
February 2001 NDPSC Meeting Oral vaccines to be listed in S4 and Part 1 in accordance with the general principle that whenever possible drugs and poisons should be listed separately in the Schedules.

The October 2007 NDPSC Meeting considered whether to include HPV under the current Schedule 4 generic entry "*VACCINES for human use **except** when separately specified in this Schedule*" or to foreshadow the inclusion of HPV as a separate entry in Schedule 4 for consideration at the February 2008 NDPSC Meeting.

In exercising its powers under section 52E of the *Therapeutic Goods Act 1989*, the Meeting agreed that HPV was clearly a Schedule 4 medicine. It is a new therapeutic substance with low dependence and abuse potential and its indication of use requires professional medical diagnosis, management or monitoring.

The Meeting agreed that there was no reason for not including it under the generic 'vaccines' entry. It was also agreed that it might be setting a precedent to include separate entries for every vaccine.

The Meeting agreed that vaccines for infectious diseases should generally be considered for listing under the Schedule 4 'vaccines' entry whilst vaccines not for infectious diseases should generally be considered for separate Schedule 4 listing.

As HPV is indicated for immunization against an infectious disease, the Committee agreed that HPV should be included under the Schedule 4 generic 'vaccines' entry.

RESOLUTION 2007/51 – 40

The Committee:

- noted the March and June 2007ADEC consideration of the new medicine human papillomavirus vaccine; and
- decided that human papillomavirus vaccine falls under the Schedule 4 generic entry "VACCINES for human use **except** when separately specified in this Schedule."

14. OTHER MATTERS FOR CONSIDERATION

14.1 CHILD RESISTANT PACKAGING

PURPOSE

The Committee noted progress on the Standards Australia review of the child resistant packaging standards.

BACKGROUND

The October 2006 NDPSC Meeting noted the recommendations of the South Australian (SA) Coroner and the actions since taken by the TGA in regard to child resistant packaging (CRP) for morphine and similar medicines.

The February and June 2007 NDPSC Meetings noted the current position regarding Standards Australia's review of the child-resistant packaging standard/s and agreed that it be kept informed of progress.

At the June 2007 NDPSC Meeting, XXXXX asked XXXXX to peruse the draft Order *Child-Resistant Packaging of Therapeutic Products* on the ANZTPA web site and provide comment to the October 2007 NDPSC Meeting.

DISCUSSION – SUBMISSIONS

XXXXX advised that from a consumer point of view, there were a number of issues of concern in the Therapeutic Goods Order 65 Child Resistant Packaging for Therapeutic Goods (TGO65), but that these have been addressed in the ANZTPA draft Order. In particular age of babies/children/adolescents.

XXXXX representing XXXXX on the Standards Australia Committee HE-016 Child Resistant Packaging informed the Meeting that:

- the Committee last met on 21 June 2007;
- XXXXX;
- Committee worked through amendments to the close-to-final revision of *AS 1928-2001 Child-resistant packages*;

- Committee further considered the development of potential new standards for child resistant non-reclosable packaging for pharmaceutical and non-pharmaceutical products, based on the existing European Standards;
- Committee agreed that more information was needed, with Committee members and Standards Australia to bring new information to the next meeting for discussion;
- the close-to-final draft *AS1928-200X Child-resistant packaging - Requirements and testing procedures for reclosable packages* was circulated to Committee members in July 2007 with agreement sought to the adoption of the document as an Australian Standard through the Postal Ballot process;
- the pre-publication draft revision of AS1928 became available to Committee members in early September 2007;
- the new edition of AS1928 was in the Standards Australia publishing system in late September 2007 and is expected to be published in mid October 2007;
- Standards Australia has not scheduled the next meeting of Committee HE-016.

The October 2007 NDPSC Meeting was also informed that:

- the Standards Australia CRP Committee HE-016 intends to prescribe the testing methodology, with a ministerial order intended to specify when that is to apply;
- with the postponement of ANZTPA negotiations in July 2007, it is understood that the ANZTPA draft Order will not be progressed;
- the ANZTPA draft Order has picked up all of the SUSDP requirements for CRCs;
- the current TGO65 has been in place for some years and is quite separate and distinct from the ANZTPA draft Order and the Standards Australia CRP Standard, i.e. that the TGA Order states when packaging must apply whereas the Joint Agency CRP standard states what that packaging should be;
- the TGO65 will refer to the new Standards Australia CRP Standard.

RESOLUTION 2007/51 – 41

The Committee:

- noted the progress made by the Standards Australia Committee HE-016 Child - Resistant Packaging;
- noted the impending release of *AS1928-2007 Child-resistant packaging - Requirements and testing procedures for reclosable packages*;
- decided that the SUSDP [Part 1 Interpretation “child-resistant packaging”] be updated at the next consolidation of the Standard in 2008.

ACTION

– *Monitor progress of AS1928-200X Child-resistant packaging - Requirements and testing procedures for reclosable packages*

– *Include in consolidation of SUSDP23*

14.2 APPENDIX D

PURPOSE

The Committee considered a review of the SUSDP Appendix D with regard to ADEC pregnancy category X medicines.

BACKGROUND

The June 2007 NDPSC Meeting XXXXX.

XXXXX had raised the issue of inconsistencies between the SUSDP's Appendix D and ADEC's "Prescribing Medicines in Pregnancy" booklet with respect to Category X medicines. XXXXX noted that the Australian categorisation of risk of drug use in pregnancy was to provide information to intending prescribers whilst the inclusion of medicines in Appendix D was to impose controls over possession and supply.

The June 2007 NDPSC Meeting noted a comparison of the SUSDP's Appendix D and the ADEC's *"Prescribing Medicines in Pregnancy"* booklet and that the NDPSC Secretariat would undertake a review of the inconsistencies for consideration at the October 2007 NDPSC Meeting.

Medicine	**ADEC Pregnancy Category X**	**SUSDP Appendix D listing for use in pregnancy**
Acitretin	√	√
Bexarotene	Not listed	√
Bosentan	√	√
Dienoestrol	√	Not listed
Dutasteride	√	Not listed
Etretinate	√	√
Finasteride	√	Not listed
Isotretinoin	√	√
Leflunomide	√	Not listed
Misoprostol	√	Not listed
Raloxifene	√	Not listed
Ribavirin	√	Not listed
Thalidomide	√	√
Tretinoin (oral)	√	√ (human oral use)

The October 2007 NDPSC meeting noted the following during its consideration:

BEXAROTENE

Bexarotene is:

- listed in the SUSDP Appendix D;
- not listed in ADEC's prescribing medicines in pregnancy booklet;
- a member of the antineoplastic, dermatological and retinoid classes of drugs, indicated for the treatment of primary cutaneous T-cell lymphoma and also used to treat AIDS-related Kaposi's sarcoma;
- not listed on the ARTG - no registered products in Australia.

Scheduling history

The August 2001 NDPSC Meeting:

- noted that bexarotene was a new therapeutic substance not approved or registered in Australia, but available through the TGA Special Access Scheme when used for the treatment of T-cell lymphoma;
- included bexarotene in Schedule 4, Appendix D, Appendix F Part 3 and Part 3 Miscellaneous Regulations;
- included bexarotene in Appendix D on the grounds that additional controls on possession and supply were warranted to prevent diversion and inappropriate use of the substance which was consistent with the controls placed on the retinoid group of drugs.

Contraindications/precautions

Micromedex records the following:

- bexarotene is a USFDA Pregnancy category X medicine;
- Black Box Warning: Bexarotene capsules are a member of the retinoid class of drugs that is associated with birth defects in humans. Bexarotene capsules must not be administered to a pregnant woman;
- bexarotene has caused malformations in animal studies. Because it is a retinoid, human teratogenicity would be expected. The manufacturer recommends a pregnancy test be performed within one week prior to initiating bexarotene therapy and repeated monthly while treatment continues. Women of childbearing potential who take bexarotene are strongly advised to use two forms of effective contraception, with one method being non-hormonal. Contraception should be used for one month prior to therapy, during therapy and for at least one month following discontinuation.

Male patients with partners of childbearing potential must use condoms during intercourse while taking bexarotene and for one month following.

Pharmaceutical Benefits Scheme – bexarotene is not listed under the PBS.

RESOLUTION 2007/51 – 42

The Committee:

- confirmed that the inclusion of bexarotene in SUSDP Appendix D remains appropriate; and
- noted that bexarotene is not included in the ADEC *Prescribing Medicines in Pregnancy* booklet.

DIENOESTROL (DIENESTROL)

Dienoestrol (dienestrol) is:

- not listed in the SUSDP Appendix D;
- listed as an ADEC pregnancy category X medicine;
- a synthetic nonsteroidal estrogen indicated for the treatment of postmenopausal atrophic vaginitis.

Scheduling History

The November 1988 DPSC Meeting included a number of substances, including dienoestrol, in Schedule 4 after noting that sex hormones and anabolic steroids used for humans and/ or animals were subject to abuse/ misuse by weight-lifters.

Product registration

- The ARTG records that Australian registration was cancelled by the sponsor in 2001.
- A hospital pharmacy newsletter of November 2000 reports that dienoestrol cream would no longer be available in Australia from September 2000, with conjugated oestrogens recommended as an alternative preparation.
- MedSafe records state that New Zealand registration of dienoestrol vaginal cream was discontinued (date unknown).
- USA approval was withdrawn in 2004 at the request of the sponsor, as Dienoestrol Cream was no longer marketed.
- Medbroadcast.com website reports that dienestrol vaginal cream is no longer manufactured in Canada nor is available under any brand names.

Contraindications/precautions

Micromedex records the following:

- dienestrol is chemically related to diethylstilbestrol which has been associated with an increased risk of genital cancer in women exposed to diethylstilbestrol in utero;
- the FDA maintains that estrogens should not be used during pregnancy and also warns that there is an increase in congenital defects in foetal reproductive organs associated with estrogen use during pregnancy;
- estrogens increase the risk of endometrial cancer;
- dienestrol is associated with an increased risk of breast cancer.

The RX List (The Internet Drug Index) records that the incidence rate of endometrial cancer has increased, which may be related to the rapidly expanding use of estrogens during the last decade. Estrogen users were 4.5 to 13.9 times at greater risk of endometrial cancer than nonusers, and appears to depend both on duration of treatment and on estrogen dose.

Nomenclature

Dienestrol is the INN and it is NDPSC policy to include INNs in the SUSDP.

Pharmaceutical Benefits Scheme – dienoestrol (dienestrol) is not listed under the PBS.

Discussion

Based on the FDA statement that oestrogens should not be used during pregnancy, a Member suggested that a class entry for oestrogens be included in Appendix D. However, as dienestrol appeared to be the only high risk oestrogen in ADEC pregnancy category X, the Committee agreed that Appendix D listing as a class was not warranted.

The Committee agreed that it would not be unlikely that dienestrol might be compounded for topical use for treatment of such conditions as atrophic vaginitis.

Because it is chemically related to diethylstilbestrol, it was considered that dienestrol may require additional controls on possession and supply. Compounding [of medicines] is consumer driven and inclusion in Appendix D would ensure that compounding chemists would be required to conform to States and Territories legislative restrictions as to who could prescribe Appendix D substances.

It was recommended, and the Committee agreed, that dienoestrol (dienestrol) did warrant full consideration for listing in Appendix D. The Committee also agreed that consideration should also be given to listing in Appendix F Part 3 and Part 3 Miscellaneous Regulations Dispensed Medicines.

The Committee also agreed that the INN dienestrol be included in the SUSDP.

RESOLUTION 2007/51 – 43

The Committee:

- decided to foreshadowed for consideration at the February 2008 NDPSC Meeting the inclusion of dienestrol in Appendix D, Part 3 Miscellaneous Regulations Dispensed Medicines and Appendix F Part 3; and
- decided to editorially amend the 'dienoestrol' Schedule 4 entry to reflect the INN 'dienestrol'.

Schedule 4 – Amendment

DIENOESTROL – amend entry to read:

DIENESTROL.

DUTASTERIDE

Dutasteride is:

- not listed in SUSDP Appendix D;
- an ADEC Pregnancy Category X medicine;
- an inhibitor of type 1 and 2 testosterone-5a-reductase, indicated for men only for the treatment of benign prostatic hyperplasia.

Scheduling History

The February 2003 NDPSC Meeting:

- included dutasteride in Schedule 4, after ADEC had recommended approval of a product containing dutasteride;
- noted that dutasteride was contraindicated for use in women and that the PI carried a precaution that the drug is absorbed through the skin and that women and children must avoid contact with leaking capsules;
- noted that the risk of accidental exposure to dutasteride by women and children was insignificant as the drug was not indicated for use in women.

Contraindications/Precautions:

Micromedex records that dutasteride is:

- contraindicated in women and children;

- absorbed through the skin and women should not handle capsules when they are pregnant or may potentially become pregnant due to the possibility of absorption and the subsequent potential risk to a male fetus.

Pharmaceutical Benefits Scheme – dutasteride is not listed under the PBS.

Discussion

A Member informed the Meeting that there was no record of this substance being marketed in Australia.

The Committee agreed that due to its specialist indication, it is unlikely to be prescribed for women, it is suitable to remain in Schedule 4 only and it does not warrant inclusion in Appendix D. Furthermore, dutasteride is specifically contraindicated in women.

The Committee confirmed the decision of February 2003 NDPSC Meeting in that the risk of accidental exposure to the product by women and children was insignificant as the drug was not indicated for use in women.

RESOLUTION 2007/51 – 44

The Committee decided that dutasteride did not warrant inclusion in Appendix D at this time.

FINASTERIDE

Finasteride is:

- not listed in SUSDP Appendix D;
- an ADEC Pregnancy Category X medicine;
- a 5-alpha reductase inhibitor indicated for benign prostatic hyperplasia and male pattern alopecia.

NDPSC scheduling consideration

The November 2003 DPSSC Meeting:

- included finasteride in Schedule 4, after ADEC had recommended approval of a product containing finasteride;
- noted that finasteride acts as dihydrotestosterone in vivo and as a potent androgen, with dihydrotestosterone thought to promote hypertrophy of the male prostate gland in men of advancing age.

The May 1998 NDPSC Meeting:

- confirmed the Schedule 4 listing of finastride after noting ADEC's approval of a new strength tablet.

Contraindications/Precautions

Australian CMI for Propecia (finasteride) records the following:

- women who are pregnant or may be pregnant must not take Propecia, handle crushed or broken tablets or handle tablets with wet hands;
- if the active ingredient in Propecia is absorbed after swallowing the tablet or through the skin by a woman who is pregnant with a male baby, it may cause the male baby to be born with abnormalities of the sex organs;
- whole tablets are coated to prevent contact with the active ingredient during normal handling, provided that the tablets haven't been crushed or broken;
- if a pregnant woman swallows Propecia, handles crushed or broken tablets or handles tablets with wet hands, her doctor must be consulted immediately;
- do not give Propecia to children or women.

Micromedex records the following:

- finasteride is contraindicated in pregnancy and not indicated for use in women and children;
- animal studies have demonstrated abnormalities in male offspring when finasteride was administered during the gestational period;
- crushed finasteride tablets should not be handled by women who are pregnant or may potentially be pregnant because of the possibility of absorption and the subsequent potential risk to the male fetus.

Pharmaceutical Benefits Scheme

- Finasteride is listed under the PBS.
- Prescribing restrictions (as extracted from the on-line PBS Schedule) are:

> Proscar – finasteride 5 mg tablet
> Authority required - Treatment of benign prostatic hyperplasia where surgery is inappropriate, or where other drug treatment has failed or is contraindicated.
> Cautions: Nil

Discussion

The Committee noted that there was the possibility of off-label use in women for an unapproved indication, although it would only be prescribed by specialist endocrinologists who would be aware of the pregnancy contraindication.

Due to its specialist indication, that it would only be prescribed by a specialist and that there is adequate warning that it is not for use in women, the Committee agreed that finasteride is suitable to remain in Schedule 4 only and does not warrant inclusion in Appendix D.

RESOLUTION 2007/51 – 45

The Committee decided that finasteride did not warrant inclusion in Appendix D at this time.

LEFLUNOMIDE

Leflunomide is:

- not listed in SUSDP Appendix D;
- an ADEC Pregnancy Category X medicine;
- a dihydroorotate dehydrogenase inhibitor and immune suppressant indicated for the treatment of rheumatoid or psoriatic arthritis.

NDPSC scheduling consideration

The August 1999 NDPSC Meeting included leflunomide in Schedule 4, after ADEC had recommended approval of a product containing leflunomide.

The February 2000 NDPSC Meeting:

- included leflunomide in Appendix F, Part 3 and Part 3 'Miscellaneous Regulations Dispensed Medicines' after considering additional requirements for labelling and/or availability of leflunomide with regard to teratogenicity;
- did not consider that inclusion in Appendix D was warranted as the potential group was not restrictive to women of child bearing age, but also to all men. It could be anticipated from the toxicity profile of the drug that treatment would be initiated with due care by any prescriber and the patient would be made well aware of its profile by direct consultation and the CMI;
- noted that some jurisdictions did not adopt Appendix D by reference; the requirements of Appendix D were taken in various ways by regulation; the proposal would be resource intensive to maintain within the jurisdictions; in some jurisdictions it would be difficult to deal with initiation by a specialist with later prescribing under the order of a GP.

Contraindications/Precautions

Australian CMI for Arava (leflunomide) records the following:

- You must not take Arava if you are pregnant or plan to become pregnant. Arava must not be used in pregnant women or in women who are not using reliable birth control because Arava may increase the risk of birth defects. Women of child bearing potential must use reliable contraception while taking Arava. You must not become pregnant while taking Arava and for a certain period of time after stopping Arava. If you wish to become pregnant after you stop taking Arava, you must consult your doctor first. Your doctor will discuss a wash-out procedure with you. If you suspect that you are pregnant while taking Arava, consult your doctor immediately.
- You must not take Arava if you wish to father a child: To prevent any risk to the developing baby, men taking Arava should consider stopping Arava and undergoing a wash-out procedure. Your doctor will discuss the wash-out procedure with you.

Micromedex records the following:

- Black Box Warning: pregnancy must be excluded before the start of treatment with leflunomide. Leflunomide is contraindicated in pregnant women, or women of childbearing potential who are not using reliable contraception. Pregnancy must be avoided during leflunomide treatment or prior to the completion of the drug elimination procedure after leflunomide treatment.
- Although no adequate studies exist in human pregnancy, leflunomide is contraindicated during pregnancy due to instances of teratogenicity and embyo-fetal toxicity in animals administered doses approximately equivalent to that given to humans. It is unknown if the drug crosses the placental barrier, but with a molecular weight of approximately 270 Daltons, it would be expected. It is also unknown if the active metabolite crosses the placenta, or if the fetus is capable of metabolizing the parent compound to the active metabolite. Pregnancy should be excluded prior to beginning leflunomide in women of child-bearing potential. Adequate contraception to prevent pregnancy should be encouraged in women of child-bearing age. Women becoming pregnant while taking leflunomide should discontinue the drug immediately, participate in the drug elimination procedure involving administration of cholestyramine 8 grams three times daily for 11 days, and verify the procedure achieved serum levels of the M1 metabolite below 0.02 mg/L. Male-mediated fetal toxicity due to paternal use of leflunomide has not been confirmed in humans; animal data are not available. To minimize any potential risk, men wishing to father a child should consider discontinuing leflunomide and take cholestyramine 8 grams 3 times daily for 11 days prior. Women wishing to conceive should wait for three menstrual cycles after the washout.
- Literature Reports: Teratogenicity (anophthalmia, microphthalmia, and internal hydrocephalus) occurred in rats at oral leflunomide doses of 15 mg/kg (this dose is approximately 1/10 the human exposure level based on the AUC). Leflunomide also caused decreased maternal body weight and an increase in embryolethality with a decreased body weight for surviving fetuses. Oral leflunomide administration in rabbits, during organogenesis, of 10 mg/kg, resulted in fused, dysplastic sternebrae

(the exposure level at this dose is essentially equivalent to the maximum human exposure level based on AUC).

- Patient Instructions: Warnings While Using This Medicine – This medicine may cause birth defects if it is taken by the mother while she is pregnant, or by the father when his sexual partner becomes pregnant. Use two forms of birth control to avoid pregnancy while you are using this medicine and for several weeks after your treatment ends. This is very important whether you are a man or a woman.

Pharmaceutical Benefits Scheme

- Leflunomide is included under the PBS.
- Prescribing restrictions (as extracted from the on-line PBS Schedule) include:

> Caution**:** Leflunomide is a category X drug and must not be given to pregnant women. Pregnancy should be avoided for two years after cessation of therapy, unless special wash-out procedures are carried out.
> Arava - 3 tablets leflunomide 100 mg and 30 tablets leflunomide 20 mg
> Authority required - Initial treatment of severe active rheumatoid arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician;
>
> Initial treatment of severe active psoriatic arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician
> Arava and Arabloc - leflunomide 10mg and 20mg
> Authority required - Initial treatment/treatment of severe active rheumatoid arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician;
> Initial treatment/treatment of severe active psoriatic arthritis where other disease modifying anti-rheumatic drugs (including methotrexate) are ineffective and/or inappropriate. Treatment must be initiated by a physician.

Discussion

As there was no further evidence of risk since the February 2000 NDPSC consideration, a Member recommended that leflunomide did not warrant inclusion in Appendix D. As discussed in February 2000, as it is contraindicated in both men and women intending to have children, all patients would require screening if added to Appendix D and this would be resource intensive.

A Member recommended that leflunomide be included in Appendix D due to a higher incidence of rheumatoid arthritis in women, the inconsistency compared with retinoids and no prescribing restrictions. The Committee agreed that while there is inconsistency there is a reason for it, given that retinoids are much more likely to be initiated by GPs to women of child-bearing age.

The Committee noted that where only specialists could prescribe under the PBS, Appendix D was not considered necessary.

The Committee confirmed the decision of the February 2000 NDPSC Meeting not to include leflunomide in Appendix D as the potential group was not restrictive to women of child bearing age, but also to all men; it could be anticipated from the toxicity profile of the drug that treatment would be initiated with due care by any prescriber; and the patient would be made well aware of its profile by direct consultation and the CMI.

It was noted that the product would be adequately labelled with warning statements under leflunomide's listing in SUSDP Appendix F Part 3.

RESOLUTION 2007/51 – 46

The Committee decided that leflunomide did not warrant inclusion in SUSDP Appendix D at this time.

MISOPROSTOL

Misoprostol is:

- not included in SUSDP Appendix D;
- an ADEC Pregnancy Category X;
- an endocrine-metabolic agent and prostaglandin indicated for the treatment of gastric and duodenal ulcers, to prevent development of NSAID-induced gastric ulcers and prevent post-operative bleeding in the stomach or upper intestine in hospital patients.

NDPSC scheduling consideration

The May 1986 DPSC Meeting included misoprostol in Schedule 4, after ADEC had recommended approval of a product containing misoprostol.

The August 1986 DPSC Meeting considered the issue of including specific prostaglandin entries in Schedule 4 and amending the Appendix D rider. This was due to a new prostaglandin product indicated to treat gastric or duodenal ulcers, but contraindicated for use in pregnancy and restricted for use by the Appendix D 'prostaglandins' class entry for specialist prescriptions. The matter was deferred to November 1986.

The November 1986 DPSC Meeting:

- agreed that prostaglandin preparations for routine therapy be available in Schedule 4 with specialised use products (obstetrics, gynaecology, endocrinology) confined to specialist use;

- favoured individual Appendix D entries and retention of the Schedule 4 'prostaglandins' class entry
- deleted the 'prostaglandins' class entry from the SUSDP Appendix D.

The February 1990 DPSC Meeting included misoprostol in Appendix F, Part 2 with new Warning Statement 53 *CAUTION (name of substance) should not be used by pregnant women).*

Misoprostol is also listed in Part 3 Miscellaneous Regulations, Dispensed Medicines sub-paragraph 45. This entry was first published under Part 3 paragraph 75 in SUSDP Amendment No.10/3, which contained out-of-session recommendations of December 1995 based on recommendations made at the November 1995 NDPSC Meeting. However, the Secretariat can find no record in the NDPSC's archival minutes of consideration of this entry.

Contraindications/precautions

Australian CMI for Cytotec (misoprostol) records the following:

- Do not take Cytotec if you are pregnant, or there is a possibility you may be pregnant, or if you intend to become pregnant.
- Tell your doctor if you become pregnant while you are taking Cytotec. The effects of Cytotec may be harmful to a developing baby (fetus).
- If it is possible for you to become pregnant, you should use adequate contraception while you are taking Cytotec. Examples of adequate contraception are oral contraceptives ("the pill") or intra-uterine devices (IUDs).
- Cytotec must not be used by pregnant women as it may cause miscarriage, and this could lead to potentially dangerous bleeding, hospitalisation, surgery, infertility or death.
- You should not become pregnant while taking Cytotec.

Micromedex records the following:

- Black Box Warning: Misoprostol administration to women who are pregnant can cause abortion, premature birth, or birth defects. Uterine rupture has been reported when misoprostol was administered in pregnant women to induce labor or to induce abortion beyond the eight week of pregnancy. Misoprostol should not be taken by pregnant women to reduce the risk of ulcers induced by nonsteroidal anti-inflammatory drugs (NSAIDs).
- Patients must be advised of the abortifacient property and warned not to give the drug to others.
- Misoprostol should not be used for reducing the risk of NSAID-induced ulcers in women of childbearing potential unless the patient is at high risk of complications

from gastric ulcers associated with use of the NSAID, or is at high risk of developing gastric ulceration. In such patients, misoprostol may be prescribed if the patient:

- has had a negative serum pregnancy test within 2 weeks prior to beginning therapy
- is capable of complying with effective contraceptive measures
- has received both oral and written warnings of the hazards of misoprostol, the risk of possible contraception failure, and the danger to other women of childbearing potential should the drug be taken by mistake
- will begin misoprostol on the second or third day of the next menstrual period

Pharmaceutical Benefits Scheme

- Misoprostol is listed under the PBS.
- Prescribing restrictions (as extracted from the on-line PBS Schedule) include:

Cytotec - misoprostol 200 mcg
Caution: Misoprostol is a prostaglandin analogue. It should not be used in pregnant women
Authority required:
Reduction in the incidence of gastrointestinal complications in patients who have a history of peptic ulcer disease and where NSAID therapy is essential;
Duodenal ulcer (including pyloric and stomal ulcers), proven by current or prior x-ray, endoscopy or surgery. The date and the method by which the ulcer was proven must be documented in the patient's medical records when treatment is initiated;
Gastric ulcer, proven by x-ray, endoscopy or surgery within the previous 2 years. The date and the method by which the ulcer was proven must be documented in the patient's medical records when treatment is initiated

Arthrotec - diclofenac sodium with misoprostol tablet 50 mg--200 micrograms
Authority required: Patients requiring an NSAID in whom a risk of upper gastrointestinal complications is high or with a history of peptic ulcer disease.

Discussion

The Committee noted that this misoprostol has been available since mid to late 1980s with no data on adverse events to date. That is to say that, regardless of the fact that there are a wide range of potential adverse outcomes for pregnant women, 20 years of clinical experience has not resulted in any ADRs being brought to the Committees' attention.

There was concern that it could be prescribed by a general practitioner. However, it was noted that regardless of the substance's original packaging, it requires a label warning statement under its SUSDP Appendix F Part 3 listing.

RESOLUTION 2007/51 – 47

The Committee decided that misoprostol did not warrant inclusion in SUSDP Appendix D at this time.

RALOXIFENE

Raloxifene is:

- not listed in SUSDP Appendix D
- an ADEC Pregnancy Category X medicine
- a selective estrogen receptor modulator. It is indicated for the treatment of breast cancer and postmenopausal osteoporosis.

NDPSC scheduling consideration

The August 1998 NDPSC Meeting included raloxifene in Schedule 4, after ADEC had recommended approval of a product containing raloxifene.

Contraindications/precautions

The Australian CMI for Evista (raloxifene hydrochloride) records that Evista is only for use by women after menopause and must not be taken by women who could still have a baby.

Micromedex records that raloxifene is contraindicated in women who are or may become pregnant. No human studies of pregnancy outcomes after exposure to raloxifene have been published and there are no reports of outcomes after inadvertent exposure during pregnancy. Given the medication's indications for postmenopausal women, such human studies are not expected.

Pharmaceutical Benefits Scheme

- Raloxifene is listed under the PBS.
- Prescribing restrictions (as extracted from the on-line PBS Schedule) include:

> Evista – raloxifene 60 mg tablets
> Authority required: Treatment as the sole PBS-subsidised anti-resorptive agent for established post-menopausal osteoporosis in patients with fracture due to minimal trauma. The fracture must have been demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be documented in the patient's medical records when treatment is initiated. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.
> Note**:** Anti-resorptive agents in established osteoporosis include alendronate sodium, risedronate sodium, disodium etidronate, raloxifene hydrochloride and strontium ranelate

Discussion

The Committee noted that raloxifene was rarely used for anything other than post-menopausal osteoporosis and that this is its only approved indication in Australia.

The Committee also noted that raloxifene was currently being trialled for the treatment of breast cancer and there was the possibility of off-label use in women. However, it was also noted that this treatment would be on the order of a specialist physician who would be aware of the pregnancy contraindication.

Due to its specialist indication for postmenopausal osteoporosis and that there is adequate CMI warnings of its pregnancy contraindication , the Committee agreed that raloxifene did not warrant inclusion in Appendix D.

RESOLUTION 2007/51 – 48

The Committee decided that raloxifene did not warrant inclusion in SUSDP Appendix D at this time.

RIBAVIRIN

Ribavirin is:

- not listed in SUSDP Appendix D
- an ADEC Pregnancy Category X medicine
- a synthetic nucleoside analog, consisting of D-ribose attached to a 1,2,4 triazole carboxamide. It is an anti-viral drug with a wide spectrum of antiviral activity in vitro against both RNA and DNA viruses.
- never used alone but always in combination with interferon alfa or peginterferon alfa, and of which is the standard of care for the treatment of chronic hepatitis C.

NDPSC scheduling consideration

The July 1987 DPSSC Meeting included ribavirin in Schedule 4, after ADEC had recommended approval of a product containing ribavirin.

Contraindications/precautions

Pregnancy

The Australian CMI for Pegatron XXXXX, a combination therapy containing Peg-intron (peginterferon alfa-2b) and Rebetol (ribavirin), records the following:

- Do not use Pegatron combination therapy if you are or your partner is pregnant or planning to become pregnant – this applies to both female patients and to partners of male patients using Pegatron combination therapy. It is very important that you or your partner avoid becoming pregnant during treatment and for 6 months after treatment. This is because Rebetol capsules can affect the sperm as well as the unborn child.

- If you are or your partner is a woman of childbearing age, you or your partner must have a negative pregnancy test before treatment with Pegatron combination therapy starts. Your or your partner must also have a negative pregnancy test each month during treatment and for the 6 months after treatment is stopped.
- Two effective forms of contraception must be used, one by each partner, male and female, during treatment with Pegatron combination therapy for the 6 months after treatment is completed. Rebetol can cause harm to the unborn child if a pregnant woman takes Rebetol herself during pregnancy or has unprotected sex (sex without using a condom) with a man who is taking Rebetol. Rebetol can damage the sperm and the embryo (unborn child).

The CMI for Pegasys RBV XXXXX, a combination therapy containing Pegasys (peginterferon alfa-2a) and Copegus (ribavirin) records the following:

- Do not take Copegus if you are pregnant or you are a male and your female partner is pregnant.
- Copegus may cause birth defects and/or death of an unborn baby.
- Extreme care must be taken to avoid pregnancy during treatment and for 6 months after completion of treatment. Effective contraception must be used during this time.

Micromedex records the following:

- Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.
- Using this medicine while you are pregnant can harm your unborn baby. The medicine may also cause birth defects if the father is using it when his sexual partner becomes pregnant. If a pregnancy occurs while you are using this medicine, tell your doctor right away. To make sure you are not pregnant, your doctor may ask you to have a pregnancy test before you start using this medicine. You should test for pregnancy every month while you are using this medicine, and for 6 months after your treatment ends. While you are using this medicine, use two forms of birth control to avoid getting pregnant. Keep using two forms for at least 6 months after your treatment ends. This is very important for both men and women. Men using ribavirin might need to use a condom with a spermicide such as nonoxynol-9 as one form of birth control.
- Black Box Warning – Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has multiple-dose half-life of 12 days, and so it may persist in non-plasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and in female partners of male patients who are

taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the 6-month post treatment follow-up period.

- Do not have pregnant family members or friends nearby when you are having your treatments. They may breathe in enough of the medicine to put their unborn baby in danger [by breathing with the use of a small particle aerosol generator for treatment, usually in a hospital, of severe lung infections caused by respiratory synctial virus]
- Women who are or who may become pregnant should avoid environmental exposure (inhalation of aerosolized drug emanating from infant treatment). Nurses, respiratory therapists and other care-givers should preferably not administer ribavirin if they are pregnant. If pregnant health care workers cannot avoid close patient contact ribavirin should be administered in a negative pressure room with adequate ventilation (at least 6 air exchanges per hour); administer ribavirin in aerosol scavenging devices; turn off the SPAG-2 for 5 to 10 minutes before prolonged patient contact; and wear an appropriate respiratory filter mask. Surgical masks will not adequately filter ribavirin particles. Administering ribavirin at a high dose (60 milligrams/milliliter) over a 2-hour period 3 times per day for up to 5 days may reduce environmental exposure.

Mental health

The CMI for Pegasys RBV records that [some of] the most serious possible side effects include mental health problems … mood or behavioural problems … irritability … depression … anxiety … aggressive behaviour … suicidal thought.

The CMI for Pegatron records that Pegatron combination therapy should not be used if you have or have had severe nervous or mental problems such as severe depression or thoughts of suicide.

Micromedex records the following:

- An increased risk of suicidal ideation or attempt, particularly in adolescents and paediatric patients during therapy and during off-therapy follow-up.
- For some children and teenagers, this medicine can increase thoughts of suicide. All of the warnings in this leaflet are true for a child or teenager who is using this medicine. Tell your doctor right away if you start to feel more depressed. Also tell your doctor right away if you have thoughts about hurting yourself. Report any unusual thoughts or behaviours that trouble you, especially if they are new or get worse quickly. Make sure your caregiver knows if you have trouble sleeping, get upset easily, have a big increase in energy, or start to act reckless. Also tell your doctor if you have sudden or strong feelings, such as feeling nervous, angry, restless, violent, or scared. Let your doctor know if you or anyone in your family has bipolar disorder (manic-depressive) or has tried to commit suicide.

Pharmaceutical Benefit Scheme (PBS) Schedule

- Ribavirin is listed under the PBS.

- Prescribing restrictions (as extracted from the on-line PBS Schedule) are

> Pegasys – ribavirin 200 mg tablets and peginterferon alfa-2a 135-180 mcg
> Pegatron – ribavirin 200 mg tablets and peginterferon alfa-2b 50-150 mcg
>
> Caution: Treatment with peginterferon alfa has been associated with depression and suicide in some patients. Patients with a history of suicidal ideation or depressive illness should be warned of the risks. Psychiatric status during therapy should be monitored.
>
> Caution: Ribavirin is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 6 months period after cessation of treatment.
>
> Private Hospital Authority Required: Treatment, managed by an accredited treatment centre, of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no prior interferon alfa or peginterferon alfa treatment for hepatitis C and who satisfy all of the following criteria:
> (1) Documented chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive);
> (2) Female patients of child-bearing age are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner). Male patients and their partners are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant.
> Note: Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C:
> (a) a nurse educator/counsellor for patients; and
> (b) 24 hour access by patients to medical advice; and
> (c) an established liver clinic; and
> (d) facilities for safe liver biopsy.

Discussion

The Committee noted that ribavirin was not likely to be prescribed by a general practitioner, but only by health professionals in specialist care who would be aware of the contraindications. It was also noted that there were mechanisms under the PBS controlling use of this substance (Section 100). Therefore, it was agreed that ribavirin did not warrant listing in SUSDP Appendix D at this time as there were other mechanisms in place to limit who prescribes it.

There was concern that hepatitis C patients may share the medications so it was agreed that consideration should be given to assigning adequate warning statements through the inclusion of ribavirin in Appendix F Part 3, and possibly Part 3 Miscellaneous Regulations Dispensed Medicines.

RESOLUTION 2007/51 - 49

That the Committee:

- decided that ribavirin does not warrant inclusion in Appendix D at this time; but

- decided to foreshadow ribavirin for inclusion in Part 3 Miscellaneous Regulations Dispensed Medicines and Appendix F Part 3, for consideration at the February 2008 NDPSC Meeting.

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

Nil items.

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 MCC NEW MEDICINES

16.1.1 DABIGATRAN

PURPOSE

The Committee considered the scheduling of the new chemical entity dabigatran.

BACKGROUND

Dabigatran etexilate is a low-molecular-weight direct thrombin inhibitor delivered by the oral route. Following oral administration, dabigatran etexilate is rapidly converted to its active form, dabigatran.

The 37th MCC meeting, held in May 2007 agreed to classify dabigatran etexilate as a Prescription Medicine. The following information was considered by MCC:

- Dabigatran etexilate is indicated for the prevention of venous thromboembolic events in patients who have undergone major orthopaedic surgery.

DISCUSSION - SUBMISSIONS

The 37th MCC meeting considered that, given its indications and patterns of use, dabigatran should be classified as a prescription medicine.

The NDPSC discussed the indications of use for the substance, noting that it was to be used in patients who would be in a hospital setting. This is relevant under S52E (1)(h). The NDPSC also noted the side effect profile of the substance. This is relevant under S52E (1)(b).

DISCUSSION – ADDITIONAL INFORMATION RELEVANT UNDER 52E

The Committee noted that New Zealand had scheduled the salt dabigatran etexilate and not the parent compound. The Committee discussed whether to schedule the salt, which is a pro-drug, or whether to schedule the active substance dabigatran. The Committee

agreed that it should schedule the active substance dabigatran rather than the salt as other salts may come to market in the future. This is relevant under S52E (1)(e) dosage and formulation.

Members also noted that this was a new substance and there was no experience with it its use in Australia. This was noted as relevant under S52E (1)(d) extent and patterns of use.

RESOLUTION 2007/51 - 50

The Committee decided to include dabigatran in Schedule 4 of the SUSDP.

Schedule 4 – New Entry

DABIGATRAN.

16.1.2 METHOXAMINE

PURPOSE

The Committee considered the scheduling of methoxamine.

BACKGROUND

Methoxamine is a sympathomimetic with mainly direct effects on adrenergic receptors. It has alpha-adrenergic activity entirely; beta-adrenergic activity is not demonstrable and beta-adrenoceptor blockade may occur at high doses. Methoxamine hydrochloride has been used parenterally for its pressor action in the management of hypotensive states, particularly in anaesthesia, and also in the management of paroxysmal supraventricular tachycardia. It has also been used topically as a vasoconstrictor in the management of nasal congestion.

At the June 1970 PSSC Meeting a new Schedule 3 entry was created for “Methoxamine except preparations containing 0.5% or less of methoxamine and except in preparations for external use containing 1% or less of methoaxamine.”

The February 1987 DPSSC Meeting foreshadowed that the Schedule 2 entry for methoxamine be amended to remove reference to the exemption for 0.5% or less of methoxamine for internal use. This recommendation was confirmed at the November 1987 Meeting.

At the August 1999 NDPSC Meeting, the Committee noted that methoxamine was generally used via injection or spinal anaesthesia and that, given this, the TTHWP recommended there should be a Schedule 4 entry for the substance. The Committee also noted that methoxamine is used for the management of nasal congestion and that this use

was captured by Schedule 2. The Committee recommended to New Zealand that they harmonise on the scheduling of this substance. The Committee, at the November 1999 Meeting, agreed to amend the Schedule 2 entry for methoxamine and create a Schedule 4 entry for preparations for injection.

As part of the TTHWP considerations, the June 2006 NDPSC Meeting noted that the Prescription Medicines entry for methoxamine in New Zealand captured all uses except for external use. The NDPSC agreed to recommend to New Zealand that they harmonise with Australia on the scheduling of this substance.

DISCUSSION - SUBMISSIONS

At their May 2007 Meeting, the MCC considered the NDPSC recommendation that they harmonise on the scheduling of methoxamine. The MCC raised the following points:

- The Schedule 2 and General Sale entries for this substance are already harmonised with Australia and there are currently no products registered in New Zealand which contain methoxamine.
- The MCC noted that the NZ Schedule 4 entry already captured injectable products, but also captured internal use products, which the Australian entry did not and thus, in Australia any internal use products would be unscheduled. The Committee, however, noted that currently in Australia all internal use products apart from preparations for injection are captured by the Schedule 2 entry.
- The MCC noted that, although the substance appeared to have no use pattern for oral administration, the NZ entry provided more comprehensive coverage and recommended that the NDPSC harmonise on this entry. The MCC also noted that this harmonisation would be in line with the policy for medicines to be prescription medicines if there were no products available with the substance in either country.

The Committee noted that there had been no submissions by any sponsors of methoxamine products.

XXXXX provided a pre-Meeting comment in which XXXXX stated that XXXXX had no objection to the MCC's recommendation.

DISCUSSION – ADDITIONAL MATTERS RELEVANT UNDER 52E

The Committee agreed that harmonising the scheduling of methoxamine with New Zealand would be in line with the principals of trans-Tasman Harmonisation as set out in the NCCTG Principles of Harmonisation. These NCCTG guidelines were ones which the Committee must take into account as set down in S52E (2) of the *Therapeutic Goods Act 1989*.

RESOLUTION 2007/51 - 51

The Committee decided to include a parent entry for methoxamine in Schedule 4 and to amend the Schedule 2 entry accordingly. The Committee also noted that this would harmonise the scheduling of methoxamine with New Zealand.

Schedule 2 – Amendment

METHOXAMINE– Amend entry to read:

METHOXAMINE in preparations for external use **except** in preparations containing 1 per cent or less of methoxamine.

Schedule 4 – Amendment

METHOXAMINE– Amend entry to read:

METHOXAMINE **except:**

(a) when included in Schedule 2; or

(b) in preparations for external use containing 1 per cent or less of methoxamine.

16.1.3 DEXTROMETHORPHAN

PURPOSE

The Committee considered the MCC's request regarding the scheduling of dextromethorphan.

BACKGROUND

Dextromethorphan hydrobromide is a cough suppressant used for the relief of non-productive cough; it has a central action on the cough centre in the medulla. It is also an antagonist of N-methyl-D-aspartate (NMDA) receptors. Although structurally related to morphine, dextromethorphan has no classical analgesic properties and little sedative activity and is not included in the *United Nations Single Convention on Narcotic Substances*.

The July 2000 Trans Tasman Harmonisation Working Party (TTHWP) Meeting recommended that New Zealand (NZ) and Australia adopt TTHWP Recommendation 13/6, following the rescheduling of single-active preparations of dextromethorphan from S4 to S2 in February 1998. This amendment allowed in S2, both compounded and single-active preparations containing 30 mg or less of dextromethorphan for divided preparations and 0.3% or less of dextromethorphan for undivided preparations, when labelled with a recommended dose not exceeding 30 mg of dextromethorphan.

Recommendation 13/6 was based on the view that imposing a pack size restriction of 600 mg in S2 was necessary to minimise the abuse and misuse potential associated with dextromethorphan products, particularly with the OTC availability of single-active preparations.

The February 2001 NDPSC Meeting endorsed TTHWP Recommendation 13/6 and recommended that MCC consider adopting this recommendation to harmonise with Australia. However, the NDPSC omitted to take further action to adopt TTHWP Recommendation 13/6 into the SUSDP and the Schedule 2 entry for dextromethorphan remained unchanged.

The May 2002 MCC Meeting considered TTHWP Recommendation 13/6 but did not agree to adopt this recommendation on the basis that abuse of dextromethorphan was not an issue in NZ, even for General Sale preparations. The October 2002 NDPSC Meeting noted the May 2002 MCC Minutes and agreed to reconsider TTHWP Recommendation 13/6 at the February 2003 meeting.

The February 2003 NDPSC Meeting reconsidered the TTHWP Recommendation 13/6, and agreed to adopt the TTHWP recommendation, and not harmonise with New Zealand, on the basis of concerns regarding the appropriateness of making more easily available products with a long history of being abused or diverted for illicit purposes. At the June 2003 Meeting, the Committee agreed to delete the recommended dose limit for divided preparations and include a recommended daily dose limit of 120 mg of dextromethorphan for all preparations in Schedule 2. The basis of this decision was to provide a consistent approach for all preparations covered by the Schedule 2 entry and to minimise the potential for inappropriate use, abuse or accidental overdosage.

As part of the TTHWP considerations, the June 2006 NDPSC Meeting noted that the Schedule 2 and Pharmacy Only entries for dextromethorphan were unharmonised as the New Zealand entry specifically exempts liquids containing 0.25% or less or solid dose forms containing 15mg or less (i.e., these items are general sale in New Zealand). The NDPSC agreed to recommend to New Zealand that they harmonise with Australia on the scheduling of this substance.

DISCUSSION - SUBMISSIONS

At their May 2007 Meeting, the MCC considered the NDPSC recommendation that they harmonise of the scheduling of dextromethorphan. The MCC made the following considerations:

- It recalled that in May 2000 it declined to harmonise with Australia on the scheduling of this substance as it could see no safety grounds for reclassifying the General Sale products. The MCC noted that it did not recommend to the NDPSC that they harmonise on this substance at this time.
- There are approximately 20 dextromethorphan containing general sale products included on SMARTI.

- The MCC had received no further information which would cause it to review its previous decision not to harmonise and recommended to the NDPSC that they consider harmonising on the less restrictive scheduling for this substance.

XXXXX provided a pre-meeting comment in which XXXXX recalled the principles of trans-Tasman harmonisation, especially the principle of harmonising to the least restrictive schedule. Given this, XXXXX stated that Australia should adopt the less restrictive New Zealand classification for this substance.

XXXXX provided a pre-Meeting comment in which XXXXX stated that XXXXX disagreed with the MCC's recommendation. XXXXX stated that Australia and New Zealand had been fortunate not to experience the same dextromethorphan abuse problems as the USA and referred the Committee to the FDA Talk Paper, #T05-23, of 20 May 2005. XXXXX also noted that dextromethorphan interacted with a number of other medicines, including antidepressants and stated that XXXXX felt labelling alone was not a sufficient control.

XXXXX provided a pre-Meeting comment in which XXXXX stated that XXXXX agreed with the MCC's recommendation under the policy of trans-Tasan harmonisation to the least restrictive schedule.

XXXXX provided a submission which stated that the NDPSC should agree to harmonise with New Zealand on this substance. The following points were made:

- The current Australian and New Zealand schedule entries were referred to, as was the TTHWP and NDPSC recommendation history for the substance. Particular mention was made of the Committee's February 2003 decision to include an S2 pack size limit (based on toxicity data, not evidence of abuse) and the fact that harmonisation was not part of this consideration. It was noted that MCC included this pack size limit in their General Sale and Pharmacy Only classifications.
- XXXXX stated that XXXXX agreed with the MCC that there was lack of evidence of abuse of the substance and stated that, since the Committee last considered harmonisation, further measures had been introduced to limit the risk of accidental overdose or misuse of dextromethorphan. XXXXX did not state what these measures were.
- XXXXX also referred to the *Principles of Harmonisation of Scheduling of Drugs and Poisons*, particularly the policy of harmonising to the least restrictive schedule.

A PubMed search of the literature relating to the abuse of dextromethorphan turned up a number of articles relating to this subject. Most of the articles related to the abuse of dextromethorphan by adolescents and noted that this was becoming a national (US) health concern (including "Pharming": the abuse of prescription and over-the-counter drugs in teens, Levine DA. *Curr Opin Pediatr. 2007 Jun;19(3):270-4;* Abuse of over-the-counter dextromethorphan by teenagers, Murray S et al. *South Med J. 1993 Oct;86(10):1151-3;* Abuse of Dextromethorphan, Cranston J. *Arch Fam Med Vol 8,*

MAR/ APR 1999.) Two separate papers outlining case reports of dextromethorphan abuse and addiction, one in the United States and one in Thailand (Chronic Addiction to Dextromethorphan Cough Syrup: A Case Report, Desai S et al. *JABFM May–June 2006 Vol. 19 No. 3;* Dextromethorphan abuse in Thai adolescents: A report of two cases and review of literature, Manaboriboon B et al. *J Med Assoc Thai. 2005 Nov;88 Suppl 8:S242-5*), were found. Both of these case studies detail the ADRs associated with dextromethorphan abuse and noted that the acute toxicity generally abates within 24 hours. A study into dextromethorphan safety issues by Bem et al (Dextromethorphan. An overview of safety issues, Bem JL, Peck R. *Drug Saf. 1992 May-Jun;7(3):190-9)* found that abuse appeared to be the most significant hazard identified by analysis of spontaneous adverse event reporting. Bem also concluded that the adverse drug reactions for dextromethorphan, when used normally, were infrequent and usually not severe. A further retrospective study into the trend of dextromethorphan abuse in Californian adolescents over a 6 year period (Dextromethorphan Abuse in Adolescence: An Increasing Trend: 1999-2004, Jodi K. Bryner et al. *Arch Pediatr Adolesc Med/Vol 160, Dec 2006*) found that between 1999 and 2004 there had been a 10-fold increase in abuse cases reported to the California Poisons Control System and that of these, 74.5% were in adolescents aged 9 to 17 years (which indicated a 15-fold increase in cases for this age group over the study period).

Members noted that the other Schedule 2 entries for opiate substances (codeine, dihydrocodeine, ethylmorphine and pholcodine) all included a daily dose limit and differentiated between divided and undivided preparations (except for dihydrocodeine, which is only allowed to be compounded with aspirin in divided preparations).

Members agreed that the main provisions of S52E relevant to this consideration were (1)(a) toxicity and safety, (1)(b) risks and benefits, (1)(f) need for access, (1)(g) potential for abuse and (1)(h) purpose of use.

Members discussed the data obtained from the PubMed search, including the individual case report and the data which showed that there had been a 10-fold increase in reports of abuse of dextromethorphan in the period 1999 – 2004. A Member questioned whether such data was relevant to Australia, given that is was from a study conducted in the United States and case reports from other countries. Members felt that this data showed that dextromethorphan was being abused in its own right, if not in Australia currently, then certainly in overseas markets and, thus, it does have a potential for abuse in this country. (S52E (1)(g) potential for abuse)

The Committee noted that a member of XXXXX was concerned that allowing open sale of some products containing dextromethorphan would be likely to lead to abuse, as abuse of dextromethorphan is currently rife in the US, and is increasing in Australia.

Members discussed XXXXX comments about general sale availability of a drug that can cause serotonin syndrome when taken in combination with other drugs that increase serotonin levels. A Member noted that other general sales substances also have drug/ drug interactions. Members discussed this and agreed that this type of potential

interaction with dextromethorphan was of concern. (S52E (1)(c) potential hazards associated with use).

DISCUSSION – ADDITIONAL MATTERS RELEVANT UNDER 52E

A Member stated that there was information available on the internet about how to extract dextromethorphan from mixtures. This was found to be relevant to S52E (1)(g) potential for abuse.

XXXXX Member noted that there had been anecdotal reports of abuse of dextromethorphan in their jurisdiction. Another Member stated that there had been reports in XXXXX of attempts by young people to buy large volumes of dextromethorphan liquids from pharmacies and that the XXXXX police had reported that dextromethorphan tablets were appearing on the party scene, possibly as an ecstasy substitute. S52E (1)(g) potential for abuse was noted once again. Members felt that substitution of dextromethorphan for ecstasy or its inclusion as a potential adulterant in ecstasy tablets was of concern.

Members discussed the safety of dextromethorphan, particularly taking into account that, in high doses, it has an active metabolite dextrorphan which antagonises the N-methyl-D-aspartate (NMDA) receptor. Members noted that, due to its similar pharmacology to phencyclidine and ketamine, dextrorphan, and to a lesser extent dextromethorphan, produces dissociative hallucinations at high doses (>240 mg, one source was noted as stating 600 mg.) S52E (1)(a) toxicity and safety was noted. Members also considered the toxicity of the substance, noting that high dose or overdose with dextromethorphan could result in significant toxicity including somnolence, hyperexcitability, ataxia, nystagmus, tachycardia, hypertension, convulsions and loss of consciousness.

Members agreed that when used in recommended doses and with access to advice from a healthcare professional, dextromethorphan is a relatively safe and effective cough suppressant. However, Members considered whether cough suppressants should be available as general sale items given that productive coughs should not be suppressed. Members felt that such substances should only be provided when there is access to medical advice to help determine whether cough suppression is appropriate. S52E (1)(f) need for access was noted.

Members agreed that the decision not to harmonise the scheduling of this substance was in line with harmonisation policy as the policy states that when the decision not to harmonise is taken due consideration must have been given to public health issues.

RESOLUTION 2007/51 - 52

The Committee decided that the current scheduling of dextromethorphan remained appropriate and agreed that the scheduling of this substance would remain unharmonised with New Zealand.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

17.1 [ITEM DELETED]

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

No items.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 EDITORIALS AND ERRATA – FORMIC ACID AND ETRETINATE

PURPOSE

The Committee considered editorial amendments to formic acid and etretinate.

DISCUSSION - SUBMISSIONS

During publication of SUSDP 21, the numbers 1, 4 and 8 in the Appendix F formic acid entry were inadvertently relocated from the "Safety Directions" column into the "Warning Statements" column. The error was republished in SUSDP 22.

- The Appendix F entry for formic acid in SUSDP 20 included the numbers 1, 4 and 8 under the "Safety Directions" column. No Committee decision had subsequently been made to move the numbers.
- As it stands, the entry for formic acid in Appendix F has 3 warning statements: 1. Highly corrosive; **4. Strongly alkaline** [clearly incorrect]; and 8. WARNING – May be fatal to children. If these number indicators were to be returned to the Safety Directions column, the safety directions would be: 1. Avoid contact with eyes; 4. Avoid contact with skin; and 8. Avoid breathing dust (or) vapour (or) spray mist.

During publication of SUSDP 22, the numbers 7, 62 and 76 in the Appendix F etretinate entry were inadvertently relocated from the "Warning Statements" column into the "Safety Directions" column.

- Warning Statements 7, 62 and 76 were first allocated to etretinate after a decision made at the November 1996 NDPSC meeting (published in SUSDP 21). No Committee decision has subsequently been made to move the numbers.
- Also, the numbers 62 and 76 do not exist as Safety Directions (Appendix F, Part 2).

- As warning statements, the numbers indicate the following: 7. WARNING – Causes Birth Defects; 62. Do not use if pregnant; 76. Do not become pregnant during use or within *x month(s)* of stopping treatment.

RESOLUTION 2007/51 - 57

The Committee decided to amend the Appendix F, Part 3, entry for formic acid by moving the existing numbers 1, 4 and 8 from the "Warning Statements" column to the "Safety Directions" column.

Appendix F, part 3 – Amendment

Formic acid – Amend entry to read:

POISON	WARNING STATEMENTS	SAFETY DIRECTIONS
Formic acid		1,4,8

The Committee decided to amend the Appendix F, part 3, entry for etretinate by moving the existing numbers 7, 62 and 76 from the "Safety Directions" column to the "Warning Statements" column.

APPENDIX F, Part 3 – Amendment

Etretinate – Amend entry to read:

POISON	WARNING STATEMENTS	SAFETY DIRECTIONS
Etretinate	7,62,76	

21.1.2 HYDROCORTISONE

PURPOSE

The Committee considered editorial amendments to hydrocortisone.

BACKGROUND

The February 2007 NDPSC meeting agreed to amend the scheduling of hydrocortisone in both Schedule 2 and Schedule 4. These changes were the result of 2 separate considerations at the one meeting:

- Following consideration of a human therapeutic submission, a statement including hydrocortisone in combination with an anaesthetic for rectal use was added to the Schedule 2 entry (Decision 2007/49 – 21).
- Following consideration of an agvet submission, hydrocortisone for veterinary use in dogs was included in the Schedule 4 entry (Decision 2007/49 – 13).

The June 2007 NDPSC Meeting subsequently varied the February decision to specify human use in both the Schedule 2 and Schedule 3 entries for hydrocortisone. The Schedule 4 entry was also amended to capture all veterinary use, not just use on dogs.

DISCUSSION – SUBMISSIONS

The Committee noted that the entry for hydrocortisone in Schedule 2 contained the human use amendment from June 2007 but not the rectal use amendment from February 2007. The hydrocortisone Schedule 2 amendment from February 2007 was inadvertently omitted when the entry was considered in June 2007. Members agreed the entry did not reflect the decision made in February 2007 that hydrocortisone ≤0.5% plus local anaesthetic for rectal use should be in Schedule 2.

The Committee agreed to rectify this error and a Member proposed a simultaneous rewording of the entry for hydrocortisone to improve its readability and consistency with other schedule entries. It was considered logical that this rewording also apply to the Schedule 3 entry for consistency.

RESOLUTION 2007/51 - 58

The Committee decided to include the statement referring to human rectal use of hydrocortisone in the Schedule 2 entry for hydrocortisone as per the February 2007 NDPSC decision (2007/49 – 21).

Schedule 2 – Amendment

HYDROCORTISONE AND HYDROCORTISONE ACETATE – Amend entry to read:

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 0.5 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or

(b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent **except** unscheduled astringents:

(i) in undivided preparations in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories.

Schedule 3 – Amendment

HYDROCORTISONE AND HYDROCORTISONE ACETATE – Amend entry to read:

HYDROCORTISONE and HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations for human therapeutic use containing 1 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations, containing no other therapeutically active constituent other than an antifungal substance; or

(b) for rectal use when combined with a local anaesthetic substance but no other therapeutically active constituent **except** unscheduled astringents:

(i) in undivided preparations in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories,

except when included in Schedule 2.

21.1.3 LEVAMISOLE

PURPOSE

The Committee considered editorial amendments to levamisole.

BACKGROUND

Levamisole is an anthelmintic that has been widely used in treatment of worm infestations in both humans and animals. It has also been used as an adjuvant in malignant disease.

At the August 1973 PSSC meeting, levamisole for veterinary use was included in Schedule 6. In May 1974 preparations containing 10% of levamisole were included in Schedule 5 and at the November 1975 meeting a cut-off at 15% was agreed. At the November 1982 meeting, levamisole for the treatment of heartworm in dogs was included in Schedule 4.

DISCUSSION – SUBMISSIONS

It was brought to the Secretariat's attention that there may be an inconsistency in the scheduling of levamisole.

- Currently, part (b) of the Schedule 6 entry exempts preparations for the treatment of ornamental birds or fish when in packs with ≤ 10 mg levamisole. This exemption was introduced at the November 1987 DPSSC Meeting where it was specifically stated that this was to be exempt from scheduling.
- The current Schedule 5 entry is levamisole in preparations containing ≤ 15 % (for the treatment of animals) and has existed since the recommendation of the November 1975 DPSSC Meeting.
- As it stands, if a preparation is less than 15% levamisole it falls under Schedule 5, even if it is for the treatment of ornamental birds or fish in a pack of less than 10 mg (i.e. still scheduled). If a preparation is greater than 15% levamisole, but in packs of 10 mg or less and for the treatment of ornamental birds or fish, it is exempt from scheduling.
- It was suggested that the Committee address this minor inconsistency by replicating the levamisole Schedule 6 ornamental birds or fish (when ≤ 10 mg) exemption in the Schedule 5 entry.

RESOLUTION 2007/51 - 59

The Committee decided to amend the levamisole entry in Schedule 5 to include an exemption for the treatment of ornamental birds or ornamental fish in packs of 10 mg or less of levamisole.

Schedule 5 – Amendment

LEVAMISOLE – Amend entry to read:

LEVAMISOLE in preparations containing 15 per cent or less of levamisole for the treatment of animals **except**:

(a) when included in Schedule 4; or

(b) in preparations for the treatment of ornamental birds or ornamental fish, in packs containing 10 mg or less of levamisole.

21.1.4 AMINACRINE

PURPOSE

The Committee considered editorial amendments to aminacrine.

BACKGROUND

Prior to the June 2005 NDPSC Meeting, aminacrine was listed in Appendix B.

The June 2005 NDPSC meeting decided to include aminacrine for veterinary use in Schedule 5 and Schedule 7. Non-veterinary use remained unscheduled. It appears that the consequential removal of aminacrine from Appendix B was overlooked at the time.

DISCUSSION – SUBMISSIONS

As a substance should not be included in Appendix B if it has been included in a schedule entry, the Committee considered deleting the Appendix B entry for aminacrine.

RESOLUTION 2007/51 - 60

The Committee decided to delete the Appendix B entry for aminacrine.

APPENDIX B – Amendment

AMINACRINE – Delete entry

21.2 SUSDP 22 AMENDMENT 2 – VARIATIONS TO DIBROMOPROPAMINE, PARACETAMOL, PROMETHAZINE, PROPAMIDINE AND TRIMEPRAZINE

PURPOSE

The Committee noted corrections to the draft SUSDP 22 Amendment 2.

DISCUSSION - SUBMISSIONS

The amendments arising from decisions made by the Committee at its June 2007 meeting (except where separately specified) were consolidated in the draft SUSDP 22 Amendment 2 for consideration by the October 2007 NDPSC Meeting.

DISCUSSION – ADDITIONAL MATTERS RELEVANT TO 52E

A Member tabled a list of possible minor editorial changes to SUSDP 22 Amendment 2. The Committee generally agreed that the following proposed variations be referred to the Drafting Advisory Panel for clearance:

Dibromopropamide and propamidine

- The June 2007 NDPSC Meeting agreed to include dibromopropamide for opthalmic use in Schedule 2 and all other uses in Schedule 4 (2007/50-24). The agreed wording of the Schedule 4 entries agreed was "…for therapeutic use **except** where included in other schedules".

- The tabled proposal was to increase the specificity of this wording through a direct reference to the only other schedule entry (Schedule 2) i.e. "…for therapeutic use **except** when included in Schedule 2".

Paracetamol

- The June 2007 NDPSC Meeting agreed to amend the Schedule 2 entry for paracetamol (2007/50-14). A Member noted that part c of this entry included "…active constituent other than (other than phenylephrine…" and proposed that the superfluous other than be removed.

Promethazine and trimeprazine

- The June 2007 NDPSC Meeting agreed to amend the Schedule 3 entries for promethazine and trimeprazine to exclude preparations for the treatment of children under 2 years of age (2007/50-11). A Member noted that part (b) of the trimeprazine entry had inadvertently dropped the reference to "per 5 mL". The Member also tabled a number of possible editorials for these entries. These proposed changes are underlined below:

PROMETHAZINE in oral preparations **except**:

(a) when included in Schedule 2; or

(b) in preparations for the treatment of children under 2 years of age.

TRIMEPRAZINE:

(a) in solid oral preparations **except** when included in Schedule 2; or

(b) in liquid oral preparations containing 10 mg or less of trimeprazine per 5 mL,

except in preparations for the treatment of children under 2 years of age.

RESOLUTION 2007/51 - 61

The Committee decided that those proposed variations to the draft SUSDP 22 Amendment 2 cleared by the Drafting Advisory Panel would be included in SUSDP 22 Amendment 2.
[Subsequent to the October 2007 NDPSC Meeting the Drafting Advisory Panel cleared the proposed editorial changes.]

Schedule 2 – Amendment (Variation of Decision 2007/50-14)

PARACETAMOL – Amend entry to read:

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 or when combined with effervescent agents) when:

(i) enclosed in a primary pack that contains not more than 12 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; or

(c) in tablets or capsules each containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine 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 25 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.

Schedule 3 – Amendment (Variation of Decision 2007/50-11)

PROMETHAZINE – Amend entry to read:

PROMETHAZINE in oral preparations **except**:

(a) when included in Schedule 2; or

(b) in preparations for the treatment of children under 2 years of age.

TRIMEPRAZINE – amend entry to read:

TRIMEPRAZINE:

(a) in solid oral preparations **except** when included in Schedule 2; or

(b) in liquid oral preparations containing 10 mg or less of trimeprazine per 5 mL,

except in preparations for the treatment of children under 2 years of age.

Schedule 4 – New Entries (Variation of Decision 2007/50-24)

DIBROMOPROPAMIDINE for therapeutic use **except** when included in Schedule 2.

PROPAMIDINE for therapeutic use **except** when included in Schedule 2.

.....
Dr Margaret Hartley Date / /
Presiding Member
National Drugs and Poisons Schedule Committee