



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

59th Meeting
22-23 June 2010

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GLOSSARY

<i>ABBREVIATION</i>	<i>NAME</i>
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicines Evaluation Committee [CMEC])
ACNMP	Advisory Committee on Non-Prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable Daily Intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ArfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils Of Australian Governments
CRC	Child-Resistant Closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	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 Act 1982
FS22-23 June ANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-Intestinal Tract
GP	General Practitioner
HCN	Health Communication Network
INN	International Non-proprietary Name
ISO	International Standards Organization

LC ₅₀	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD ₅₀	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
MCC	Medicines Classification Committee (NZ)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-Prescription Medicines [ADNPM])
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
NOEAC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCSEH	Office of Chemical Safety and Environmental Health
ODBT	Office of Devices, Blood and Tissues
OOS	Out of Session

OMA	Office of Medicines Authorisation (formerly Office of Prescription Medicines [OPM] and Office of Non-Prescription Medicines [ONPM])
ONPM	Office of Non-Prescription Medicines (now Office of Medicines Authorisation [OMA])
OPM	Office of Prescription Medicines (now Office of Medicines Authorisation [OMA])
OTC	Over-the-Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted Flow Insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons

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

1. PRELIMINARY MATTERS

1.6 PROCEDURAL MATTERS

XXXXX.

1.6.2 TRANSITION ARRANGEMENTS

The Committee noted the transition arrangements for the February and June 2010 decisions. Members also noted that the following notice was:

- published on the NDPSC webpage (www.tga.gov.au/ndpsc/ndpsc1006.htm) on 27 May 2010;
- emailed to the June 2010 NDPSC meeting applicants and pre-meeting respondents on 27 May 2010; and
- included in an email to subscribers of the listserver email notification service provided through the NDPSC website on 4 June 2010.

Important notice: Matters for consideration at the June 2010 NDPSC meeting

Have you:

- submitted a scheduling application for consideration at the June 2010 meeting of the National Drugs and Poisons Schedule Committee (the NDPSC); or
- submitted, or intend to submit, a public comment in response to matters mentioned in the June 2010 pre-meeting notice <<http://www.tga.gov.au/ndpsc/ndpscgan.htm>>

If either of the above applies to you, it is important you please consider the following regarding the June 2010 NDPSC meeting.

Please note that the following Checklist actions do not apply to those decisions from the February 2010 NDPSC meeting which will not have been implemented by 1 July 2010 (unless it was also a matter mentioned in the June 2010 pre-meeting notice). Details regarding this situation are provide below under the heading Transition Arrangements in relation to February 2010 decisions by the NDPSC.

Checklist

Please read the information below and, for each matter where you are the applicant or where you have submitted a public comment, please advise the NDPSC Secretariat (before 11 June 2010) whether you are:

- requesting consideration of an implementation date later than 1 September 2010, should a change of scheduling result from the June 2010 consideration; and/or
- whether you:
 - are willing to accept a June 2010 decision as final even if the decision results in a scheduling change that does not align with your request (allowing the matter to be concluded); or
 - are requesting that any such decision not be considered final (noting that this would likely mean that consideration will need to start afresh under the new arrangements and may mean no final decision before the end of 2010).

Details**New scheduling arrangements from 1 July 2010**

New scheduling arrangements will come into force on 1 July 2010 and the NDPSC will be replaced by the Secretary of the Department of Health and Ageing (DoHA) - or her delegate - as the decision maker for the scheduling of medicines and chemicals. Two new expert advisory committees, the Advisory Committee on Medicines Scheduling and the Advisory Committee on Chemicals Scheduling, will be established to provide advice and make recommendations to the Secretary (or delegate) on medicines and chemicals scheduling decisions. The finer details of the revised scheduling process are currently being developed but are expected to be made available shortly. More information on these new scheduling arrangements can be found on the NDPSC website <http://www.tga.gov.au/ndpsc>.

Consequences for matters before the June 2010 NDPSC meeting

Transition provisions are set out in Schedule 1, Item 13 of the Therapeutic Goods Amendment (2009 Measures No. 2) Act 2009 (the Amendment Act). These include that the Secretary, or her delegate, must have regard to any decisions made by the NDPSC after 1 January this year (ie at the February or June 2010 meetings) which have not been incorporated in a legislative instrument that either:

- amends the current Poisons Standard (the legal title for the current SUSDP); or
- is a document which is a new Poisons Standard substituting the current Poisons Standard, before 1 July 2010.

Transition arrangements in relation to February 2010 decisions by the NDPSC

Decisions made by the NDPSC at the February 2010 meeting which were to result in an amendment to the current Poisons Standard (including any changes from reconsideration of some of these decisions at the June 2010 NDPSC meeting) will be considered by the Secretary or her delegate for inclusion in the first Poisons Standard legislative instrument under the new arrangements (the 'first instrument').

It is currently intended that the first instrument will be registered in the Federal Register of Legislative Instruments (FRLI) prior to September 2010 so as to allow the February 2010 NDPSC decisions to be implemented on 1 September 2010 (the normal implementation date for NDPSC decisions from the February 2010 meeting had the existing scheduling arrangements continued past 1 July 2010).

Transition arrangements for June 2010 decisions by the NDPSC

IMPORTANT – It is possible for the first instrument to encompass different commencement dates for a particular category or group of scheduling decisions. The proposed commencement date for the first instrument is likely to be 1 September 2010, significantly earlier than usually expected for June NDPSC decisions. As outlined above in the Checklist, it is important that any request to consider an implementation date later than 1 September 2010 be provided to the secretariat as soon as possible (deadline is 11 June 2010).

Decisions at a June meeting of the NDPSC would normally be implemented 1 January of the following year to allow time for consideration of further public submissions on the June decision at the subsequent October meeting. However, the transitional arrangements set out under the Amending Act include no provisions for further submissions on NDPSC decisions made at the June 2010 meeting, other than a subsequent request for scheduling/rescheduling under the new arrangements. As a consequence, matters to be considered at the June 2010 NDPSC meeting are expected to fall into one of the following categories:

No pre-meeting submissions - can be finalised

Under the current process, if an interested party has made a valid pre-meeting public submission in relation to a proposed scheduling decision and in response to a notice under subregulation

42ZCU(1) of the Therapeutic Goods Regulations 1990, they are invited to make further submissions on an amendment to the Poisons Standard following an NDPSC decision. This invitation is included in the Gazette notice under subsection 52D(4) of the Act. These arrangements are currently provided for under subregulation 42ZCY(1).

Therefore, decisions at the June 2010 NDPSC meeting for matters where no pre-meeting comments were received would not be required to undergo further reconsideration. The NDPSC would not require further submissions in relation to these matters had the current scheduling arrangements continued after 1 July 2010. These decisions will be considered by the Secretary, or her delegate, for inclusion in the first instrument. As discussed above, it is important that you provide to the Secretariat as soon as possible (deadline is 11 June 2010) any request to consider an implementation date later than 1 September 2010.

Pre-meeting submissions and application align with decision – can be finalised

Some June 2010 NDPSC decisions may result in scheduling changes consistent with both the application and any/all pre-meeting comments provided by interested parties. These decisions will be considered by Secretary or her delegate for inclusion in the first instrument (again noting the need to provide to the Secretariat as soon as possible (deadline is 11 June 2010) any request to consider an implementation date later than 1 September 2010).

Scheduling change appears to be in dispute

Other June 2010 NDPSC decisions may result in scheduling changes that are not consistent with either the application or some/all pre-meeting comments lodged in response to a notice under subregulation 42ZCU(1). As discussed above, had the NDPSC process proceeded past 1 July 2010 such decisions would have been reconsidered and an invitation to make a further public submission would have been made to those persons who provided valid public submissions for the June 2010 NDPSC meeting. However, as discussed above, there will be no avenue for making further submissions on June 2010 decisions by the NDPSC under the current regulatory framework.

Consequently, unless those parties whose position is not consistent with the scheduling change agree to accept a June 2010 decision by the NDPSC as final (allowing the matter to be concluded) then it is likely that such matters will not be concluded at the June 2010 meeting. If not concluded, these matters will be referred to the Secretary or her delegate for consideration under the new arrangements. This may mean no final decision is reached before the end of 2010.

IMPORTANT – As outlined in the Checklist above, could you please advise the NDPSC Secretariat (before 11 June 2010) whether you:

- are requesting that, if a decision would result in a scheduling change that does not align with your preferred position, such a decision should not be considered final (noting that this would likely mean that consideration will need to start afresh under the new arrangements and may mean no final decision before the end of 2010); or
- are willing to accept that any such decision be considered final even if the decision results in a scheduling change that does not align with your preferred position (allowing the matter to be concluded).

Amendments required to change SUSDP 24 into SUSMP 1

The current Poisons Standard consists of the Poisons Standard 2009 and the three amendments made to that Poisons Standard. The Poisons Standard 2009 consists of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) No. 24 and three subsequent amendments (referred to as Poisons Standard Amendment No. 2 of 2009, Poisons Standard Amendment No. 3 of 2009 and Poisons Standard Amendment No. 1 of 2010 in FRLI).

Under the revised scheduling arrangements, the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) will be replaced by the Standard for the Uniform Scheduling of Medicines

and Poisons (SUSMP). The proposed SUSMP has been developed by the National Co-ordinating Committee on Therapeutic Goods (NCCTG) (as the committee which oversees scheduling policy). This process included public consultation, with submissions on the proposed SUSMP being invited during May22-23 June xxxx 2009.

The transitional amendments required to change the SUSDP 24 (and the three subsequent amendments to it as incorporated by the Poisons Standard amendments outlined above) into SUSMP 1 have now been referred to the June 2010 NDPSC meeting for consideration. It is a practical necessity for transitioning to the new arrangements that the NDPSC makes a decision on this matter at the June 2010 meeting and that the SUSDP 24 (and amendments to it) be considered by the Secretary or her delegate for inclusion in the first instrument. **PLEASE NOTE** – this will occur regardless of whether these changes are disputed in pre-meeting comments (pre-meeting comments will, as is always the case, be taken into consideration by the June 2010 meeting in reaching its decision).

It should be noted, however, that unlike many matters going before NDPSC, these proposed amendments, and a summary of reasons for these changes, have been made available on the NDPSC website at Transitional amendments: SUSDP 24 to SUSMP 1 <http://www.tga.gov.au/ndpsc/cons-susmp1.htm>. This advice was included in the June 2010 pre-meeting notice <http://www.tga.gov.au/ndpsc/ndpscgan.htm>. As such, interested parties should be in a position to provide detailed and considered pre-meeting submissions on this issue.

Finally, it is always open for interested parties to submit a rescheduling application under the new process, should they wish to request a change to any aspect of these transitional amendments (finalised at the June 2010 NDPSC meeting, and incorporated into the first instrument made by the Secretary or her delegate under the new scheduling arrangement).

1.7 NDPSC WORKING PARTIES

No items.

1.8 PROPOSED ROUTINE CHANGES TO THE SUSDP

1.8.1 STANDARD FOR THE UNIFORM SCHEDULING OF MEDICINES AND POISONS NO. 1

PURPOSE

The Committee considered the transitional amendments required to change the *Standard for the Uniform Scheduling of Drugs and Poisons No. 24* (SUSDP 24) into the *Standard for the Uniform Scheduling of Medicines and Poisons No. 1* (SUSMP 1), being the new Poisons Standard under the revised scheduling arrangements commencing 1 July 2010.

BACKGROUND

The *Review of Drugs, Poisons and Controlled Substances Legislation* (the Galbally Review) made a number of recommendations regarding the Poisons Standard. The Review considered each section of the Poisons Standard and subsequently a number of amendments were proposed to implement these recommendations.

In particular, the Review considered that the term ‘medicine’, rather than ‘drug’, would better reflect the substances used for therapeutic purposes covered by the Standard and proposed that the title of the *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP) be changed to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

The proposed changes submitted to the Committee for consideration were made publicly available in the June 2010 pre-meeting Gazette Notice. Prior to this, these proposals had been subjected to extensive public consultation and review.

The Committee considered each of the proposed changes to the Poisons Standard either individually or in groups of similar content, with Resolutions relevant for each section presented. These sections were:

1.8.1.1: Name, Use of Drug vs Medicine and Preface

1.8.1.2: Introduction and Principles of Scheduling

1.8.1.3: Interpretation – Definitions

1.8.1.4: Labels and Containers

1.8.1.5: Miscellaneous Regulations

1.8.1.6: Appendices

1.8.1.7: Other changes to note

When considering the above, the Committee also recalled from item 1.6.2 that it would be impractical not to finalise amendments to transition to the SUSMP at this meeting. Stakeholders were advised prior to the June 2010 Committee meeting that it is a practical necessity for transitioning to the new arrangements that the Committee makes a decision on this matter at the June 2010 meeting regardless of whether these changes are disputed in pre-meeting comments. It was accepted that stakeholders and interested parties have had ample opportunity to provide comment on the proposed amendments.

Where the resolutions refer to “for the transition to the SUSMP” the decision will be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for inclusion in the first instrument (SUSMP 1) under these new arrangements, with the specified implementation date.

1.8.1.1 NAME, USE OF “DRUG” VS “MEDICINE” & PREFACE

The title of the Poisons Standard was recommended to change to “*Standard for the Uniform Scheduling of Medicines and Poisons*”.

Any reference to “drug” was proposed to change to “medicine” and, where necessary, be preceded by “human” or “veterinary”, depending on use.

The information that was in the preface of the SUSDP was proposed to be incorporated into the introduction (see 1.8.1.2) to simplify the structure of the Standard and to aggregate like information under common headings.

Pre-Meeting Submissions

None received on this item.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

The Committee agreed that the proposed changes were reasonable and required no additional amendments.

RESOLUTION 2010/59 - 1

The Committee agreed to:

- change the title of the Poisons Standard to the “*Standard for the Uniform Scheduling of Medicines and Poisons*”;
- replace all references to “drug” to “medicine”, preceded by “human” or “veterinary” as necessary;
- remove the Preface of the current SUSDP, for the transition to the SUSMP.

1.8.1.2 INTRODUCTION AND PRINCIPLES OF SCHEDULING

The “Introduction” and “Principles of Scheduling” sections of the Poisons Standard were rewritten to provide a more comprehensive context for the new scheduling standard, to aggregate material under common headings and to improve public understanding of scheduling and its implications.

Within the “Principles of Scheduling” section a table was added for clarification of the role of the Appendices. This table characterises each of the appendices, its title and regulatory purpose.

Pre-Meeting Submissions

XXXXX suggested that as the SUSMP applies to both medicines and poisons this should be made clear from the start of the Introduction. They expressed concern that the first mention of ‘medicines’ is in ‘Principles of Scheduling’. It was suggested that the each occurrence of ‘poison(s)’ be amended to ‘medicine(s) and poison(s)’ throughout the

introduction. Members noted, however, that the definition of “poison” in the proposed SUSMP remains the same as in the current SUSDP 24, i.e. “means any substance or preparation included in a Schedule to this Standard”.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members discussed the proposal from XXXXX, in particular the benefits and disadvantages of referring to medicines and poisons throughout the text. Members agreed that a clarifying statement should be added to the first paragraph explaining that the term poison captures medicines.

Members also identified a number of typographical errors in the text.

RESOLUTION 2010/59 - 2

The Committee agreed to the proposed amendments to the “Introduction” and “Principles of Scheduling”. The Committee further agreed to the following changes (highlighted in the amended text below, for ease of reference only – this will be removed prior to publication of SUSMP 1):

- Addition of the reference to section 52D of the *Therapeutic Goods Act 1989*.
- After “poison” included the statement “noting that the definition of poison includes medicine.”
- Removed the proposed reference “These are listed below on page 3”.
- Removed the proposed reference to “other relevant APVMA legislative instruments”.
- Removed the space between training and the comma.
- Removed the full stop at the end of the heading
- Table of appendices: inserted a closing bracket after “laboratory use” in the column relating to “Purpose/controls imposed” for Appendix F.

Introduction and Principles of Scheduling – Amend to read:

INTRODUCTION

The *Standard for Uniform Scheduling of Medicines and Poisons* (the Standard) or (SUSMP) is established under Section 52D of the *Therapeutic Goods Act 1989*, and is a compilation of the decisions made under Section 52D of the same Act. The SUSMP should be read in conjunction with the *Scheduling Policy Framework* (SPF) of the National Coordinating Committee on Therapeutic Goods. Further information on the scheduling amendments and the SPF can be accessed from the following website:

www.tga.gov.au. Refer to Part 1 Interpretation on page XX below, for definitions of specific terms used in this document including “medicine” and “poison” (noting that the definition of poison includes medicine). The predecessor to this document, the *Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)*, as decisions of the former National Drugs and Poisons Schedule Committee, formed the basis of this Standard. The *SUSMP* serves two key purposes.

Firstly, the *SUSMP* contains the decisions of the delegates regarding the classification of poisons into Schedules, as recommendations to Australian States and Territories. The scheduling classification sets the level of control on the availability of poisons. The scheduling of poisons is implemented through relevant State and Territory legislation. Certain advertising, labelling and packaging requirements may also be a consequence of scheduling but are the subject of other Commonwealth registration schemes.

Secondly, the *SUSMP* includes model provisions for labelling, containers, storage and possession of poisons in general, which are intended to be adopted for use in each jurisdiction of Australia, according to local requirements and local law. Appropriate labelling and container requirements for products, other than therapeutic goods and agricultural and veterinary chemical products, are imposed through adoption of Parts 1, 2 and 3 of the *SUSMP* into State or Territory legislation. Other government agencies may also impose controls on certain products, for example cosmetics.

The requirements for labelling and containers in the *SUSMP* are intended to integrate with existing legislative instruments for labelling and containers. Advertising, labelling and packaging of therapeutic goods and agricultural and veterinary chemicals are also dealt with through the respective product registration schemes provided for in Commonwealth legislation.

Poisons which are packed and sold solely for industrial, manufacturing, laboratory or dispensary use are exempt from all labelling requirements included in the *SUSMP* as they are covered by the Safe Work Australia *National Code of Practice for the Labelling of Workplace Substances*¹ (the SWA Code). Note, however that this exemption does not extend to controls on supply of these poisons.

The *SUSMP* is presented with a view to promoting uniform:

- scheduling of poisons throughout Australia;
- signal headings on labels for poisons throughout Australia;
- labelling and packaging requirements for poisons throughout Australia;
- additional controls on the availability and use of poisons in Australia.

The various Commonwealth legislative instruments which integrate with the *SUSMP* include:

¹The SWA Code (NOHSC:2012 (1994)) can be accessed from www.safeworkaustralia.gov.au

- the *Agricultural and Veterinary Chemicals Code Act 1994*
- the *Agricultural and Veterinary Chemicals Code Regulations 1995*
- the *Therapeutic Goods Act 1989*
- TGO 65 – *Child-resistant packaging for therapeutic goods*
- TGO 69 – *General requirements for labels for medicines*
- TGO 80 – *Child-Resistant Packaging Requirements for Medicines*
- *Required Advisory Statements for Medicine Labels (RASML)*

CLASSIFICATION

22-23 June

Poisons are classified according to the Schedules in which they are included. The following is a general description of the Schedules. For the legal definitions, however, it is necessary to check with each relevant State or Territory Authority.

Schedule 1.[This Schedule is intentionally blank.]

Schedule 2. Pharmacy Medicine – Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.

Schedule 3. Pharmacist Only Medicine – Substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.

Schedule 4. Prescription Only Medicine, or Prescription Animal Remedy – Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.

Schedule 5. Caution – Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.

Schedule 6. Poison – Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.

Schedule 7. Dangerous Poison – Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.

Schedule 8. Controlled Drug – Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.

Schedule 9. Prohibited Substance – Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities.

PRINCIPLES OF SCHEDULING

PRINCIPLES OF SCHEDULING

Poisons are not scheduled on the basis of a universal scale of toxicity. Although toxicity is one of the factors considered, and is itself a complex of factors, the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance.

This Standard now lists poisons in nine Schedules according to the degree of control recommended to be exercised over their availability to the public.

Poisons for therapeutic use (*medicines*) are mostly included in Schedules 2, 3, 4 and 8 with progression through these schedules signifying increasingly restrictive regulatory controls.

For some medicines, agricultural, domestic and industrial poisons, Schedules 5, 6 and 7 represent increasingly strict container and labelling requirements with special regulatory controls over the availability of the poisons listed in Schedule 7. Products for domestic use must not include poisons listed in Schedule 7.

Schedule 9 contains substances that should be available only for teaching, training, medical or scientific research including clinical trials conducted with the approval of Commonwealth and/or State and Territory Health Authorities. Although appearing as a Schedule in this Standard the method by which it is implemented in the States and Territories may vary.

Substances in products which have been considered for scheduling but have been exempted from this Standard may be listed in either Appendix A (general exemptions) or Appendix B (substances considered not to require control by scheduling).

Appendix C contains a list of substances or preparations, the sale, supply or use of which should be prohibited because of their known dangerous properties. It is recommended that provisions of this appendix be put into effect through inclusion of the substances in appropriate State and Territory legislation.

READING THE SCHEDULES

Schedule entries have been designed to be as simple as possible while retaining readability, legal integrity and as much freedom from ambiguity and contradiction as possible. As a result they are expressed in a number of ways, though this number has been kept to a minimum. It is necessary to keep this variety of expression in mind when searching or interpreting Schedule entries.

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Firstly, poisons are now scheduled individually using their approved names wherever practicable although exceptions are necessary in some cases. Some of those are mentioned overleaf. Older group entries are being revised and replaced by individual entries as time permits although in some of these cases a group term has also been retained to deal with any members of the group or class that may have escaped attention but should be scheduled.

Secondly, schedule entries have been expressed in either positive or negative terms and care must be taken to distinguish between the two different forms of expression. Thus, selenium is in Schedule 6 only when one of the clauses in this schedule entry applies, while fluorides are in Schedule 6 unless one of the exempting clauses applies.

Where exceptions are included in an entry these have been emphasised by printing the word “except” in bold type.

Where the schedule entries for a poison make a specific exclusion or exemption, the requirements of this Standard do not apply to that poison within the constraints of that exclusion or exemption although controls under other legislation such as pesticide registration may apply.

Where a Schedule entry for a poison requires a specific statement to be included on a label as a condition for a product to qualify for an exemption (‘reverse scheduling’), then in cases where it is impracticable for a supplier to use the exact wording of such a statement, its wording may be varied provided that the full intent and meaning of the statement is not changed.

Where a poison has been included in more than one Schedule the principal entry, where practicable, has been included in the most restrictive Schedule with references to the other Schedule(s) involved.

It is important to remember that a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise. (See Interpretation PART 1 [paragraph 1(2)]).

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.

Finally, when using the Standard to determine the scheduling status of a poison it may be necessary to search each relevant Schedule as well as Appendices A, B and C and the Index. In this process if the poison is not found under its “approved name” it may be shown under a group term such as:

Group	Example
the parent acid of salts	“oxalic acid” to find sodium oxalate
the radical of a salt	“chromates” to find potassium chromate
the element	“arsenic” to find arsenic trioxide
a chemical group with similar toxicological or pharmacological activity	“hydrocarbons, liquid” to find kerosene
a pharmacological group	“anabolic steroidal agents” to find “androsterone”

Availability of poisons

The purpose of classification is to group substances into Schedules that require similar regulatory controls over their availability.

These Schedules have been developed over a long period and contain poisons that may be obsolete for various reasons. Also as part of the move to harmonise the Australian and New Zealand classifications many substances have been added to the Schedules for that purpose, irrespective of their availability in either country.

Inclusion of a poison in a Schedule indicates the degree of control required if it is marketed. It does not indicate:

- that the poison is available; nor

- that it has been approved or is efficacious for any use that may be specified in a Schedule; nor
- does it negate any obligation for registration of a therapeutic good, or agricultural or veterinary chemical product containing that poison.

Preparations containing poisons listed in two or more Schedules

If a preparation contains two or more poisons, the provisions relating to each of the Schedules in which those poisons are included apply.

Where it is not possible to comply both with a provision relating to one of those Schedules and with a provision relating to another of those Schedules, the provision of the more restrictive Schedule applies, unless a contrary intention is indicated in the Schedules or relevant legislation.

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The Schedules listed in order of greatest to least restriction on access and availability are 9, 8, 4, 7, 3, 2, 6, 5.

Schedule 1 is not currently in use.

Some substances in certain circumstances are also subject to exemptions or additional restrictions as described in the Appendices to this Standard. The table below summarises the purpose of each of the appendices and the controls imposed on substances included in them.

Appendix	Title	Purpose/ controls imposed
Appendix A	General exemptions	List of classes of products or uses exempted from this <i>SUSMP</i>
Appendix B	Substances considered not to require control by scheduling	List of poisons exempted from scheduling
Appendix C	Substances, other than those included in Schedule 9, of such danger to health as to warrant prohibition of sale, supply and use	List of poisons prohibited from sale, supply or use because of their known potential for harm to human and/or animal health
Appendix D	Additional controls on possession or supply of poisons included in Schedule 4 or 8	List of medicines included in Schedule 4 or Schedule 8 where additional controls apply – these controls are specified in the appendix
Appendix E	First aid instructions for poisons	First aid instructions for poisons (other than agricultural and veterinary chemicals and chemicals packed and sold solely for industrial, dispensary, manufacturing or laboratory use)

Appendix	Title	Purpose/ controls imposed
Appendix F	Warning statements and general safety directions for poisons	Warning statements and general safety directions for poisons (other than human medicines, agricultural and veterinary chemicals and chemicals packed and sold solely for industrial, dispensary, manufacturing or laboratory use)
Appendix G	Dilute preparations	Concentration cut-offs for specified poisons, below which the requirements of the Standard do not apply
Appendix H	Schedule 3 medicines permitted to be advertised	Schedule 3 medicines that are permitted to be advertised to the public
Appendix I	Uniform paint standard	Requirements to apply to poisons included in paints or tinters
Appendix J	Conditions for availability and use of Schedule 7 poisons	List of Schedule 7 poisons where additional specified conditions apply to their availability and use
Appendix K	Human medicines required to be labelled with a sedation warning	List of human medicines required to be labelled with a warning regarding their sedation potential
Appendix L	Requirements for dispensing labels for medicines	Requirements applying to labels attached to medicines at the time of dispensing

1.8.1.3 INTERPRETATION – DEFINITIONS

As part of the implementation of Recommendation 22 of the Galbally Review, NCCTG has endorsed that controls on advertising, packaging and labelling of human medicines and agricultural and veterinary chemicals (except signal headings) will be progressively transferred from the Poisons Standard to Commonwealth legislation as it is developed.

As a consequence of the above, and to provide clarity and ensure the use of the term is in accord with the meaning of the terms used in the *Agricultural and Veterinary Chemicals Code Act 1994*, a number of new definitions, and several amendments to current definitions were proposed for Part 1 – Interpretation.

Pre-Meeting Submissions

XXXXXX suggested the following amendment to part (b) of the definition of 'label' to ensure that it is consistent with the definition of 'label' in the *Therapeutic Goods Act 1989*:

- (b) in relation to a therapeutic good, includes a display of printed information about the product:
 - (i) on, or attached to the good; or

- (ii) on, or attached to, a container or primary pack in which the good is supplied ~~with such a container or pack~~; or
- (iii) supplied with such a container or pack.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members discussed the pre-meeting proposal from XXXXX, and generally agreed that the proposal would provide consistency for the definition of ‘label’.

Members also agreed to amend the reference to the Victorian Department of Human Services, in the definition of “Appropriate authority”, to the Department of Health.

Members further accepted the editorial amendments proposed by the Secretariat.

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The Committee agreed to the inclusion of the new definitions and the amendments to the current definitions in Part 1 – Interpretation of the Poisons Standard. Members further agreed to amend the definition of label to remove the reference to “with such a container or pack”. The Committee also agreed to the editorial amendments (below) for the transition to the SUSMP.

Editorial amendments

- The heading “Agricultural chemical” to be in bold font.
- Only the heading “Medicine” to be bold font for the new medicine entry.
- The new entry for “Therapeutic good” requires a full stop at the end.
- Part (f) of the veterinary chemical definition to refer to a product declared to be a veterinary chemical product (was previously agricultural).

Interpretation – New Entries

“**Agricultural chemical**” means a substance that is represented, imported, manufactured, supplied or used as a means of directly or indirectly:

- (a) destroying, stupefying, repelling, inhibiting the feeding of, or preventing infestation by or attacks of, any pest in relation to a plant, a place or a thing;
- (b) destroying a plant;

- (c) modifying the physiology of a plant or pest so as to alter its natural development, productivity, quality or reproductive capacity;
- (d) modifying an effect of another agricultural chemical;
- (e) attracting a pest for the purpose of destroying it; or
- (f) any active ingredient included in a product declared by regulation under the Agricultural and Veterinary Chemicals Code Act 1994 to be a veterinary chemical product,

but does not include:

- (g) a veterinary chemical.

“Agricultural chemical product” has the meaning defined in the *Agricultural and Veterinary Chemicals Code Act 1994*.

“Animal” means any animal (other than a human being), whether vertebrate or not, and whether a food producing species or not, and includes mammals, birds, bees, reptiles, amphibians, fish, crustaceans and molluscs.

“Authorised prescriber” means a registered medical, dental or veterinary practitioner or such other person authorised by the appropriate authority.

“Dispensing label” means the label attached to the immediate container of a substance for therapeutic use at the time of dispensing.

“Medicine” means any poison for therapeutic use.

Note: To be preceded by “human” or “veterinary” where restriction of the “medicine” to human or animal use is intended.

“Therapeutic good” has the meaning defined in the *Therapeutic Goods Act 1989*.

“Veterinary chemical” means a substance that is represented as being suitable for, or is manufactured, supplied or used for, administration or application to an animal by any means, or consumption by an animal, as a way of directly or indirectly:

- (a) preventing, diagnosing, curing or alleviating a disease or condition in the animal or an infestation of the animal by a pest;
- (b) curing or alleviating an injury suffered by the animal;
- (c) modifying the physiology of the animal:

- (i) so as to alter its natural development, productivity, quality or reproductive capacity; or
- (ii) so as to make it more manageable;
- (d) modifying the effect of another veterinary chemical;
- (e) any vitamin, mineral substance, or additive, if, and only if, the vitamin, substance or additive is used for a purpose mentioned in paragraph (a), (b), (c) or (d); or
- (f) any active ingredient included in a product declared by regulation under the *Agricultural and Veterinary Chemicals Code Act 1994* to be a veterinary chemical product;

but does not include:

- (g) an agricultural chemical.

“Veterinary chemical product” has the meaning defined in the *Agricultural and Veterinary Chemicals Code Act 1994*.

Interpretation – Amend entries to read:

“Appropriate authority” means:

- (a) in the Australian Capital Territory, ACT Health;
- (b) for the purpose of providing an exemption from sections 2-12 of this Standard by the Australian Pesticides and Veterinary Medicines Authority, the Chief Executive Officer or their delegate;
- (c) in New South Wales, the Director-General of New South Wales Health;
- (d) in the Northern Territory, the Chief Health Officer of the Department of Health & Families;
- (e) in Queensland, the Chief Executive of Queensland Health;
- (f) in South Australia, the Chief Executive of the Department of Health;
- (g) in Tasmania, the Secretary of the Department of Health and Human Services;

- (h) for the purpose of providing an exemption from sections 2-12 of this Standard by the Therapeutic Goods Administration, the National Manager or their delegate;
- (i) in Victoria, the Secretary to the Department of Health;
- (j) in Western Australia, the Chief Executive Officer of the Department of Health.

“Label” means:

- (a) a written statement on a container of a poison; and
- (b) in relation to a therapeutic good, includes a display of printed information about the product:
 - (i) on, or attached to, the good;
 - (ii) on, or attached to, a container or primary pack in which the good is supplied; or
 - (iii) supplied with such a container or pack.

“Main label” means, where there are two or more labels on a container or a label is divided into two or more portions:

- (a) the part of a label that is most likely to be displayed, presented, shown, or examined under ordinary or customary conditions of display; and
- (b) where there are two or more labels or two or more portions of a single label – that label or portion of the label where the product name is more or most conspicuously shown; or
- (c) where the product name is equally conspicuous on two or more labels or portions of a label – each such label or portion.

“Paint”, without limiting the ordinary meaning, includes any substance used or intended to be used for application as a colouring or protective coating to any surface but does not include graphic material or paints for therapeutic use.

“Required Advisory Statements for Medicine Labels” means the document made under subsection 3(5A) of the *Therapeutic Goods Act 1989* by the Therapeutic Goods Administration.

“Therapeutic use” means use in or in connection with:

- (a) preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in human beings or animals;
- (b) influencing, inhibiting or modifying a physiological process in human beings or animals;
- (c) testing the susceptibility of human beings or animals to a disease or ailment;
- (d) influencing, controlling or preventing conception in persons or animals;
- (e) testing for pregnancy in persons or animals; or
- (f) the replacement or modification of parts of the anatomy in persons or animals.

1.8.1.4 PART 2: LABELS AND CONTAINERS

Various provisions in Part 2: Labels and Containers of the Poisons Standard have been proposed for amendment as a result of the Galbally Review. The changes and the explanation for the change are listed in the table below, which was made available for public comment prior to the June 2010 meeting.

SUSDP Provision	Changed to SUSMP provision	Explanation
7(l)(g)	Amend to commence with “for an unregistered poison”	As part of the implementation of Recommendation 22 of the Galbally Review, controls on advertising, packaging and labelling of human medicines and agricultural and veterinary chemicals (except signal headings) will be progressively transferred to from the SUSDP to Commonwealth legislation as it is developed. Some labelling provisions have already been moved to either the <i>Required Advisory Statements for Medicines</i> (RASML) or Therapeutic Goods Order 69 (General requirements for labels for
7(l)(m)	Amend to commence with “for an unregistered poison”	
7(l)(n)	Amend to commence with “for an unregistered poison”	
7(l)(o)	Amend to commence with “for an unregistered poison”	
9(1)	amended to insert a new sub-section to exclude therapeutic goods labelled in accord with TG legislation	
10(1)	amended to insert a new sub-section to exclude therapeutic goods labelled in accord with TG legislation	
11(1)	amended to insert a new sub-section to exclude therapeutic goods labelled in accord with TG legislation	

		<p>medicines) – and it is proposed that these can now be removed from the Poisons Standard. Changes have only been recommended where existing Commonwealth legislation enables the removal of a provision from the Poisons Standard. Further provisions will be recommended by NCCTG for transfer as the appropriate Commonwealth legislation is amended.</p>
13(2)	amended to reflect the current reference for the <i>National Code of Practice for the Labelling of Workplace Substances</i>	<p>Clarification of the scope and conditions under which a temporary exemption from labelling requirements can be granted. Provision was to be made to mutually recognize decisions by appropriate authorities in relation to exemptions from labelling and packaging controls.</p>
13A	<p>Paragraph 13A was proposed due to the following Council of Australian Government's (COAG) decision. At its meeting of 26 March 2008 COAG signed an Intergovernmental Agreement on the Australian health workforce, for the first time creating a single national registration and accreditation system. Ten health professions will be included in the national system as of 1 July 2010. These are: chiropractors; dental care practitioners; medical practitioners; nurses and midwives; optometrists; osteopaths; pharmacists; physiotherapists; podiatrists; and psychologists. References to particular health professions in the Standard have been generalised where appropriate, in recognition of these Commonwealth legislative changes.</p>	
14	<p>The new Appendix L will list all of the requirements for dispensing labels previously included in the body of the SUSDP. All remaining matters for dispensed medicines have been aggregated under a single heading in Part 2 of the Standard: "Dispensed</p>	<p>Recommendation 24 was that model legislation should be developed for adoption by reference by states and territories. The review proposed that model legislation include all</p>

	Medicines” – Paragraph 14.	provisions which relate to the supply of medicines for therapeutic purposes and to supply of domestic chemicals. While not supporting the adoption of model legislation for achieving uniformity in these areas, the NCCTG agreed to develop a uniform approach. The new Appendix L will list all of the requirements for dispensing labels previously included in the body of the Poisons Standard.
25	Amended to exclude poisons included in therapeutic goods when packaged in accordance with TG legislation. To provide clarification of an “authorised prescriber” the term “a medical practitioner or dentist” was replaced with “an authorised prescriber”.	Clarification under the new definition of “authorised prescriber”
31A		To complement paragraph 31

Pre-Meeting Submissions

XXXXXX suggested that Paragraph 13A (2) may need to be reconsidered. The proposed wording indicates that the labelling exemptions granted by an appropriate authority will only be effective for 12 months. It was argued that there are cases where more than 12 months labelling exemptions are warranted, and as the authorities have previously set the appropriate effected date, the wording should be revised to indicate that exemption is effective for 12 months, or as indicated by an appropriate authority.

XXXXXX additionally suggested that there are certain authorisations that can be issued by an appropriate authority, such as those listed in paragraph 7(1)(m)(ii)(B) and that the intent was not to capture these authorisations in paragraph 13A(2). It was suggested that these sections be revised to make this clear. [Members noted that ‘appropriate authority’ is defined in Part 1 of the SUSMP and is applicable in each instance identified here.]

XXXXXX advised that they were not happy with the wording of paragraph 14(2) as it is restricted only to human medicines which are prepared and supplied by a pharmacist. XXXXXX argued that it was unreasonable that other health practitioners, such as dispensing doctors, who may supply patients, whether on prescription or not, are not required to ensure that appropriate warning statements regarding sedation, or as otherwise

specified in Appendix L Part 2, are displayed on the medicine. XXXXX applying the Quality Use of Medicines principles, suggested that the words “by a pharmacist” be removed from paragraph 14(2) to ensure that all medicines supplied by health practitioners to all patients be labelled to ensure their safe use. XXXXX advised that the remainder of paragraph 14 was reasonable and raised no further concerns.

XXXXX noted that paragraph 14(2)(b) requires sedation warnings to be in bold red print, and strongly suggested that this requirement be removed. XXXXX asserted that this requirement is not consistent with the relevant Cautionary and Advisory Labels (CALs) in the Australian Pharmaceutical Formulary and Handbook (APF). XXXXX argued that the standards and specifications of CALs were reviewed by a working group and subsequently approved by the APF Editorial Board. From consultation with Vision Australia, one clear piece of advice for the CALs was that “coloured text should only be used on large text such as headlines and headings”. While XXXXX supported the use of sedation warnings on appropriate medicines, XXXXX asserted that the needs of visually impaired people must be taken into account.

XXXXX supported the position of XXXXX regarding the use of bold red print in paragraph 14(2)(b).

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members agreed that the amendments to paragraphs 7(l)(g), 7(l)(m), 7(l)(n), 7(l)(o), 8(3), 9(1), 10(1), 11(1), 25(1) and 31A were appropriate.

The Committee discussed the various proposals for amending paragraph 13 and 13A, including:

- The wording of the heading for paragraph 13A, as paragraphs 7-12 cover labelling requirements beyond just signal headings. Members agreed that the heading should be amended to “Exemptions from label requirements in certain circumstances”.
- Members debated the proposed amendment to paragraph 13 and generally agreed that the motivation was for mutual recognition of labelling exemptions.
- The Committee further debated the proposed entry for paragraph 13A(2), in particular its relationship with paragraph 7(1)(m)(ii)(B). One Member questioned how this would apply to exemptions granted for longer than 12 months, in particular permanent exemptions for pack inserts under 7(1)(m)(ii)(B). Members debated whether this was sufficiently addressed by mutual recognition between the jurisdictions or whether the exemption was at the discretion of the regulator. One Member asserted that issues of mutual recognition between the states and territories do not routinely occur and this perhaps is an issue that could be addressed by the regulator or perhaps it was covered by the definition of “appropriate authority”. In

order to clarify how paragraph 13A applies to exemptions under 7(1)(m)(ii)(B), the Committee agreed to add the following clause to 13A: (3) For the avoidance of doubt, this paragraph does not apply to exemptions issued under 7(1)(m)(ii)(B) of this Standard.

Members were concerned that the proposed paragraph 14 entry did not adequately capture the requirements for sedation warnings and that the provision did not cover the intent of including the requirements from Appendix K. Members generally agreed that under the original paragraph 14 there were three categories with exemptions from labelling requirements, and in paragraph 45 (which is being incorporated into Appendix L) these are referred to as “additional” labelling requirements and Members felt that the new paragraph 14 needed to reflect this. Members agreed that paragraph 14 should be redrafted to include an exemption in relation to a medicine that is prepared and supplied by a pharmacist and labelled in accordance with Appendix L Part 1 of the Poisons Standard. Members redrafted paragraph 14 to reflect the intention of paragraph 45 of the SUSDP.

The meaning of “authorised prescriber” was also debated. It was noted in particular that the definition in the SUSMP is different to that in Section 19 of the *Therapeutic Goods Act 1989*. Several jurisdictions agreed that the new SUSMP definition was more appropriate in the context of the SUSMP. There was debate about changing the specific examples of authorised prescriber in the definition, in line with current Government policy, to include nurse practitioners. Members generally agreed that it was not necessary to change the definition of “authorised prescriber”.

Members also considered the proposal to remove the requirement for bold red print in paragraph 14 and agreed that this requirement was not helpful and should be removed.

Members discussed the inclusion of midwife in paragraph 25A(2)(c) and 25A(2)(d) and generally agreed that reference to a midwife should be included where there is reference to a nurse.

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Members agreed to the proposed amendments to the labels and containers section of the Poison Standard for the transition to the SUSMP with the changes listed below:

- The term sanserif to be changed to sans serif throughout.
- The term nurse *or* midwife is to be included in paragraph 25A(2)(c) and 25A(2)(d).
- The heading for paragraph 13A to read “Exemptions from label requirements in certain circumstances”.
- Inclusion of the extra provision to paragraph 13A: (3) For the avoidance of doubt, this paragraph does not apply to exemptions issued under 7(1)(m)(ii)(B) of this Standard.
- Agreed to amend paragraph 14 to include an exemption in relation to a medicine that is prepared and supplied by a pharmacist and labelled in accordance with Appendix L Part 1 of the Standard. And further agreed that a person must not supply a dispensed

medicine for human use containing (a) a substance listed in column 1 of the table at Appendix L Part 2 of this Standard unless it is clearly labelled with the warning statement(s) specified in column 2 of that table; or (b) a substance listed in Appendix K unless it is clearly labelled with a sedation warning as specified in Appendix F Part 1 of this standard.

- Remove the requirement for bold red print for labels under paragraph 14(2).

PART 2: Labels and Containers – Amend entries to read:

7. (1)(g) for any poison other than a poison for human therapeutic use labelled in accordance with the *Required Advisory Statements for Medicine Labels*, if safety directions are required on the label by sub-paragraph 7(1)(n), with the cautionary statement –
7. (1)(m) for any poison other than a poison for human therapeutic use labelled in accordance with Therapeutic Goods Order 69 *General requirements for labels for medicines* or in an agricultural or veterinary chemical product labelled in compliance with the *Agricultural and Veterinary Chemicals Code Act 1994*, if the poison is prepared, packed or sold for a specific purpose, with clear and adequate directions for use unless:
7. (1)(n) for any poison other than a poison for human therapeutic use labelled in accordance with the *Required Advisory Statements for Medicine Labels*, if use of the poison may be harmful to the user, with appropriate safety directions (see Appendix F), grouped together as a distinct section of the label and prefaced by the words –
7. (1)(o) for any poison other than a poison for human therapeutic use labelled in accordance with the *Required Advisory Statements for Medicine Labels*, if any warning statement or statements are required for the poison (see Appendix F), with that warning statement or those statements grouped together:
8. The statement of the quantity, proportion or strength of a poison must be expressed in the most appropriate of the following forms:...
 - (3) if the poison is a solution of a mineral acid, the proportion of the acid (un-neutralised by any bases present in the preparation) in a preparation may be expressed as the un-neutralised mass of the acid per stated mass of the preparation;
9. The requirements of paragraph 7 do not apply to an immediate container that is a

measure pack or a selected container (other than an ampoule, a pre-filled syringe or an injection vial to which paragraphs 10 or 11 apply) when:

- (1) the immediate container is for a therapeutic good and is labelled in the manner prescribed by orders made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or
- (2) the immediate container is:
 - (a) packed in a primary pack labelled in accordance with paragraph 7; and
 - (b) labelled with:
 - (i) the signal word or words relating to the Schedule in which the poison is included and the purpose for which it is to be used, as shown in the table to sub-paragraph 7(1)(a); and
 - (ii) the approved name of the poison and the quantity, proportion or strength of the poison in accordance with paragraph 8; and
 - (iii) the name of the manufacturer or distributor or the brand name or trade name used exclusively by the manufacturer or distributor for the poison; and
 - (iv) if the poison is for the treatment of animals, with the cautionary statement –

FOR ANIMAL TREATMENT ONLY

written in sans serif capital letters.

10. The requirements of paragraph 7 do not apply to a selected container, or an ampoule (other than an ampoule to which paragraph 11 applies) when:

- (1) the selected container or ampoule is for a therapeutic good and is labelled in the manner prescribed by orders made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or
- (2) The selected container or ampoule is:
 - (a) packed in a primary pack labelled in accordance with paragraph 7; and

(b) labelled with:

- (i) the approved name of the poison and the quantity, proportion or strength of the poison in accordance with paragraph 8; and
- (ii) with the name of the manufacturer or distributor or the brand name or trade name used exclusively by the manufacturer or distributor for the poison; and
- (iii) if the poison is for the treatment of animals, with the cautionary statement –

FOR ANIMAL TREATMENT ONLY

written in sans serif capital letters.

11. The requirements of paragraph 7 do not apply to a selected container that is a plastic ampoule that is continuous with a strip of the same material and opens as it is detached from the strip when:

- (1) the selected container is a plastic ampoule that is continuous with a strip of the same material and opens as it is detached from the strip, is for a therapeutic good and is labelled in the manner prescribed by orders made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*; or
- (2) the selected container is a plastic ampoule that is continuous with a strip of the same material and opens as it is detached from the strip, is:
 - (a) packed in a primary pack labelled in accordance with paragraph 7; and
 - (b) the strip is labelled in accordance with paragraph 10; and
 - (c) the ampoule is labelled with:
 - (i) the approved name of the poison or the trade name of the product; and
 - (ii) the quantity, proportion or strength of the poison in accordance with paragraph 8.

Dispensary, industrial, laboratory and manufacturing poisons

13. The labelling requirements of this Standard do not apply to a poison that:

- (1) is packed and sold solely for dispensary, industrial, laboratory or manufacturing purposes; and
- (2) is labelled in accordance with *Worksafe Australia's National Code of Practice for the Labelling of Workplace Substances* [NOHSC: 2012 (1994)].

Exemptions from label requirements in certain circumstances

- 13A.** (1) The labelling requirements of sections 7- 12 do not apply to a poison where an appropriate authority has granted a labelling exemption in whole or in part for these sections for a specified product; and
- (2) the labelling exemption from an appropriate authority referred to in subparagraph (1) is limited to no more than 12 months from the effective date of the decision for retail supply of the product; and
 - (3) for the avoidance of doubt this paragraph does not apply to exemptions issued under 7(1)(m)(ii)(B) of this Standard.

Dispensed medicines

14. Unless otherwise specified by regulation:

- (1) The labelling requirements of this Standard do not apply to a medicine that:
 - (a) is supplied by an authorised prescriber or other person authorised to supply and is labelled in accordance with the requirements of Appendix L Part 1 of this Standard; or
 - (b) is supplied on and in accordance with a prescription written by an authorised prescriber and is labelled in accordance with the requirements of Appendix L Part 1 of this Standard; or
 - (c) is prepared and supplied by a pharmacist for an individual patient and is labelled in accordance with the requirements of Appendix L Part 1 of this

Standard.

(2) A person must not supply a dispensed medicine for human use containing:

(a) a substance listed in column 1 of the table at Appendix L Part 2 of this Standard unless it is clearly labelled with the warning statement(s) specified in column 2 of that table; or

(b) a substance listed in Appendix K unless it is clearly labelled with a sedation warning (being statement 39, 40 or 90 as specified in Appendix F Part 1 of this Standard).

Child-resistant closures

25. (1) If a poison, other than a poison included in a therapeutic good packaged in a manner compliant with orders made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*, listed in column 1 of the following table is sold or supplied in a container having a nominal capacity specified for that poison in column 2 it must be closed with a child-resistant closure.

Schedule 8 poisons

25A.(1) A person who supplies any Schedule 8 poison must ensure that the Schedule 8 poison is packaged in such a way that its primary pack is so sealed that, when the seal is broken, it is readily distinguishable from other sealed primary packs.

(2) This paragraph does not apply to the supply of a Schedule 8 poison by an:

(a) authorised practitioner or other authorised supplier;

(b) pharmacist on the prescription of an authorised prescriber;

(c) pharmacist employed at a hospital, on the written requisition of a medical practitioner, a dentist or the nurse or midwife in charge of the ward in which the Schedule 8 poison is to be used or stored; or

(d) nurse or midwife on the direction in writing of an authorised prescriber.

31A. A person must not sell any poison in a container used expressly for any food,

drink or condiment.

1.8.1.5 PART 3: MISCELLANEOUS REGULATIONS

A proposal to include Appendix C substances in the prohibition of advertising, as approved by NCCTG, was made. The proposed amended entry was:

- 33** A person must not include any reference to a substance included in Schedule 9 or Appendix C of this Standard in any advertisement.

Paragraph 45 was proposed to be consolidated within paragraph 14; paragraph 45 was therefore proposed to be deleted.

Pre-Meeting Submissions

None received for this item.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members debated the intention of the “reference to a substance included in” with regard to the proposed addition of a reference to Appendix C in paragraph 33. Members generally agreed to the amendment of paragraph 33, providing it was understood that the intention was that it applied only when the substance was captured by Appendix C.

RESOLUTIONS 2010/59 - 5

The Committee agreed to the amend paragraph 33 to include substances captured by Appendix C in the prohibition of advertising, for the transition to the SUSMP.

Part 3: Miscellaneous Regulations, Paragraph 33 – Amend entry to read:

- 33** A person must not include any reference to a substance included in Schedule 9 or Appendix C of this Standard in any advertisement.

1.8.1.6 PART 5: APPENDICES

It was proposed that the header for Appendix E be amended to exclude poisons for human therapeutic use when compliant with *Required Advisory Statements for Medicine Labels* (RASML), as is currently the case for the Appendix F header. The justification for this stems from Recommendation 22 of the Galbally Review. As part of the implementation of Recommendation 22 of the Galbally Review, controls on advertising, packaging and labelling of human medicines and agricultural and veterinary chemicals

(except signal headings) will be progressively transferred from the Poisons Standard to Commonwealth legislation as it is developed.

Galbally Recommendation 24 was that model legislation should be developed for adoption by reference by states and territories. The review proposed that the model legislation include all provisions which relate to the supply of medicines for therapeutic purposes and to supply of domestic chemicals. While not supporting the adoption of model legislation for achieving uniformity in these areas, NCCTG agreed to develop a uniform approach.

The new Appendix L, for the requirements for dispensing labels for medicines and dispensed veterinary chemicals, has been proposed to list all of the requirements for dispensing labels previously included in the body of the Poisons Standard. All remaining matters for dispensed medicines have been aggregated under a single heading in Part 2 Paragraph 14: "Dispensed Medicines".

Pre-Meeting Submissions

XXXXXX agreed that the specifications for dispensing labels described in Appendix L Part 1 and the warning statements described in Part 2 are reasonable and do not vary significantly from those contained in existing Western Australian poisons legislation.

XXXXXX queried the need for advisory statements for medicines for human use to still be included in Appendix F. It was argued that since the transfer of label advisory statements from the SUSDP to RASML has been completed there was no longer a need to maintain the list of statements in Appendix F.

XXXXXX also queried the need for Part 2 of Appendix L which requires the dispensing label to include mandatory advisory statements. It was argued that like other medicines requiring mandatory advisory statements, the medicines listed in Appendix L, Part 2 are included in RASML and require the equivalent Appendix F statements to be printed and grouped together on labels. It was suggested that individual schedule entries be amended to include a statement requiring compliance with RASML and Part 2 of Appendix L be deleted. Members noted that requiring compliance with RASML has implications beyond the requirements of Appendix L Part 2. Given the number of entries currently in Appendix L, the purpose of Appendix L was to create a single location for requirements for dispensing labels.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members discussed whether Appendix F was still required with the addition of Appendix L, or if duplicated entries between the two should be removed. Some of the jurisdictions asserted that entries in Appendix F were still required for enforcement, so duplications

between the two should not be removed just yet. Other Members agreed that Appendix F was still relevant where substances were not supplied in their original packaging.

Members generally agreed to the changes to the header for Appendix E and the inclusion of Appendix L in the SUSMP.

RESOLUTION 2010/59 - 6

The Committee agreed to the amendment of the Appendix E header and to the inclusion of the new Appendix L for the transition to the SUSMP.

Appendix E – Amend header to read:

APPENDIX E

FIRST AID INSTRUCTIONS FOR POISONS

[other than agricultural and veterinary chemicals (including pesticides) registered by the Australian Pesticides and Veterinary Medicines Authority and medicines for human use when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*]

Part 5: Appendices – New entry:

APPENDIX L

REQUIREMENTS FOR DISPENSING LABELS FOR HUMAN AND VETERINARY MEDICINES

PART 1

(See Part 2 Sub-paragraph 14(1))

GENERAL REQUIREMENTS FOR DISPENSING LABELS

(1) All details, words and other required information on a label on a container of a substance for therapeutic use must be in the English language in letters at least 1.5 millimetres in height.

(2) All symbols, numbers and words on a label must be in durable characters.

(3) The label on a container of a substance for therapeutic use must contain the following details:

(a) the name, address and telephone number of the dispenser supplying the substance;

(b) the approved name of the substance and / or its proprietary name (unless it is a preparation compounded in accordance with the dispenser's own formula);

(c) adequate directions for use;

- (d) the strength and form of the substance;
 - (e) the total quantity of the goods in the container;
 - (f) the words “KEEP OUT OF REACH OF CHILDREN” in red on a white background;
 - (g) if the substance is intended for external use only, the word “POISON”, or the words “FOR EXTERNAL USE ONLY”, in red on a white background;
 - (h) if the substance is a medicine, the name of the person for whom it was dispensed; and
 - (i) if the substance is a veterinary chemical, the species of animal, the name of the animal’s owner and the words “FOR ANIMAL TREATMENT ONLY”.
- (4) The label on a container of a medicine or veterinary chemical that is supplied on prescription must also include:
- (a) the prescription reference number;
 - (b) the date on which the prescription was supplied (unless that date is clear from the prescription reference number); and
 - (c) the directions for use set out in the prescription.

PART 2

ADDITIONAL LABELLING REQUIREMENTS FOR CERTAIN HUMAN MEDICINES

(See Part 2 Sub-paragraph 14(2))

Medicines required to be labelled with certain warning statements

A substance listed in Column 1 of the following table must be labelled with the warning statement in Appendix F, Part 1 as specified opposite in Column 2.

Column 1 Substance	Column 2 Warning statement
Acitretin:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Adapalene:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Bexarotene:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Dienestrol.	67

Etretinate:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Isotretinoin:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Leflunomide.	7, 62 and 87
Lenalidomide.	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Levocabastine.	62
Misoprostol.	53
Thalidomide:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77
Tretinoin:	
(i) for oral use;	7, 62 and 76
(ii) for topical use.	62 and 77

1.8.1.7 OTHER CHANGES FOR THE COMMITTEE TO NOTE

There are a number of minor editorial changes correcting or amending presentation, spelling or other minor errors in the existing entries in the Standard. These were not specifically tabled for consideration in detail by the Committee.

Amendments 1-3 of SUSDP 24 were included in the proposed version of the SUSMP which was tabled for consideration.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under Section 52(E)(1) were (i) any other matter that the Committee considers necessary to protect public health.

Members generally agreed that it would be sensible that the Secretariat should make any minor editorial changes to prepare the Poisons Standard for publication and distribution.

RESOLUTION 2010/59 - 7

The Committee agreed that any minor editorials/errata should be corrected by the Secretariat in preparing SUSMP 1 for consideration by the delegate under the new scheduling arrangements commencing 1 July 2010 for inclusion in the first SUSMP.

**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

No items.

2.2 SUSDP, PART 2

No items.

2.3 SUSDP, PART 3

2.3.1 AMBRISENTAN

PURPOSE

The Committee considered the scheduling of ambrisentan.

BACKGROUND

Ambrisentan is an endothelin receptor antagonist with selectivity for the endothelin type-A (ET-A) receptor. Ambrisentan blocks the vasoconstriction and cell proliferation effects of ET-A in the vascular smooth muscle and endothelium, which in turn relaxes the blood vessels and reduces right arterial pressure in patients with pulmonary arterial hypertension.

At the February 2009 meeting, the Committee considered the scheduling of ambrisentan and decided to include it in Schedule 4 with an entry in Appendix D, paragraph 6.

DISCUSSION - SUBMISSIONS

Application

XXXXXX requested that the Committee consider the requirements for warning statements on labels for medicines for human use containing endothelin receptor antagonists, specifically ambrisentan, bosentan and sitaxentan.

The request proposed that due to its potential to cause birth defects, ambrisentan be listed in Part 3, paragraph 45, and in Appendix F, Part 3 specifying warning statements 7, 62 and 76, consistent with the current Appendix F, Part 3 entry for bosentan.

- 7. WARNING - Causes birth defects.
- 62. Do not use if pregnant.
- 76. Do not become pregnant during use or within (Insert number of months as per approved product information) month(s) of stopping treatment.

The application noted that:

- At the October 2009 States, Territories and New Zealand Health Authorities (STANZHA) meeting, it was agreed that if a substance is added to Appendix D, it could automatically be added to paragraph 45 of Part 3, with the relevant Appendix F, Part 1 warning statements, unless it was labelled in accordance with the *Required Advisory Statements for Medicine Labels* (RASML).
- The RASML did not include any warning label requirements for ambrisentan.
- Ambrisentan was not listed in Appendix F, Part 3.

XXXXXX advised that if the Committee's decision resulted in a scheduling change, XXXXXX would be willing to accept the matter as final with an implementation date of 1 September 2010.

Impact of the changes from SUSDP to SUSMP

The proposed changes from the SUSDP to the SUSMP were discussed at item 1.8.1. As part of these proposed changes, paragraph 45, under Part 3 was removed and its intent incorporated into paragraph 14, under Part 2.

In the new SUSMP, Appendix L lists the requirements for dispensing labels for human and veterinary medicines. Appendix L, Part 2 specifies additional labelling requirements for certain human medicines. The purpose of Appendix F remains unchanged from the SUSDP, and lists the warning statements and general safety directions for poisons, other than for medicines when compliant with RASML.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (c) potential hazards and (i) other matters including labelling and packaging.

The Committee discussed the need for an Appendix L entry for ambrisentan. A Member asserted that although the regulatory authority ensures that medicines are manufactured with appropriate labelling, there are no regulations which compel a pharmacist to dispense that medicine in its registered packaging. An Appendix L entry would ensure that ambrisentan would be dispensed with the appropriate warning statements. Members generally agreed that these statements should mirror those listed in the Appendix F, Part 3 entry for bosentan (i.e. 7, 62 and 76).

Members discussed the need for an Appendix F entry for ambrisentan. A Member noted that an Appendix F entry may be redundant as appropriate labelling of prescription medicines is a matter for the regulatory authority. Other Members asserted that due to the potential hazards associated with ambrisentan, an Appendix F entry would be

appropriate to ensure consistency and clarity in the interpretation of labelling requirements.

A Member noted that to avoid any unwanted regulatory impact on existing ambrisentan products, an implementation date later than 1 September 2010 would be required for the proposed Appendix F entry.

RESOLUTION 2010/59 - 8

The Committee agreed that:

- ambrisentan be included in Appendix L, specifying warning statements 7, 62 and 76, with an implementation date of 1 September 2010;
- ambrisentan be included in Appendix F, Part 3, specifying warning statements 7, 62 and 76, with an implementation date to be determined; and
- these decisions be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument.

Appendix F – New entry

POISON	WARNING STATEMENTS	SAFETY DIRECTIONS
Ambrisentan	7,62,76	

Appendix L – New entry

Column 1 Substance	Column 2 Warning statement
Ambrisentan.	7, 62 and 76

2.3.2 BOSENTAN

PURPOSE

The Committee considered the scheduling of bosentan.

BACKGROUND

Bosentan is an endothelin-receptor antagonist and has a two-fold higher affinity for ETA receptors than ETB receptors. By blocking both receptors, bosentan reduces the effect of endothelin 1 and improves pulmonary haemodynamics in animal models of pulmonary

hypertension, decreasing pulmonary pressure and reducing the proliferation of pulmonary vascular smooth muscle.

At the February 2003 meeting, the Committee decided to include bosentan in Schedule 4 with entries in Appendix D, paragraph 6 and Appendix F, Part 3. The Committee specifically noted that the inclusion of pregnancy warning statements in Appendix F was necessary to alert women to the high potential for birth defects to occur from exposure to bosentan during pregnancy.

DISCUSSION - SUBMISSIONS

XXXXXX requested that the Committee consider the requirements for warning statements on labels for medicines for human use containing endothelin receptor antagonists, specifically ambrisentan, bosentan and sitaxentan.

The application proposed that due to its potential to cause birth defects, bosentan be listed in Part 3, paragraph 45. The application noted that:

- At the October 2009 States, Territories and New Zealand Health Authorities (STANZHA) meeting, it was agreed that if a substance is added to Appendix D, it could automatically be added to paragraph 45 of Part 3, with the relevant Appendix F Part 1 warning statements, unless it is labelled in accordance with the *Required Advisory Statements for Medicine Labels* (RASML).
- The RASML included a requirement for warning statements on labels of medicines for human use containing 'bosentan' [sic].
- Unlike ambrisentan and sitaxentan, bosentan had an Appendix F, Part 3 entry, listing warning statements 7, 62 and 76.
 - 7. WARNING - Causes birth defects.
 - 62. Do not use if pregnant.
 - 76. Do not become pregnant during use or within (Insert number of months as per approved product information) month(s) of stopping treatment.

XXXXXX advised that if the Committee's decision resulted in a scheduling change, XXXXXX would be willing to accept the matter as final with an implementation date of 1 September 2010.

Impact of the proposed changes from SUSDP to SUSMP

The proposed changes from the SUSDP to the SUSMP were discussed at item 1.8.1. As part of these proposed changes, paragraph 45, under Part 3 was removed and its intent incorporated into paragraph 14, under Part 2.

In the new SUSMP, Appendix L lists the requirements for dispensing labels for human and veterinary medicines. Appendix L, Part 2 specifies additional labelling requirements

for certain human medicines. The purpose of Appendix F remains unchanged from the SUSDP, and lists the warning statements and general safety directions for poisons, other than for medicines when compliant with RASML.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (c) potential hazards and (i) other matters including labelling and packaging.

The Committee discussed the need for an Appendix L entry for bosentan. A Member asserted that although the regulatory authority ensures that medicines are manufactured with appropriate labelling, there are no regulations which compel a pharmacist to dispense that medicine in its registered packaging. An Appendix L entry would ensure that bosentan would be dispensed with the appropriate warning statements. Members generally agreed that these statements should mirror those currently required by its Appendix F, Part 3 entry (i.e. 7, 62 and 76).

RESOLUTION 2010/59 - 9

The Committee agreed that:

- bosentan be included in Appendix L, specifying warning statements 7, 62 and 76; and
- this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Appendix L – New entry

Column 1 Substance	Column 2 Warning statement
Bosentan.	7, 62 and 76

2.3.3 SITAXENTAN

PURPOSE

The Committee considered the scheduling of sitaxentan.

BACKGROUND

Sitaxentan is an endothelin-1 receptor antagonist indicated for the treatment of pulmonary arterial hypertension in patients with WHO Functional Class III symptoms to improve exercise capacity.

At the June 2007 meeting, the Committee decided to include sitaxentan in Schedule 4 with an entry in Appendix D, paragraph 6, stating that the condition being treated would necessitate appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional.

DISCUSSION - SUBMISSIONS

Application

XXXXXX requested that the Committee consider the requirements for warning statements on labels for medicines for human use containing endothelin receptor antagonists, specifically ambrisentan, bosentan and sitaxentan.

The application proposed that due to its potential to cause birth defects, sitaxentan be listed in Part 3, paragraph 45, and in Appendix F, Part 3 specifying warning statements 7, 62 and 76 consistent with the current Appendix F, Part 3 entry for bosentan.

- 7. WARNING - Causes birth defects.
- 62. Do not use if pregnant.
- 76. Do not become pregnant during use or within (Insert number of months as per approved product information) month(s) of stopping treatment.

The application noted that:

- At the October 2009 States, Territories and New Zealand Health Authorities (STANZHA) meeting, it was agreed that if a substance is added to Appendix D, it could automatically be added to paragraph 45 of Part 3, with the relevant Appendix F, Part 1 warning statements, unless it is labelled in accordance with the *Required Advisory Statements for Medicine Labels* (RASML).
- The RASML did not include any warning label requirements for sitaxentan.
- Sitaxentan was not listed in Appendix F, Part 3.

XXXXXX advised that if the Committee's decision resulted in a scheduling change, XXXXX would be willing to accept the matter as final with an implementation date of 1 September 2010.

Impact of the proposed changes from SUSDP to SUSMP

The proposed changes from the SUSDP to the SUSMP were discussed at item 1.8.1. As part of these proposed changes, paragraph 45, under Part 3 was removed and its intent incorporated into paragraph 14, under Part 2.

In the new SUSMP, Appendix L lists the requirements for dispensing labels for human and veterinary medicines. Appendix L, Part 2 specifies additional labelling requirements for certain human medicines. The purpose of Appendix F remains unchanged from the

SUSDP, and lists the warning statements and general safety directions for poisons, other than for medicines when compliant with RASML.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (c) potential hazards and (i) other matters including labelling and packaging.

The Committee discussed the need for an Appendix L entry for sitaxentan. A Member asserted that although the regulatory authority ensures that medicines are manufactured with appropriate labelling, there are no regulations which compel a pharmacist to dispense that medicine in its registered packaging. An Appendix L entry would ensure that sitaxentan would be dispensed with the appropriate warning statements. Members generally agreed that these statements should mirror those listed in the Appendix F, Part 3 entry for bosentan (i.e. 7, 62 and 76).

Members discussed the need for an Appendix F entry for sitaxentan. A Member noted that an Appendix F entry may be redundant as appropriate labelling of prescription medicines is a matter for the regulatory authority. Other Members asserted that due to the potential hazards associated with sitaxentan, an Appendix F entry would be appropriate to ensure consistency and clarity in the interpretation of labelling requirements.

A Member noted that to avoid any unwanted regulatory impact on existing sitaxentan products, an implementation date later than 1 September 2010 would be required for the proposed Appendix F entry.

RESOLUTION 2010/59 - 10

The Committee agreed that:

- sitaxentan be included in Appendix L, specifying warning statements 7, 62 and 76, with an implementation date of 1 September 2010;
- sitaxentan be included in Appendix F, Part 3, specifying warning statements 7, 62 and 76, with an implementation date to be determined; and
- these decisions be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument.

Appendix F – New entry

POISON

WARNING STATEMENTS

SAFETY DIRECTIONS

Sitaxentan

7,62,76

Appendix L – New entry

**Column 1
Substance**

**Column 2
Warning statement**

Sitaxentan.

7, 62 and 76

2.4 SUSDP, PART 5

No items.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

3. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY(1)(c))

No items.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 CARBENDAZIM

PURPOSE

The Committee considered the scheduling of carbendazim.

BACKGROUND

Carbendazim is a broad-spectrum benzimidazole fungicide. In addition to its agricultural applications, carbendazim is also used as a fungicide in paints, jointing compounds and sealants.

At the November 1982 meeting, the Committee agreed to reschedule benomyl from the exempt list (now Appendix B) to Schedule 6 due to developmental toxicity, genotoxicity and carcinogenicity concerns. Carbendazim is the primary metabolite and alleged mutagenic compound of benomyl. At the February 1983 meeting, the Committee decided to also reschedule carbendazim from the exempt list to Schedule 6.

At the February 1989 meeting, the Committee considered a request to exempt paints containing benomyl or carbendazim at 1 per cent or less. Members agreed that, while small amounts of fungicide for preservation of dried film should present no hazard, the exact manner of their use was needed in order to word the schedule entries correctly. At the August 1990 meeting, the Committee again considered fungicides in paints and agreed to an exemption cut-off for paints containing 0.5 per cent or less of carbendazim or benomyl.

At the June 2008 meeting, the Committee considered an extension of the 0.5 per cent exemption from the carbendazim Schedule 6 entry for paints to also include construction materials. A Member noted that, given the broad general use of paint, the exposure risk from this use was likely to be lower. The Committee agreed to broaden the exemption for paints to also include jointing compounds and sealants containing less than or equal to 0.5 per cent carbendazim.

At the October 2008 meeting, the Committee considered a review of benomyl prepared as part of the APVMA Chemical Review Program. This review:

- Recommended that benomyl be rescheduled to Schedule 7 as it was a developmental toxicant in laboratory animals in the absence of maternal toxicity and that the mechanism of action may be relevant to humans. The Committee agreed.
- Concluded that the hazard from applying paint containing 0.5 per cent benomyl was not significant, nor was any hazard anticipated from dried paint, given the low vapour pressure of benomyl and that it would be encapsulated within the paint film. The Committee decided to maintain the 0.5 per cent or less exemption for paint but did agree to also include benomyl in Appendix F Part 3 with Warning Statement 46 'WARNING – Contains (name of substance) which causes birth defects in laboratory animals. Women of child bearing age should avoid contact with (name of substance)'.

At the October 2009 meeting, the Committee considered a review of carbendazim and thiophanate-methyl prepared by XXXXX as part of the APVMA Chemical Review Program. Carbendazim was nominated for review based on concerns over its potential to cause impairment of reproduction and development. This review recommended, and the Committee agreed, that carbendazim should be rescheduled to Schedule 7 as it was a developmental toxicant in laboratory animals in the absence of maternal toxicity and that the mechanism of toxicity may be relevant to humans. The evaluator also advised that, from calculations based on published data, accidental oral ingestion of as little as 3.5 mg of carbendazim would be sufficient to reach the acute reference dose (ARfD) for testicular toxicity for an adult. At a concentration of 0.5 per cent in paint, the ARfD could be exceeded by accidentally swallowing 0.7 mL of the paint during the course of a days work. On this basis, Members concluded that an exemption for paints, jointing compounds or sealants containing 0.5 per cent or less of carbendazim was no longer appropriate.

At the February 2010 meeting, the Committee considered a number of comments which asserted that the impact of the October 2009 carbendazim decision would be disastrous for the Australian paint industry as carbendazim is found in nearly all exterior paints sold in Australia. Key arguments from XXXXX, which were re-iterated in several other industry comments, were:

- the need for access to an effective film biocide in Australian conditions and at this point in time no suitable alternatives to carbendazim have been identified;
- the financial impact of the decision would be catastrophic for the manufacturers of paints, jointing compounds and sealants in Australia and importers of these products;
- XXXXX
- any new cut-off should be consistent with the European Union Adaptation to Technical Progress (ATP) of the Dangerous Substances Directive (less than 0.1 per cent).

The Committee also considered further advice from the evaluator, including the toxicological implications of a cut-off of 0.1 per cent.

Given the significant impact that the October 2009 decision to reschedule carbendazim from Schedule 6 to Schedule 7 with no exemptions would have on industry, the Committee agreed to defer the implementation date of this decision until 1 January 2011. The Committee then foreshadowed for the June 2010 meeting a consideration of a Schedule 7 parent entry for carbendazim with an exemption cut-off of 0.1 per cent for carbendazim in paints, jointing compounds and sealants.

DISCUSSION - SUBMISSIONS

XXXXX

XXXXX proposed a new exemption cut-off of 0.1 per cent. The key points of this submission were raised at the February 2010 meeting as summarised above.

XXXXX

XXXXX supported a 0.1 per cent exemption. Members noted the following points from the submission:

- While carbendazim may have harmful effects via ingestion, it is a useful chemical for protecting buildings from mould and fungal degradation. Defacement by mould and algal growth can result in many thousands of dollars in maintenance costs to building owners, and is an issue faced by most regions of Australia.
- At common usage rates in paints there is little risk of harm given the quantity of paint that would need to be ingested, 3.5 mL, to reach the ARfD of 0.05 mg / kg bw over the course of the day (noting the use of a 1000-fold safety factor in determining this limit).
- It was asserted that the risk of harm is effectively reduced by the lack of evidence that carbendazim is retained in the body.
- The submission reiterated that while alternatives to carbendazim are being investigated, no suitable replacements had been identified.
- It was argued that it would be sensible to have limits consistent with those in the 29th ATP of the Dangerous Substance Directive in the European Union (0.1 per cent).
- The submission also argued that the Schedule 6 status of carbendazim should be maintained as it avoided the need for usage licenses thus minimizing further compliance costs for businesses. The submission argued that in manufacturing there is little risk of ingestion as all operators are trained in handling chemicals of all types and wear appropriate personal protective equipment. Members noted that it was unclear if this was in addition to the exemption cut-off, or if the assumption was that the exemption was from Schedule 7 to Schedule 6 for this use.

XXXXX

XXXXX also supported the proposed 0.1 per cent exemption. Members noted the following points from the submission:

- There are currently no suitable alternative biocides available for use.
- Given the nature of sealants and jointing compounds, their packaging and use, oral ingestion of any significant amounts of the formulated products during application and use appears unlikely. Further asserted that the oral ingestion of 3.5 mL of sealants and jointing compounds appears to be an unlikely exposure scenario.
- Highlighted that on the Hazardous Substances Information System (HSIS) administered by SafeWork Australia, at concentrations of less than 1 per cent of carbendazim, there are no specified risk statements required for labelling of products.
- Supported a cut-off for carbendazim that is consistent with the European Union and Australian workplace health and safety standards.

XXXXX

The submission from XXXXX was received after the deadline for pre-meeting submissions; however the same points were raised by the valid pre-meeting submission from XXXXX which supported the proposed 0.1 per cent exemption. Members also noted the following points:

- Reiterated that there are no tested dry film biocide alternatives available.
- Highlighted the current usage of carbendazim in XXXXX paints is typically between 0.05 – 0.5 per cent carbendazim by weight. For topcoats it is unusual to exceed 0.054 per cent carbendazim by weight. Levels between 0.054 and 0.5 per cent were generally found in stains and primers where additional fungicide protection was required. These levels were the result of the previous exemption of 0.5 per cent or less.
- Asserted that XXXXX current practice is typically below the European Union cut off for carbendazim in paints (less than 0.1 per cent) and that international harmonisation would be welcome.
- Argued that a 24 month period to implement a threshold of less than 0.1 per cent would be required to ensure product stability.

XXXXX

XXXXX also supported the proposed 0.1 per cent exemption. Members noted the following points from the submission:

- Reiterated that there is no suitable biocide alternative currently available.
- Raised concerns about restrictions that may be placed on users of the raw material in production. The submission highlighted that there may be licensing requirements in

the various jurisdictions for Schedule 7 substances and these requirements may differ between the jurisdictions. The submission asserted that there may be operational implications as a consequence of these different requirements.

XXXXXX

XXXXXX argued against the Schedule 7 listing of all uses of carbendazim on the basis that the toxicological endpoints used by the APVMA and the Committee to establish exposure thresholds of carbendazim in paints were not appropriate. Members noted the following points from the submission (the points raised were based on the October 2009, not the February 2010 consideration of carbendazim):

- Reiterated that no suitable alternatives to carbendazim exist that are as effective against fungal contamination.
- Asserted that the use of carbendazim at less than 0.5 per cent in paint would not cause unreasonable risk to Australian applicators and consumers.
- Asserted that the toxicology of carbendazim should not be associated with benomyl, arguing that the US EPA had developed end points for each substance individually.
- Argued that the use of an acute high dose study that included male reproductive endpoints to assess occupational risks was unusual, and in particular questioned the appropriateness of the symptom relied upon.
- Disputed the likelihood of a worker ingesting 0.7 mL of paint during the course of the day. Highlighted that professional painters use hats and other protective clothing to minimise exposure and that they, or other painters, do not apply paint with their mouths open, as is postulated in the current approach. [Members noted that the Committee's main concern was not professional users, but home / domestic users].
- Provided a US EPA risk assessment of carbendazim. This assessment used a NOEL of 0.96 mg / kg / day for exposure assessment which was derived from a 90 day rat inhalational study with benomyl. The conclusion of this assessment was to allow industrial uses of carbendazim for paints, coatings, stuccos and construction products.
- Provided a European Union risk assessment of carbendazim. The key point of this assessment was that a threshold concentration was established for mutagenicity.
- Provided an internal risk assessment and proposal for paints and coatings.
- Suggested a concentration cut-off of 0.35 per cent of carbendazim to harmonise with US EPA and Canadian PMRA.
- Stressed that the toxicity of carbendazim as a reproductive toxicant and potential mutagen was not in dispute, but asserted that these effects could be properly managed.

February 2010 Considerations

Members also recalled the following from the February 2010 meeting:

Evaluator's comment

Advice was sought from the evaluator with regard to the oral ingestion risk of carbendazim in light of the proposal for a 0.1 per cent cut-off. Members particularly noted the following:

- The ARfD for carbendazim is 0.05 mg / kg bw. For an adult (70 kg), this represents 3.5 mg of carbendazim ($0.05 \times 70 \text{ kg} = 3.5 \text{ mg}$).
- At a concentration of 0.5 per cent the ARfD could be reached by accidentally swallowing 0.7 mL of product ($3.5 \text{ mg} / 5 \text{ mg} / \text{mL} = 0.7 \text{ mL}$) during the course of a days work.
- At 0.1 per cent, this becomes an accidental swallow of 3.5 mL of product during a day.

Members recalled that the ARfD of 0.05 mg / kg bw was based on developmental and testicular toxicity. In particular:

- In two XXXXX gavage developmental toxicity studies, increased incidence of malformations affecting the head, spine and ribs were seen at doses of XXXXX and higher. These occurred in the absence of maternal toxicity and the NOEL for these effects was 10 mg / kg bw / d.
- Testicular toxicity was observed in two separate XXXXX studies following a single gavage dose of XXXXX. Effects included premature release of immature germ cells 2 days post-exposure, atrophy of seminiferous tubules, decreased seminiferous tubule diameter, abnormal growth of efferent ductules and increased frequencies of micronuclei were observed in spermatids. In each case, this was the lowest dose tested.
- Since testicular toxicity can potentially arise following a single exposure, it is considered to be an appropriate toxicological endpoint to establish an ARfD.
- A 1000-fold safety factor, incorporating 10-fold each for intra and interspecies variation and an additional factor of 10, to account for the use of a LOEL, was used to establish the ARfD.

Members' Discussion

Members also recalled the following from the February 2010 discussion:

- Members agreed that there appeared to be potential for significant regulatory impact from the October 2009 decision. Members additionally noted that it appeared that there was a real need for this material and that, at this time, no alternatives were available.
- Several Members recalled that the European Union had set a cut off at 0.1 per cent carbendazim.

- The Committee debated whether there were grounds for reintroducing a low concentration exemption for certain uses (paints, jointing materials and sealants), particularly noting new evidence from the evaluator that at 0.1 per cent an ingestion of at least 3.5 mL was required to reach the ARfD (over the course of a day).
- Several Members suggested that the risk of ingesting 3.5 mL of paint, jointing material or sealant was significantly less than the risk of ingesting 0.7 mL (the amount needed to reach the ARfD from a 0.5 per cent carbendazim preparation). One Member also asserted that the ARfD safety factor of 1000 may be too conservative, noting that the end point of concern, testicular cancer, was only observed in a single species, with no adverse effects observed in any other species. The Member suggested that a safety factor of 100 may be more appropriate, noting that if this figure were used the ingestion volume would become an improbable 35 mL. Another Member argued that the safety factor was appropriately high because the ARfD was based on a LOEL rather than a NOEL as no clear end point could be established.
- Members generally agreed that a cut-off of 0.1 per cent for use in paints, jointing materials and sealants seemed appropriate.

TRANSITIONAL CONSIDERATIONS

XXXXXX indicated that an implementation date of 1 September 2010 was acceptable and were prepared to accept the decision from June 2010 Meeting.

XXXXXX indicated that an implementation date of 1 January 2011 would be acceptable and if the decision is consistent with XXXXX position the matter could be finalised.

XXXXXX advised that if the decision did not align with XXXXX preferred position, it should not be considered final.

XXXXXX requested an implementation date later than 1 September 2010. Further requested that the June 2010 decision not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (c) potential hazards, (d) extent and patterns of use and (e) dosage and formulation.

Members agreed that the October 2009 decision to reschedule carbendazim from Schedule 6 to Schedule 7, with an implementation date of 1 January 2011, remained appropriate. Members further agreed that consideration of an appropriate cut-off point for carbendazim in paints, jointing compounds and sealants was required.

Members discussed the merits of proceeding with the foreshadowed 0.1 per cent exemption, noting that there was general agreement from XXXXX to the proposed cut-off point of 0.1 per cent. The only opposition to this proposal came from a single,

XXXXX pre-meeting submission which maintained that a cut-off point of less than 0.5 per cent would not pose inappropriate risk, but they would also support a cut-off point of 0.35 per cent.

A Member suggested that the Committee be pragmatic in applying its transition arrangements to this decision and argued that the Committee finalise a carbendazim decision given that:

- the pre-meeting submission supporting a cut off point of 0.5 per cent included references to data that was not officially available until August 2010 and thus had not been submitted to or assessed by XXXXX;
- the rebuttal provided was in relation to the October 2009 Record of Reasons, not the February 2010 Record of Reasons. As the October 2009 decision had already been open to the full reconsideration process, the Committee agreed that it was reasonable to finalise this matter; and
- there was widespread support for the proposed 0.1 per cent exemption from all other pre-meeting submissions which included XXXXX, noting that this single objection did not appear to be from XXXXX.

Members generally agreed that it would be appropriate to include an exemption for paints, jointing compounds and sealants containing 0.1 per cent or less of carbendazim. The Committee also agreed with the argument that this decision be referred to a delegate under the new scheduling arrangements commencing for consideration of inclusion into the first instrument, with an implementation date of 1 January 2011. This implementation date would allow time for industry to make the necessary arrangements, noting that this was the previously expected implementation date for the October 2009 carbendazim decision.

RESOLUTION 2010/59 - 11

The Committee agreed that Schedule 7 is the appropriate parent entry for all uses of carbendazim. The Committee further agreed to an exemption cut-off from Schedule 7 for paints, jointing compounds and sealants containing 0.1 per cent or less of carbendazim.

The Committee agreed that this recommendation be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 January 2011.

Schedule 6 – Delete Entry

CARBENDAZIM.

Schedule 7 – New Entry

CARBENDAZIM **except** in paints, jointing compounds and sealants containing 0.1 per cent or less of carbendazim.

4.2 LAURETH CARBOXYLIC ACIDS

PURPOSE

The Committee considered the scheduling of laureth carboxylic acids (LCA).

BACKGROUND

LCA is the International Nomenclature Cosmetic Ingredients (INCI) name for a set of polymers containing, among others, polyethylene glycol-5 lauryl ether carboxylic acid (PEG-5 lauryl ether carboxylic acid) and PEG-6 lauryl ether carboxylic acid; also known as laureth-5 carboxylic acid and laureth-6 carboxylic acid respectively. LCA is a member of the alkylethercarboxylic acid class of chemicals which in turn is a member of the anionic surfactant group of chemicals.

LCA is used internationally as a surfactant and cleansing agent in a number of cosmetic and household products.

At the November 1999 meeting, the Committee noted the toxicity profile of a specific LCA salt, sodium laureth-6 carboxylate, in particular its severe eye irritancy potential, and agreed to list this specific LCA salt in Schedule 5 except for preparations containing 1 per cent or less.

At the February 2010 meeting the Committee considered a review of LCA prepared by NICNAS following a company notification. The Committee decided to include LCA in Schedule 6 with a cut-off to Schedule 5 of 10 per cent or less LCA with an exemption from scheduling for 1.5 per cent or less LCA. However, given the widespread use of LCA in cleaning and cosmetic products, there was significant potential for unintended regulatory impact from this decision. The Committee agreed to foreshadow the decision for consideration at the June 2010 meeting to allow time for additional public consultation, particularly with regard to the proposed cut-offs. The Committee also agreed to consider whether additional labelling requirements were warranted for LCA at the June 2010 meeting.

DISCUSSION - SUBMISSIONS

Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX

Argued that LCA should be treated in the same manner as sodium lauryl sulfate (SLS, Item 4.3) on the basis that the two substances have similar eye irritancy profiles. The submission argued that the proposed scheduling for LCA is inconsistent with other similar substances such as SLS. It also highlighted that LCA has a long history of safe use. Members particularly noted the following from the submission:

- Regulation (EC) No 1223/2009 of the European Parliament (November 2009) on cosmetic products does not list LCA in any of its annexes. The New Zealand Cosmetic Products Group Standard 2009 takes up the European Union cosmetic amendments (last updated 28 July 2009) and has no restriction on LCA.
- Presented evidence that the eye irritancy of LCA is considerably lower than the severe classification that formed the basis of the proposed Scheduling entry. It asserted that the Bovine Cornea Opacity Permeability (BCOP) test was a suitable screening method for hazard identification for eyes, and is an OECD approved test (No 437), having been adopted on 7 September 2007. A 1999 study was also supplied which found that BCOP irritation scores for a range of shampoos containing SLS were comparable to Draize irritation scores for the same substances.
- Presented data indicating that a formulation containing 10 per cent LCA in water or as a shampoo was a mild eye irritant in a BCOP test. Skin irritancy tests with similar substances in an EpiDerm test also produced mild irritation scores. A BCOP study testing a shampoo containing 11 per cent LCA found that after a 30 minute exposure a score of 16.7 for a 10 per cent diluted sample in water was obtained. This score was within the range (10-25) for moderately irritating.

Members noted that according to the OECD Guideline No 437, BCOP is only considered reliable for corrosive and severe eye irritants. The intention of this method is to screen for corrosive and severe eye irritants. A substance that tests negative (not corrosive or a severe irritant) in this method should be tested in rabbits using a sequential testing strategy. The accuracy and reliability for substances classified as less than corrosive or severe irritant in a BCOP test, as defined by the EPA, EU and GHS, have not been formally evaluated. Data obtained for a test substance that is not corrosive or a severe irritant may be useful when considered in conjunction with test data from the *in vivo* rabbit eye test or from an adequately validated *in vitro* test. Similarly regarding EpiDerm studies for skin irritation, results indicating mild irritation cannot be relied upon. The OECD Guideline (439) for this study is still in draft form, but is expected to be adopted soon.

XXXXX

Did not support the proposed scheduling of LCA as the proposal did not take into account the risk associated with the use of these substances in cosmetics, and it would result in unique requirements that would be detrimental to Australian business. Members also noted the following from the submission:

- It was argued that LCA had been used for many years in many different types of cosmetics with no safety concerns. Consequently, including LCA in schedules 5 and 6 was inappropriate.
- It was further asserted that the required label statements from any such scheduling would cause unnecessary alarm to consumers and would be inappropriate for cosmetic products.
- Proposed that a Schedule 6 entry consistent with that proposed for SLS would be appropriate for LCA, such as:

**LAURETH CARBOXYLIC ACIDS (excluding derivatives) for human topical use
except:**

- (a) in wash off preparations containing 30 per cent or less of laureth carboxylic acids; or
- (b) in leave on preparations containing 1.5 per cent or less of laureth carboxylic acids.

XXXXX

Also supported consideration of LCA in the same manner as SLS for scheduling. It was asserted that the February 2010 consideration had over-estimated the severity of the eye irritancy for LCA and argued that it should be considered as only a moderate irritant. Specifically:

- Submitted information indicated that 100 per cent LCA was severely irritating to rabbit eyes and that irritation persisted for the duration of the observation period.
- It was argued that if the BCOP test data is to be considered then a 1.5 per cent or less solution of LCA was considered to be a moderate irritant. The submission argued that this is a similar level of irritancy to that of SLS that is a slight irritant at 1.25 and 2 per cent and a moderate irritant at 2.5 – 5 per cent.
- It was also noted that as ethoxylation of LCAs increased, irritancy, generally, decreased.

February 2010 Considerations

Members' Discussion

The Committee recalled the following from the February meeting:

- Members first considered the existing scheduling of sodium laureth-6 carboxylate (a sodium salt of a single specific LCA). The Committee agreed that the current consideration should remain focused on the scheduling of LCA and that it did not wish to reconsider the scheduling of sodium laureth-6 carboxylate at this time.

- A Member suggested that, according to the scheduling guidelines, a Schedule 6 parent entry would be appropriate for a substance that was clearly a severe eye irritant. Another Member argued, however, that the guidelines should be considered “on balance”, i.e. that the complete toxicological profile be considered, noting both that there were no other significant toxicological concerns and the long history of use of LCA preparations without concern. Members generally agreed, however, that the long history of use was an argument more relevant to consideration of cut-offs or exemptions than for setting a parent entry. The Committee agreed that a parent entry in Schedule 6 was appropriate.
- Members discussed if an exemption or cut-off to Schedule 5 may be warranted. A Member asserted that if LCA was to be scheduled, Australia would be the only country in the world to do so. The Member noted that in this case there could be significant regulatory burdens as any required labelling on imported products would be uniquely Australian. The Member also reiterated that LCA was widely used with no history of adverse events. On this basis, the Member suggested that if scheduling was considered appropriate, an exemption cut-off of 15 per cent should apply.
- Several Members remained concerned, however, by the potential for irritancy at 15 per cent, noting that the NICNAS report identified that severe eye irritation at concentrations greater than 10 per cent could not be ruled out. Additionally, Members noted that the NICNAS report also identified that preparations containing less than 10 per cent were also likely to exhibit eye irritation (although less likely to be severe). A Member suggested, and the Committee generally agreed, that a Schedule 6 to Schedule 5 cut-off for 10 per cent or less was therefore appropriate.
- Several Members continued to argue that there was sufficient information to also consider a low level exemption from scheduling. These Members asserted that, despite some deficiencies in the protocol for the irritation studies in the NICNAS report, it still provided reasonable support for considering that the irritancy potential of LCA was significantly reduced at 1.5 per cent or less. The Committee generally agreed therefore to exempt preparations containing 1.5 per cent or less from scheduling.
- Members also discussed whether additional labelling was warranted (such as Appendix E entries). The Committee was of the view, however, that this was best left to the June 2010 meeting as this needed to be informed by any additional arguments submitted in response to the foreshadowed scheduling of LCA.

NICNAS Report

The Committee also recalled the following from the NICNAS report:

Public Health Standards

- When used in cosmetic and household products, LCA is not considered to pose an unacceptable risk to public health if used at less than 10 per cent with appropriate label statements regarding the potential for eye irritation.

Label statements

- Products should be labelled with a warning against eye contact, and directions on first aid measures if the product enters the eye (e.g. avoid contact with the eyes, in case of contact with eyes, rinse immediately with plenty of water and seek medical advice).
- The following warning statements have been recommended for products/mixtures containing LCA:
 - 10 per cent or more: Risk of serious damage to eyes
 - Between 5 and 10 per cent: Irritating to eyes.

Toxicology

- LCA (undiluted) was found to be a severe irritant in an eye irritation test in rabbits, with corneal and iridial effects observed up to the end of the 20 day observation period. A BCOP test was conducted on a product containing < 15 per cent LCA. The test substance was applied as a 10 per cent solution (therefore < 1.5 per cent LCA). This diluted solution was found to be moderately irritating.
- LCA was also found to be slightly irritating to the skin of rabbits when applied undiluted with evidence of inflammation persisting for greater than 10 days.

Occupational health and safety

- Irritation is the primary risk presented by the notified chemical to workers in occupational settings. Eye, and to a lesser degree, skin irritation, are potential risks to reformulation and/or transportatiworkers because of their handling of LCA (80-90 per cent) prior to and during reformulation. Appropriate handling techniques and the use of PPE should be in place to ensure the likhood of exposure is very low so that the risk to workers would not be considered unacceptable.
- Hairdressers and beauty therapists will encounter repeated dermal exposure to cosmetic products, such as shampoos, containing LCA (\leq 15 per cent). The risk of eye exposure is not considered likely given the hairdresser will normally be standing up during application of the shampoo. While it is unknown whether skin irritation is likely after exposure at 15 per cent or less, it is assumed that significant irritation would be unlikely given the rinse-off nature of the products.

Public health

- Members of the public will experience widespread and frequent exposure to LCA through daily use of cosmetic and household products (\leq 15 per cent) which will involve direct contact with the skin and hair. There is potential for accidental eye exposure while using shampoo products containing the LCA and this could lead to eye irritation. This exposure could be either to the \leq 15 per cent formulation, or to a diluted shampoo solution.
- As severe eye irritancy was observed with undiluted LCA the potential for severe eye effects at concentrations greater than 10 per cent cannot be ruled out. At concentrations less than 10 per cent there is likely to be eye irritation, but this is less

likely to be severe. Therefore although LCA may cause some eye irritation when used in cosmetic and household products the risk of serious eye damage may be minimised by restricting the concentration to less than 10 per cent and by clear and appropriate directions for use and safety precautions to avoid eye contact.

- First aid information should also be included on product packaging to minimise adverse effects if eye contact occurs. Extensive dermal exposure to LCA in cosmetic and household products at ≤ 15 per cent is not considered to present an unreasonable risk of skin irritation given that LCA was found to be only slightly irritating and was primarily intended for use in rinse-off products.
- A maximum systemic exposure of 0.79 mg/kg bw/day was estimated. As no repeat dose toxicity studies have been conducted, a NOAEL could not be established for LCA. Therefore a quantitative risk assessment could not be conducted. However, given the expected low systemic toxicity after repeated use and the current low introduction volume, LCA is not expected to pose an unacceptable risk of systemic toxicity to the public when used in cosmetic and household products at 15 per cent or less.

Hazard Classification

- LCA was not listed in the HSIS database of hazardous substances. On the basis of the available data and using the 2004 NOHSC Approved Criteria for the Classifying Hazardous Substances, the assessor classified LCA as hazardous with the following risk phrase: Xi; R41 Risk of serious eye damage.

February Pre-meeting Submissions

Members recalled that these submissions highlighted that LCA had safely been used as a surfactant in numerous cosmetic and home care products in Australia and overseas. Submissions either opposed scheduling of LCA in personal and home care products entirely or else suggested exemptions below an appropriate lower limit.

TRANSITIONAL CONSIDERATIONS

- XXXXX requested that if the decision made at the June 2010 meeting did not align with its preferred position, it should not be considered final.
- XXXXX requested that any decision should not be considered final and that the matter should be reconsidered under the new arrangements.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members generally agreed that relevant matters under Section 52E (1) included (a) toxicity and safety, (c) the potential hazards and (d) the extent and patterns of use.

A Member noted the similarity of SLS (item 4.3) and LCA use patterns and risk profile and argued that similar scheduling should apply to both. A Member noted that LCA

appeared to be somewhat more irritating than SLS, but that there was some uncertainty on this given the problems associated with relying on the BCOP results.

A Member noted that the principle concern appeared to be human topical use and argued that scheduling should be limited to this use, with appropriate cut-offs. Other Members argued, and the Committee generally agreed, that LCA's potential for serious eye irritation warranted a parent entry in Schedule 6 for all uses.

A Member then argued that this parent entry should be limited to LCA only, i.e. exclude salts and derivatives. The Committee agreed that this was appropriate to avoid unintended regulatory consequences.

Members then discussed potential cut-offs.

A Member recalled that the intent of the February 2010 meeting when it proposed the foreshadowed cut-offs was to take a pragmatic approach that accommodated the toxicity information tabled to date (especially the eye irritancy) while recognising the long history of safe use of many existing LCA products. Additionally, the similarity of SLS (item 4.3) and LCA was again noted and it was argued that similar cut-offs should apply to both. Several Members noted that there was no significant opposition to this intent from the pre-meeting submissions, only suggestions which would better align the cut-offs with this intent. In particular:

- *Use in leave-on products.* While one Member advocated limiting the leave-on limit to 1 per cent or less, the Committee generally agreed that there was little harm in extending the foreshadowed 1 per cent cut-off to 1.5 per cent to better reflect the current usage of LCA.
- *Cleaning products not intended for skin contact.* A Member suggested a blanket exemption for cleaning products. Other Members were concerned about not having an upper limit when high concentrations of LCA had significant eye irritancy potential. It was noted that the risk from these products would be less than that from wash-off preparations, and the foreshadowed cut-off for wash-off preparations was ≤ 30 per cent. The Committee agreed that it would be appropriate to increase the "other preparations" cut-off to ≤ 30 per cent.

Several Members noted that this new scheduling appeared to reflect the spirit of the various positions in the pre-meeting submissions. These Members argued, therefore, that it was possible to finalise the scheduling of LCA. The Committee agreed that this decision (but not the labelling issue discussed below) could be referred to a delegate for consideration of inclusion in the first legislative instrument under the new arrangements. Members did agree, however, that a delayed implementation date of 1 January 2011 was appropriate to allow time for industry to prepare for this new scheduling.

Other Labelling

Members then discussed whether additional labelling was warranted (such as Appendix E entries). A Member suggested that the main eye irritancy concern for LCA was similar to that of SLS (item 4.3) i.e. for preparations containing greater than 5 per cent. The Member suggested that any preparations above this threshold should comply with the Appendix E standard statement E1 “if in eyes wash out immediately with water” due to eye irritancy. The Member also suggested that perhaps the Appendix E standard statement S1 “if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water” would be appropriate for cleaning products containing greater than 5 per cent SLS.

Other Members suggested that this labelling need only apply as conditions for the exemptions from Schedule 6, and that anything captured by Schedule 6 would already adequately warn users as it would be labelled as “Poison”. Therefore:

- wash-off preparations, > 5 and ≤ 30 per cent, exempt only when labelled with “if in eyes wash out immediately with water”;
- leave-on preparations, ≤ 1.5 per cent – no additional labelling required; and
- all other preparations, > 5 and ≤ 30 per cent, exempt only when labelled with “if in eyes wash out immediately with water” and “if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water”.

The Committee discussed the merits of these proposals and generally agreed that it would be appropriate to consider some additional labelling for preparations containing greater than 5 per cent LCA. However, all the tabled suggestions diverged in some respect from the positions preferred by some stakeholders. Members therefore agreed that the issue of additional labelling should be referred to a delegate as a new consideration under the new scheduling arrangements, noting the concerns of the Committee that preparations with greater than 5 per cent LCA may require some additional labelling.

One Member expressed concern regarding the possibility that household products containing LCA that have significant potential to cause serious eye injury, as well as moderate acute oral toxicity, may be exempted from Schedule 6 without the mandatory requirement for appropriate warning statements and first aid instructions.

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The Committee decided to include laureth carboxylic acids (excluding salts and derivatives) in Schedule 6 with exemptions for:

- leave-on preparations, 1.5 per cent or less;
- wash-off preparations, 30 per cent or less; or
- in all remaining preparations, 30 per cent or less of laureth carboxylic acids.

The Committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 January 2011.

The Committee further decided to refer the matter of possible inclusion in Appendix E and application of appropriate labelling statements to a delegate for consideration under the new scheduling arrangements commencing 1 July 2010.

Schedule 6 – New entry

LAURETH CARBOXYLIC ACIDS (excluding its salts and derivatives) **except:**

- (a) in leave-on preparations containing 1.5 per cent or less of laureth carboxylic acids;
- (b) in wash-off preparations containing 30 per cent or less of laureth carboxylic acids; or
- (c) in other preparations containing 30 per cent or less of laureth carboxylic acids.

4.3 SODIUM LAURYL SULFATE

PURPOSE

The Committee considered the scheduling of sodium lauryl sulfate (SLS).

BACKGROUND

SLS is the approved ISO common name for the chemical sodium dodecyl sulfate (IUPAC). The chemical has a tail of 12 carbon atoms, attached to a sulfate group, giving the molecule the amphiphilic properties required of a detergent.



SLS is an anionic surfactant used in emulsifiable and suspension concentrates, liquid tablet and wettable powder formulations. SLS has a long history of use in industry, personal care products, as a pharmaceutical excipient and as a food additive. SLS has been used in cosmetics including shampoos at 10-30 per cent and is currently listed on the Australian Inventory of Chemical Substances.

At the February 2010 Meeting the Committee proposed including SLS in Schedule 6 with exemptions for:

- wash-off preparations containing 30 per cent or less SLS;

- leave-on preparations containing 1 per cent or less SLS; or
- in other preparations containing 2 per cent or less SLS.

However, given the widespread use of SLS in an extensive range of products, Members recognised that there was significant potential for unintended regulatory impact. The Committee agreed to foreshadow this proposed scheduling for consideration at the June 2010 meeting to allow time for additional public consultation, particularly with regard to the proposed cut-offs. The Committee also agreed to consider whether additional labelling requirements were warranted for SLS products at the June 2010 meeting.

DISCUSSION – SUBMISSIONS

Pre-meeting Submissions

Pre-meeting submissions were received from:

XXXXX.

XXXXX

Disagreed with the foreshadowed SLS scheduling, arguing that it did not reflect the human experience from widespread use of SLS. Members noted the following from the submission:

- The submission reiterated their position from February 2010 which was based on the NICNAS Existing Chemicals Sheet for SLS, namely that SLS posed a low risk to human health.
- Asserted that the foreshadowed entry for “other preparations” with a cut-off of 2 per cent was very conservative, arguing that non skin contact products, for example cleaning products, containing more than 2 per cent SLS would inappropriately be captured by Schedule 6.
- It was proposed that products which were not for skin contact should be exempted from scheduling, as there seem to be no problems associated with this use pattern.

XXXXX

Disagreed with the proposal to include SLS in Schedule 6, arguing that SLS has been safely used in topical cosmetics and therapeutics for decades without serious incident. However, it conceded that with the proposed exemptions the new entry for SLS would be without regulatory or commercial consequences to XXXXX. The submission also made a number of comments regarding inclusion of SLS in Appendix E, including:

- For cosmetics and therapeutics, including toothpastes, shampoos, bath soaps, shaving cream, foundations and other make-up preparations, etc, it is generally understood that these are for topical use and not for ingestion.
- Where SLS is used in food and ingestible therapeutics, requiring warning statements for action in case of swallowing would be confusing to the consumer and

commercially damaging to the product carrying such warnings. [Members noted that Appendix E does not apply to medicines compliant with the *Required Advisory Statements for Medicine Labels* as discussed under item 1.8.1.] Appendix E basic and general statements are not considered appropriate qualifying criteria for these products to be exempt from Schedule 6.

- E1 (If in eyes wash out immediately with water) is considered appropriate for wash off preparations and words to the effect of E1 are already common place in industry for wash off products. However, the use of E1 on products such as toothpastes, dried egg foods or dentifrices would not be helpful and may be confusing to the customer.
- E2 (If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor, or for at least 15 minutes.) is not considered appropriate as under normal conditions a compliant product should not cause ocular damage if the eyes are rinsed immediately, i.e. E1 is sufficient.
- Products containing SLS are generally not at risk of being inhaled and as such respiratory warnings would be inappropriate.
- The majority of the products containing SLS, which qualify for the foreshadowed exemptions, are for use on the skin, thus skin statements are not appropriate.
- It would also not be appropriate to require special purpose standard statements on products that qualified for the foreshadowed Schedule 6 exemptions.

XXXXX

Agreed with the foreshadowed SLS scheduling. It was highlighted that capsules that use less than 2 per cent SLS as a lubricant should not be affected.

XXXXX

Noted the long history of safe use of SLS and requested alternative exemptions to recognise the current use in toothpaste. Members particularly noted the following from the submission:

- Reiterated that the Cosmetic Ingredient Review (CIR), OECD Screening Information Data Sheet and NICNAS reports on SLS all concluded that it was safe for use in cosmetics. In addition, the CIR concluded that SLS was safe for use in preparations designed for brief use followed by rinsing of the skin contact area.
- Noted that many toothpastes have SLS at concentrations greater than 2 per cent, and would thus be captured by the foreshadowed Schedule 6 entry. In addition to affecting the Australian market, this could create trade barriers and potentially inhibit commercial global sourcing activities.

- Proposed either amending the “other preparations” from 2 to 5 per cent SLS to allow toothpaste to remain unscheduled, or creating an additional specific exemption for toothpaste containing less than 5 per cent SLS.

XXXXX

Reiterated the arguments above regarding the long history of safe use. It was also argued that since the intention of the foreshadowed decision was to minimise impact on industry, the Committee should reconsider the classification of toothpaste as an “other preparation”. Reiterated suggestions to either raise the exemption for other preparations from 2 to 5 per cent, or add a specific exemption for toothpastes.

XXXXX

Also reiterated the long history of safe use of SLS and argued that this should carry more weight in risk management assessments. Members particularly noted the following from the submission:

- Suggested that the scheduling entry could be specific for a 7 per cent solution for intradermal injection for animal use. However, if this preferred position was not adopted, argued that the primary concern for SLS was in topical products so other products not intended for topical use should be exempted from scheduling.
- Highlighted the confusion regarding toothpastes, especially if they were “wash off” or “other” preparations. Argued that since irritation was the main concern, oral care should be considered “wash off”, especially when toothpaste contains up to 5 per cent SLS.

XXXXX

Highlighted that there may be some unintended consequences of the foreshadowed scheduling. Members noted the following from the submission:

- Argued that liquid laundry detergents would be inappropriately classified as Schedule 6 by the foreshadowed scheduling as they would be considered an “other preparation” and these contain considerably greater than 2 per cent SLS (noting that SLS is not deliberately included but rather was an unavoidable component of sodium lauryl ethoxy sulfate (SLES), which is one of the main surfactants used in liquid laundry detergents in Australia).
- Mandatory label statements required for Schedule 6 would be disproportionate to the in-use risk of liquid laundry detergents.
- As these products are not intended for skin contact or ingestion, it was proposed that the schedule entry should be revised to only capture the primary concern of SLS in topical products.

XXXXX

The submission addressed the points from Section 52E, including:

(a) *Toxicity and safety*:

- SLS has a long history of safe use as an excipient. Asserted that the consideration before the Committee arises from a new use pattern (animal injection) rather than any safety issue arising from the current use patterns.

(d) *Extent and purpose*:

- Referred to its February 2010 submission which covered the broad use of SLS.

(e) *Dosage and formulation*:

- Argued that the foreshadowed Schedule 6 entry did not fully reflect the deliberations of the Committee according to the Record of Reasons, particular where some Members had concerns regarding potential overlap of the “other preparations” with “wash-off” and “leave-on”. For example, oral hygiene products may be considered a topical oral product that is washed off or an “other preparation” (as discussed above). Suggested a cut off for oral hygiene products, namely toothpastes, at 5 per cent.
- Advised that the foreshadowed 1 per cent limit for “leave on” preparations may mean registered topical medicines with between 1 – 1.5 per cent SLS would be Schedule 6, requiring “poison” on the label which may be misleading as well as potentially commercially unviable. The submission suggested that the “leave on” limit should be increased to 1.5 per cent.
- Regarding possible inclusion in Appendix E, the submission highlighted that at 2 per cent SLS was only a slight irritant, but with increasing concentration the irritancy increased. It was suggested that it may be beneficial to apply Appendix E standard statements to some of the exempt categories where appropriate for the use pattern.
- Discussed that the E1 statement would be appropriate for higher concentration “wash off” preparations where the product may accidentally contact the eyes and suggested that this would be appropriate for concentrations greater than 5 per cent.

February 2010 Meeting Discussion

The Committee recalled the following from the February 2010 discussion:

- Based on the toxicological information provided, the Committee generally agreed that a parent entry in Schedule 6 was appropriate for SLS given its potential for serious eye and skin irritation.
- The Committee then debated whether there should be exemptions to this general parent entry. It was noted, however, that there would be difficulties setting a low level cut-off because, while apparently justified by the extensive use of SLS at low concentrations without significant adverse events, the data provided appeared to be less robust with regard to setting a particular cut-off.

- A Member noted that the effects mentioned in the NICNAS review were concentration dependent and asserted that this, together with the long history of safe use at lower concentrations, should allow the Committee to arrive at some reasonably justifiable cut-offs for exemptions from scheduling. Members debated the appropriate concentration levels for the various uses of SLS, including wash off products, leave on cosmetics and other products, including toothpaste.
- The Committee generally agreed that, based on the information tabled to date and taking a pragmatic approach that recognised the long history of safe use of many existing products, concentrations of ≤ 30 per cent for wash off products, ≤ 1 per cent for leave on products and ≤ 2 per cent for other products appeared appropriate for exemption from the Schedule 6 parent entry. There was some debate as to whether these cut-offs should specifically relate to cosmetic use. However, it was agreed that the risk largely related to concentration and whether it was a 'leave on', 'rinse off' or 'other use', regardless of whether or not it was a cosmetic.
- A Member noted, however, that given the widespread use of SLS in many sectors, there was significant potential for unintended regulatory impact from this decision. The Committee agreed that it was appropriate to foreshadow the proposed SLS scheduling for consideration at the June 2010 meeting to allow time for additional public consultation.
- Members also discussed whether additional Appendix E standard statements or labelling criteria to qualify for the proposed exemptions were warranted. The Committee was of the view, however, that this was a debate best left for the June 2010 meeting.

February 2010 Pre-meeting submissions

There were 12 pre-meeting submissions for the February 2010 meeting. These submissions generally raised similar issues as summarised below:

- Emphasised the wide range of products for human therapeutic, hygiene and cosmetic use.
- Scheduling of SLS in Australia would severely limit the manufacture and use of these products.
- Asserted that such a limitation was unjustified in view of its widespread continuous use throughout the world for a long period of time in low concentrations, without any significant reporting of adverse effects.
- Asserted that no other regulatory agency in the world restricts the use of SLS in the aforementioned products.

February 2010 Evaluation Report

The Committee also recalled the following from the XXXXX report considered at the February 2010 meeting:

- The application was for the approval of a new technical grade active constituent (TGAC), SLS. The applicant was also seeking registration for a new product XXXXX containing SLS at XXXXX.

Public Health Standards

- The ADI for SLS was established at 0.1 mg/kg bw/d based on a NOEL of 100 mg/kg bw/d from a 28-day rat oral study and using a safety factor of 1000.
- No ARfD for SLS has been established and no suitable data was available to enable an ARfD to be set.
- Based on its oral acute toxicity and severe eye and skin irritation potential, SLS was recommended to be included in Schedule 6.

Label Statements

- New statements, including 'Will damage skin and eyes' and 'Attacks skin and eyes'.
- General Safety Precaution Statements also included 'Avoid contact with the eyes and skin', 'If product on skin, immediately wash area with soap and water' and 'If product in eyes, wash it out immediately with water'.

Toxicology

- The toxicity assessment was based on information primarily from the NICNAS Existing Chemicals Information Sheet – Sodium Lauryl Sulfate, 9 October 2007, 'International Chemical Safety Card 0502' for SLS, International Programme on Chemical Safety, August 1997 and published literature including a 'Cosmetic Ingredient Review 1983' provided by the applicant.

TGAC

Absorption, distribution, metabolism and excretion in mammals – no data available	
Acute toxicity	
Rat oral LD ₅₀ (mg/kg bw)	1200
Rat dermal LD ₅₀ (mg/kg bw)	No data
Rabbit dermal LD ₅₀ (mg/kg bw)	Approximately 600
Rat inhalation 4-hr LC ₅₀ (mg/m ³)	>3900 (one hour exposure)
Skin and eye irritation	Severe irritant
Skin sensitisation	Unknown, but unlikely to be sensitising
Short-term toxicity	
Target/critical effect	Liver toxicity
Lowest relevant oral NOEL (mg/kg bw/d)	100
Lowest relevant dermal NOEL mg/kg bw/d)	No data
Genotoxicity	Unlikely to be genotoxic <i>in vitro</i> or <i>in vivo</i>
Long-term toxicity	No data available
Carcinogenicity	No evidence of a carcinogenic potential
Reproductive toxicity	Not a reproductive toxicant
Developmental toxicity	Not a developmental toxicant.

Human safety experience

- The Cosmetic Ingredient Review of 1983 contained cosmetic experience submissions for shampoos containing SLS. The data are shown below:

Per cent SLS present in shampoo	Sales of shampoo per year in the USA	Total number of applications per year in the USA	Number of safety-related complaints
10	390,000 units	8,580,000	None in two years
14.5	Not reported	200,000	17 in 7 years
30	398,000 units	4,852,620	One in 2 years

- The evaluator further advised that the USFDA list SLS as a food additive and has exempted it from the requirement of a food additive tolerance. They also consider SLS as Generally Recognized as Safe (GRAS).
- In Australia, the Australia New Zealand Food Standards Code does not list all food additives approved for use in Australia but instead states the acceptability of additives listed in the GRAS lists of flavouring substances published by the Flavour and Extract Manufacturers' Association of the United States (which currently includes SLS). In Europe, SLS is listed in Annex II of Council Regulation (EEC) No 2377/90 meaning that no maximum residue limit (MRL) is required for a food product.
- The evaluator drew attention to the OECD SIDS Initial Assessment Report on Sodium Dodecyl Sulfate (1997) which concluded that, at present, SLS is of no concern for the general public and for workers. The evaluator also noted that the Cosmetic Ingredient Review of 1983 concluded that SLS appeared to be safe in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with skin, concentrations should not exceed 1 per cent.
- The evaluator concluded the discussion of human safety by stating that the amounts of SLS used in cosmetics, and hence the potential human exposure, are significantly smaller than that used in animal studies. Consequently, considering the human health effects associated with SLS together with data indicating potentially extensive use in both industrial and consumer areas, it appears that for consumers and workers, the human health hazards are low.

TRANSITIONAL CONSIDERATIONS

XXXXXX requested that if the decision made at the June 2010 meeting did not align with their preferred position it should not be considered final.

XXXXXX also added that without being aware of the outcome of decisions made by the June Meeting, they could not provide an unconditional agreement to accept a decision made at this meeting as final.

XXXXXX argued that the Committee's decision on this matter should not be considered final for various reasons, the most pertinent being that it would be inappropriate to proceed to a schedule entry without further opportunity for comment.

XXXXXX commented that they were happy with a Schedule 6 parent entry or the proposed Schedule 6 entry with exemptions. They requested that the issue be finalised at the June 2010 meeting, with an implementation date of 1 September 2010, XXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members generally agreed that relevant matters under Section 52E (1) included (a) toxicity and safety, (c) the potential hazards and (d) the extent and patterns of use.

A Member, reiterating that SLS had been used for a long time in a broad range of products with no evidence of adverse incidents, suggested limiting any scheduling to the new use identified by the XXXXX evaluation report (animal use for injection). The Member noted XXXXX was reconciled to a Schedule 6 classification. Another Member also agreed that Schedule 6 was warranted given the lack of data provided on product packaging for this use.

Several other Members agreed that the use examined in the XXXXX evaluation report should be Schedule 6 but disagreed that this should be the only use scheduled, noting that the foreshadowed scheduling had already made many concessions regarding current products. The Committee generally agreed that, based on the toxicological information provided, a Schedule 6 parent entry was appropriate for SLS given its potential for serious eye irritation.

A Member then argued that this parent entry should be limited to SLS only, i.e. excluding its salts and derivatives, noting a range of surfactant by-products and precursors which would otherwise potentially be scheduled. The Committee agreed that this was appropriate to avoid unintended regulatory consequences.

Members then discussed potential cut-offs.

A Member recalled that the intent of the cut-offs proposed at the February 2010 meeting was to take a pragmatic approach that incorporated the toxicity information tabled to date (especially the eye irritancy) while recognising the long history of safe use of many existing SLS products. Several Members noted no significant opposition to this intent in the pre-meeting submissions, but suggestions were made that would more closely align the cut-offs with this intent. In particular:

- *Use in toothpaste up to 5 per cent.* Members generally agreed that a cut-off for this use was appropriate. Members further agreed that this cut-off should also apply to all oral hygiene products.

- *Use in leave-on products.* Members generally agreed that there was little harm in extending the foreshadowed 1 per cent cut-off to 1.5 per cent to accommodate existing use in some topical therapeutic products.
- *Cleaning products not intended for skin contact.* One Member suggested a cut-off of 15 per cent might be appropriate, noting that there was very little data about this use pattern. Other Members noted that this would be somewhat incongruous given that the risk from these products would be less than that from wash-off preparations, and the foreshadowed cut-off for wash-off preparations was 30 per cent or less. The Committee agreed that it would be appropriate to increase the “other preparations” cut-off to 30 per cent or less.

Several Members noted that this new scheduling appeared to reflect the spirit of the various positions in the pre-meeting submissions. These Members argued, therefore, that it was possible to finalise the scheduling of SLS. The Committee agreed that this decision (but not the labelling issue discussed below) could be referred to a delegate for consideration of inclusion in the first legislative instrument under the new arrangements. Members did agree, however, that a delayed implementation date of 1 January 2011 was appropriate to allow time for industry to prepare for this new scheduling.

Other Labelling

Members then discussed whether additional labelling was warranted (such as Appendix E entries). A Member suggested that the main eye irritancy concern was for preparations containing greater than 5 per cent SLS. The Member suggested that any preparations above this threshold should comply with the Appendix E standard statement E1 “if in eyes wash out immediately with water” due to eye irritancy. The Member also suggested that the Appendix E standard statement S1 “if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water” would be appropriate for cleaning products containing greater than 5 per cent SLS.

Other Members suggested that this labelling need only apply as conditions for the exemptions from Schedule 6, and that anything captured by Schedule 6 would already adequately warn users as it would be labelled as “Poison”. Therefore:

- wash-off preparations, > 5 and ≤ 30 per cent, exempt only when labelled with “if in eyes wash out immediately with water”;
- leave-on (≤ 1.5 per cent), toothpaste and oral hygiene preparations (≤ 5 per cent) and other animal use (≤ 2 per cent) – no additional labelling required;
- all other preparations, > 5 and ≤ 30 per cent, exempt only when labelled with “if in eyes wash out immediately with water” and “if skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water”.

The Committee discussed the merits of these proposals and generally agreed that it would be appropriate to consider some additional labelling for preparations containing greater than 5 per cent SLS. However, all the tabled suggestions diverged in some respect from

the positions preferred by some stakeholders. Members therefore agreed that the issue of additional labelling should be referred to a delegate as a new consideration under the new scheduling arrangements, noting the concerns of the Committee that preparations with greater than 5 per cent SLS may require some additional labelling.

One Member expressed concern regarding the possibility that household products containing SLS that have significant potential to cause serious eye injury, as well as moderate acute oral toxicity, may be exempted from Schedule 6 without the mandatory requirement for appropriate warning statements and first aid instructions.

RESOLUTION 2010/59 - 13

The Committee decided to include sodium lauryl sulfate (excluding salts and derivatives) in Schedule 6 with exemptions for:

- wash-off preparations, 30 per cent or less;
- leave-on preparations, 1.5 per cent or less;
- toothpaste and oral hygiene preparations, 5 per cent or less;
- in other preparations for animal use, 2 per cent or less; or
- in all remaining preparations, 30 per cent or less of sodium lauryl sulfate.

The Committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 January 2011.

The Committee further decided to refer the matter of possible inclusion in Appendix E and application of appropriate labelling statements to a delegate for consideration under the new scheduling arrangements commencing 1 July 2010.

Schedule 6 – New entry

SODIUM LAURYL SULFATE (excluding its salts and derivatives) **except:**

- (a) in wash-off preparations containing 30 per cent or less of sodium lauryl sulfate;
- (b) in leave-on preparations containing 1.5 per cent or less of sodium lauryl sulfate;
- (c) in toothpaste and oral hygiene preparations containing 5 per cent or less of sodium lauryl sulfate;

- (d) in other preparations for animal use containing 2 per cent or less; or
- (e) in other preparations containing 30 per cent or less of sodium lauryl sulfate.

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

5.1 SUSDP, PART 4

5.1.1 BROMHEXINE

PURPOSE

The Committee considered the scheduling of bromhexine.

BACKGROUND

Bromhexine is a mucolytic substance that is used to decrease viscosity of sputum with consequent ease of expectoration. It is used for this purpose in both humans and animals.

Bromhexine was originally included in Schedule 4 in 1969 due to a lack of adequate data. In Appendix XV – Amendments to the Uniform Poisons Standard, April 1977, bromhexine was deleted from Schedule 4 and included in Schedule 2 for all uses. Previously requested toxicity information is presumed to have been provided to the Committee at that time however, the Committee records do not contain this detail.

In May 1986, an attempt was made to have bromhexine for animal use rescheduled from Schedule 2 to Schedule 6, on the grounds that it was a veterinary poison. This was not considered by the Committee as the request was not received in time for consideration at the next meeting, nor was any supporting data for such a request submitted. This does not appear to have been subsequently pursued.

There are 12 products currently available, as listed on PUBCRIS, for animal therapeutic use containing only bromhexine or bromhexine in combination. Of these, 10 are labelled as “Prescription [Only] Animal Medicine”. The other 2 are labelled “Pharmacy Medicine. For Animal Treatment Only” with the instruction “for use by or under direction of a registered vet”. In both instances, the labels may be beyond the current Schedule 2 requirements for bromhexine.

DISCUSSION - SUBMISSIONS

Recently, the 77th Meeting of the NCCTG set out new policy principles relating to Schedules 2 and 3, in particular that these two schedules should be reserved exclusively for human medicines. Members of NCCTG decided that veterinary medicines should not

be included in Schedule 2 or 3 and that the current inclusion of veterinary medicines in these schedules should be phased out. It was argued that not all pharmacists would be able to provide relevant information on the veterinary use of these products.

The NCCTG has therefore requested that the Committee reconsider the entry for bromhexine in Schedule 2, with a view to not capturing animal use in this entry.

There was concern that removing bromhexine, and similar substances, from Schedule 2 and 3 would result in these products becoming unscheduled, making the imposition of child-resistant packaging or supply controls more difficult. It was suggested that this could be managed by instead including these products in Schedule 4, 5, 6 or 7.

Pre-meeting Submissions

XXXXX identified numerous products containing bromhexine that were not for animal use and requested that this information be considered to avoid any unintended impact on their availability.

XXXXX also highlighted that there are many products containing bromhexine currently available for human therapeutic use. In addition XXXXX would support clarifying the current entry with the words “for human therapeutic use”.

XXXXX also submitted a (not exhaustive) list of Schedule 2 human OTC medicines containing bromhexine and stressed that any amendment to the current entry for bromhexine must not impact on the existing scheduling arrangements for human OTC medicines.

XXXXX requested clarification of the Gazette Notice, given that there are bromhexine products for human therapeutic use in Schedule 2.

TRANSITIONAL CONSIDERATIONS

XXXXX requested that if the final decision differs from their position, it should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (f) the need for access to a substance, and (h) the purposes for which a substance is to be used.

The Committee noted that the premise of NCCTG’s request, that the only bromhexine products listed in Schedule 2 were solely veterinary products, was incorrect.

As it appeared that nearly all of the currently registered bromhexine products for animal use are treated as prescription products, Members considered whether a Schedule 4 parent entry for bromhexine for animal use may be appropriate.

The Committee generally agreed however that a Schedule 4 entry for bromhexine for animal use would be inappropriate, given the general safety of bromhexine. However, several Members argued that some professional advice was required for pet owners.

Members discussed whether labelling from inclusion in Schedule 5 or 6, together with APVMA requirements, might sufficiently address this need. There was discussion regarding the merits of a Schedule 5 or 6 listing for animal use. The Committee generally agreed that more information was required before inclusion in Schedules 5 or 6 could be supported, particularly on:

- the availability and need for bromhexine for veterinary use (noting that current animal products appear to be labelled as prescription [animal] preparations and it is unclear at this stage whether such a restriction is required);
- specific products used;
- what controls would be required, such as professional veterinary intervention; and
- the availability of toxicity data on this substance.

There was general agreement from Members that the scheduling of bromhexine should remain unchanged until this further information is provided.

RESOLUTION 2010/59 - 14

The Committee acknowledged the request of NCCTG, has considered the rescheduling of bromhexine and resolved that the current scheduling should remain unchanged pending further exploration of:

- the need for access within a veterinary setting; and
- the availability of toxicity data about this substance.

Members agreed that this matter should be referred to the Delegate for reconsideration under the new scheduling arrangements.

5.1.2 LIGNOCAINE

PURPOSE

The Committee considered the scheduling of lignocaine.

BACKGROUND

Lignocaine is a local anaesthetic which acts by reversible inhibition of nerve impulse generation and transmission. It is used in local, surface and topical anaesthetics. A low dose topical formula, for human therapeutic use, has been used for the management of teething in infants, in the treatment of transient mouth ulcers, minor oral injury, new dentures and inflammation of the gums, palate and tongue.

Erythema may occur after topical use of some lignocaine formulations while transient blanching of the skin is frequent after application of eutectic lidocaine/prilocaine mixtures to the skin. True hypersensitivity reactions, including dermatitis, rarely occur. Methaemoglobinaemia has occurred after the topical application of a eutectic preparation of prilocaine and lignocaine. After the use of this mixture in infants and children, some infants may be particularly susceptible to induced methaemoglobinaemia during the first 3 months of life probably due to their limited enzyme capacity.

In animals, lignocaine is used as an anaesthetic in the ear, nose and throat, and in dermatological preparations, either as the sole active ingredient or in combination with other substances.

Scheduling considerations for lignocaine have been in relation to human therapeutic use. The most recent consideration of the scheduling of lignocaine was at the October 2008 meeting when the Committee considered a proposal to broaden the current Schedule 2 exemption for dermal use (less than or equal to 2 per cent) to also exempt use on gums. At this time the Committee decided that the current Scheduling remained appropriate.

There is no record of a scheduling consideration for lignocaine for animal use. There are 15 products on PUBCRIS currently listed for animal use containing only lignocaine or lignocaine in combination. Thirteen of these products are currently labelled as "Prescription [Only] Animal Medicine". One is labelled "Pharmacy Medicine For Animal Treatment Only". One is labelled "Caution For Animal Treatment Only".

DISCUSSION - SUBMISSIONS

Applicant's Submission

Recently the 77th Meeting of the NCCTG set out new policy principles relating to Schedules 2 and 3, in particular that these two schedules should be reserved exclusively for human medicines. Members of NCCTG decided that veterinary medicines should not be included in Schedule 2 or 3 and that the current inclusion of veterinary medicines in these schedules should be phased out. It was argued that not all pharmacists would be able to provide relevant information on the veterinary use of these products.

The NCCTG has therefore requested that the Committee reconsider the entry for lignocaine in Schedule 2, with a view to not capturing animal use in this entry.

There was concern that removing lignocaine, and similar substances, from Schedule 2 and 3 would result in these products becoming unscheduled, making the imposition of child-resistant packaging or supply controls more difficult. It was suggested that this could be managed by including these products in Schedule 4, 5, 6 or 7.

Pre-meeting Submissions

XXXXXX advised that lignocaine is an active ingredient in many products in Schedule 2 for human use. This contradicts the wording of the Gazette Notice that the only known products captured by the Schedule 2 lignocaine listing are indicated exclusively for veterinary use.

XXXXXX highlighted two topical products containing lignocaine that are not indicated exclusively for animal use.

XXXXXX also noted numerous products containing lignocaine that are not for animal use and requested that this information be considered to avoid any unintended impact on their availability.

XXXXXX also highlighted that there are many products containing lignocaine currently available for human therapeutic use. In addition, XXXXXX would support clarifying the current entry with the words “for human therapeutic use”.

XXXXXX requested clarification of the Gazette Notice, given that there are lignocaine products for human therapeutic use in Schedule 2. There are 33 products containing lignocaine listed on the ARTG.

TRANSITIONAL CONSIDERATIONS

XXXXXX requested that if the final decision differs from their position, it should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety; (f) the need for access to a substance, and (h) the purposes for which a substance is to be used.

The Committee noted that the premise of NCCTG’s request, that the only lignocaine products listed in Schedule 2 were solely veterinary products, was incorrect.

As it appears that nearly all of the currently registered lignocaine products for animal use are treated as prescription products, Members considered whether a Schedule 4 parent entry for lignocaine for animal use may be appropriate.

The Committee generally agreed however that a Schedule 4 entry for lignocaine for animal use was not appropriate, given that no adverse drug reactions had been reported to date.

A Member then suggested that lignocaine for animal use be rescheduled to Schedule 6. Other Members remained concerned however that there was a need for veterinary intervention when using lignocaine animal products. The Committee generally agreed

that there was inadequate information to support the rescheduling of lignocaine for animal use to Schedules 4, 5 or 6 given:

- No toxicological data was submitted to support a rescheduling proposal;
- Advice from the veterinary profession would also need to be obtained to support a rescheduling proposal; and
- Consideration of appropriate warning labels needed further discussion.

The Committee therefore agreed that the matter should be referred to a delegate for reconsideration under the new scheduling arrangements.

RESOLUTION 2010/59 - 15

The Committee acknowledged the request of NCCTG, has reconsidered the rescheduling of lignocaine and resolved that the current scheduling should remain unchanged pending further exploration of:

- the need for access within a veterinary setting; and
- the availability of toxicity data about this substance.

Members agreed that this matter should be referred to the Delegate for reconsideration under the new scheduling arrangements.

5.2 SUSDP, PART 5

No items.

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

No items.

7. MATTERS REFERRED BY OFFICE OF CHEMICAL SAFETY (OCS) OR THE NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME (NICNAS)

7.1 TRICLOSAN

PURPOSE

The Committee considered the scheduling of triclosan.

BACKGROUND

5-Chloro-2-(2,4-dichlorophenoxy)phenol, commonly known as triclosan, is used in the formulation of cosmetics and personal care products, cleaning agents, therapeutics,

pesticides and veterinary products as a preservative or anti-bacterial. It is also used to treat textiles and in plastics due to its antimicrobial activity.

Triclosan was declared a Priority Existing Chemical (PEC) for full chemical assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* (ICNA Act), because of environmental concerns in 2003. The widespread use of triclosan provided a number of ways for the chemical to enter the environment and tests showed that it may be toxic to algae and other aquatic species. The chemical properties also indicate that triclosan may be bioaccumulative and persistent in the environment.

Prior to August 1989 triclosan had been listed in Appendix B (or its equivalent). At the August 1989 meeting, the Committee reconsidered triclosan on the basis of new toxicology data, and confirmed that Appendix B remained appropriate, i.e. a compound of low toxicity not requiring control by scheduling.

Appendix B was subsequently removed from the SUSDP in the mid 1990s. A new Appendix B was reintroduced into the SUSDP in the early 2000's, but did not include a number of substances that had previously been in Appendix B as the Committee was unable to locate data for these substances to continue justifying such a listing.

At the June 2005 meeting, it was noted that triclosan was not included in Appendix B when it was reinstated. A change to the scheduling of triclosan was proposed based on a toxicology assessment, however, the Committee agreed to defer any scheduling consideration until the NICNAS PEC review was completed.

DISCUSSION - SUBMISSIONS

Application

NICNAS referred its triclosan PEC Assessment Report (http://nicnas.gov.au/Publications/CAR/PEC/PEC30/PEC_30_Full_Report_PDF.pdf) with a request for a scheduling consideration. The PEC Review recommended that a maximum level for triclosan as a preservative in cosmetic and personal care products be set. Prior to the June 2010 meeting NICNAS clarified its position by explicitly recommending that cosmetics and personal care products should only be allowed to contain a maximum of 0.2 per cent triclosan for leave-on, rinse-off and oral care products (discussed in detail under the "NICNAS subsequent recommendation" heading below).

The PEC report included a risk assessment on public health, occupational health and safety and environmental effects of triclosan. Triclosan in pesticides and veterinary medicines and therapeutic products was not assessed as these uses were outside the scope of the ICNA Act. Members particularly noted the following PEC conclusions:

- It is appropriate to have a maximum concentration limit for triclosan across various cosmetic products due to the potential for health effects from aggregate exposure.

This is consistent with other countries which have also set maximum allowable concentrations for cosmetics containing triclosan.

- The EU maximum concentration level of 0.3 per cent or less for triclosan in cosmetic and personal care products was suggested as being protective to public and promoting international harmonisation.
- However, the most current EU Scientific Committee on Consumer Products (SCCP) opinion on triclosan (2009) considered the current concentration of 0.3 per cent in all cosmetic products as unsafe for the consumer because of the magnitude of aggregate exposure. This safety evaluation was based on a conservative NOAEL of 12 mg/kg bw/day based on haematotoxicity and decreased absolute and relative spleen weights.
- Based on inhalation toxicity and the additional acute effect of respiratory irritation, triclosan in pure form meets the criteria for Schedule 6. The skin and eye irritation potential of triclosan meets the criteria for Schedule 5.
- Due to the low concentration of triclosan in consumer products, the risk of an acute adverse effect (acute toxicity or irritation) following exposure to triclosan containing products is low. However, health effects (liver) may occur in some individuals from triclosan exposure through the repeated use of a single product containing high levels or combined use of multiple cosmetic and personal care products containing triclosan.
- The risk of health effects in babies and children following repeated use of a subset of products containing triclosan is low. Also, risks of chronic effects from exposure through breast-milk containing triclosan were low.
- Public use of triclosan products, and hence potential exposure, was widespread.
- Under normal conditions of consumer use the risk of adults and children being exposed to levels of triclosan that would lead to adverse health effects such as inhalation toxicity, skin, eye and respiratory irritation and chronic effects was low.
- However, the use patterns of triclosan-containing products vary greatly among individuals. Some studies in humans showed a high level of exposure following use of a single cosmetic or personal care product. This raises concerns that chronic health effects may potentially occur in some individuals through the combined use of a range of cosmetic and personal care products containing triclosan, or use of certain products containing relatively high concentrations of triclosan. However, these limited incidences were not reflective of general consumer exposure.

Members also noted the following toxicology summary from the PEC report:

Acute toxicity

- Triclosan has low acute oral toxicity in rats and dogs ($LD_{50} > 5000$ mg/kg bw) and low acute dermal toxicity in rabbits ($LD_{50} > 9300$ mg/kg bw). For inhalation toxicity, in a 21 day repeat dose inhalation study more than half of treated rats died following a single 2 hour nose-only exposure to a triclosan aerosol at 1300 mg/m³. The LC_{50} for triclosan is therefore < 1300 mg/m³ in rats.

- Triclosan produces both skin and eye irritation in rabbits but is not phototoxic in guinea-pigs. It also induces severe respiratory irritation based on observations from a 21-day repeat dose inhalation toxicity study in rats. Triclosan is not a skin sensitiser in guinea-pigs. No data was available on the respiratory sensitisation potential of triclosan.
- Human volunteer studies of triclosan show skin irritation in the absence of phototoxicity. Furthermore, available human data indicates that triclosan may be a very weak skin sensitiser. There is very limited evidence of photo-sensitisation.

Repeat dose toxicity

- Overall, data from several animal species indicate that the principal effects following repeated oral exposure to triclosan are hepatic effects. Oral NOAELs of 40 mg/kg bw/day (males) and 56 mg/kg bw/day (females) were established in a well conducted 2-year rat carcinogenicity study based on clinical chemistry and histological changes in the liver in males.
- In a 90-day rat dermal study, degenerative changes in the liver and kidney (not dose related) and occult blood in the urine were also observed in some animals. These findings were seen in the absence of other significant clinical chemistry or haematological changes or treatment related histopathological changes and a NOAEL of 80 mg/kg bw/day was identified. For local irritant effects, a NOAEL could not be identified and a LOAEL of 10 mg/kg bw/day was established.
- In the only repeat dose inhalation study available (21 day rat study), severe signs of systemic toxicity (muscle spasms, acute inflammation with focal ulceration of the mucous membranes of the nasal cavity and trachea, haemorrhage and severe acute congestion and oedema of the lungs) and deaths were observed during the first week of treatment. A NOAEC of 50 mg/m³ was identified based on irritation of the nasal tract and changes in clinical chemistry parameters.
- Available human data provides no reliable information to identify a robust NOAEL or profile the systemic toxicity of triclosan.

Genotoxicity and carcinogenicity

- Overall, available *in vitro* and *in vivo* genotoxicity studies in bacteria, fungi or mammalian cells indicate that triclosan is not genotoxic. Similarly, carcinogenicity studies in rats and hamsters provided no evidence of a carcinogenic potential.

Developmental toxicity

- No evidence of fertility effects was seen in a two-generation dietary study in the rat or numerous repeat dose studies of 90-days or longer duration. Similarly, no evidence of developmental effects was seen in robust studies in the rat or rabbit at triclosan doses up to those that produced marked maternal toxicity.

Absorption and distribution

- Triclosan is readily absorbed following oral and dermal administration in both humans and animals. Human data indicated that at least 97 per cent and 14 per cent of triclosan was absorbed by oral and dermal routes, respectively. Dermal absorption was dependent on the formulation in which triclosan was delivered with greater absorption seen following delivery in a solution than in cream. Human oral and dermal data provided no evidence of a bioaccumulation potential. However, enterohepatic circulation has been demonstrated in rats with limited evidence for such in mice and hamsters.
- There are no data to allow a quantitative estimation of absorption of triclosan following inhalation exposure. However, the observation of clinical signs of systemic toxicity in a 21-day repeat dose inhalation study in the rat indicates that absorption via the inhalation route can occur.
- Triclosan and/or its metabolites have been observed in human breast milk. First pass metabolism and relatively rapid elimination of triclosan suggests that the potential for transfer to the foetus and bioaccumulation may be limited.

Public exposure

- Exposure can occur through the use of consumer products such as cosmetic and personal care products, household cleaning products, paint, plastics and textiles.
- Given the types of triclosan products available, the main route of exposure is dermal. However, oral exposure may occur through accidental ingestion of cosmetic and personal care products such as lip balm, toothpaste or mouthwash formulations. Inhalation exposure may occur through breathing aerosols from the use of cosmetic, personal care or cleaning products.
- Cosmetics and personal care products: A variety of cosmetic and personal care products contain triclosan. These include aerosols, rinse-off or leave-on products, oral care products and wipes. The concentration of triclosan in these products ranges considerably from less than 0.01 to 0.5 per cent. The highest concentration of triclosan was observed in rinse-off products (up to 0.5 per cent) whereas most other products contained less than 0.3 per cent of triclosan.
- Cleaning products: Triclosan is present in a number of household cleaning products, at concentrations ranging from 0.04 per cent to 0.3 per cent. These include dishwashing detergents, laundry detergent, surface cleaners, and commercial and hospital grade cleaners. Currently the level of exposure from this source is relatively low with less than 1 tonne/year being used for these applications.
- Textiles and plastic articles: Textiles containing triclosan include insulation batts, bedding, quilts and blankets, pillows, curtains and blinds and clothing. Triclosan is also used as an antimicrobial additive in plastics. No data are available on the leaching of triclosan from plastic and textile products and therefore the potential oral or dermal exposures and health risks from these products are particularly uncertain.

- Other industrial uses: Triclosan is also used in certain industrial products such as antimicrobial treatments for air-conditioning heat exchange coils, tile grouts and tile and laminate paints.

Risk

- The majority of cosmetic products used in Australia contain 0.3 per cent or less of triclosan. However, some rinse-off products, such as shower/bath gels, body washes, face washes and face masks contain up to 0.5 per cent triclosan.
- The table below provides overall body burden and margin of exposure (MOE) calculations for estimated triclosan exposures from combined use of cosmetics and personal care products at various cut-off concentrations.

Triclosan (%)	Inhalation (µg/kg bw/d)	Dermal (µg/kg bw/d)	Oral (µg/kg bw/d)	Internal dose (µg/kg bw/d)	MOE (based on NOAEL of 40 mg/kg bw/d)
0.1	6 - 18	93	8	107 - 119	374 - 336
0.2	12 - 36	186	16	214 - 238	187 - 168
0.3	18 - 54	279	25	321 - 357	125 - 112

- These calculations are based on a realistic worst case scenario where exposure is assumed from multiple cosmetic and personal care products containing triclosan by all exposure routes.
- At concentration cut-offs of 0.1 or 0.2 per cent, MOEs are noticeably greater than 100 indicating low risk. However, at a concentration cut-off of 0.3 per cent, the MOE is as low as 112. NICNAS asserts that this raises a concern that health effects may be likely in individuals through combined use of multiple cosmetic products containing triclosan up to this concentration. [Several Members questioned this “may be likely” conclusion given that the MOE was still above 100, the usually accepted standard for “low risk”.]
- Available volunteer studies show considerable variations in plasma steady state levels of triclosan following use of different products and high levels following repeated use of single products containing triclosan. The lowest MOE seen was 179 in males following the repeated use of a single hand wash product containing 1 per cent triclosan. Similarly, MOEs of 258 and 311 were seen in female and male volunteers following the repeated use of a toothpaste containing 0.3 per cent of triclosan. MOEs would be even lower than those observed in some individuals through combined use of multiple products and/or products containing higher concentrations of triclosan.

NICNAS subsequent recommendation

NICNAS also provided subsequent recommendations:

- To ensure an adequate MOE for health effects from repeated exposures to triclosan, it is recommended that cosmetics and personal care products contain a maximum allowable cut-off concentration of 0.2 per cent triclosan for leave-on, rinse-off and oral care products.
- Table 2 shows a breakdown of internal doses and estimated MOEs for use of these product types.

Exposure	Product type	Recommended triclosan content (%)	Internal dose (µg/kg bw/d)
Dermal	Leave-on	0.2	184
	Rinse-off	0.2	2
Oral	All oral products	0.2	16
Inhalation	Spray	0.2	12 - 36
Combined internal dose (use of all products)			214 - 238
Combined MOE based on NOAEL of 40 mg/kg bw/d			187 - 168

- The MOE for a combined exposure scenario assuming use of multiple cosmetic and personal care products is estimated to be 187 – 168 and is considered representative of an acceptable risk at this proposed concentration cut-off.
- Recommended that triclosan not be used in cosmetic or personal care products above 0.2 per cent. The Committee should consider appropriate scheduling for triclosan in cosmetics and personal care products with risk mitigation measures that are adequately protective above the recommended cut-off concentration.

Pre-meeting Submissions

Pre-meeting submissions were received from:

XXXXX.

There was general support for a 0.3 per cent cut off for triclosan as a preservative in cosmetics and personal care products. However, the majority of submissions raised concerns that they had not been consulted on NICNAS's final recommendation of 0.2 per cent.

XXXXX

Argued that the current status of triclosan was appropriate. Any changes in scheduling could result in widespread commercial and regulatory implications as it is used in hand washes, toothpastes, acne products and bath oils. Advised that a search of the TGA's

website identified 17 therapeutic products containing triclosan (mainly antibacterial hand washes).

XXXXX

While there was tentative support XXXXX for a 0.3 per cent cut-off for triclosan in cosmetics, the submission questioned the need for scheduling of triclosan when it was indicated in the PEC that there are currently no health concerns associated with triclosan. Members noted the following points from the submission:

- Cited the European Union Cosmetics Directive (76/78/EEC) which specifically approves triclosan as a preservative for use in all cosmetic products at levels up to 0.3 per cent. Further highlighting that an additional EU review of triclosan is expected at the end of 2010.
- Highlighted that the US FDA had previously found triclosan safe for use in consumer products, noting that triclosan in consumer products is currently under review.
- Argued that since it had taken so long for NICNAS to make a recommendation to the Committee on triclosan, there was little concern for public safety regarding the current use of triclosan.
- Suggested that the Committee may wish to defer a decision on the scheduling of triclosan until the EU and US FDA reports are available.

XXXXX

Reiterated the above points. Also advised that triclosan is used in a number of its products that have been sold in Australia for approximately 8 years and they have yet to receive a consumer safety complaint.

XXXXX

Recommended deferring a decision until NICNAS had discussed its final recommendation with industry or until the USFDA review of triclosan was finalised.

XXXXX

Members noted the following from this submission:

- Argued that there seemed to be no basis for the suggested 0.3 per cent cut off from any of the data evaluated in the report and there seemed to be low risk for chronic human health risks.
- Highlighted that the concentration of triclosan in various imported cosmetic and personal care products is 0.00125 – 0.87 per cent, and was likely to be similar in locally manufactured products.
- Suggested that if triclosan was to be scheduled then the cut-off from scheduling should be much higher than the suggested 0.3 per cent.

XXXXX

Provided a list of concentrations of triclosan used in a range of its products. Also noted that the recommendation from the PEC report quoted the EU maximum allowable concentration of triclosan as a preservative at 0.3 per cent in all cosmetic products. It was also noted that the New Zealand Cosmetic Product Group Standard lists the maximum allowable concentration for triclosan (as a preservative) as 0.3 per cent.

The submission supported the proposal for 0.3 per cent in line with harmonisation.

XXXXX

Highlighted that triclosan was used in some registered anti-bacterial soaps and anti-acne facial washes at levels of up to 1 per cent. Members noted the following points from the submission:

- Asserted that the EU SCCP and NICNAS (in the PEC review) determined that triclosan was a safe and effective ingredient in dental, medical, cosmetic and household products.
- Suggested that in relation to oral and cosmetic products, the use of triclosan up to 0.3 per cent dose did not represent a safety concern.
- Provided triclosan strengths for a number of current products which included cosmetics containing 0.25 per cent and medicated soap containing 1 per cent.
- Suggested that for medicated soaps that contain 1 per cent triclosan, an entry in Schedule 5 or 6 or an entry in Appendix C (with appropriate exemptions) could be appropriate.
- However, it was highlighted that the signal headings associated with Schedules 5 and 6 could be alarming, noting that the affected product has been on the ATRG for many years with no recorded safety related issues. As this proposal could result in confusion regarding the safety of the product, it was requested that the Committee consider the commercial implications and impact of any scheduling change.

XXXXX

Supported international harmonisation and was concerned that Australia did not create a unique set of limits for triclosan. Members considered the following points from the submission:

- Argued that if different limits were to be set for triclosan (other than the 0.3 per cent proposed in the PEC report) the scientific basis would need to be validated.
- Asserted that if triclosan was to be scheduled, the use of the substance other than in cosmetic products should be accommodated through exemptions.

- Emphasised that if the final recommendation from NICNAS was different from the PEC recommendation, then a decision should be deferred until industry had a chance to consider the proposal.

XXXXXX

Advised that their submission was prepared in response to the recommendation in the PEC report of 0.3 per cent and had not had a chance to consider the implications of a 0.2 per cent cut-off in cosmetics. Members noted the following points from the submission:

(a) Toxicity and safety

- Reiterated a number of points from the PEC report regarding public health and safety. Noted that the NICNAS recommendation for scheduling was an attempt to mitigate any risk from potential aggregate use of triclosan. However, the nature of the potential chronic health risk was not clear.

(d) Extent and purpose of use

- Highlighted that triclosan had a long history of safe use in therapeutic goods as an antimicrobial, either as an active ingredient or as a preservative.

(e) Dosage and formulation

- Highlighted that as an active ingredient in wash-off preparations the maximum triclosan concentration was 1 per cent, in leave-on preparations 0.3 per cent and in oral hygiene preparations 0.3 per cent (noting that this should not be considered exhaustive).

(f) Need for access

- Asserted that triclosan was an effective substance suitable for use on the skin. In spite of widespread use, triclosan did not appear to be the subject of any significant concerns of microbial resistance. It was therefore considered a valuable substance to which restriction from access for inclusion in medicines would be an unfortunate consequence.
- Noted that triclosan is used in cleaning products but assumes that such products were not intended to be scheduled. The submission reiterated the arguments above regarding the Schedule 5 and 6 signal headings being excessive for the current use patterns and urged the Committee to consider the implications of any schedule entry.
- Further highlighted that the US FDA report on triclosan was due to be released in 2011 and requested that the Committee defer a final decision on this item to allow an informed and considered comment on any proposed schedule entry.

Transitional considerations

XXXXXX requested that if the proposed scheduling did not align with their position the decision should not be considered final (i.e. if current products are affected).

XXXXXX also added that without being aware of the outcome of decisions made by the June 2010 meeting, they could not provide an unconditional agreement to accept a decision made at this meeting as final.

XXXXXX requested an implementation date of June 2011 if the scheduling threshold of triclosan was less than 0.3 per cent and requested that if the decision made was an exemption of less than 0.3 per cent it should not be considered final.

XXXXXX requested that the Committee's decision should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members generally agreed that relevant matters under Section 52E (1) included (a) toxicity and safety, (c) the potential hazards and (d) the extent and patterns of use.

A Member noted that the concern from the NICNAS PEC report appeared limited to cosmetic use and the Member therefore suggested just scheduling 0.3 per cent or more for cosmetic use as Schedule 6. Other Members noted that parent entries should generally capture all uses, especially if concerns include an acute toxicity end point (such as the inhalation toxicity of triclosan). The Committee agreed that a parent entry of Schedule 6 was appropriate given the toxicological information provided. The Committee also agreed that an exemption cut-off was warranted.

A number of Members suggested a 0.3 per cent general cut-off as a starting point given that this seemed to align with various overseas regulatory systems and seemed to have broad support from pre-meeting submissions. Other Members noted that while 0.3 per cent would currently align with various overseas regulators, many of these were in the process of reviewing this level (particularly the EU and USFDA).

Members noted that the cut-off considerations were mainly driven by concerns regarding subtle liver effects from chronic exposure to triclosan, as evidenced by liver histopathology results. One Member suggested, however, that these liver effects might be physiological rather than pathological (particularly noting no evidence of necrosis). The Member noted that it appeared that the liver changes stopped once exposure ceased and, while readily absorbed, that triclosan was not cumulative in the body. The Member remained unconvinced that these subtle liver changes would result in any actual public health issue. XXXXXX responded that the effects were considered to be a potentially significant human health risk as they were not observed in any of the controls.

Members revisited the NICNAS arguments for a 0.2 per cent cut-off. The first point was that a 0.3 per cent cut-off resulted in an MOE only just above 100. In addition, human trials showed evidence of significant plasma levels of triclosan in some volunteers after use of a single product containing 1 per cent triclosan over several months (sufficient to give MOEs as high as 175). It was argued that, at the least, these results from repeat exposure to a single product were indicative of a sensitive subpopulation potentially at risk from widespread exposure to triclosan. It was asserted that this risk could be

mitigated by restricting exposure through cosmetic use to 0.2 per cent or less. However, a Member asserted that, as triclosan is found in so many everyday products, the human trial results may not accurately reflect the effects of exposure to a single product.

Several Members observed that a cut-off of 0.3 per cent gave an MOE in the range of 112-125, above the normal value (100) indicative of a safe exposure level, which presumably reflected a worst case scenario. A Member also reiterated that the health implications of the subtle liver changes remained unclear, and queried whether the observed haematological effects should be of greater concern. The Member was advised that the blood changes were very mild and that the subtle liver effects were of central concern to NICNAS. The Member asserted that this effect was not sufficiently serious to be the basis for restricting a cut-off to 0.2 per cent and suggested that this matter be referred to a delegate under the new arrangements to allow time for additional information to be sought.

A Member noted the concern in pre-meeting submissions that NICNAS had recommended a 0.2 rather than 0.3 per cent per cent cut-off with assertions that this was without industry consultation. This Member asserted that engagement with the PEC stakeholders prior to submitting a recommendation on scheduling may have been more appropriate. The Member particularly noted that many stakeholders appeared to have been under the impression that NICNAS was going to recommend a 0.3 per cent cut-off which may have affected the June 2010 pre-meeting public consultation process.

A Member also noted that the PEC review did not examine in detail the use of triclosan for therapeutic use. Also absent were any recommendations for non-cosmetic use (such as cleaning products or as a preservative). A Member noted that there were currently products on the market with more than 1 per cent triclosan e.g., therapeutic and non-therapeutic products. A Member also noted advice that about a quarter of current triclosan products contained more than 0.2 per cent triclosan (noting that this came from 2003 data and may not reflect the current situation). The Committee therefore generally agreed that scheduling would need to be careful about unintended regulatory impact. A Member also suggested that these concerns warranted additional public consultation i.e. should be referred for consideration under the new arrangements.

The Members generally agreed that the above issues required careful consideration. It was also noted that the cosmetic industry currently works to the 0.3 per cent limit, indicating that perhaps there was no great immediate risk. As such, Members agreed that this matter should be referred for consideration under the new arrangements, with the delegate being advised that while the Committee agreed that triclosan warranted a Schedule 6 parent entry, it was unable to settle on an appropriate cut-off.

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The Committee agreed that it was unable to come to a decision with respect to the scheduling of triclosan at this time, noting that this matter should be referred for consideration under the new scheduling arrangements commencing 1 July 2010.

8. OTHER MATTERS FOR CONSIDERATION

8.1 XXXXX

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

No items.

PHARMACEUTICALS

10. MATTERS ARISING FROM THE MINUTES OF THE PREVIOUS MEETING (CONSIDERATION OF POST-MEETING SUBMISSIONS UNDER 42ZCY(1)(c))

10.1 NICOTINE

PURPOSE

The Committee considered a post-meeting submission regarding the February 2010 decision to exempt nicotine preparations for oral mucosal spray use from scheduling.

BACKGROUND

The first-line pharmacological intervention for nicotine dependence from cigarette smoking is nicotine replacement therapy (NRT) - available as chewing gum, transdermal patches, inhalers, nasal sprays, sublingual tablets, and lozenges. Combination therapy with different types of NRT has also been tried as a means of increasing efficacy.

In June 1991, the Schedule 4 entry for nicotine was amended to include all preparations (except Schedule 3 chewing tablets) which could be used as an aid in smoking cessation, containing between 2 and 4 mg of nicotine or roll-on devices with 0.65 per cent or less of nicotine e.g. transdermal patches.

At the August 1993 meeting, the Committee rejected a proposal to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and 4 mg sublingual tablets rescheduled from Schedule 4 to Schedule 3.

At the November 1993 meeting, the Committee agreed that Schedule 4 remained appropriate for patch formulations. Subsequently, at the November 1997 meeting, transdermal patches were included in Schedule 3.

Nicotine 2 mg chewing tablets were rescheduled to Schedule 2 in February 1997. However, the Committee decided that the higher dosage (4 mg) should only be rescheduled to Schedule 3 to facilitate the counselling of heavy smokers by a pharmacist.

Inclusion of nicotine gum and transdermal patches in Appendix H was agreed to at the August 1998 meeting.

At the February 1999 meeting, the Committee amended the Schedule 3 nicotine entry to 'Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use.' At the August 2001 meeting, the Committee agreed that nicotine lozenges would have a comparable safety profile to that of sublingual tablets, and so it

was appropriate to also include lozenges in Schedule 3. Subsequently, lozenge preparations were down scheduled to Schedule 2 in June 2003.

Down scheduling of nicotine for oral inhalation to Schedule 3 and inclusion in Appendix H was decided at the November 1998 meeting. Subsequently, nicotine inhalers were rescheduled from Schedule 3 to Schedule 2 in February 2002.

At the February 2010 meeting, the Committee considered a request from XXXXX to broaden the current exemptions for specified NRT buccal dosage formats i.e. chewing gum and lozenges, to buccal preparations in general. The Committee decided, however, to restrict the additional exemption to preparations for oromucosal spray use.

DISCUSSION - SUBMISSIONS

Post-meeting submission

XXXXX argued that the February 2010 decision (to limit the additional exemption from scheduling to NRT for oromucosal spray use) should instead be broadened to all oral use NRT.

XXXXX also proposed an alternative for consideration should the Committee reject the first proposal – to broaden the exemption to all oral mucosal products which were bioequivalent to currently marketed oral dose formats. The basis for this proposal was that no information was available to suggest that oral use of NRT products, which are bioequivalent to the currently marketed oral dose formats, were less safe or effective.

XXXXX post-meeting submission reiterated XXXXX February 2010 position, including that:

- Dose formats for oral nicotine use should not be differentiated as all current registered formats are for ‘oromucosal use’ and the absorption of nicotine from chewing gum, lozenge and sublingual tablet is through the oral mucosa in the same way as it is for the spray.
- A broader exemption for oromucosal products would give smokers the choice of innovative NRT formats as smokers often seek convenient and discrete forms of NRT to assist with their needs for quitting.
- The appropriateness of the format of an oromucosal OTC nicotine product should be the remit of the regulator and not necessarily a condition placed on the scheduling of a substance.
- Oral nicotine formulations were the most popular form of NRT.

In addition, XXXXX noted some points from the February 2010 Records of Reasons, including that:

- The Committee had set a precedent within the NRT category of down scheduling dosing formats from Schedule 3 to Schedule 2 based on a safety profile which is consistent with the currently marketed NRT.
- The Committee had previously taken steps to promote and facilitate wider access to NRT so as to encourage more smokers to quit smoking.

XXXXXX concluded that:

- Smokers often sought convenient and discreet forms of NRT to assist with quitting. Oral formats which are discreet, fast dissolving and do not require any particular technique for use, are ideal.
- Extending the current nicotine scheduling to oromucosal or oral formats, which are bioequivalent to current oral formats, would facilitate access to innovative effective and safe formats.

February 2010 Meeting

Application

Members recalled that XXXXX February 2010 application requested a broadening of the current exemptions for NRT from specified buccal dosage formats i.e. chewing gum and lozenges, to buccal preparations in general. The applicant's arguments are summarised as follows:

- Preparations for sublingual or transdermal use were currently in the same scheduling, and not differentiated by the specific dosage format.
- Buccal preparations and sublingual preparations had comparable safety and efficacy, hence the argument for grouping buccal preparations seemed reasonable given this principle was already applied to the sublingual format.
- Oromucosal spray products are sprayed directly into the mouth (rather than specifically under the tongue), making the route of administration buccal. The plasma levels following a single-dose of oromucosal spray (1-2 mg nicotine) were within the range of those for marketed buccal preparations such as nicotine 2 mg and 4 mg chewing gum and nicotine 2 mg and 4 mg lozenge.
- Studies demonstrated that nicotine from oromucosal spray administered via buccal (oral transmucosal) or sublingual routes would produce the desired efficacy, with no incidents or trends indicating that the adverse event profile of oromucosal spray might differ significantly from buccal preparations.

Members' Discussion

Members recalled the following from the February 2010 meeting discussion:

- Members noted that the proposed extension to the NRT exemptions would allow for new, innovative formats, such as, for example, oromucosal spray. A potential benefit in encouraging new options would particularly be for those few who were unable to chew, maintain a lozenge in the mouth or maintain a patch on the skin. Several Members, however, felt that an exemption for all buccal preparations would be too broad and could potentially see it expand to less suitable formats such as mouthwashes and toothpastes.
- Members generally agreed that the only potential addition for exemption at this time, for which data had been presented, was a specific exemption for oromucosal spray formats.
- There was concern regarding the risks of ingestion by consumers, particularly children, of a dose of liquid containing nicotine from a spray format. Members noted, however, that both the systemic availability of nicotine and the concentration of nicotine in a spray would be low, which would reduce any risk of unwanted systemic effects.
- Members also confirmed that the exemption for oromucosal spray use was not intended to exempt the current Schedule 2 NRT inhalers.

Evaluation Report

The evaluation report recommended approval of an exemption for oromucosal spray products, pending supportive evidence of safety and efficacy. The evaluator argued that should such data be provided, and an exemption be considered for all buccal preparations, then for greater clarity, the following wording should be used “for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal absorption”. However, the evaluator noted that the data in the application was not sufficient to support the proposal.

The main points from the applicant’s response to the evaluation report were:

- The main difference between oromucosal spray and other oral forms of NRT was the speed of absorption. XXXXX.
- Treatment-related adverse events from oromucosal spray were transient and generally well tolerated and similar to those seen for gum and lozenge preparations.
- The absorption of nicotine from oromucosal 1 mg spray was more rapid than that from gum and also showed superiority versus lozenge. The maximum concentration was generally reached 10 minutes after dose with oromucosal spray as compared with 45 minutes with lozenge and 30 minutes with gum.

Pre-meeting Submissions

Members recalled the following points from pre-meeting submissions to the February 2010 meeting:

- XXXXX were not opposed to the proposal to exempt from scheduling more general 'buccal preparations'.
- XXXXX also asserted that, based on an anatomical approach, it seemed reasonable to broaden the current exemption to 'buccal preparations'.
- XXXXX noted that a broadening to 'buccal' could also exempt other buccal products such as mouthwashes or similar and therefore did not support the general exemption.
- XXXXX asserted that professional intervention on NRT supply enhanced patient outcomes and was more cost-effective for the consumer and did not support a general exemption for this reason. Also questioned whether exemption of NRT from scheduling had resulted in increased and sustained smoking cessation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (d) extent and pattern of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

A Member asserted that no new information had been provided to the Committee in the post-meeting submission that had not already been considered by the Committee in making its decision in February 2010.

Given this, the Committee confirmed the February 2010 decision to amend the scheduling of nicotine to exempt oromucosal spray use as an aid in withdrawal from tobacco smoking.

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The Committee confirmed the February 2010 resolution (2010/58-20) to amend the scheduling of nicotine to exempt oromucosal spray use as an aid in withdrawal from tobacco smoking. The Committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 September 2010.

10.2 FLURBIPROFEN

PURPOSE

The Committee considered a post-meeting submission regarding the February 2010 decision to broaden the Schedule 2 flurbiprofen entry to include undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

BACKGROUND

Flurbiprofen was first included in Schedule 4 in November 1993.

The Committee decided to reschedule flurbiprofen in divided preparations for topical oral use containing 10 mg or less of flurbiprofen per dosage unit from Schedule 4 to Schedule 3 in February 2000. Subsequent rescheduling to Schedule 2 for this type of preparation followed in October 2002. The Committee's decision was based on post-marketing safety data demonstrating that the preparation had a very low potential for causing adverse effects and no evidence of abuse or misuse.

Currently, in Australia, flurbiprofen products are available as lozenges for the treatment of sore throats (Schedule 2) and eye drops for the treatment of intraoperative miosis (Schedule 4).

At the February 2010 meeting, the Committee considered a request from XXXXX to exempt from scheduling divided and undivided preparations of flurbiprofen for topical oral use. The Committee generally felt that the case for unscheduled access to topical flurbiprofen had not been made. The Committee decided however, that there was sufficient information to support rescheduling of undivided flurbiprofen for topical use from Schedule 4 to Schedule 2 "in undivided preparations containing 0.25 per cent or less, or 10 mg or less per dose, of flurbiprofen".

DISCUSSION - SUBMISSIONS

Post-meeting submission

XXXXXX requested a reconsideration of the February 2010 decision in light of arguments discussed below. These largely focused on supporting an exemption from scheduling for flurbiprofen lozenges. These arguments addressed points from the February 2010 Record of Reasons, and include:

Regarding potential to cause harm to patients with cardiovascular, renal and gastrointestinal conditions:

- Although the daily dose of this flurbiprofen use is much lower than the daily oral systemic anti-inflammatory dose, inclusion of precautions on the label for patients with these conditions was considered prudent.

Regarding being a Category C medicine in pregnancy:

- While flurbiprofen is a Category C medicine in pregnancy it should be recalled that there are currently other exempted substances which are Category D medicines, such as nicotine formats for buccal use.
- Also advised that flurbiprofen for ophthalmic preparations is classified as Category B2 by the *Prescribing Medicines in Pregnancy 4th Edition*.

- Noted that warnings for use in pregnancy were not initially required when flurbiprofen lozenges were first registered in 1999. It only became a requirement after the *Required Advisory Statements of Medicines Labels* (RASML) was updated on 23 April 2008, as a consequence of flurbiprofen being grouped with other non-steroidal anti-inflammatory drugs (NSAIDs).
- Asserted that these RASML warnings were consistent with those of aspirin and ibuprofen which have been available in unscheduled products for many years.

Category C medicines: drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

Category D medicines: drugs which have caused, are suspected to have caused or may be expected to cause, an increase incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

Category B2 medicines: drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animal are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

General perception by the public that lozenges have little potential to do harm:

- Argued that there was no reported evidence that consumers might confuse flurbiprofen lozenges as a 'lolly'.
- XXXXX. Asserted that consequently, flurbiprofen lozenges were specifically registered as XXXXX to provide differentiation for consumers. Asserted that a TV advertisement campaign (2008-2009) was intended to educate consumers that, unlike non-medicated lollies, the flurbiprofen lozenges contained active ingredients.
- Reiterated its previous argument that the dose absorbed is unlikely to have a systemic effect on the body for the following reasons:
 - Very small dosage of flurbiprofen per dosage unit (10 mg) in comparison with its oral OTC dose when used for a systemic anti-inflammatory effect (150 mg – 300 mg)
 - Mean systemic bioavailability after buccal flurbiprofen lozenge relative to oral systemic administration is about 10.6 per cent or less.
 - A study demonstrated that the lozenge dissolved over approximately 12 minutes and was cleared from the mouth into the throat. A constant level of activity was maintained in the throat during dissolution of the lozenge.

Need for Access was not demonstrated. Alternatives are available unscheduled:

- Asserted that XXXXX contained an antibacterial and a local anaesthetic whereas flurbiprofen lozenges had anti-inflammatory properties.

- Affirmed that although the dosage form of flurbiprofen and XXXXX were the same, the local anaesthetic numbing sensation and short-acting nature of the latter differs from flurbiprofen lozenges.
- Stated that a study submitted in the original application had identified paracetamol and ibuprofen as the only products which can provide longer-term (more than 24 h) effective treatment for the relief of a severe sore throat. The action of flurbiprofen is better than that of paracetamol or ibuprofen.

Reason for the proposed restriction against use by children 12 years of age or less:

- Contended that there have not been any clinical trials conducted with flurbiprofen lozenges in children aged 12 or less, therefore the product was not recommended in children when it was registered i.e. not due to concern that children would use the product as a lolly as suggested in the February 2010 Record of Reasons. Asserted that the following evidence supports that flurbiprofen had been promoted to the correct target population:
 - No evidence from safety reviews suggesting that flurbiprofen lozenges have been used in children.
 - Only a single report of a 4-year old child who complained of urticaria after using flurbiprofen spray.

If topical oral flurbiprofen is exempted, individuals with more serious conditions may be further delayed in having a health professional intervention which could lead to complications:

- Contended that as flurbiprofen lozenges are indicated for use in adults and children over 12 years, and sore throat is a common occurrence every year, these patients would be able to self-diagnose and self-medicate.
- Asserted that it could be considered as a safer alternative to taking an oral dosage form of paracetamol or ibuprofen.
- Stated that the current labelling statement (below) is sufficient to address any such risk as it urged consumers to seek advice from their health professional:
 - *Do not take for more than 3 days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.*
 - *If symptoms persist, talk to your pharmacist or doctor.*

February 2010 Meeting

Application

Members recalled XXXXX arguments from XXXXX application to exempt flurbiprofen for all topical oral use (divided lozenges and undivided i.e. XXXXX) from scheduling. A summary of the main points included:

- Preparations for topical oral use have been marketed for over 7 years with no instances of misuse or abuse recorded.
- Flurbiprofen at a dose of 8.75 mg in a lozenge formulation had been shown to be effective in relieving the symptoms of sore throat. Self-management with an NSAID-containing product would be preferable to treating an acute sore throat with prescription antibiotics. In addition, lozenges act locally on the pharyngeal mucosa with little or no systemic side effects.
- The use of a mouthwash or a throat spray preparation similarly would be very unlikely to lead to systemic adverse effects.
- XXXXX.

Members' February 2010 Discussion

Members recalled the discussion on whether there were sufficient grounds for exempting all flurbiprofen for topical oral use, as requested. In particular:

- Members generally felt that a better justification needed to be made regarding the public health benefits of unscheduled flurbiprofen. The Committee agreed that preparations of flurbiprofen for topical oral use (10 mg or less) should remain in Schedule 2.
- A Member noted that flurbiprofen lozenges as Schedule 2 had been available in Australia since 2002 and that there had been few reports of adverse events or systemic toxicity. The Member argued that flurbiprofen lozenges (10 mg or less) would be a safer alternative than ibuprofen (or other NSAID) for managing sore throat symptoms, noting that the majority of people self-medicate for relieving these symptoms. Another Member contended, however, that this benefit would only be tenuous and any real benefit of flurbiprofen lozenges over NSAID tablets could not be quantified from the information tabled.
- A Member noted that XXXXX had developed public education campaigns to emphasise the presence of active compounds in lozenges. Also asserted that the lolly argument was unsubstantiated and, in any case, the risk of harm was quite low and a product presentation would still need to be approved by the regulator. Another Member contended that it was intuitive for children to see lozenges as lollies, and this was a major reason that companies felt the need to develop education campaigns in the first place. The Member also asserted that this may have been a reason for the applicant's proposed restriction against OTC flurbiprofen use by children 12 years of age or less.
- Members generally contended that the applicant's argument that an exemption from scheduling would facilitate access for communities in rural / remote areas in Australia, had little basis as jurisdictions had arrangements in place for supplying Schedule 2 products outside pharmacies.
- A number of Members asserted that products with a Category C pregnancy risk should not be available unscheduled.

- Members generally concluded that the applicant did not provide convincing data to support the need for unscheduled flurbiprofen for topical oral use, noting that there were alternatives already available.
- Members generally agreed, however, that there was sufficient information to support rescheduling low concentration undivided flurbiprofen formulations, for topical oral use, in line with the current Schedule 2 of some divided preparations. By setting a low concentration cut-off (0.25 per cent), even if the whole content was ingested from mouthwash preparations, the total flurbiprofen dose would still be too low to cause systemic toxicity.
- Members noted that the indication for use was not consistent among the different formulations. While the indication for flurbiprofen lozenges was for the relief of sore throat symptoms, the indication for mouthwash and spray, such as were available in Italy, appeared to be for conditions such as pharyngitis, stomatitis and gingivitis.

Evaluation

The evaluation report supported a flurbiprofen exemption for oral topical use from scheduling noting that in doing so, there should be an upper limit for the concentration for undivided preparations. In general, the evaluator asserted that:

- Flurbiprofen was effective in the symptomatic treatment of sore throat (lozenges) at a dose (8.75 mg, up to 8 times a day) much lower than the recommended daily systemic anti-inflammatory dose of 150 – 300 mg.
- The application demonstrated that the indication and the products were suitable for self-identification and self-treatment without professional advice, and that the safety profile indicated that there would not be any significant risk to consumers during self-management of sore throat.

Pre-meeting Submissions

Members recalled that the various pre-meeting submissions opposed an exemption for all oral topical flurbiprofen. Generally, it was suggested that lozenges and other formulations should remain in Schedule 2. There was support for certain undivided preparations of flurbiprofen to also be included in Schedule 2 in line with the current scheduling for divided preparations.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (e) dosage and formulation and (f) need for access.

Members discussed the merits of the arguments presented in the post-meeting submission relating to flurbiprofen as a Category C medicine in pregnancy. A Member supported the argument that this classification should not preclude unscheduled access as there are Category D medicines available as OTC medicines e.g. nicotine in nicotine replacement therapy (NRT) products. Another Member asserted that the NRT example was not a

good comparator as the risk of using NRT in pregnancy was balanced against the detrimental effects of smoking in pregnancy, a mitigating factor that does not apply to flurbiprofen use in pregnancy.

Members then discussed in detail the ongoing concern that the public does not generally perceive lozenges as medicines, which could exacerbate the inherent risk of these types of products. A Member stated that there was no evidence that lozenges are regarded as lollies by consumers. Another Member reiterated that industry had gone to great lengths to educate consumers that 'therapeutic lozenges' contain active ingredients and stated that there were other comparable NSAIDs available unscheduled with similar toxicological concerns as flurbiprofen and other unscheduled lozenges such as XXXXX.

However, another Member asserted that the perception that lozenges are not medicines was inherent in the general community. The Member further emphasised that the public was habituated to presentations such as tablets being medicines but this was not the case for lozenges and asserted that the presentation of flurbiprofen in lozenge form is a risk which must be considered in the Committee's decision.

Another Member emphasised that although the relative toxicity was comparable to other unscheduled products, each scheduling decision must be based on its own merits and, in the case of flurbiprofen, the risk of idiosyncratic reactions was of concern.

The Committee generally agreed that, while some of the arguments presented in the post-meeting submission were valid, the concerns of the February 2010 meeting were not sufficiently addressed. Given this, the Committee confirmed the February 2010 decision to broaden the Schedule 2 flurbiprofen entry to include undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

RESOLUTION 2010/59 - 19

The Committee confirmed the February 2010 resolution (2010/58 – 19) to:

- Retain the Schedule 2 entry for divided preparations for topical oral use containing 10 mg or less per dosage, and
- To broaden the Schedule 2 entry by including undivided preparations containing 0.25 per cent or less or 10 mg or less per dose of flurbiprofen.

The Committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 September 2010.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

No items.

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

12.1 SUSDP, PART 4

12.1.1 ALPRAZOLAM

PURPOSE

The Committee considered the scheduling of alprazolam.

BACKGROUND

Alprazolam is a short-acting triazolobenzodiazepine with general properties similar to those of diazepam. It is used in the short-term treatment of anxiety and in the treatment of panic disorder, with or without agoraphobia. Like other benzodiazepines, alprazolam's pharmacological effects include sedation, muscle relaxation, reduction in anxiety, and prevention of convulsions.

Alprazolam was first scheduled in Schedule 4 in November 1981.

XXXXX.

Flunitrazepam is mainly used in the short-term management of insomnia (anxiolytic sedatives, hypnotics and antipsychotics), as a premedicant in surgical procedures, and for induction of anaesthesia (general anaesthetics).

At the May 1997 meeting, the Committee considered the rescheduling of flunitrazepam from Schedule 4 to Schedule 8. A Schedule 8 entry for flunitrazepam was foreshadowed. Subsequently, at the November 1997 meeting, Members agreed that there was an on-going public health issue associated with the abuse and misuse of flunitrazepam, and decided to reschedule this substance from Schedule 4 to Schedule 8.

DISCUSSION - SUBMISSIONS

XXXXX expressed concerns about the misuse / abuse of alprazolam, and requested the rescheduling of alprazolam from Schedule 4 to Schedule 8. Members noted the following arguments made by the applicant:

- The rescheduling of alprazolam would align with another benzodiazepine, flunitrazepam, which was upscheduled to Schedule 8.

- There is strong evidence to suggest that alprazolam is addictive, and once dependent, withdrawal is markedly unpleasant and may be fatal.
- Even after small doses, memory loss, uncharacteristic behaviour, sedation and coma may develop.
- It is over-represented in deaths or injury from overdose, suicide, motor vehicle collisions and crimes. It has been used as a 'date rape' drug.
- Alprazolam is prescribed for panic disorder, a relatively rare condition, yet high rates of prescriptions are reportedly dispensed in Australia. Several safer and more efficacious treatments for panic disorder are available.
- General practitioners can prescribe alprazolam without professional psychiatric opinion. Asserted that GPs were pressured to prescribe this medication.
- Asserted that up-scheduling flunitrazepam resulted in immediate benefit.
- Both the colleges of psychiatry and general practice discouraged the profligate prescribing of substances known to cause dependence.

Members also noted some pharmacological characteristics extracted from the Martindale monograph for alprazolam:

Overdosage

- A retrospective analysis of 2063 hospital admissions for benzodiazepine overdosage in one region of Australia between January 1987 and October 2002 found that patients who overdosed on alprazolam were about twice as likely to require admission to intensive care as those taking other benzodiazepines.
- Given the apparently greater toxicity of alprazolam in overdosage, its increasing rate of prescribing to groups at risk of self-poisoning was of concern.

Precautions

Abuse

- High doses of alprazolam taken after maintenance doses of methadone produced a 'high' without pronounced sedation; alprazolam is also misused by non-opioid drug abusers.
- The usual urine toxicology screens for benzodiazepines often give false-negative results for alprazolam because of the extremely low concentrations of metabolites excreted, making abuse of this substance difficult to detect.
- A review considered that the literature did not support the belief that alprazolam had a greater liability for abuse than other benzodiazepines, but the possibility could not be discounted.

Breast feeding

- The American Academy of Paediatrics considers that, although the effect of alprazolam on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since anxiolytic drugs do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Hepatic impairment

- Alprazolam, in common with other benzodiazepines, undergoes oxidative metabolism, and accumulates to a greater extent in patients with alcoholic cirrhosis than in healthy subjects; the daily dose of alprazolam may need to be reduced by half in this population.

Porphyria

- Alprazolam is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in vitro* systems. Members noted that porphyrias are a group of inherited or acquired disorders of certain enzymes in the heme biosynthetic pathway. Porphyrias primarily affect the nervous system, resulting in abdominal pain, vomiting, acute neuropathy, muscle weakness, seizures, and mental disturbances, including hallucinations, depression, anxiety, and paranoia.

Paradoxical reactions

- Although unusual, there has been reports of muscle twitching and tremors, aggression, rage, hostility, mania, agitation, hyperactivity and restlessness associated with the use of alprazolam (Michel L *et al*, 2003 'Benzodiazepines and forensic aspects', *Encephale* vol 29, pp 479–85; Rapaport, M and Braff, D, 1985 'Alprazolam and hostility', *The American journal of psychiatry* vol 142 pp 146; Arana, Gw *et al*, 1985, 'Alprazolam-induced mania: two clinical cases.', *The American journal of psychiatry* vol 142, pp 368–9).

Other uses

- Alprazolam has been used in the management of anxiety disorders (anxiolytic sedatives, hypnotics and antipsychotics).
- Benzodiazepines are not usually considered appropriate for the treatment of depression; however, alprazolam has been used.
- Produces a marginal to good response in premenstrual syndrome however, the role of benzodiazepines is limited by their adverse effects.
- Alprazolam has been used in the management of tinnitus.

Members noted the current classification status of alprazolam internationally:

- Alprazolam is included in Schedule IV of the United Nations Convention on Psychotropic Substances. Flunitrazepam is included in Schedule III. The Convention scheduling of controlled substances ranges from Schedule I (most restrictive) to Schedule IV (least restrictive):

- Schedule I includes drugs claimed to create a serious risk to public health, whose therapeutic value was not currently acknowledged, including psychedelics such as LSD, ecstasy, and tetrahydrocannabinol (THC).
 - Schedule II includes stimulants of the amphetamine type, deemed to have limited therapeutic value, as well as some analgesics such as morphine.
 - Schedule III includes barbiturate products with fast or average effects, which have been the object of serious abuse even though useful therapeutically, **flunitrazepam, temazepam, nimetazepam** and some analgesics like buprenorphine.
 - Schedule IV includes some weaker barbiturates and other hypnotics, hypnotic and anxiolytic benzodiazepines (**except** flunitrazepam, temazepam, nimetazepam), and some weaker stimulants.
- Under the UK Drug Misuse classification system, alprazolam is a class C4 drug (the least restrictive within C1-C4) which includes, but is not limited to, tranquilisers, some painkillers, gamma hydroxybutyrate (GHB) and ketamine. Flunitrazepam was class C3.
 - In NZ, alprazolam, flunitrazepam, nimetazepam and temazepam are classified as C5 controlled substance (lowest abuse potential within C1-C5).
 - In the US, alprazolam is a prescription drug and is assigned to the Controlled Substances Act by the Drug Enforcement Administration. It is included in the Schedule IV medically useful category of drugs that have less potential for abuse or addiction than those of Schedules I [e.g. LSD], II [e.g. cocaine], and III [barbiturates and amphetamines]).
 - In Canada, it is captured under the Controlled Drugs and Substances Act and is included in C4 i.e. the least restrictive (CDSA IV). Although it is not an offence to possess a Schedule IV substance for personal use, the CDSA states that "no person shall seek or obtain a substance or authorization from a practitioner to obtain a substance in Schedules I through IV." C4 substances include anabolics, benzodiazepines (except flunitrazepam), cathine, most barbiturates and others. Flunitrazepam is included in the more restrictive CDSA III class.

Pre-meeting Submissions

XXXXXX opposed the rescheduling of alprazolam from Schedule 4 to Schedule 8. In general the following arguments were made:

- Argued that according to the NDPSC Guidelines, a Schedule 8 poison is a substance that is dependence-producing and / or likely to be abused or misused. The Assessment Factors for a Schedule 8 poison are inclusion in Schedule I or II of the WHO Single Convention on Narcotic Medicines and inclusion in Schedule II or III of the WHO Convention on Psychotropic Substances (likely to present a substantial risk

of abuse, dependence or misuse for illegal purposes). Alprazolam is not currently included in Schedule II or III of the WHO Convention on Psychotropic Substances.

- Also asserted that alprazolam was included in Schedule IV of this convention on the basis that it had a comparable risk-benefit profile to other benzodiazepines which were already included in the WHO Schedule IV.
- XXXXX were not aware of any evidence to show that alprazolam was being over-prescribed or has been the subject of abuse or misuse.
- Asserted that there was a long and established history of safe and effective use of alprazolam in Australia.
- Contended that a rescheduling to Schedule 8 was an unnecessary step that would be inconsistent with current international practice. Furthermore, rescheduling in isolation to other benzodiazepines would not address the concerns of abuse or dependency.

XXXXX were aware that alprazolam was being misused and was sometimes inappropriately prescribed. However, XXXXX generally did not support the proposal to upschedule alprazolam to Schedule 8. XXXXX considered rescheduling to Schedule 8 to be a significant amendment which warranted careful consideration, and felt XXXXX not in a position to provide a definitive position based on the limited information available.

XXXXX did not object, in principle, to the proposal if the abuse and / or misuse of alprazolam was demonstrated to be a significant national problem and consideration had been given to drug tendencies for the other benzodiazepines and pharmacies' Schedule 8 storage capacity.

Further general views from some specific pre-meeting submissions include:

XXXXX

- Claimed that XXXXX adverse events (AEs) database identified a total of 16 AEs, with no reports of abuse, dependence or intentional misuse for this product for the period January 2008 to present XXXXX.
- Contended that rescheduling was being considered due to the potential for abuse, but a decision needed to be carefully weighted against the need for patient access.
- Acknowledged the need for education in relation to the prescribing and ongoing use of this medicine, and proposed a review of campaigns such as Project STOP for pseudoephedrine, and the utility of such a model for the prescription and ongoing use of alprazolam.
- Also claimed that XXXXX was not aware of sufficient evidence that would allow alprazolam to be described as being at substantial risk of abuse, dependence or misuse. This was further supported by the fact that XXXXX was not aware of any other country imposing stricter scheduling than that equivalent to Schedule 4 in Australia.

XXXXX

- Claimed that XXXXX had received no reports of abuse, dependence or misuse for XXXXX alprazolam XXXXX.
- Contended that rescheduling of alprazolam would not substantively address the concerns of potential for abuse, dependence or misuse within this drug class.

XXXXX

- Claimed that a review XXXXX indicated that there had been no reports of abuse, dependence or misuse for XXXXX alprazolam XXXXX.
- Stated that it was aware of some recent media attention surrounding alprazolam use and would caution any action based on unsubstantiated media claims.

XXXXX

- Asserted that rescheduling of alprazolam to Schedule 8 would not deter those who intended to use the drug illegally.
- Contended that this proposed rescheduling and level of control would be unique to Australia, as no other regulatory jurisdiction had made a similar recommendation / decision to date.
- Asserted that the alprazolam Product Information (PI) and Consumer Medicine Information (CMI) contained numerous sections which emphasised its appropriate prescribing.

Safety

- The PSUR (XXXXX) reported that out of XXXXX cases, there were XXXXX reports of abuse, XXXXX reports of misuse and XXXXX relevant reports of drug dependence with alprazolam.
- The safety report concluded that it considered the benefit-risk of alprazolam unchanged and favourable when used in accordance with the approved product labelling.

Supporting evidence

- A search in EMBASE and MEDLINE using the terms 'alprazolam' and 'abuse' did not produce conclusive evidence that alprazolam had a higher risk of abuse than other benzodiazepines.
- A study showed that deaths due to alprazolam ingestion alone were rare and that most fatalities result from a drug cocktail having been ingested.
- Evidence from the US showed a growing trend of alprazolam abuse in Texas over the period 1998-2004.
- A review of literature on this subject revealed that it did not conclusively support the widely held belief that alprazolam had a greater liability for abuse than other

benzodiazepines. The author stated that the findings were not conclusive and that further research was required to verify or refute this.

Medical vs. illicit use of alprazolam

- Noted that it had recently been reported in the media that alprazolam was being sold on the streets illegally and abused by drug users, most often in combination with other medications. Believed that the impact of rescheduling alprazolam in isolation from other benzodiazepines would result in minimal impact on the illicit use of this agent, as those who were motivated to use benzodiazepines would find other means to access it, and / or source other more readily available benzodiazepines.
- Considered that efforts to prevent abuse of benzodiazepines through rescheduling would only be sustainable if all benzodiazepines were rescheduled as Scheduled 8 substances.
- Stated that the rescheduling of alprazolam would be detrimental to patients who required it for the appropriate treatment of a diagnosed medical condition.

Alternative Solution

- XXXXX proposed the following solutions:
 - Changes to the CMI to specifically make patients aware of the potential risks of taking benzodiazepines, including drug dependence.
 - The development of an online patient education booklet. XXXXX would be willing to contribute to XXXXX the development of this online patient information initiative.
 - Letters to healthcare practitioners and pharmacists – discouraging doctors from prescribing and pharmacists dispensing more than a single pack at one time and promoting awareness of patients potentially at a high risk for abuse and dependence.
 - Health practitioner education – a XXXXX sponsored CPD-accredited education initiative to educate doctors about safe and appropriate prescription of benzodiazepines, such as a fact sheet about appropriate prescribing, as well patient-centred material contained within the leaflet.
 - Inclusion of specific benzodiazepines on the Project STOP initiative.

XXXXX

- Stated that experience has shown that abuse of particular substances such as the benzodiazepines, comes in and out of vogue. Oxazepam was a favoured drug of abuse in Australia in the 1980s and more recently, temazepam. Clonazepam also had some favour on the illicit market because, unlike other benzodiazepines, it was available in quantities of 200 tablets.

- Contended that Schedule 8 should not be used as a classification to house drugs whose abuse patterns may be transient and which places Australia out of alignment with other countries unless there was compelling local evidence.
- Asserted that it was not aware of robust data to show that alprazolam had a special propensity for dependence over related substances. The transfer of occasional problem drugs to Schedule 8 would devalue the status of the Schedule.
- Claimed that state law already caters for trafficking of benzodiazepines; e.g. in Victoria, under Schedule 11 of the *Drugs, Poisons and Controlled Substances Act 1981*. There were already extra obligations placed on medical practitioners and pharmacists in prescribing and dispensing benzodiazepines.
- Considered it more appropriate for medical boards, through their newsletters, to advise doctors to treat requests for alprazolam circumspectly and acquaint them with their legal and professional obligations under present law.

Members noted that XXXXX sent an additional comment to its pre-meeting submission, which noted the following:

- XXXXX reported some disquiet among pharmacists at the quantities and the number of repeats written as “Authority to Prescribe” prescriptions under the Pharmaceutical Benefits Scheme.
- In addition to XXXXX proposed educative approach to doctors, XXXXX also suggested that the state departments of health should maintain a watching brief on usage patterns of alprazolam.

XXXXX

- Understood that there was considerable variation between jurisdictions in prescribing patterns for alprazolam, although the reasons for this were unclear.
- Where close monitoring of alprazolam use was desirable, believed other measures should be instituted before rescheduling to Schedule 8, such as:
 - Concerted communication with prescribers and dispensers about any unusual or alarming trends in use and the problems resulting from this.
 - Placing restrictions (through regulation) on: the maximum quantity and / or repeat interval per supply, the period of validity of the prescription or disallowing emergency supplies.
 - Requiring prescribers to obtain an authority to prescribe.
- Suggested that another option would be the real-time electronic recording of the dispensing of alprazolam which would allow monitoring of its use and early detection (and prevention) of possible overuse.

- Requested further background information on the proposal to reschedule alprazolam to Schedule 8 and sought the opportunity to provide comments once it had reviewed the information.

XXXXX

- Asserted that consideration needed to be given to the following, before upscheduling to Schedule 8:
 - Whether restricted access to alprazolam would resolve the issue or result in those with drug seeking tendencies to turn their attention to other benzodiazepines. If the latter, developing a real-time-recording (RTR) system to monitor alprazolam and other drugs prone to misuse, and integrating its capabilities with the proposed Appendix N of the SUSMP, may be more efficient and effective. [Members noted that the proposed Appendix N was to list notifiable substances and, at this time, has not been included in the SUSMP].
 - Reiterated that if alprazolam was to be stored in the drug-safe, this may create medicine crowding and could potentially hinder accurate product selection, increasing the risk of dispensing error for these medicines.
 - Suggested a classification similar to Tasmania's S4D (declared restricted substances) would avoid these storage issues, whilst applying other Schedule 8-level restrictions.
- It also made particular reference to matters under section 52E as follows:

(a) Toxicity and Safety

- Evidence exists that alprazolam is more toxic than other benzodiazepines. A database of consecutive poisoning admissions to the XXXXX toxicology service was examined, XXXXX. Based on comparative measures including length of stay in hospital, intensive care admission, flumazenil administration, coma and requirement for mechanical ventilation, they concluded that, in overdose, alprazolam was significantly more toxic than other benzodiazepines
- The authors also considered data concerning benzodiazepine-related fatalities in the US, NZ and Britain and found it to be consistent with these findings. The authors stated that this greater toxicity appeared to be due to the intrinsic toxicity of alprazolam and alprazolam overdose should be regarded as more significant than other benzodiazepines.

(b) Risks and Benefits

- Alprazolam was effective for treating acute symptoms, but produced a range of adverse effects, such as drowsiness, sedation and memory problems. There were concerns of physical dependence with long term use.

- Review of literature has found that alprazolam may impair performance in a variety of skills in healthy volunteers, as well as in patients. This behavioural impairment limited the safe use of alprazolam in patients routinely engaged in potentially dangerous daily activities, such as driving a car.
- Elderly patients were particularly susceptible to the sedative effects of benzodiazepines and associated giddiness, ataxia and confusion, which may increase the risk of a fall.
- Benzodiazepines should be avoided if possible during pregnancy, particularly large doses and regular use, as a risk of growth restriction and neonatal withdrawal syndrome was identified. Repeated doses should also be avoided whilst breastfeeding as it could cause lethargy and poor feeding in the infant.
- Argued that the use and risks / benefits of alprazolam / benzodiazepines were well established and do not, on their own, provide any cause for re-evaluation of scheduling.

(c) Potential Hazards

- Physical and psychological dependence have occurred with recommended doses of benzodiazepines, and caution must be exercised in administering alprazolam to individuals known to be addiction-prone.
- The most prominent concerns in Australia regarding alprazolam currently surrounded the illicit misuse / abuse of the agent, as distinct from concerns of deliberate self-poisoning.
- The use of intravenous alprazolam in conjunction with methadone to achieve a 'heroin-like' high was of particular concern as this practice presented a very serious risk of overdose.
- Pharmaceutical Benefits Scheme (PBS) data suggests that alprazolam prescribing in Tasmania is significantly higher than the national average. Alprazolam has been listed as a declared restricted substance (S4D) and queried whether data suggested an improvement in this problem, and if those abusing alprazolam were seeking other benzodiazepines as an alternative.
- Argued that a decision to reschedule a drug to Schedule 8 would resolve the issue and not transfer the problem to another Schedule 4 benzodiazepine or other substances.

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

- Noted that alprazolam was listed on the PBS as an authority item for panic disorder where other treatments had failed or were inappropriate.
- Available in tablet form in strengths from 250 micrograms up to 2 mg.
- Benzodiazepines may increase depression in some patients and may contribute to deterioration in severely disturbed schizophrenic patients with confusion and

withdrawal. Suicidal tendencies may be present or uncovered and protective measures may be required.

- As panic disorder has been associated with depression, precautions should be exercised when using higher doses of alprazolam for these patients.

(g) Potential for abuse

- Referred to excerpts from the NDPSC guidelines concerning the classification of Schedule 4 and Schedule 8 substances as previously cited by some other pre-meeting submissions.
- Stated that significant concerns existed around the abuse of alprazolam in Australia, making it difficult to reconcile a description of 'low to moderate abuse potential' (Schedule 4) and that it seems a more consistent description would be 'likely to be abused or misused' or 'likely to present a substantial risk of abuse, dependence or misuse for illegal purposes' (Schedule 8).
- Particularly noted the concurrent abuse of alprazolam / benzodiazepines with prescription opiates. A *National Drug Law Enforcement Research Fund's* paper presented a picture of active illicit markets in Melbourne, Hobart and Darwin for benzodiazepines and pharmaceutical opioids.
- Asserted that the alprazolam prescribing guidelines in Australia and NZ state that:
 - the effects of alprazolam were increased when combined with other CNS depressants such as methadone and other opiate-related medications;
 - benzodiazepines and opiates used together increase the risk of fatal overdose and similarly the use of methadone and benzodiazepines increases the risk of sedation;
 - the mortality and harm associated with abuse of opioids prescribed in the community was an important emerging issue and associated with that is the concurrent abuse of alprazolam; and
 - the harm associated with the use of this drug is increasing in line with the steadily increasing medical use of opioids.
- With concern over the high number of alprazolam prescriptions dispensed, Tasmania has implemented education measures for general practitioners, stricter regulation surrounding its supply from September 2007, and the subsequent roll-out of a Commonwealth-funded real time recording system for Schedule 8 substances and alprazolam.

(i) Additional matters

- Reiterated that for Schedule 8 substances, pharmacies must store medicines in a drug-safe that meets jurisdictional legislative requirements. Such drug-safes have a limited storage capacity and, with more products being restricted to Schedule 8, pharmacies must assess and resolve any storage issues.

- Consideration should also be given to the access of alprazolam by legitimate patients, particularly in rural areas where stock delivery might not be as frequent as in metropolitan areas.
- Advised that the decision to reschedule alprazolam to Schedule 8 could set a precedent to other benzodiazepines which has the potential to significantly impact the Schedule 8 storage capacity of a pharmacy. Stated that an alternative to a Schedule 8 restriction for alprazolam was required.
- Stated that the current Tasmanian classification for alprazolam of Schedule 4 “declared restricted substance”, commonly known as S4D21 could provide an interim solution in jurisdictions most affected, until a more effective national solution is available as discussed below.

Real Time Recording (RTR)

- Asserted that rescheduling as a mechanism for addressing misuse / abuse of medicines is problematic, as it would impose greater bureaucratic and other burdens, without necessarily targeting the cohort of people involved.
- Noted that the RTR systems were a specific tool to address misuse, alerting the relevant agencies who monitor the problem and providing clinicians with an effective decision support tool.
- In Tasmania, the access to dispensing information in real time had increased the capacity for pharmacists to identify potential problems, and to make clinically significant interventions to promote best practice / improve public health outcomes.
- Suggested the use of RTR be considered as part of the proposed Appendix N (notifiable medicines) of the *Standard for the Uniform Scheduling of Medicines and Poisons*, which was described in the draft Scheduling Policy Framework released by the National Co-ordinating Committee on Therapeutic Goods in 2009.

Transitional Considerations

XXXXXX requested that opportunity be given to further discuss XXXXX proposed alternative solution and that any decision on alprazolam made at the June 2010 meeting not be final.

XXXXXX requested that, if a decision results in the rescheduling of alprazolam to Schedule 8, such a decision should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) risks and benefits, (f) need for access, and (g) the potential for abuse.

Members discussed the need to amend the scheduling of alprazolam given the potential for abuse and dependence of this substance. A Member asserted that at this time there was insufficient evidence before the Committee to support the proposal to amend the scheduling of alprazolam from Schedule 4 to Schedule 8. Another Member stated that up-scheduling alprazolam to Schedule 8 would be the most restrictive scheduling status of this substance in the world. It was also noted that all benzodiazepines, apart from flunitrazepam, are currently Schedule 4. A Member asserted that more restrictive access to alprazolam would not deter those intending to abuse benzodiazepines, unless all were up-scheduled to Schedule 8. Another Member noted that local information indicated that alprazolam is a widely abused benzodiazepine, especially among intravenous drug users, is the drug of choice on forged prescriptions and detection in heroin associated deaths has increased since 2000.

Members discussed the merits for inclusion of alprazolam under Project STOP noting that any such move was not a scheduling matter. A Member asserted that Project STOP was designed to assist in inhibiting diversion of pseudoephedrine for illegal use, such as in the manufacture of amphetamines. Such diversion was not the main concern for alprazolam. It was suggested that RTR, as opposed to Project STOP, could be of some benefit in terms of obtaining a better indication of the prevalence of use and abuse of alprazolam.

A Member asserted that the abuse of alprazolam seemed to vary significantly between jurisdictions and there was insufficient evidence to indicate that a national response through additional scheduling controls was necessary at this time. The Member suggested that States and Territories further investigate this issue and, if appropriate data to support a rescheduling application became available, this matter could be referred to the delegate under the new arrangements.

Members generally agreed that there was insufficient evidence to support a Schedule 8 restriction for alprazolam, at this stage. Members further agreed that until such information is provided to support a rescheduling application, the current Schedule 4 entry for alprazolam remained appropriate.

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

12.1.2 5-AMINOLEVULINIC ACID (5-ALA)

PURPOSE

The Committee considered the scheduling of 5-aminolevulinic acid (5-ALA).

BACKGROUND

Methylaminolevulinate (MAL) is used in photodynamic therapy to treat cancerous and pre-cancerous cells. MAL is currently listed in Schedule 4, with no specified cut-offs or use limits. MAL is the methyl ester of 5-aminolevulinic acid (5-ALA).

As 5-ALA is the active principle of MAL, it is expected that it would normally be captured by the Schedule 4 entry of MAL, since a Schedule entry captures “every salt, active principle or derivative of the substance, including esters”, as set out under Part1(2)(c). However, in October 2003, the Committee determined that, until such time as a product was available in the Australian market, 5-ALA should remain unscheduled. There is no record of any subsequent reconsideration of this position.

DISCUSSION - SUBMISSIONS

In February 2010 XXXXX raised concerns with the TGA about the scheduling status of 5-ALA and its current use by beauty therapists for photodynamic therapy (PDT).

The February 2010 letter from XXXXX raised the following concerns:

- Asserted that PDT is promoted for treatment of sun-damaged skin within the beauty profession without the relevant medical and clinical guidelines.
- Because 5-ALA is unscheduled, non-medical personnel can provide skin cancer treatment to the general public without the appropriate training, diagnostic skills, follow-up or monitoring.

This issue was therefore referred for consideration at the June 2010 meeting by XXXXX.

Pre-meeting Submissions

With the exception of the submissions from XXXXX, all submissions were in support of a Schedule 4 entry for 5-ALA. Members noted the following points from the submissions:

- XXXXX reiterated a number of the points raised in XXXXX initial letter and further highlighted the lack of training of beauty therapists to adequately diagnose or treat sun-damaged skin. The submission also discussed the types of lesions that are able to be treated by PDT in order to highlight the need for professional intervention.
- XXXXX also highlighted the concern of correct diagnosis of potential skin cancers before undertaking PDT treatment.
- XXXXX was alarmed that beauty therapists, who had minimal training in the treatment and recognition of skin cancer, have access to 5-ALA.
- XXXXX highlighted that interactions with medications, such as tetracycline antibiotics, griseoflucin and diuretics were of particular concern as it is common for patients seeking PDT to be taking these substances.

- XXXXX, fully supported the concerns raised by XXXXX with regard to the possible dangers surrounding use of 5-ALA.

XXXXX

XXXXX argued that there was no scientific basis for the restriction of PDT due to perceived threat to public safety. Members noted the following points from the submission:

- Beauty therapists are made aware of the potential for a client to present with skin cancers through training at XXXXX and XXXXX accredited training bodies and to seek medical advice before treating any skin with abnormalities.
- 5-ALA enhances the effects of laser, intense pulse light (IPL) and light emitting diodes (LED) treatments and these treatments have been used safely for years.
- Asserted that XXXXX does not train in the removal of skin cancers with PDT, noting that there a different treatment protocol that is left strictly to the medical profession.
- XXXXX training stipulates that any pigmented skin be medically assessed for skin cancer and cleared before PDT skin rejuvenation treatments are offered.
- Asserted that the vast majority of “non-medical” health practitioners freely and swiftly refer clients to doctors for assessment and treatment where there is even the slightest possibility of a skin cancer condition.
- Strongly opposed the scheduling of 5-ALA as it would severely limit public access to a safe and effective treatment offered by the wider aesthetic industry.

XXXXX

The submission disputed the need for scheduling on the grounds of public safety for 5-ALA, arguing that the proposal was based on a business focus of some medical groups. Members noted the following points from the submission:

History of 5-ALA and PDT

- PDT has long been considered the domain of the medical profession, as a specific form of 5-ALA, MAL is only available on prescription. In the USA another prescriptive form is 5-ALA hydrochloride. Both these forms tend mainly to be used for squamous and basal cell carcinoma treatments on face and body areas. MAL appears to be a much more aggressive treatment path.

Background: 5-ALA

- 5-ALA is a naturally occurring substance found within the human body. It is involved in porphyrin biosynthesis.
- By applying 5-ALA (or MAL) to the skin, it bypasses a rate-limited enzyme reaction so that there is a build-up of intermediates of porphyrin synthesis, namely PpIX -

which is photoactive. Thus, when a light source is applied, it gives off reactive oxygen species (ROS) that then destroy the cell (which is good when it is a skin cancer or poor quality or defective tissue).

Literature review of PDT, XXXXX

Asserted that:

- The study identified all known literature worldwide to identify any possible side effects and complications. Broadly speaking, this comprehensive study located only two adverse outcomes related to the use of ALA-PDT.
- The study stated that “PDT has demonstrated high efficacy, minimal side effects and improved cosmetic outcome when used for the treatment of actinic keratoses (AK), basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and photaging...” And, that there are clearly identified wide ranging cosmetic benefits “to soften the appearance of acne scars, fine lines and wrinkles...”

Current usage of 5-ALA in Australia – medical and non medical

Asserted that:

- There have been no serious adverse events reported to date by either Beauty Therapists or Doctors in Australia or New Zealand of PDT treatments using 5-ALA and various light energy sources.
- Often Doctors were uncertain as to the correct clinical parameters on the use of PDT and the “learning curve” was considered a lengthy one taking up to 12 months or more. However, with correct clinical training and access to TGA listed (or registered) light devices, a health practitioner could rapidly become competent and extremely safe in the patient assessment and use of PDT treatment.
- Based on some simple survey sampling, the total number of Australian clinics offering PDT to the public may be around 200 – 240 centres (primarily medical clinics). These clinics appear to prefer using 5-ALA rather than the more aggressive MAL, primarily used by a small number of dermatologists specifically for treatment of cancerous and pre-cancerous tissue identified in patients.

Risk profile

- Asserted that, based on the detailed literature review of XXXXX, “there are few reports of significant adverse outcomes using ALA-PDT. Two cases of skin cancer possibly related to PDT have been reported. The report states “PDT is generally considered to have a low risk of carcinogenicity.....”
- Widely accepted by Doctors and others, PDT has an extremely low risk profile, and is an ideal tool for a variety of skin conditions and complaints, some medical and others not.
- Asserted that, while there are several arguments to support the scheduling of 5-ALA, these can be rebutted, as follows:

1. Asserted that there was no scientific evidence to support the claim that an improvement in skin cancer prone tissue treated by a health professional other than a Doctor might “mask” or hide a skin cancer leading to serious adverse effects for the patient at a later date.
 2. Many clinics distribute cancer council literature and the vast majority appear to have appropriate arrangements for referring clients to local doctors for skin assessment and treatment.
 3. Asserted that the medical profession are concerned that the public be protected by “scheduling” 5-ALA and have been running campaigns to discredit health operators with less training in the broad areas of IPL and laser operation despite there being many thousands of IPL systems now safely in use in Australia and no evidence of widespread or serious negligence or malpractice. Many dermal clinicians and beauty therapists have substantial IPL clinical experience.
 4. Asserted that there has been a concerted attempt by a small sector of the medical community to institutionalise a very simple, very safe and highly effective cosmetic treatment. The scheduling of 5-ALA will certainly lead to a severe future restriction of this excellent treatment without any corresponding benefit in terms of safety of the public.
 5. The public already have adequate access to PDT treatments for serious sun damaged and marked (pigmented) skin and asserted that the average cosmetic doctor has little time to carefully consider the wider benefits of PDT and other reliable long lasting treatments.
- The submission discussed clinical applications, methods of application, public benefits and risks and the commercial pressure influencing doctor statements.
 - The submission also included letters from beauty therapists with experience using PDT and 5-ALA, all supporting XXXXX position that 5-ALA should not be scheduled.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits of use, and (d) extent and patterns of use.

A Member asserted that the extent of non-medical use of 5-ALA was difficult to determine and that the risks and benefits of use of this substance in this context should be considered in making a scheduling decision. The Member specifically noted the risk of potentially delaying diagnosis of cancer in relation to potential aesthetic benefits.

Another Member argued however, that a scheduling decision must be based on the inherent risk of the substance and not be used to restrict access in a particular setting without appropriate toxicological data to support that restriction. The Member also

cautioned that there were different uses of the term “sun-damaged skin” which was contributing to the confusion in this debate. For the beauty profession, this often means “signs of ageing” such as wrinkles, whereas for the medical profession, the term usually relates to skin in a “pre-cancerous” condition. Another Member suggested it was possible that the wide use of the weaker form (5-ALA vs. MAL) in a less regulated market (i.e. the beauty industry) could in fact lead to greater exposure for patients for referral to Doctors.

A Member stated that given there are now products containing 5-ALA available on the Australian market, the October 2003 decision to leave 5-ALA unscheduled “until such time as a product was available in the Australian market” was no longer appropriate. The Member also noted that XXXXX supported a Schedule 4 listing.

A Member asserted, and the Committee generally agreed, that 5-ALA should, by any objective determination, be captured by the Schedule 4 methylaminolevulinate (MAL) entry, given that 5-ALA is the active principle of MAL (and MAL is a derivative of 5-ALA). Members noted however, that a number of pre-meeting submissions opposed such a scheduling change and, in accordance with the transition arrangements discussed under item 1.6.2, agreed that this item could not be finalised at this meeting. The Committee therefore agreed that the matter should be referred to a Delegate for reconsideration under the new scheduling arrangements with the recommendation that a new Schedule 4 entry for 5-ALA be created.

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The Committee decided that it would be appropriate to include 5-aminolevulinic acid (5-ALA) in Schedule 4. Members agreed that this recommendation should be referred to the Delegate for reconsideration under the new scheduling arrangements.

12.1.3 AMOROLFINE

PURPOSE

The Committee considered the scheduling of amorolfine.

BACKGROUND

Amorolfine is a morpholine derivative with antifungal activity. It acts by interfering with the synthesis of sterols essential for the functioning of fungal cell membranes. It is active *in vitro* against a wide variety of pathogenic and opportunistic fungi including dermatophytes, *Blastomyces dermatitidis*, *Candida* spp., *Histoplasma capsulatum*, and *Sporothrix schenckii*. Amorolfine also has variable activity against *Aspergillus* spp. Despite its *in vitro* activity, amorolfine is inactive when given systemically which has limited its use to topical applications for superficial infections.

In February 1995, amorolfine was first scheduled in Schedule 4 following consideration of its use in the treatment of dermatomycoses caused by dermatophytes, and cutaneous candidiasis.

At the February 1998 meeting, the Committee rejected rescheduling of amorolfine from Schedule 4 to Schedule 2 when in topical preparations containing 5 per cent or less of amorolfine (nail lacquer), for the treatment of infections of the nail. The Committee was concerned with the ability of the consumer to self diagnose, that an inaccurate diagnosis may delay the appropriate treatment of other conditions and also that inappropriate treatment could be used for an extended period. Further, there were safety concerns on embryotoxic potential, and the possibility of accumulation in long term use.

An application containing additional information in support of a request to reschedule topical preparations containing amorolfine to Schedule 2 was considered at the August 1998 meeting. The Committee agreed, based on the information provided, that the potential for adverse effects associated with long-term use of nail lacquer was sufficiently low to support rescheduling to Schedule 2.

As a result of a Trans-Tasman Harmonisation Working Party recommendation, the Committee decided to harmonise with NZ to include amorolfine for topical use in preparations containing 0.25 per cent or less of amorolfine in Schedule 2, in August 1999. There was no indication that this was to apply specifically to nails or any non-dermal surface. The Committee also agreed to include amorolfine in Appendix H.

At the October 2005 meeting, the Committee noted that there were no significant safety issues associated with the use of amorolfine topical cream applied on the nails or on the foot. It was further noted that at the June 2005 meeting, Members agreed to exempt from scheduling certain antifungal agents indicated for the treatment of tinea pedis to harmonise with NZ but these did not include amorolfine. On the basis of amorolfine's safety profile, the Committee agreed to foreshadow a decision to harmonise with NZ on the scheduling of amorolfine. Subsequently, in February 2006 the foreshadowed decision to exempt amorolfine for the treatment of tinea pedis from scheduling was confirmed.

Other topical antifungals available unscheduled in Australia for the treatment of tinea pedis include the imidazoles, ciclopirox, selenium sulphide, tolnaftate, undecenoic acid, benzoic acid, salicylic acid, povidone iodine. The imidazoles (e.g. clotrimazole, miconazole) were also listed in Schedule 2 for application to the nails. Ciclopirox and amorolfine were restricted to Schedule 3 for application to the nails (noting that ciclopirox was not available as a nail application in Australia).

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested the rescheduling of amorolfine preparations for topical use (regardless of strength) from Schedule 3 to Schedule 2. The applicant argued that amorolfine fit all of the criteria for Schedule 2, given that:

- Amorolfine was suitable for self-treatment of onychomycosis (a minor ailment capable of being recognised and monitored by the consumer).
- Low potential for harm from inappropriate use and very low abuse potential.
- Low or well characterised incidence of adverse effects and contra-indications for which advice or counselling is available.
- No interactions with commonly used substances or food.
- High therapeutic index and a wide therapeutic window.
- The risk of masking a serious disease and of compromising medical management of a disease was extremely low.
- The use of the product did not require ongoing or close medical diagnosis or management.
- The condition was easily recognisable by the consumer, was amenable to short-term treatment and was capable of being monitored and self-managed by the consumer, with advice and counselling if necessary.
- Positive benefits for consumers if amorolfine was included in Schedule 2:
 - The product and its packaging would be available for perusal by consumers before making a decision to purchase.
 - It would be readily available to those consumers who may be embarrassed by their condition and unwilling to discuss their symptoms with a pharmacist.
 - Pharmacist or pharmacy assistant advice would still be available to those consumers who require it.
- Rescheduling would have no effect on the ability of sponsors to advertise products as amorolfine was already included in Appendix H.
- Rescheduling would be consistent with other current Schedule 2 imidazole antifungals for application to the nails.

The applicant provided an overview of amorolfine use as follows:

- For the treatment of nail infections caused by dermatophytes, yeasts and moulds, a lacquer containing 5 per cent amorolfine, painted onto the affected nail once or twice weekly until the nail has regenerated (usually 6 to 12 months).

- For skin infections, including dermatophyte, a cream containing the equivalent of 0.25 per cent amorolfine, applied once daily for at least 2 to 3 weeks and continued for 3 to 5 days after clinical cure is achieved.
- In Australia, amorolfine was marketed as nail lacquer amorolfine 50 mg / mL. This product was registered by the TGA in 1996 for the treatment of onychomycosis caused by dermatophytes, yeasts and moulds. At this time, there were no other amorolfine products registered in Australia.
- Onychomycosis is one of the most common dermatological conditions. It accounts for one third of all fungal skin infections and one half of all nail disease. The infection occurs predominantly in adults and is rarely found in children, with incidence increasing with age.
- The amorolfine nail lacquer product has been marketed in about 60 countries worldwide. It has been available without prescription in the UK since 2006, NZ, Germany, Austria and Singapore.

The applicant also addressed matters under section 52E, outlined below under the Evaluation Report section.

Evaluation Report

The evaluator did not support the applicant's requested Schedule 2 entry for amorolfine for topical use. In the evaluator's opinion, the applicant did not adequately justify XXXXX claim that onychomycosis was a self-diagnosable condition, and also emphasised the significance of pharmacist intervention to aid the assessment of the patient and referral to a doctor if no proper diagnosis could be made. Members noted the main points raised by the evaluator:

- Onychomycosis was responsible for only 50 to 60 per cent of abnormal appearing nails and the identification of fungus was primordial before establishing antimycotic treatment, as white superficial onychomycosis responds well to topical treatment, whereas distal subungual onychomycosis and total dystrophic onychomycosis required oral treatment. Pharmacist intervention before purchase of amorolfine nail lacquer ensured that patients had been properly diagnosed before starting up to 12 months of treatment.
- The applicant's claim that onychomycosis was self-diagnosable was doubtful. It was noted that nail dystrophies, often clinically indistinguishable from distal subungual onychomycosis, could occur with psoriasis, eczematous conditions, senile ischaemia (onychogryphosis), trauma, and lichen planus.
- While the labelling provided additional information to help consumers recognise the condition, use the product and seek assistance from their pharmacist or doctor if they were unsure about the diagnosis or treatment, the evaluator reiterated that a proper assessment by a healthcare provider was still necessary to evaluate the condition.

- While the applicant claimed that there might be a public health benefit associated with prompt treatment of onychomycosis, the evaluator noted that amorolfine was currently listed in Appendix H, which meant direct-to-consumer advertising, which could result in increased community awareness. The evaluator was uncertain as to what additional public health benefits could be gained by the down scheduling of amorolfine to Schedule 2. A down scheduling would mean that some patients might trial the product prior to receiving proper medical assessment.
- The applicant stated that a Schedule 2 arrangement would be a positive benefit for sufferers who may be unwilling to submit to questioning by a pharmacist, particularly in an open shop situation. The evaluator argued that while the potential psychological impacts of onychomycosis could not be disputed, it was uncertain whether permitting patients to purchase the product without a prior consultation with a health professional was beneficial. Reiterated that treatment with amorolfine needed to be continued for 12 months and was associated with considerable medical costs. Therefore, a proper diagnosis to ensure appropriate use was important.

In the evaluator's opinion, the following arguments made by the applicant appeared appropriate:

- Minimal amount of amorolfine topical preparation was absorbed systemically, therefore treatment with amorolfine rarely produced systemic events and was only associated with local skin reaction, noting that the treatment for onychomycosis was topical.
- The pattern of use of amorolfine lacquer and creams was extensive in Australia.
- While some consumers may request advice with the first purchase, it would usually not be required for repeat purchases over the period of treatment (of up to 12 months). The applicant's claim that amorolfine for topical use did not require professional advice with every purchase was appropriate.
- Overall, the applicant's claim that data illustrated that amorolfine was safe was supported. In particular:
 - XXXXX.
 - The Committee reviewed a report of the Adverse Drug Reactions Advisory Committee -ADRAC (now replaced by the Advisory Committee on Safety of Medicines - ACSOM) 2005 and concluded that there were no significant safety issues associated with the use of amorolfine topical cream on the nails or on the foot. A recent search of ADRAC identified one additional report since 2005 involving loss of smell in a 69 year old male.
- There was satisfactory discussion of the background of amorolfine on its antimicrobial action, uses and administrations, the prevalence, causes and risk factors of onychomycosis (main indication of amorolfine).
- Other agents available for topical treatment of onychomycosis such as imidazoles (e.g. clotrimazole, miconazole) were included in Schedule 2 for application to toe

nails. Ciclopirox, similar to amorolfine, was restricted to Schedule 3 for application to the nails (noting that ciclopirox was not available as a nail application in Australia).

The evaluator further assessed the application against matters under 52E as follows:

(a) Toxicity and Safety

- The evaluator noted that this had been well addressed by the applicant. Supported the applicant's assertion that the data illustrated that amorolfine was safe.

(b) Risks and Benefits

Treatment options

- Agreed with the applicant that systemic treatment was not suitable for all patients, and that:
 - Oral treatments such as terbinafine could cause gastrointestinal disturbances and an increase in liver enzyme.
 - The main benefit of topical anti-mycotic agents was direct application and action of the drug at the site of infection.
 - The potential for interaction with other medications was also limited and undesirable effects were generally localised.
 - The systemic absorption of amorolfine even after prolonged use was negligible.
 - It was suggested that white superficial onychomycosis responded well to topical treatment.

Potential for resistance

- Noted that the applicant mentioned an *in vitro* study with respect to the frequency and appearance of resistant mutants to amorolfine. Four hundred strains of *Candida* spp. and *Trichophyton* were used to test resistance frequency and selection of resistant mutants. Under the test conditions, none of the 400 strains tested for sensitivity showed primary resistance to amorolfine and no fully resistant strains were detected. In the evaluator's opinion these claims appeared to be appropriate.

(c) Potential Hazards

Adverse effects

- Noted that very rare cases of skin irritations and allergic sensitivity have been reported, including dermatitis, eczema, rash, pruritis, bullous reaction and skin atrophy.
- Agreed with the applicant's claims that the symptoms of skin irritation and allergic sensitivity were easily recognisable by the consumer and that appropriate advice to discontinue treatment and seek medical help for these symptoms was provided in the CMI / package insert.

Contraindications

- Noted that amorolfine was not indicated for use in children less than 18 years, or during pregnancy and lactation as there were no specific data relating to use in these groups.
- Also noted further claims that onychomycosis very rarely occurred in children or young adults and any unintended use during pregnancy was unlikely to present a direct danger to the foetus due to the very low systemic absorption of topical amorolfine.
- There were no listed drug interactions for amorolfine and it has been safely used in combination with oral antifungals. The concomitant use of nail varnish or artificial nails was not recommended. This was also stated in the CMI / package insert.

Other potential hazards

- Considered that the assertion by the applicant that the risk of masking an underlying serious medical condition through topical treatment of onychomycosis was negligible since onychomycosis alone was rarely, if ever, a symptom of an underlying serious pathology, was appropriate.
- Argued that the applicant did not identify the potential hazards to patients of misdiagnosed onychomycosis due to lack of medical intervention, and thus delaying patient access to appropriate treatment.

(d) Extent and Pattern of Use

- XXXXX.

(e) Dosage and Formulation

- Amorolfine nail lacquer comprised amorolfine 5 per cent dissolved in a lacquer base. The solvents evaporate quickly leaving a thin durable film of amorolfine lacquer on the nail surface.
- The CMI was accompanied by a series of illustrations showing consumers how the lacquer should be applied.

(f) Need for Access, taking into account toxicity compared with alternatives

- Noted that the toxicity of amorolfine was low, similar to the toxicity of other antifungals used topically in Australia (including the imidazoles, ciclopirox, selenium sulphide, tolnaftate, undecenoic acid, benzoic acid, salicylic acid, povidone iodine).
- Also noted that most other antifungals were unscheduled or Schedule 2 for topical use. The imidazoles clotrimazole, econazole and miconazole were Schedule 3 for vaginal use. Miconazole was also Schedule 3 for oral candidiasis. The imidazoles were Schedule 2 for application to the nails.

- The applicant asserted that reclassifying amorolfine XXXXX in Schedule 2 would be consistent with the classification of the imidazoles.

(g) Potential for misuse / abuse of substance

- Noted that the potential for misuse or abuse of amorolfine was extremely low. There have been isolated reports of individuals applying amorolfine nail lacquer more frequently than the recommended once or twice weekly. Two cases of overuse were published where the lacquer had been applied once daily for 2 months. Both cases reported discolouration of the nail with no other adverse effects and the discolouration resolved fully within 2 months of discontinuing treatment.
- Following prolonged overuse it might generally be expected that the frequency and intensity of local skin irritations would increase, but there were unlikely to be any serious consequences from this kind of misuse.
- The applicant reiterated that there was negligible or no risk of systemic effects resulting from overuse of amorolfine topical administration.
- Amorolfine nail lacquer has been available for over 13 years and was sold in over 50 countries worldwide without any indication of harm from misuse or abuse. In countries where OTC amorolfine was available there have been no suggestions of increased misuse or abuse of the product.
- There has not been a single case reported of potential addiction or possible dependence with any amorolfine containing preparation. Amorolfine does not produce any stimulant or other addictive effects.

(h) Purpose

- Noted the applicant's assertion that given the current availability in Australia of products containing amorolfine, the only purpose for which this substance would be used was as a 5 per cent nail lacquer for the treatment of onychomycosis.

Applicant's Response to the Evaluation Report

The applicant responded to the evaluator's recommendation not to reschedule amorolfine for fungal nail infections from Schedule 3 to Schedule 2, as summarised below:

- Disagreed with the evaluator's conclusion that the submission had not adequately justified its claim that onychomycosis was a self-diagnosable condition. Contended that the basis for the application was that onychomycosis, like many other topical fungal skin conditions, was able to be successfully treated by consumers.
- Argued that subungual onychomycosis could be differentiated from psoriasis, eczematous conditions, senile ischaemia (onychogryphosis), trauma, and lichen planus, which were associated with other symptoms involving the skin and or nail distinguishing them from fungal infections. Psoriasis usually presents as psoriatic plaques on other susceptible areas of the skin such as the scalp, elbows and knees. People with skin conditions such as psoriasis, eczema, senile ischaemia and lichen

planus would usually be under the care of a medical practitioner and could be expected to refer any associated nail condition to their doctor.

- In the unlikely event that onychomycosis was misdiagnosed and amorolfine nail lacquer was used inappropriately, there was negligible risk to health.
- Contended that the rate of false negatives at first culture test was high and the actual proportion of cases of onychomycosis was higher than the 50 – 60 per cent quoted by the evaluator. A report demonstrated that 38 per cent of patients were positive (after first negative test), and that 26.7 per cent were positive on the third mycological evaluation.
- In relation to the evaluator's comment that a mycological test was essential before starting an antimycotic treatment, the applicant argued that while treatment by a medical practitioner following confirmation of fungal infection was the gold standard, the likelihood of consumers misdiagnosing their condition was low and the consequences of mistakenly treating another condition as fungal, or delaying treatment of another condition were not significant.
- Asserted that consequently most antifungals were unscheduled (e.g. amorolfine topical less than 0.25 per cent for the treatment of tinea pedis) or Schedule 2 (e.g. the imidazoles for application to the nails). Contended that Schedule 2, as applied to the imidazoles for application to the nails was equally applicable to amorolfine 5 per cent for application to the nails.
- Also asserted that market research indicated that many consumers were treating their fungal nail infections inappropriately with antifungals that were available on open shelves (e.g. antifungal creams). The availability of amorolfine nail lacquer on shelves alongside these products would give consumers a more rational choice of product.
- Argued that while there were benefits to having "pharmacists act as a screen" for Schedule 3 medicines, amorolfine nail lacquer in Schedule 2 would provide additional benefits in allowing consumers to make a direct choice between the various alternative treatments without necessarily involving the pharmacist.
- The evaluator commented that due to the appearance of an infected nail, consumers may feel embarrassed to consult with a pharmacist. The evaluator was uncertain whether permitting patients to purchase amorolfine products without prior health professional consultation was beneficial. The evaluator suggested that this would be associated with considerable medication costs as amorolfine treatment needs to be continued for 12 months. The applicant argued that although the initial unit cost of amorolfine was high relative to the imidazoles, the product was only used once weekly (in contrast to the imidazoles that were used twice daily) and one pack would treat one to two nails for up to 12 months.
- Acknowledged that differential diagnosis of distal subungual onychomycosis from more unusual conditions of the nails, as specified by the evaluator, was difficult. Requested the following points to be taken into consideration:

-
- Differential diagnosis of any kind of fungal condition can be difficult (e.g. tinea vs. dermatitis and other conditions such as pityriasis rosea and granuloma annulare).
 - The only certain way of diagnosing a fungal condition was to perform mycological testing, however this would need to be done by a medical practitioner and results would not be available for 3 – 4 weeks and even then a false negative result could occur in a large number of cases.
 - The Committee had previously recognised the ability of consumers to self-diagnose and treat common fungal conditions such as tinea of the feet without involvement of a pharmacist or doctor.
 - Other antifungals for the treatment of fungal nail infections were already in Schedule 2 e.g. miconazole (tincture) and clotrimazole (solution).
 - The information on product packaging was of critical importance in assisting consumers in knowing whether the product was appropriate for them and how to use it correctly.
 - The amorolfine nail lacquer packaging would be modified to make it clear when to use the product, when not to use it and how to use it correctly.
 - Emphasised that pharmacists were not able to provide a proper diagnosis of any fungal condition because this required pathology testing which was not usually available in pharmacies. Acknowledged the importance of pharmacist advice being available if required but noted that consumers were already making decisions on treatments for onychomycosis in purchasing the Schedule 2 imidazoles.
 - Reiterated that pharmacist intervention was not required with every sale of antifungal nail products and this has been recognised by the Committee in the classification of the imidazoles as Schedule 2.
 - XXXXX.
 - Claimed that XXXXX was working with pharmacy organisations to develop appropriate educational materials to support pharmacists and pharmacy assistants in managing the change to Schedule 2.
 - Noted the evaluator agreed that:
 - Amorolfine for topical use did not require professional advice with every purchase.
 - Amorolfine was safe.
 - There was a role for topical anti-mycotic agents in the treatment of onychomycosis.
 - There was a negligible risk of masking an underlying medical condition.
 - The potential for abuse was low.

Pre-meeting Submissions

XXXXXX did not oppose the proposal to reschedule amorolfine 5 per cent from Schedule 3 to Schedule 2 while maintaining the current exemption for tinea pedis. XXXXX concurred that amorolfine for topical use fits the classification for a Schedule 2 entry and noted that it may already be advertised directly to consumers as it was currently listed in Appendix H.

XXXXXX also noted that other topical preparations used for the treatment of fungal nail infections were unscheduled or in Schedule 2.

XXXXXX recommendation was based on amorolfine's safety profile with limited contraindications and comprehensive training materials being developed for pharmacy assistants XXXXX. XXXXX believed such training would allow pharmacy assistants to effectively support consumers in amorolfine nail lacquer use and to effectively triage patients for referral to the pharmacist when required. In addition, particular matters under section 52E were addressed, as summarised below:

(a) Toxicity and Safety

- Amorolfine has a reasonable safety profile with the only contraindication being hypersensitivity to the product.
- For both pregnancy and lactation, there was evidence of AEs in animals, but not for humans. As such, it was listed as a Category B3 for use in pregnancy and was not recommended for use during either pregnancy or lactation. For both instances, pharmacy assistants were trained to enquire about such status with women for referral to the pharmacist.

[Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.]

- Amorolfine has limited and relatively minor adverse reactions, predominantly itching and erythema (0.6 per cent) when used as monotherapy. Rare cases of nail disorders such as nail discolouration, brittle or broken nails have been experienced, but this may also be linked to the condition being treated.

(d) Extent and Patterns of Use

- Topical treatment of onychomycosis may take several months. XXXXX.

(f) Need for Access

- Other non-prescription products available for the treatment of onychomycosis included miconazole 2 per cent tincture (Schedule 2) and undecenoic acid / chloroxylenol solution (unscheduled). The once or twice weekly application of amorolfine provided greater ease of application than these other products.

- While amorolfine 5 per cent was available as a Schedule 3 product, rescheduling as Schedule 2 would permit storage with the other products which would increase consumer awareness of the range of available products to treat nail infections.
- Asserted, however, that amorolfine 5 per cent should remain as a scheduled medicine as it was essential to maintain access to health professional support to ensure patients at risk of complications are supported. Onychomycosis was more common in people with diabetes, and it is important to ensure that these patients have access to professional support.
- The high cost of the product was likely to inhibit consumers from trialling the product without assessment or recommendation by pharmacy personnel.

Transition Arrangements

Members noted that XXXXX requested that if the Committee's decision resulted in a scheduling change that did not align with the proposed position (i.e. Schedule 2), such a decision should not be considered final.

XXXXX advised that XXXXX was willing to accept that any decision for amorolfine be considered final even if the decision results in a scheduling change that did not align with XXXXX preferred position.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits and (f) need for access.

Members noted the risks associated with use of amorolfine. A Member queried whether the public was able to correctly self-diagnose onychomycosis. Another Member asserted that if the condition was misdiagnosed, there was the potential for a 12 month delay in appropriate treatment. However, other Members generally agreed that such a delay did not pose a significant risk. Another Member noted the contraindications associated with amorolfine, especially for use in pregnancy and diabetes.

Members discussed the contraindications of amorolfine in comparison with similar substances available for this use. A Member asserted that the risks associated with amorolfine were similar to those for existing Schedule 2 antifungal products. The Member further asserted that the addition of amorolfine to Schedule 2 would not impact the existing level of risk to the public.

A Member queried whether this level of risk was appropriate and whether other Schedule 2 products should instead be rescheduled to Schedule 3. A Member asserted that, as with other products, this risk may be addressed by labelling and there had been no indication that the Committee would need to consider an up-scheduling of similar products.

The Committee decided that that all amorolfine topical preparations should be rescheduled from Schedule 3 to Schedule 2, whilst maintaining the exemption for the treatment of tinea pedis. Members noted that as a Schedule 2 product, advice from a pharmacist would still be available if required.

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The Committee agreed to reschedule all amorolfine topical preparations from Schedule 3 to Schedule 2. The Committee also agreed that the exemption from scheduling for preparations containing amorolfine for treatment of tinea pedis remained appropriate.

The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 2 – Amendment

AMOROLFINE – Amend entry to read

AMOROLFINE in preparations for topical use **except** in preparations for the treatment of tinea pedis.

Schedule 3 – Amendment

AMOROLFINE – Delete entry.

Schedule 4 – Amendment

AMOROLFINE **except**:

- (a) when included in Schedule 2; or
- (b) in preparations for the treatment of tinea pedis.

12.1.4 IODINE

PURPOSE

The Committee considered the scheduling of iodine.

BACKGROUND

Potassium iodide or potassium iodate may be taken by mouth for radiation protection to saturate the thyroid when uptake of radio-iodine by the gland is not desired. Therapeutically, potassium iodide may also be used as an antifungal, an expectorant and in veterinary medicine as a treatment of actinobacillosis, actinomycosis and simple goiter.

Non-therapeutic uses include the manufacture of photographic emulsions, as well as in animal and poultry feeds.

Since its first scheduling in May 1956, iodine has been considered at numerous meetings. Most significantly, at the August 1984 meeting, the Schedule 2 iodine entry was refined, adding a specification for iodine preparations for human therapeutic use. At the May and November 1987 meetings, the Committee considered reports of iodine intake exceeding recommended levels and agreed to include warning labels for iodine containing preparations. The Schedule 2 iodine entry was last amended at the May 2001 meeting, reflecting the current scheduling.

DISCUSSION - SUBMISSIONS

Application

XXXXXX requested an exemption from scheduling for oral iodine when used for prophylaxis and treatment of radioactive iodine exposure under an emergency plan approved by an appropriate authority. The application noted that:

- Currently all States and Territories, which have approved anchorages for visiting nuclear powered warships, hold stocks of 65 mg potassium iodine tablets as prophylaxis for exposure to radioactive iodine during a nuclear emergency. As part of Commonwealth port approval, the States and Territories must have plans in place that would allow the distribution of these tablets in the unlikely event of a nuclear emergency.
- The Tasmanian plan allows for the iodine tablets to be distributed by Ambulance Service officers and / or public health physicians and nurses. This is consistent with the requirements of the *Tasmanian Poisons Act 1971* for the distribution of Schedule 2 substances.
- The requested exemption would ensure further supply options (i.e. from fire service officers), should the Ambulance Service be unable to execute the distribution plan due to unforeseen emergencies. The current legislation would not allow this as an option while Schedule 2.
- XXXXXX has advised of its support for greater flexibility in distribution arrangements.

International use

According to the Martindale monograph for iodine, giving a radiologically stable form of iodine to saturate the thyroid gland confers thyroid protection from iodine radionuclides. In the event of a nuclear accident:

- US authorities recommend an adult dose of 130 mg of oral potassium iodide daily (including in pregnant and lactating women). Daily doses should be given until risk of exposure has passed and adjunctive measures have been implemented.

- UK authorities recommend an adult dose of 100 mg of stable iodine (as 170 mg of potassium iodate) for adults (including pregnant women and women who are breast feeding) as soon as possible after exposure and before evacuation.

Pre-meeting submissions

XXXXXX supported the proposed exemption.

XXXXXX asserted that iodine has a history of safe use as a supplement in multivitamin and mineral preparations. It was also asserted that, as an essential trace element referenced in the NHMRC Nutrient Reference Values for Australia and New Zealand, access to iodine in supplements should not be further restricted by changing the current scheduling arrangements.

XXXXXX noted that iodine is used in a number of complementary medicines and requested further details on how the proposed scheduling for iodine would affect current scheduling requirements.

XXXXXX requested clarification of the proposal to exempt iodine when used as a prophylaxis for radioactive exposure and queried how this exemption would affect current iodine scheduling and exemptions.

Transitional arrangements

XXXXXX requested an implementation date of later than 1 September 2010 should a change in scheduling result from the June 2010 meeting and that these decisions not be considered final. XXXXXX also requested that any decision from the June 2010 meeting not be considered final.

Following approval from the Committee, XXXXXX confirmed with XXXXXX that their transitional comments referred to changes to scheduling of complementary medicines containing iodine. Both XXXXXX agreed that they would accept the Committee's decision to exempt iodine when used as a prophylaxis and treatment in the event of radioactive iodine exposure under an emergency plan approved by an appropriate authority.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (f) need for access and (h) purpose of use.

Members discussed the need to amend the scheduling of iodine to facilitate appropriate access in the event of radiation exposure. A Member noted that Queensland state legislation allows access to iodine in these situations. A Member also noted that several other states and territories also had mechanisms in place which allow for the emergency distribution of therapeutic products. However, Members generally agreed that an

exemption from scheduling would ensure a nationally consistent approach for emergency access to iodine, and would not impact on its other uses.

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The Committee agreed to exempt oral preparations of iodine for use in prophylaxis and treatment in the event of radioactive iodine exposure under an emergency plan approved by an appropriate authority. The Committee agreed that this decision would be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 2 – Amendment

IODINE – Amend entry to read:

IODINE:

- (a) in preparations for human internal therapeutic use containing 300 micrograms or more of iodine per recommended daily dose; or
- (b) in preparations for human external therapeutic use containing more than 2.5 per cent of available iodine (excluding salts, derivatives or iodophors),

except in oral preparations for use in prophylaxis and treatment in the event of radioactive iodine exposure under an emergency plan approved by an appropriate authority.

12.1.5 LEPTOSPERMUM SCOPARIUM OIL

PURPOSE

The Committee considered the scheduling of *Leptospermum scoparium* oil (manuka oil).

BACKGROUND

Leptospermum scoparium oil (*L. scoparium* oil, also commonly known as manuka oil) is derived from the *L. scoparium* shrub, which is abundant throughout New Zealand and, to a lesser degree, Australia. *L. scoparium* is also commonly known as tea tree, sharing its name with the related melaleuca plant.

Between 1995 and 2000, the scheduling of essential oils was considered at numerous Committee meetings. The Essential Oils Working Party (EOWP) was established to provide scheduling recommendations for consideration by the Committee. The EOWP

advised that wherever possible, oils should be scheduled or exempted individually on the basis of the toxicity of the oil and that restricted flow inserts be implemented to minimise hazard of child poisoning. The EOWP also developed tables listing constituents of essential oils, recommended as either warranting scheduling controls or the consideration of scheduling controls.

Individual essential oils are listed in Schedules 5 and 6 (dependent upon their specific toxicity), with exemptions based on restricted-flow inserts, restricted volumes, and labelling requirements. Individual essential oils are also included in Part 2, section 25(1), (capacity-based child-resistant closure [CRC] requirements), and in Appendix E, part 2 (first aid instructions).

Members noted that as part of the SUSMP changes discussed at item 1.8.1, the proposed new Part 2, section 25(1) states:

If a poison, other than a poison included in a therapeutic good packaged in a manner compliant with orders made under section 10(3) of the Commonwealth *Therapeutic Goods Act 1989*, listed in column 1 of the following table is sold or supplied in a container having a nominal capacity specified for that poison in column 2 it must be closed with a child-resistant closure.

A search of the ARTG did not show any current products containing *L. scoparium* oil. An online search revealed that 100 per cent *L. scoparium* oil was available commercially in containers ranging from 6 mL to 25 kg.

DISCUSSION - SUBMISSIONS

XXXXXX referred for the Committee's consideration an evaluation report following an application from XXXXX for registration of *L. scoparium* oil as a new complementary medicine substance for use in Listed medicines.

The report noted that *L. scoparium* oil was initially considered by the XXXXX in 2006. The XXXXX evaluation report, included in XXXXX evaluation, recommended that the substance was suitable for use in Class 1 (i.e. Listed) medicines, without restrictions, subject to similar requirements associated with the scheduling conditions of essential oils in Australia, due to the potential for acute poisoning in children.

Building upon the XXXXX recommendations, the XXXXX report further recommended that, due to its toxicity profile, the main entry for *L. scoparium* oil be included in Schedule 6, noting XXXXX proposed exemptions, consistent with other essential oils, i.e. restricted-flow inserts, restricted volumes, and labelling statements.

The XXXXX report also noted that:

- *L. scoparium* oil has a highly variable chemical composition, depending on the geographical area from which the plants were sourced. Most preparations available commercially contained leptospermone (up to 20 per cent) and calamanene (up to 18

per cent) as the principal active ingredients. These preparations also consisted of lower concentrations of cadina-1,4-diene, flavesone, α -copaene, iso-leptospermone, α -cubebene, α -selinene, β -selinene (8 per cent or less of each).

- The *L. scoparium* oil evaluated was of the 'high β -triketone' type (consisting of 25-32 per cent flavesone, leptospermone, and isoleptospermone), derived from freshly chopped leaves and terminal branchlets, wild-harvested from the East Cape of New Zealand.
- Other chemotypes of *L. scoparium* oil ('high pinene' and 'complex of sesquiterpenes') were briefly included in the XXXXX evaluation, but have been omitted from the XXXXX evaluation as they were not exploited on a significant commercial scale at the time of the evaluation.

Members noted the following from the XXXXX evaluation reports:

Use patterns

- *L. scoparium* oil is regulated as a dietary supplement in New Zealand, but had not been evaluated by New Zealand regulatory authorities prior to the 2006 XXXXX evaluation.
- Internationally, *L. scoparium* oil is used as a preservative in cosmetics, replacing parabens, generally at a 2 per cent concentration. Its primary therapeutic use was for application to minor skin lesions, cuts and burns, with diluted oil preparations also used in aromatherapy and as an antiseptic mouthwash.
- The application proposed that 0.2 per cent diluted *L. scoparium* oil preparations be used as a mouthwash. The application also recommended that to achieve therapeutic levels for antimicrobial activity, preparations would need to contain 5 – 10 per cent of the oil.
- The XXXXX evaluation report further noted that it would not be unusual for a consumer to use 100 per cent pure *L. scoparium* oil dropwise topically for occasional acute treatment of small skin lesions such as minor burns, cuts and abrasions.

Pharmacology, toxicology and clinical data (high β -triketone chemotype)

- *L. scoparium* oil had a moderate oral LD₅₀ XXXXX. Skin irritation was moderate to severe XXXXX (4 hour exposure, semioccluded). The oil was not a skin sensitiser XXXXX, and was not mutagenic XXXXX (with or without metabolic activation). Dermal absorption data was not provided by the applicant.
- In *in vitro* studies, the cytotoxicity of *L. scoparium* oil was similar to Kanuka oil (*Kunzea ericoides* - a closely related species), both of which were more cytotoxic than cajuput oil and clove oil (nontoxic at 0.006 per cent). The maximum concentration at which *L. scoparium* oil was not cytotoxic was XXXXX.

- Biological activity studies demonstrated both antimicrobial and antiviral activity. *L. scoparium* oil was also found to possess XXXXX.
- Clinical data from studies where *L. scoparium* oil was used as a mouthwash XXXXX in combination with one or more other substances indicated “no adverse effects of concern”, however, the XXXXX report noted that the presence of other substances in the tested formulations detracted from their usefulness for the evaluation. The report also noted that one study had utilised oil from a different geographical area to the substance under evaluation, increasing the likelihood that its composition was considerably different from *L. scoparium* oil.
- A study on the pharmacokinetics of *L. scoparium* oil in XXXXX liver raised the possibility that ingestion of the oil may affect the hepatic metabolism of certain drugs and other exogenic compounds in humans.
- The oil, when used topically or diluted, was safe, however, inadvertent ingestion of the pure oil could pose a poisoning risk.

Other chemotypes / individual components

- It was anticipated that varieties of *L. scoparium* oil other than the high β -triketone chemotype, could be developed for commerce as demand for the oil grew. These other chemotypes (‘high pinene’ and ‘complex of sesquiterpenes’) usually contain low or zero β -triketones and relatively high monoterpenes. Of the ‘high pinene’ chemotype approximately 12 per cent of the oil consisted of components designated as ‘unknown’.
- The EOWP table of constituents warranting scheduling controls named 1,8-cineole as a restricting factor for scheduling (Schedule 6, with an exemption of 25 per cent or less of cineole). The XXXXX evaluation recorded maximum concentrations of 0.29 per cent cineole in *L. scoparium* oil.
- The EOWP table of components recommended for consideration of scheduling controls included four constituents present in *L. scoparium* oil: terpinen-4-ol (up to 1.85 per cent of the whole oil), α -pinene (up to 1.31 per cent in New Zealand, 18 per cent in Australian varieties), and β -pinene (up to 0.12 per cent), and linalool (up to 0.10 per cent). Members noted that these components were all unscheduled at this time.

α -Pinene component (unscheduled)

- Reported toxic effects of α -pinene were due to non-specific toxicity.
- Single-dose studies indicated an oral toxicity in rats with an LD₅₀ of 3.7 g / kg bw and a dermal toxicity in rabbits with LD₅₀ >5 g / kg bw (24-hr covered contact). In human studies, α -pinene had been shown to cause skin irritation and skin sensitization, particularly when allowed to oxidise. The vapour induced eye, nose and

- Inhalation toxicity was reported in some animal studies at up to 334 mg / m³, where lethargy was followed by agitation, staggering, loss of equilibrium and convulsions, and death. Autopsy revealed tissue changes in the respiratory tract and cerebral oedema (swelling). However, other studies have suggested that much higher concentrations are required to cause death. Literature on human poisoning indicated that following inhalation of α -pinene at up to 450 mg / m³ for 2 hours, total blood clearance was high, indicating that it was readily metabolised. However, a long half-time suggested that it would take more than 2 days for the body to be completely cleared of α -pinene.
- Repeat-dose rat studies indicated that 220 mg / kg bw / day for 3-5 days caused tissue changes in the liver, suggestive of microsomal enzyme induction, an increase in the amount of microsomal protein and marked increases in the activities of several liver enzymes.
- In rabbits, administration of α -pinene at up to 550 mg / kg bw / day was not associated with any overt toxic effects, and counteracted some of the adverse events of coadministered cholesterol. In one sheep, blood cells were found in the urine (possibly indicative of kidney damage) after three doses each of 1000 ml α -pinene (equivalent to 14.3 g / kg bw) and prolonged administration had marked toxic effects on the liver and kidneys.
- Carcinogenicity studies in rats indicated that administration of 500 mg / kg bw / day for 20 weeks did not significantly affect the total number or latency of mammary tumours induced by a dose of dimethylbenzanthracene (DMBA). However, a dermal study indicated that α -pinene appeared to have a weak tumour-promoting effect on mouse skin, following application of DMBA.
- Reproductive toxicity was reported in rats administered with a terpene preparation at 0.16, 0.8 or 1.6 mL / kg bw / day. Autopsy revealed decreased placental, foetal and newborn pup weights and an increase in the number of fetuses with a skeletal anomaly at the highest dose level, which also produced maternal weight loss. At the two lower levels there were no reported significant adverse effects or anomalies.
- No reports of human poisoning with pure α -pinene were found, however, poisonings with pine oil (60 per cent α -pinene) had been reported in large numbers, mostly as accidental poisoning in children.
- The XXXXX report noted that for monoterpenes such as α -pinene, but excluding D-limonene, there are no occupational exposure limits in most countries. In a publication extensively reviewing this issue, a 25 ppm (140 mg / m³) limit was proposed for all monoterpenes.

Limonene component (listed in Appendix B)

- Single-dose studies indicated an oral toxicity with LD₅₀ in rats of 5 g / kg bw. Dermal toxicity studies in rabbits produced an LD₅₀ of 5 g / kg bw, where limonene was moderately irritating to the skin, but only produced contact sensitivity in guinea pigs after oxidation in air.
- Human exposure to limonene by inhalation resulted in no reports of discomfort, irritation or other symptoms related to central nervous system effects after 2 hours exposure to the oil at 10, 225 or 450 mg / m³.
- Renal carcinogenicity occurred in male rats following chronic exposure, but was specific to this sex and in this species and did not occur in other species. The nephrotoxicity in male rats was related to the α_2 -microglobulin binding by the oil, resulting in accumulation of the protein in tubular cells leading to cytotoxicity. As this and similar proteins did not occur in the kidneys of other species, the possibility of human health hazard following exposures to limonene was considered negligible.

Other

- In the absence of human clinical trials of *L. scoparium* oil, the XXXXX report noted results from clinical trials where patients were subjected to an occlusive application of 25 per cent melaleuca oil (*Melaleuca alternifolia*) for 21 days. The study revealed that a small proportion experienced an irritation reaction, where further testing indicated that the allergens responsible were sesquiterpenes, which may also be found in certain types of *L. scoparium* oil.

Adverse reactions

- No adverse reactions to *L. scoparium* oil were found in the Australian adverse drug reaction database. One instance was reported in the Health Canada database, however, it contained insufficient detail about the composition of the product.

Pre-meeting submissions

XXXXX supported the proposed inclusion of *L. scoparium* oil in Schedule 6 with exemptions similar to other essential oils.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (d) patterns of use and (e) dosage and formulation.

Members discussed the toxicity profile of *L. scoparium* oil. A Member asserted that the toxicity profile of *L. scoparium* oil was consistent with other essential oils in Schedule 6. The Committee agreed that due to the overall similarities between *L. scoparium* oil and melaleuca oil, the two oils' scheduling cut-offs, exemption criteria and warning statements should also be consistent. Members also agreed that to reduce the risk of accidental poisoning, appropriate CRCs and labelling requirements should be

implemented. Consistent with the melaleuca entry, Members generally agreed that *L. scoparium* oil be labelled with the following Appendix E, Part 2 first aid statements:

- A For advice, contact a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766) or a doctor (at once).
- G1 Urgent hospital treatment is likely to be needed.
(Note – the words ‘at once’ to be added to instruction A).
- G3 If swallowed, do NOT induce vomiting.

The Committee discussed the proposed uses of *L. scoparium* oil. Members noted that the use of diluted essential oils in therapeutic products (as a mouthwash) has a documented history of use and results in low levels of exposure to the oil. Members also noted that the oil may be used in aromatherapy and agreed that *L. scoparium*'s inhalation toxicity was consistent with other Schedule 6 essential oils used for aromatherapy.

Members also noted that there was some potential for confusion as both melaleuca oil and *L. scoparium* oil could be referred to as “tea tree” oil. As the melaleuca oil entry specified “tea tree oil”, the inclusion of *L. scoparium* oil's common name “manuka oil” in its schedule entry would assist in differentiating between these two substances and provide greater clarity.

Members considered an appropriate date for the implementation of *L. scoparium* scheduling decisions, noting that the SUSMP No.1 was expected to have an implementation date of 1 September 2010. As products containing *L. scoparium* oil may be available commercially, Members considered a delayed implementation date of 1 January 2011 to allow for industry to make arrangements, if necessary.

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The Committee agreed:

- to include *Leptospermum scoparium* oil in Schedule 6, with exemptions consistent with other essential oils, including:
 - When fitted with restricted-flow inserts for up to 15 mL containers and additional child-resistant closures criteria for up to 25 mL containers in:
 - medicines for human therapeutic use when labelled according to *Required Advisory Statements for Medicine Labels* requirements; or
 - preparations other than for human therapeutic use when labelled with “KEEP OUT OF REACH OF CHILDREN” and “NOT TO BE TAKEN”.
 - For preparations containing 25 per cent or less of the oil;
- to include *Leptospermum scoparium* oil in Part 2, section 25(1), specifying requirements for child-resistant closures for containers with a nominal capacity of 200 mL or less;

- to include *Leptospermum scoparium* oil in Appendix E, Part 2, specifying that containers be labelled with first aid statements A, G1 and G3;
- that these decisions be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 January 2011.

Schedule 6 – New entry

LEPTOSPERMUM SCOPARIUM OIL (manuka oil) **except:**

- (a) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 15 mL or less fitted with a restricted flow insert and compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;
- (b) in medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and a child-resistant closure and compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;
- (c) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 15 mL or less fitted with a restricted flow insert and labelled with the warnings:

KEEP OUT OF REACH OF CHILDREN; and
NOT TO BE TAKEN;

- (d) in preparations other than medicines for human therapeutic use, when packed in containers having a nominal capacity of 25 mL or less fitted with a restricted flow insert and a child-resistant closure and labelled with the warnings;

KEEP OUT OF REACH OF CHILDREN; and
NOT TO BE TAKEN; or

- (e) in preparations containing 25 per cent or less of *Leptospermum scoparium* oil.

Part 2, Labels and Containers – New entry

25. (1) Child-resistant closures – New entry**Column 1****Name of the poison**

Leptospermum scoparium oil (manuka oil)
when included in Schedule 6.

Column 2**Nominal capacity**

200 millilitres or less

Appendix E, Part 2 – New entry

POISON

STANDARD

STATEMENTS

Leptospermum scoparium oil (manuka oil)

A,G1,G3

12.1.6 LOPERAMIDE

PURPOSE

The Committee considered the scheduling of loperamide.

BACKGROUND

Loperamide is a synthetic derivative of pethidine that inhibits gut motility and may also reduce gastrointestinal secretions. It is given orally as an antidiarrhoeal drug as an adjunct in the management of acute and chronic diarrhoeas and may also be used in the management of colostomies or ileostomies to reduce the volume of discharge. Available anti-diarrhoeal OTC treatments include loperamide, loperamide+simethicone combination, diphenoxylate / atropine, adsorbents (kaolin and pectin) and probiotics.

Loperamide for use in anti-diarrhoea was first considered by the Committee at the November 1978 meeting. The Committee decided to include loperamide in Schedule 4.

At the May 1983 meeting, the Committee considered rescheduling loperamide 2 mg capsules for a maximum of 2 – 3 days supply for use in chronic diarrhoea from Schedule 4 to Schedule 3. The Committee had concerns with the real need and suitability for loperamide to be available over-the-counter (OTC) and the possible risks associated with the early use of this substance. Loperamide remained scheduled as a Schedule 4 substance.

At the August 1986 meeting, the Committee again considered the down scheduling of loperamide. The application was considered to be more comprehensive than that of 1983. The Committee agreed with the evaluation report that in general loperamide appeared to be safe and no consistent pattern of adverse reactions had been detected. The Committee agreed to reschedule loperamide 2 mg in packs of 8 capsules to Schedule 3 and added an Appendix F warning statement. Subsequently, at the November 1986 meeting, the Committee confirmed its decision.

At the August 1996 meeting, the Committee considered a request to reschedule loperamide in packs of 8 dosage units, each dosage unit containing 2 mg or less of loperamide, from Schedule 3 to Schedule 2. The Committee stated that the existing scheduling of loperamide remained appropriate due to the need for professional advice at the point of sale and the potential risks associated with more widespread use resulting from the Schedule 2 advertising of the preparation.

At the November 1996 meeting, the Committee agreed to reschedule loperamide from Schedule 3 to Schedule 2 in packs of 8 dosage units or less, with each dosage unit containing 2 mg or less of loperamide. All other loperamide preparations remained in Schedule 4.

At the February 2000 meeting, the Trans-Tasman Harmonisation Working Party recommended removal of the current dose and pack size restrictions for loperamide from Schedule 2 and the inclusion of loperamide when given by injection in Schedule 4. At the August 2000 meeting, the Committee agreed that it would harmonise with New Zealand and increase the Schedule 2 pack size limit of loperamide from 8 dosage units to a maximum of 20 dosage units.

At the June 2009 meeting, the Committee decided to amend the Schedule 2 entry for loperamide to include the word 'divided' to further clarify that liquid preparations are Schedule 4.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested an exemption from scheduling of loperamide for oral use, when in a maximum pack size of 8 dosage units, with each dosage unit containing 2 mg or less of loperamide. The application contained arguments to support the exemption of loperamide from scheduling when used for the relief of acute, non-specific diarrhoea in persons aged over 12-years, although not recommended for use in pregnant or lactating women.

Members noted the applicant's arguments in support of an exemption for loperamide:

- Asserted that diarrhoea in the western world is usually acute and self limiting, with a brief duration, and does not need the advice of a healthcare professional.
- Claimed that consumers suffering from diarrhoea usually required urgent treatment of symptoms which include faecal incontinence (real or threatened) and social embarrassment and discomfort.
- Asserted that there was no evidence that treating an attack of diarrhoea prolongs the illness. In the unlikely event that there was a more serious underlying disease, control of acute symptoms and the minor delay in seeking a physician's advice was not thought to negatively impact the clinical outcome. Diarrhoea symptoms were non-ambiguous and misdiagnosis was very unlikely.
- Asserted that loperamide was a safe and effective treatment for acute diarrhoea for adults, with a very low incidence of interactions. Its contraindications would be outlined on the labelling.
- Argued that the urgency of a bout of diarrhoea was self evident and availability of effective control with a good safety profile was of community benefit. A small pack

of a maximum of one day's treatment would provide ease of access from a wide range of distributors.

- Asserted that the safety record of loperamide had been established through more than 30 years of use by adults in 137 countries as both Rx and OTC products (12 years in Australia).
- Claimed that the control and symptomatic treatment of acute non-specific diarrhoea was suitable for self treatment in the non pharmacy setting.

Members also noted the following points from the application:

Pharmacology

- Loperamide is a non-centrally acting antidiarrhoeal agent that has been shown to be effective for relief of acute and chronic diarrhoea of diverse aetiology. It binds to opiate receptors in the gut wall, which inhibits the release of acetylcholine and prostaglandins, leading to a reduction in propulsive peristalsis and an increase in intestinal transit time.
- Loperamide also reduces daily faecal volume output, inhibits intestinal secretion of fluid and electrolytes, and increases anal sphincter tone, thereby reducing incontinence and urgency.

Pharmacokinetic Profile

- In man, peak plasma levels of about 2 mg / ml of intact loperamide occurred at 4 hours. The half-life was about 11 hours with a range of 9-14 hours.

Adverse Reactions

- Reported non-serious adverse events (AEs) included abdominal pain/discomfort, nausea, vomiting, dry mouth, tiredness, drowsiness, dizziness, constipation and flatulence. These symptoms were often difficult to distinguish from undesirable drug effects.
- AEs recorded were generally of a minor and self-limiting nature. They were more commonly observed during treatment of chronic diarrhoea.

XXXXX.

The application also addressed other points under section 52E, summarised under the evaluation report discussion below.

Evaluation Report

The evaluator recommended approval of the requested exemption from scheduling for loperamide in a small pack size, provided that adequate patient information was included with the product packaging. The evaluator made the following points:

- Product information was required to address all contraindications and possible side-effects of loperamide.
- Further consideration should be given to the maximum recommended dose over 24 hours and the maximum pack size to be made available as unscheduled.

The evaluator assessed the application against section 52E. Members noted the following points:

(a) Toxicity and Safety

- The evaluator agreed with the applicant's claim that the post-marketing AE reflected 'reporting rates' which may not represent true incidence as would be seen in clinical trials or epidemiological studies, and that under-reporting was likely. The reported post-marketing AEs were summarised in the following table:

Adverse Event	Rate of adverse event
Skin and subcutaneous tissue disorders (rash, urticaria, pruritis, angioedema and bullous eruptions)	Very rare (< 1 / 10,000)
Immune system disorders (allergic and hypersensitivity reactions, anaphylaxis)	Isolated occurrences (< very rare)
Gastrointestinal disorders (abdominal pain, ileus, abdominal distension, nausea, constipation etc.)	Very rare (< 1 / 10,000)
Renal and urinary disorders (urinary distension)	Isolated occurrences
Psychiatric system disorders (drowsiness)	Very rare (< 1 / 10,000)
Nervous system disorders (loss of consciousness, dizziness)	Very rare (< 1 / 10,000)
Special senses (taste disturbance)	Very rare (< 1 / 10,000)

XXXXX

- Also agreed with the claims that review of the case details in the Periodic Safety Updated Report (PSUR) often reveals numerous confounding factors (additional medications, underlying disease states etc) which contribute to the AE, and add to uncertainty when interpreting data from a non-controlled setting.
- Noted that the data provided in the application relating to the number and type of serious AEs appeared to slightly under-represent the data provided in the application (review of the post-marketing safety profile). Noted, however, the inconsistencies did not change the overall profile as the cases occurred within a denominator of XXXXX total doses.
- Asserted that a literature search revealed no additional safety concerns other than those stated in the application. Use in children, use with fever / infection, bloody

stools and ongoing use without medical consultation were safety concerns repeated in the literature; however the conclusion that loperamide was safe for OTC use / adult self-medication was generally supported.

- The evaluator agreed with the conclusion made by the applicant that loperamide appeared to have an excellent safety profile and AEs were generally rare and of a minor nature.

Contraindications

- The evaluator had concerns that the large amount of contraindications for loperamide would require a particularly small font on the pack label and information may not be easily readable by consumers.
- Also was concerned that the Consumer Medicine Information (CMI) advised consumers to ensure that, if they have liver disease, kidney disease, AIDS, glaucoma or bladder problems, to advise their healthcare professional before they were instructed to consume loperamide. While these were precautions within a supervised setting, it may be prudent to consider whether these diseases should be contraindications in an unscheduled setting, unless specific advice had been received from a health professional.

Interactions

- Disagreed with the applicant's conclusion that there were no significant drug interactions of clinical relevance. Contended that this did not reflect the CMI advice to consumers to ensure that use of concomitant tranquilisers, alcohol and monoamine oxidase inhibitors had been considered by the healthcare professional.
- Asserted that these may be considered as potential interaction risks if loperamide was available as unscheduled, and thus may not be recommended for concomitant use unless advice had previously been received from a health professional.
- Noted the safety record of loperamide and reports noting the sale of approximately XXXXX doses each year in pharmacies in 2008 and 2009, with only two ADRAC reports being made.

Therapeutic index

- Noted that the recommended maximum dose of loperamide was 16 mg daily, which represented the proposed maximum unscheduled quantity.
- Recognised that the therapeutic index was wide with isolated reports of 144 mg and 60 doses being consumed without fatal consequence. Fatal outcomes associated with loperamide overdose in the PSUR (XXXXX) were associated with multiple drug toxicity and that the role of loperamide in causality was not defined.

(b) Risks and Benefits

- The risks of loperamide were described in *(a)* for general safety, although further information on hazards and misuse were listed in sections *(c)* and *(g)* below.
- Noted that the benefits associated with loperamide use with respect to relief of symptoms of diarrhoea were well documented. In addition, indirect benefits such as decreased absenteeism from work, and decreased social embarrassment were also reported.
- Benefits associated with increased access as a result of loperamide being available in retail outlets were described in section *(f)*.

(c) Potential Hazards

Use in Pregnancy / Breast feeding

- Agreed with the applicant's statement that the use of loperamide in pregnancy or breastfeeding in an unscheduled setting was contraindicated. Argued that the suggestion to use an icon to assist with the communication of this information to individuals with low literacy appeared reasonable and advisable.
- A literature search identified two case-control studies of loperamide use in pregnancy. Noted that neither an attributable risk, nor a conclusion of safety of loperamide in pregnancy was able to be conclusively determined from these studies. It was apparent however, that in absolute terms, any risk in pregnancy attributable to loperamide would be small.

Accidental exposure / poisoning

- The application presented NSW Poisons Information Centre 2008 data which included 46 reports of loperamide poisoning, but no reported outcomes. Of these, 39 related to exposure in children, however further information (i.e. on outcomes) was necessary to appropriately assess the risks.
- Agreed with the applicant's suggestion that accidental ingestion of loperamide by children over 2 years of age was likely to be safe. This assertion was based on licensing information from the USA and Canada (where loperamide has been licensed for children over 2 years of age).

Risk of masking serious disease or compromising medical management of a disease

- The applicant claimed that diagnosis of acute diarrhoea was non-ambiguous and apparent to the patient. It was claimed that the labelling of loperamide would list circumstances warranting further investigations rather than immediate treatment, and advice to seek medical care if self-treatment was unsuccessful after 48 hours.
- Asserted that the applicant's claim that a health professional generally relies on the patient's description to diagnose diarrhoeal disease was reasonable.
- Asserted that in the absence of health professional advice, if loperamide was unscheduled, requirements to confirm the suitability of treatment should be highly

prominent on packaging to prompt self-assessment. Argued that the application had not provided an acceptable example of pack labelling.

- Noted that the applicant claimed that a 48 hour delay in receiving medical advice was unlikely to have clinical implications, and loperamide treatment was not associated with increasing the duration or severity of diarrhoea. Agreed that this assertion appeared reasonable and was generally supported by the literature, however, argued that specific clinical advice with respect to a 48 hour delay may be warranted.

(d) Extent and Pattern of Use

- Loperamide is available in 137 countries, and in most as an OTC product. In the UK, USA and Canada it is available in grocery settings. In the UK, pack size was limited to 6 caplets, however the US and Canada have not limited the pack size in grocery settings.
- While it would appear that the maximum quantity available in the UK as a general sale product had been aligned with the maximum 24 hour dose, no further information on the rationale for setting this maximal dose had been able to be determined by the evaluator. The maximum dose recommended on the general sales' pack in the USA was 4 caplets in 24 hours, whilst Canada's recommendation allowed up to 8 caplets / 24 hours (and each have unlimited pack sizes).
- To minimise the risk of patients neglecting to obtain professional healthcare advice in circumstances where diarrhoea persists, the evaluator argued that the use of a 24 hour pack limit appeared reasonable. However given the range in maximal doses recommended, choice of the most appropriate pack size may warrant further discussion (see *(e)*).

(e) Dosage and Formulation

- Noted that loperamide was available in three formulations in Australia:
 - Loperamide hydrochloride: capsule, caplet, chewable tablet, oral solution, and fast-dissolving tablet.
 - Loperamide oxide, a pro-drug of loperamide, as a tablet.
 - Loperamide (2 mg) / simethicone (125 mg) as both a tablet and chewable tablet.
- The applicant proposed an exemption from scheduling for loperamide available in a maximum pack size of 8 dosage units (equivalent to 24 hours supply).
- Asserted that there was a discrepancy between the unscheduled dosage being sought in Australia and available general sales in the UK (maximum 6 dosage units per 24 hours) and the US (maximum 4 dosage units per 24 hours), both of which were below the Australian PI recommended maximum daily dose.
- Argued that, noting the lower dose recommendations in the grocery stores overseas and the fact that the application stated that in practice an average dose of five capsules was rarely exceeded; a smaller maximum pack size of 8 dosage units may be more

appropriate in the unscheduled setting. [Members noted that the evaluator later clarified their recommendation that the preferred recommended daily dose in Australia be aligned with the UK.]

(f) *Need for Access*

- Suggested that the unpredictable nature of acute diarrhoea and the urgency (although non-medical) with which it requires management, indicated that a community benefit may be associated with increased ease of access to loperamide. Noted that this was more pertinent in rural or remote regions, where there are fewer pharmacies or pharmacies with limited business hours.
- Asserted that as the majority of cases of diarrhoea were self-limiting and the risk of AEs associated with the misuse of loperamide was low, there may be some benefit to allowing access to smaller pack sizes of loperamide in an unscheduled environment.
- Noted that evidence to allow a comparison with the risk and benefit profiles of alternative unscheduled anti-diarrhoeal preparations, (bovine colostrum and *Lactobacillus fermentum*) was limited. The uncertain risk-benefit profile of alternatives may be relevant when considering the potential benefits of unscheduled loperamide for consumers.

(g) *Potential for Misuse / Abuse*

- Asserted that the abuse potential of loperamide has not been identified as an issue of concern.
- Noted that the PSUR (XXXXXX) reported XXXXX cases of drug abuse and misuse with loperamide OTC and in these cases, constipation was the only AE occurring more than three times. Of the XXXXX cases, XXXXX were regarded as serious, and involved intentional misuse, drug dependence, intentional overdose and withdrawal syndrome.

(h) *Purpose(s) for Use*

- Unscheduled loperamide was proposed to be used for the relief of acute non-specific diarrhoea in persons aged over 12 years (consistent with the TGA approved indication).

(i) *Other Matters*

- None were raised by the applicant, but the evaluator did discuss a number of other matters.
- XXXXX.
- No pack size was provided in the application for loperamide (2 mg) + simethicone (125 mg), however a reduced daily maximum was recommended in the PI.

- Asserted that due to the volume of information in the CMI for Schedule 2 loperamide products, it would seem necessary that an equivalent package insert would be necessary to convey equivalent information (framed in a different context where necessary) in the unscheduled setting.

The evaluator concluded that adequate PI or CMI would need to be made available to consumers concerning all contraindications and possible side-effects of loperamide.

Applicant's Response to the Evaluation Report

The applicant reiterated arguments from the application, particularly those regarding:

- The suitability of indication for self treatment in the non pharmacy setting.
- That the availability of a small pack (of a maximum of one day's treatment) exempted from scheduling will provide ease of access, which would better serve the needs of a sufferer.

The applicant also responded to particular matters raised by the evaluator including:

Toxicity and Safety

- XXXXX.
- Contended that CMI were only required to be supplied for Schedule 3 products, and may be required for products that have been down scheduled from Schedule 4 or Schedule 3. It was noted that Schedule 2 products were not required to be supplied with a CMI.
- Assured that the proposal was to exempt packs of not more than one day's supply to minimise potential safety concerns.
- Argued that a number of unscheduled products have contraindications and / or interaction risk, and Category C pregnancy risk products, which were all adequately addressed through labelling to ensure safe and correct use of the product, without the need for pack inserts or CMI's.
- XXXXX.
- Confirmed that a review of the PSURs since 2001 indicated that no regulatory actions were taken for safety reasons.

Potential Hazards

- XXXXX.
- Acknowledged that more warnings may be considered appropriate on the label in an unscheduled setting, however did not believe that all contraindications should be expressed on labelling or extended to a pack insert, especially for those that were very rare.
- XXXXX.

Extent and Pattern of Use

- Addressed the evaluator's concerns on the rationale for setting maximal doses in some countries and in Australia:
 - Contended that in the UK, historically a maximum of 6 dosage units per 24 hours had been approved and hence the resulting maximum pack size allowable for general sales was 6 tablets (one days' supply). The applicant was not aware why the maximum daily dose was 6 tablets.
 - Asserted that the dose in Canada was a maximum of 8 dosage units per 24 hours, consistent with the Australian product information. However, as highlighted by the evaluator, both the USA and Canada have unlimited pack sizes for general sales.
 - Reiterated that the proposal in Australia was one day supply, ensuring that the product was only taken for a brief duration for acute self limiting diarrhoea, noting that the TGA had approved a recommended maximum daily dose of 8 capsules or caplets.
 - Concluded that the benefit outweighed any potential risk in maintaining an unscheduled pack size consistent with the maximum daily dose.

Dosage and Formulation

- Further addressed the evaluator's concerns on the recommended dosage sought in Australia (8 dosage units) being higher than in the UK (6 dosage units) and the US (4 dosage units), as follows:
 - Highlighted that the conclusions previously drawn that '5 capsules is rarely exceeded' was correct for consumers suffering from chronic diarrhoea, not for acute diarrhoea, which loperamide was indicated for.
 - Also asserted that as loperamide was indicated for acute nonspecific diarrhoea, the recommended maximum daily dose of 8 capsules or caplets remained appropriate; given this was the maximum daily dose as approved by the TGA.
 - A maximum of one days' supply in a GSL setting ensured easy access for sufferers without promoting extended use.
- In relation to the specific packaging, the applicant stated that each dosage unit would be packaged in individual units in a blister pack which would be placed in a carton as per current loperamide products.

Pre-meeting Submissions

XXXXX opposed the proposal to exempt loperamide in packs of 8 dosage units from scheduling.

XXXXXX asserted that electrolyte replacement therapy was the cornerstone of diarrhoea treatment and was concerned about reliance being placed on loperamide, especially in cases of diarrhoea in children and the elderly.

XXXXXX argued that:

- The use and availability of loperamide as an OTC preparation for the control and symptomatic relief of acute non-specific diarrhoea was well established. However, certain precautions must be exercised, including the importance of initiating supportive treatment (e.g. fluid and electrolyte replacement, nutritional therapy); elimination, if possible, of the underlying cause of diarrhoea; and contraindications if diarrhoea was accompanied by fever or if there was blood or mucous in the stool.
- Highlighted the current warning statement for loperamide product labels '*Do not give to children under 12 years of age. Do not use beyond 48 hours or in pregnancy or lactation except on doctor's advice*'.
- Asserted that diarrhoea could be life-threatening if it is not managed appropriately. Simple factors could also exacerbate the condition (e.g. hot weather), particularly in the elderly; dehydration in this population group commonly leading to hospitalisation.
- Emphasised the importance of the pharmacist's role in monitoring medication use and referring to a medical practitioner if the condition had not improved or resolved as expected.
- Argued that exemption from scheduling would mean the consumer would not have the immediate opportunity to access advice from a pharmacist.

XXXXXX recommended that anti-motility agents such as loperamide should be used as a second line to other treatments such as rehydration. Asserted that it was critical that those most at risk of adverse outcomes, such as children, the elderly, or those with chronic health conditions, be encouraged to access advice from a health professional.

XXXXXX also addressed the following section 52E matters:

(a) Toxicity and safety

- Argued that the primary goal of treating diarrhoea, whether viral, bacterial, parasitic or non-infectious, was preventing dehydration or to provide appropriate rehydration.
- Asserted that loperamide use should be considered only in adult patients who were not febrile or experiencing bloody / mucoid diarrhoea.
- Asserted that it was also contraindicated in people with a hypersensitivity to loperamide and that inhibition of peristalsis was to be avoided.
- Stated that due to possible anticholinergic effects, loperamide should be used with caution in people with glaucoma, pyloric obstruction, significant gastric retention, or intestinal stasis.

- Contended that loperamide was known to cross the placental barrier and to be detected in milk in animals. As such it was classified as Category B3 use in pregnancy (i.e. drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed).
- Argued that short-term treatment of acute diarrhoea was better managed through a pharmacy where patients have access to professional advice.

(b) Risk and benefits

- In an epidemiological study in Italy on the prevalence of diarrhoea in old age, the most common causes were infectious diseases (19 per cent) and medicine use (16 per cent).
- Asserted that the treatment of elderly patients with diarrhoea must include rehydration and nutritional support. For these people, where causes related to infection or medicine side-effects, it was essential that they have access to advice from a health professional. This would not be encouraged by having packs of loperamide available from any retail outlet.

(c) Potential hazards

- Loperamide could cause tiredness, dizziness or drowsiness, and caution was advised when driving a car or operating machinery. Generally, such effects were more noticeable with acute, short-term treatments as the body was not accustomed to the effect.
- There was a potential interaction with tranquilisers or alcohol which may also impact on a person's ability to safely drive.
- Raised the concern that even small pack sizes may be inadvertently misused by people who do not understand the directions or the precautions.
- Claimed that in the interest of public safety, it was essential that support be aimed at people with limited health literacy. Relying solely on having information on a medicine pack was not appropriate if there was any risk of misuse.
- Argued that an exemption for a pack size of 8 would not reduce the risk of misuse as there was no restriction on the number of packs that could be purchased.

(f) Need for access

- Asserted that anti-diarrhoeals should not be used for acute diarrhoea in children as they did not reduce fluid and electrolyte loss and may delay expulsion of organisms and cause adverse effects.
- While a short course of anti-diarrhoeals may be warranted in adults to control symptoms, assessing and correcting dehydration and electrolyte disturbance was a

priority, particularly in elderly or those with diabetes, cardiovascular conditions or impaired renal function. In such cases, access to appropriate advice was more important than access to an anti-motility agent.

- Noted that loperamide was commonly included as part of a traveller's first aid kit. However, in these circumstances there was not a need for urgent access, and the traveller would benefit from interaction with pharmacy personnel who could also assist them in checking they were prepared for other medical contingencies, including vaccination and malaria prophylaxis.

Transitional considerations

- XXXXX requested that if a decision would result in a scheduling change that did not align with XXXXX position, such a decision should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risk and benefits, (c) potential hazards, (f) need for access and (g) potential for abuse.

Members generally agreed that the prevention of dehydration was the first line of treatment for diarrhoea. A Member asserted that a focus on consumer management of dehydration was especially important due to Australia's arid environment, where associated risks are greater than in other countries (i.e. Canada or the UK).

Members noted the long list of contraindications associated with loperamide and raised concerns that CMI was not required for unscheduled products. A Member asserted that although CMIs were not mandatory, this would not necessarily indicate a deficiency in the unscheduled products' label warnings. The Member argued that the regulator would ensure that labelling and warning statements were appropriate.

Another Member asserted that the public has a poor understanding of loperamide and its interactions and contraindications. The Member further argued that as a large percentage of the population does not read packet instructions there is a risk that loperamide may be used inappropriately.

A Member argued that a limited exemption for only one days' supply would minimise the potential risks. Another Member argued that there were questions as to the efficacy of one day's supply and in the absence of a desired effect consumers may continue to use loperamide, through purchase of multiple packs, without obtaining appropriate advice or information if such was not readily available. Another Member noted that there have already been reports of the misuse of loperamide, which may be indicative of a wider problem. The Member asserted that there is a risk that this misuse may be exacerbated if loperamide was to be available as unscheduled.

Members noted the claim that an exemption for loperamide would ensure access in rural areas. Several Members noted that there exist alternative supply provisions which ensure

appropriate access to scheduled substances, especially in rural areas where pharmacies may be limited or difficult to access.

Members acknowledged that consumers experience a degree of urgency when seeking access to loperamide. However, a Member asserted that it was important for consumers to be able to obtain advice and information for loperamide and that scheduling would ensure that this was available. Members generally agreed that, on balance, it was not appropriate for loperamide to be available as unscheduled.

RESOLUTION 2010/59 - 25

The Committee agreed that the current scheduling of loperamide remained appropriate, i.e. Schedule 2 when in divided preparations for oral use in packs of 20 dosage units or less, and Schedule 4 for all other preparations.

12.1.7 MAGNESIUM SULFATE

PURPOSE

The Committee considered the scheduling of magnesium sulfate.

BACKGROUND

Magnesium sulfate is often available as the heptahydrate complex, commonly called Epsom salts. Anhydrous magnesium sulfate is used as a drying agent. Oral magnesium sulfate can also be used as an osmotic or saline laxative. Epsom salts have been available for many years as an unscheduled powder with directions for use as a laxative, relaxing bath additive, fertilizer and fabric softener.

At the February 2009 meeting, the Committee agreed to foreshadow a Schedule 3 magnesium sulfate entry 'for human therapeutic use in divided oral preparations for constipation' following consideration of concerns regarding use for laxation from the Adverse Drug Reactions Advisory Committee (ADRAC, now replaced by the Advisory Committee on the Safety of Medicines - ACSM).

Subsequently, at the June 2009 meeting, the Committee decided to include magnesium sulfate in Schedule 3 for human therapeutic use in divided oral preparations i.e. did not support the February 2009 intent to limit the entry to preparations for treating 'constipation'. The Committee also agreed to exclude it from Appendix H.

At the October 2009 meeting, the Committee considered, and agreed to, a XXXXX request to exempt preparations containing 1.5 g or less of magnesium sulfate per recommended daily dose to avoid unintended regulatory impact. The Committee agreed that this cut-off limit was appropriate, noting that this would retain the status quo for existing mineral supplement products.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested an exemption from scheduling for magnesium sulfate in divided preparations containing 15 g or less of magnesium sulfate for use in laxation. Two scheduling wordings were suggested by the applicant, as follows:

- MAGNESIUM SULFATE for human therapeutic use in divided oral preparations except in preparations containing 15 g or less of magnesium sulfate per recommended daily dose; or
- MAGNESIUM SULFATE in preparations for oral use for bowel cleansing prior to diagnostic, medical or surgical procedures.

The applicant's argument is summarised as follows:

- Advised that, in line with the Committee's view that indications are best addressed by the regulator, the proposal to increase the cut-off level for exemption does not include a reference to a particular indication. However, the alternate proposed wording refers particularly to bowel cleansing indications, in line with the Schedule 3 entries for other similar substances.
- Argued that the exemption of 15 g or less of magnesium sulfate from scheduling would align it with the other osmotic laxatives of a similar nature and allow access to this easy to use, safe treatment for constipation.
- Asserted that magnesium sulfate fits all of the criteria for general sale, except when used in very large quantities as a bowel cleanser prior to diagnostic, medical or surgical procedures.
- The applicant argued that magnesium sulfate:
 - Was suitable for self treatment of constipation.
 - Had an extremely low abuse potential, and this potential was no greater than for any of the other unscheduled laxatives.
 - Had potential for harm from inappropriate use that was no greater than that of any of the other unscheduled laxative products, and was lower than many laxatives that are currently unscheduled.
 - Had very low incidence of adverse effects or side-effects.
 - Had no known interactions with commonly used substances or food.
 - Had a high therapeutic index and a wide therapeutic window.
 - The risk of masking a serious disease was extremely low, and was no greater than for any of the other unscheduled laxatives.
 - The risk of compromising medical management of a disease was extremely low.

- The use of the product did not require ongoing or close medical diagnosis or management.
 - The condition was easily recognised by the consumer, was amenable to short term treatment and was capable of being monitored and self managed by the consumer.
- Claimed the following benefits for consumers if magnesium sulfate was available as a general sale product:
 - Products and their packaging will be available for perusal by consumers before making a decision to purchase;
 - Products would be readily available to consumers who may be embarrassed by their condition and unwilling to discuss their symptoms with a pharmacist;
 - Will be consistent with the scheduling of the other osmotic laxative products.
- Noted that the more palatable encapsulated magnesium sulfate formulation was previously considered by the Committee, which agreed to a cut-off of 1.5 g or less per recommended daily dose. This cut-off was apparently determined based on magnesium sulfate content and dosage included in products on the Australian Register of Therapeutic Goods (ARTG) that were not indicated for constipation. Argued that the safety and appropriateness of higher magnesium sulfate concentrations did not appear to have been considered.
- Stated that the information in the application related to magnesium sulfate's use as a laxative (either as a treatment for constipation or as a bowel cleanser) because these are the indications of interest to the applicant.

The applicant also addressed matters under section 52E, as outlined below under the Evaluation Report summary.

Evaluation Report

The evaluator recommended consideration of whether the application has adequately justified the need for increased access for constipation to permit unsupervised sales in supermarkets, and whether any potential benefits justified the increased risks associated with medically unsupervised provision. Stated that while the applicant addressed to a degree some of the risks (of accidental ingestion by children, potential for abuse and risks of gastric erosions and obstruction) there remained concerns regarding the appropriateness of down scheduling to open sale:

- The data provided in the application on the use of magnesium sulfate for treatment of constipation was limited; hence the data available to evaluate its safety may also be limited. Noted the applicant's claim that toxicity associated with hypermagnesaemia was rare and, citing a review by the European Commission (EC), toxicity was unlikely to occur at doses of 2500 mg or less of magnesium per day (or 25 g of heptahydrate magnesium sulfate). The EC evaluation postulated that only patients

with underlying bowel disorders or those with severe renal dysfunction would be at higher risk from magnesium use.

- Contended the applicant's claim that magnesium sulfate was unlikely to have any drug interactions. The EC's Scientific Committee on Food (SCF) stated that significant interactions between iron and magnesium had been found both under experimental and clinical conditions and that interactions with zinc absorption owing to the inhibition of gastric acid by magnesium may occur, as well as interactions with certain drugs like tetracycline, penicillin and digoxin.
- Argued that there appeared to be a lack of robust evidence to support the efficacy of encapsulated magnesium sulfate (EMS) in chronic constipation compared with available unscheduled alternatives. The only clinical evidence for claims of EMS efficacy in treatment of chronic constipation was a non-randomised, single arm study; such studies are always subject to considerable bias, which renders its results unreliable.
- Asserted that the applicant's claim of a need for access to magnesium sulfate for treatment of constipation also appeared to be poorly justified. A plethora of laxatives are already available over the counter and more data had gathered regarding the use of these agents compared to magnesium sulfate.

The evaluator also reiterated the various concerns raised at the February, June and October 2009 meetings regarding the safety of the consumption of large quantities of oral EMS. In particular, XXXXX was concerned:

- About a possible resurgence of the use of magnesium sulfate as a laxative and, in turn, problems currently not seen such as hypermagnesaemia.
- That no intervention by a healthcare professional would likely lead to inappropriate use and safety risks in those with known and unknown renal impairment as well as dehydration in children, the elderly and those taking other medications.
- About the potential for gastric erosion and swallowing safety due to the large recommended dose (15 capsules) which could lead to oesophageal obstruction.
- Risk of the development of volume depletion and consequent exacerbation of renal failure in persons with chronic kidney disease as well as those with undiagnosed kidney disease especially with concurrent use of NSAIDs, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers.

The evaluator referred to the June 2009 meeting discussion. In particular, in reaching the decision to not include the indication for constipation in the Schedule 3 entry for magnesium sulfate Members noted that:

- While the substance had been unscheduled for a long time and the proposal was a significant jump to Schedule 3, it was the undivided preparation that had been historically available and that the encapsulated formulation was quite new.

- The risk arose from off-the-shelf use by the public for constipation and the associated potential for misuse. It was also noted that overuse could occur with people seeking to use this product as part of a 'cleansing diet' alternative therapy.
- The specific divided preparation that initiated this consideration was of particular concern regarding misuse as the taste of the magnesium sulfate was masked by the capsule formulation. The risks were therefore significantly different to those associated when use under medical supervision.
- The Committee generally agreed that any issue with the appropriateness of the presentation for a particular indication was best addressed by the regulator as part of the product approval process.
- In regard to Appendix H, it was noted that the risks associated with this type of magnesium sulfate preparation meant that advertising was not appropriate. Members noted that no other Schedule 3 bowel cleansers were listed in Appendix H and no convincing argument for public health benefit from advertising had been made.

The evaluator also noted that at the October 2009 meeting, the Committee reconsidered its June 2009 decision due to significant unintended regulatory impact. Points discussed included:

- Low levels of magnesium sulfate are contained in a large number of current oral human therapeutic use products (mainly as mineral supplements).
- A Schedule 3 entry would require that these products be registered, not listed.
- The Committee confirmed that the capture of such products had not been considered by the June 2009 meeting and that the risks being addressed through inclusion of magnesium sulfate in Schedule 3 would not arise from use of these low concentration products.
- Members therefore agreed that it would be appropriate to vary the June 2009 decisions to include a cut-off for exemption from scheduling.

Members also noted the evaluator's additional comments:

- A capsule presentation containing 950 mg of dried magnesium sulfate was indicated 'for weekly bowel conditioning, for the relief of constipation, for bowel preparation prior to colonoscopy'.
- However, due to safety concerns, XXXXX changed the indications to 'for the relief of occasional constipation, magnesium sulfate is a naturally occurring mineral that has been used for many centuries for bowel cleansing'.

The evaluator also made reference to the applicant's arguments against Section 52E as follows:

(a) Toxicity and Safety

- The evaluator assessed the studies provided by the applicant and concluded that this information should be interpreted in the context that the use of magnesium sulfate as a laxative has been minimal.
- Noted the applicant's claims that magnesium sulfate is poorly absorbed from the gastrointestinal tract after oral ingestion (4-11 per cent) and that, for this reason, hypermagnesaemia is rare.
- Noted that according to the EU's SCF at least two capsules of magnesium sulfate are required to produce a laxative effect. The maximum dose of XXXXX for treatment of constipation is XXXXX capsules per day (total XXXXX of elemental magnesium).
- Noted that the applicant provided references citing case studies of magnesium toxicity as well as results from three studies conducted by the applicant. The full trial reports of these studies, however, have not been provided for evaluation.
- The applicant stated that XXXXX of XXXXX magnesium sulfate products have been sold since the products were launched XXXXX, of which XXXXX per cent have been used for constipation relief, with the remainder for bowel-cleansing. The applicant also claimed that the XXXXX database (XXXXX) shows only two items where XXXXX was a suspected contributor to an adverse event. The evaluator noted that the full details of the adverse reactions were unclear.
- Noted the applicant's argument that clinical and scientific evidence for safety and toxicity are such that the exemption should be broader than that included in the current Schedule 3, and should be consistent with the scheduling of other osmotic and stimulant laxatives (unscheduled unless indicated as a bowel cleansing agent prior to diagnostic medical or surgical procedures, when it should be included in Schedule 3).
- Noted the applicant's argument that, as a minimum, the exemption from scheduling should be set at 15 g magnesium sulfate per maximum daily dose.

(b) Risks and Benefits

- Noted the applicant's claim that one benefit of encapsulated magnesium sulfate (EMS) was that it masked the unpleasant taste which had previously limited the use of magnesium sulfate as a laxative.
- Noted the argument that EMS, in comparison with other unscheduled laxatives, was associated with mild haemodilution rather than haemoconcentration. The applicant cited results of a randomised trial of EMS versus a powder formulation in bowel preparation prior to procedures, which showed that the volume of liquid consumed with EMS was significantly higher than with the powder formulation. The comparison provided, however, was not directly applicable to the current rescheduling request to limit the Schedule 3 entry to use in bowel preparation. Data comparing the safety of EMS and other unscheduled laxatives would be more informative.

- Noted that EMS would be a listed medicine and its efficacy and safety have not been subject to the stringent reviews of the registration process. Reiterated that there was a lack of rigorous evidence demonstrating efficacy of magnesium sulfate as it appeared that only one non-randomised study had been conducted in chronic constipation patients.
- Noted that the Committee had previously agreed that any issue with the appropriateness of the presentation of magnesium sulfate for a particular indication was best addressed as part of the product approval process.

(c) *Potential Hazard*

- Noted the applicant's reference to XXXXX which showed only two reports of hypermagnesaemia suspected to be related to magnesium sulfate. From this, the applicant claimed that a significant increase in hypermagnesaemia resulting from the availability of a more palatable form of magnesium sulfate was unlikely. Contended that it was uncertain whether the applicant had conducted a systematic search of the evidence and this information should also be interpreted with an understanding that use of magnesium sulfate for laxation has been limited, mainly due to its unpleasant taste.
- Noted that the current packaging of magnesium sulfate products contains XXXXX. Noted that the content of one full bottle of the magnesium sulfate product is the dose needed for use as a bowel preparation. This greatly exceeded the upper limit recommended by the EU's SCF of 2500 mg of elemental magnesium per day.

Gut Erosion

- Recalled that the Committee and XXXXX had been concerned that swallowing large amounts of EMS capsules has the potential to induce gastric erosions. Noted the applicant's statement that it could find no evidence to support this concern from either the medical literature or clinical practice.
- Advised that since the reduction in the EMS pack size to XXXXX, the Committee's concern regarding gastric erosion was somewhat lessened.

Dehydration / Volume Depletion

- Recalled that the Committee had expressed concern that in the absence of intervention by a healthcare professional, it was likely that EMS would be used inappropriately and present safety risks in those with known renal impairment, undiagnosed renal impairment and dehydration in children, the elderly and in those taking other medicines as well as magnesium sulfate.
- The evaluator expressed confusion regarding the applicant's conclusion that magnesium sulphate, even at a dosage three times that recommended for laxation, consistently induced falls in serum urea, and that a fall in serum urea is the reverse of the volume depletion. However, the applicant further argued that there were no reports in the medical literature of volume depletion caused by magnesium sulfate.

Used by the Renally Impaired

- The applicant claimed that magnesium sulfate posed little or no risk to the renal function of any patient, including patients with known chronic renal disease. Moreover, magnesium sulfate was occasionally administered for unrelated therapeutic reasons even in patients with chronic renal disease. The use of magnesium sulfate in patients with chronic renal disease was associated with an increased risk of inducing hypermagnesaemia due to reduced renal excretion of magnesium. The applicant further claimed that even in this at-risk group, magnesium toxicity was only seen at doses higher than those recommended for use in constipation. The evaluator was not able to find this claim in the application's citation.
- Recalled that at the June 2009 meeting, Members noted that abuse of magnesium sulfate would present a risk of hypermagnesemia for patients with chronic kidney disease (CKD). The greatest risk to CKD patients is the development of volume depletion and consequent worsening of renal failure. The evaluator asserted that there was also a risk for patients who may take this medication but be unaware that they have CKD especially if they are currently on NSAIDs, ACE inhibitors or angiotensin receptor blockers.

Interaction with other drugs

- Contended the applicant's claims that there are no known drug interactions with magnesium sulfate and that the recommended EMS dosage (a single dose every 3 – 7 days) substantially reduces the risk of interference with drug absorption compared with the usual frequency of laxative dosage (once or twice-daily). Asserted that significant interactions between iron and magnesium have been found. In addition, interactions with zinc absorption owing to the inhibition of gastric acid by magnesium may occur as well as interactions with certain drugs like tetracycline, penicillin and digoxin.

Accidental ingestion / overdose or misuse

- The evaluator considered that the following claims by the applicant with respect to abuse potential were reasonable:
 - No grounds to believe that patients with constipation are at particular risk of inappropriate drug usage. This concern should apply equally to any commercially available laxative preparation, many of which would be easier to ingest than EMS.
 - Consequently, these other laxatives lend themselves much more readily to intentional or accidental overdose – the tablets are smaller and hence easier to take in large numbers and they exert a far more potent laxative action per gram; almost all of these laxatives are, at inappropriate dosage, likely to induce significant fluid and electrolyte loss.
 - The large number of capsules required for the standard laxative dosage acts as an inherent brake against inadvertent over-dose. To exceed the recommended

dosage would require a conscious and repeated process of ingesting numerous capsules as well as a disregard for the instructions.

(e) Extent and Pattern of Use

- Magnesium sulfate – primarily in the form of Epsom salts – has been in common use as a laxative for approximately 400 years. The applicant claimed that despite its long history of use, reports of adverse outcomes associated with its use were rare. However, the use of magnesium sulfate as a laxative was not common in recent decades.
- The applicant claims that EMS is expected to eventually have a similar extent and pattern of use as the other available unscheduled osmotic laxatives.
- The evaluator reiterated that while magnesium sulfate had been unscheduled for a long time, the encapsulated formulation was quite new.

(e) Dosage and Formulation

- The applicant claimed that stricter restrictions have been placed on EMS compared with existing magnesium sulfate preparations. EMS:
 - was contraindicated for children under 12 years;
 - have a maximum dose for adults and children over 12 years that is slightly lower than Epsom Salts (XXXXX); and
 - have directions for use which state that approximately 250 mL fluid should be drunk with each set of five capsules – giving a total of 750 mL liquid to be taken per maximum dose.
- The applicant stated that oesophageal obstruction associated with EMS was unlikely. It was argued that, unlike particles with high water carrying capacity (such as guar gum and psyllium husks, which are unscheduled and available commercially in capsule format), magnesium sulfate dissolved completely within seconds of its exposure to water. This chemical process was rapid and there was no potential for capsule expansion. The evaluator noted that although the applicant's claim appeared to be logical physiologically, this was not backed up by objective evidence.

(f) Need for Access

- The applicant claimed that currently available laxatives fail to meet the clinical needs and expectations of the chronically constipated, and that magnesium sulfate capsules reflected a new concept in the management of constipation. The evaluator contended that the applicant drew its conclusion from a non-randomised study and that the results of such studies are associated with significant bias and provide less convincing evidence compared to results derived from randomised controlled trials.

(g) Potential for Misuse / Abuse

- The applicant claimed that the potential for abuse of magnesium sulfate would be the same as for other unscheduled laxatives (e.g., magnesium hydroxide, bisacodyl,

macrogol, sodium picosulfate), except when indicated for bowel-cleansing prior to diagnostic medical or surgical procedures. The evaluator observed that these claims appeared plausible on principle, but were not backed up by objective evidence.

(h) Purpose for Use

- Noted the claim that magnesium sulfate can have a variety of uses. Also noted that in its oral form, when unscheduled, the major use was likely to be for relief of constipation.

(i) Additional Matters

Accidental ingestion by children

- The evaluator agreed with the applicant's claim that:
 - Accidental EMS ingestion by children was unlikely because of the size of the capsules.
 - Should a young child attempt to ingest a capsule, it would likely be by chewing it. In that circumstance, the magnesium sulfate would be released and the unpalatable flavour would prevent a child from consuming more than a small quantity of magnesium sulfate (as was the case for undivided preparations, which were to remain unscheduled).
 - As an additional protective feature, the magnesium sulfate products are supplied in a bottle with a child-resistant cap.

Regulatory status of magnesium sulfate

- The evaluator noted the following statements from the applicant:
 - The safety profile of magnesium sulfate was such that inclusion in the low risk category of listed medicines was appropriate.
 - If the regulator disagreed with this view, it could amend the regulations to remove magnesium sulfate from this list or restrict the circumstances in which magnesium sulfate was eligible for use in listed medicines.
 - Therefore this factor should not be a consideration when determining the scheduling status of this substance.

Applicant's Response to the Evaluation Report

In addition to reiterating various arguments from the application, the applicant also commented specifically on the evaluation report as summarised below:

Toxicity and Safety

- Asserted that the EU's SCF have determined that the safe upper limit of a single dose of magnesium, at or below which toxicity would not be seen, was 2.5 g of magnesium.

- Stated that three studies commissioned by the applicant have also shown that there were no clinically significant adverse events in the 387 patients studied, some of whom received doses far larger than those proposed for laxation.
- The applicant responded to the evaluator's concerns that a report "postulates that patients with underlying bowel disorders such as ulcerative colitis, gastritis, colitis etc or those with severe renal dysfunction may be at higher risk of magnesium toxicity". Stated that, with the exception of "severe renal dysfunction", the remark included in the report was a postulate only, for which no supporting evidence was available, and should therefore be given little if any weight.
- Also stated that some of these conditions were associated not with constipation but with the complete reverse and, therefore, are irrelevant to the consideration of scheduling of magnesium sulfate for use as a laxative. Additionally, patients with "severe renal dysfunction" would likely be under the care of a doctor.

Benefits

- Noted that osmotic laxatives are both efficacious and free of the habit-forming effects of stimulant and herbal laxatives. The poor palatability of saline laxatives greatly limits their use in chronically constipated patients. Asserted that by encapsulating magnesium sulfate, the salt is rendered more palatable, overcoming the single biggest obstacle to its appropriate use in the management of constipation.

Efficacy

- In response to the evaluator's conclusion that there:
 - appeared "to be a lack of robust evidence to suggest the efficacy of EMS in chronic constipation compared with available unscheduled alternatives"; and
 - "the only clinical evidence from which the applicant makes its claim of efficacy of EMS in treatment of chronic constipation was a non-randomised, single arm study; which renders its results unreliable".
- The applicant asserted that:
 - The efficacy of magnesium sulfate for relief of constipation at the stated dose was well established, as demonstrated by the inclusion of recommended doses in all of the references which include those used by the TGA during product evaluations.
 - The presentation of magnesium sulfate in an encapsulated form would not affect its efficacy as it was available to the gastro-intestinal system in the same way as the undivided preparations as soon as it was released from the capsules. The results of the clinical trial performed using the encapsulated magnesium sulfate were consistent with this being the case.
- Also agreed that the gold standard method of evaluation for new treatments is the randomised controlled trial. However, a placebo-control arm would have proven difficult as the dose-finding period would almost certainly have exposed the placebo arm as ineffective. Hence, allowing patients to act as their own controls was

considered more appropriate, comparing the addition of once-weekly encapsulated magnesium sulfate to their previous therapy. Asserted that the important, scientifically valid and statistically significant observations about the impact of EMS should not be discounted on this basis. The study was one of the largest published constipation studies in terms of numbers of patients studied.

- The applicant also noted that for listed medicines, allowable claims are limited and the sponsor must hold data to the satisfaction of the TGA to support its claims. The applicant therefore contended that any further questions regarding product efficacy should be left to the product regulator.

Potential Hazard

Hypermagnesaemia

- Asserted that a systematic literature review of magnesium sulfate was conducted which showed that there are few reports of clinically significant hypermagnesaemia.

Gut erosion

- Asserted that the literature review found no evidence of gut erosion as a consequence of the ingestion of magnesium sulfate.

Dehydration / volume depletion

- Asserted that the literature search revealed no reports of volume depletion caused by magnesium sulfate, and located a study of magnesium sulfate use in bowel preparation of children which also showed no elevation of serum magnesium was seen while serum urea actually fell.

Use by the Renally Impaired

- Asserted that magnesium sulfate posed little or no risk to the renal function of any patient, including patients with known chronic renal disease. Stated that this was confirmed by the fall in serum urea and creatinine consistently seen with the use of magnesium sulfate capsules at high dosage and by the rarity of reports of adverse effects of magnesium sulfate even in patients with chronic renal disease.
- In relation to the inclusion of a study showing that the volume of liquid consumed with EMS was significantly higher than with powder formulation, the applicant argued that the purpose of inclusion of this data was to refute the position at previous Committee meetings that magnesium sulfate may cause dehydration / volume depletion. Argued that the fact that this does not occur was relevant and supported the safety of magnesium sulfate at the lower dose, as well as at the dose tested.
- In relation to potential abuse in patients with CKD leading to hypermagnesaemia, the applicant commented that abuse of any medicine by anyone was likely to lead to poor health outcomes, and that the reviewer had accepted the contention in the application that this medicine was, if anything, less likely than others to be the subject of misuse or abuse. Asserted that the probability of a patient having undiagnosed CKD and

taking NSAIDs, ACE inhibitors or ARBS and taking magnesium sulfate for constipation must surely be very low.

Interaction with other drugs

- In response to the concerns that “significant interactions between iron and magnesium have been found, and that interactions with zinc absorption owing to the inhibition of gastric acid by magnesium, as well as interactions with tetracycline, penicillin and digoxin” the applicant stated that the findings referred to were made in relation to magnesium hydroxide, not magnesium sulfate.
- Argued that observations based upon the use of magnesium hydroxide should not be extrapolated to those that might be seen with magnesium sulfate. There are substantial and significant differences in the biochemical reactions that occur when different magnesium salts come into contact with gastric acid and the efficiency of iron absorption is intimately linked to gastric pH.
- Reiterated that there were no known drug interactions with magnesium sulfate. Stated that the evaluator had mistakenly extrapolated the findings of a study involving magnesium hydroxide to apply to a substantially different molecule.

Dosage and Formulation

- Asserted that the XXXXX capsule pack size represents approximately XXXXX doses at the maximum recommended dose, or about XXXXX supply. This was consistent with (or smaller than) other comparable laxatives. Argued that EU’s SCF limits were not generally looked at as a guide for pack size. Asserted that, in addition, the bottle would be fitted with a CRC. Therefore, there should be no concerns over the pack size.

Need for access

- Noted the evaluator’s claims that a need for access to magnesium sulfate for treatment of constipation appeared to be poorly justified, and that other laxatives are already available over the counter. Responded that this statement disregards an independent report which concluded that currently available laxatives fail to meet the clinical needs and expectations of the chronically constipated.
- Asserted that most of the comparable unscheduled laxatives have been available for many years (like magnesium sulfate), and, as such, contemporary research on these substances was also likely to be limited.

Pre-meeting Submissions

XXXXX opposed the proposed down scheduling of magnesium sulfate for use in laxation. XXXXX recommended retaining the current Schedule 3 magnesium sulfate entry.

XXXXX reiterated its comment from a June 2009 post-meeting submission which recommended that the Committee consider amending the Schedule 3 entry to include a specific indication for constipation. The submission questioned the logic behind the

proposal to change the exemption of scheduling from 1.5 to 15 g when it was concerns about such a product (containing 15 g or less) XXXXX that evidently resulted in the Committee deciding on a Schedule 3 listing.

XXXXX also questioned the reason for exempting magnesium sulfate when used for laxation. Argued that this change would defeat the initial reasoning behind the scheduling of this substance.

Transitional Considerations

XXXXX requested that any decision recommended by the Committee not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) the risks and benefits, (d) the extent and pattern of use, (e) dosage and formulation and (h) the purpose for which a substance is to be used.

A Member noted that several of the evaluator's conclusions inadvertently associated data on magnesium hydroxide to magnesium sulfate outcomes. Members noted this, but agreed that the conclusions in question were not pivotal to many of the concerns arising from the June 2009 consideration.

While the applicant asserted that it had addressed all of the Committee's June 2009 concerns a number of Members remained unconvinced of this. In particular, several Members recalled concerns about increased risk of adverse events arising from the potential for overuse of large amounts of magnesium sulfate now that the unpleasant taste of magnesium sulfate could be masked.

A Member also recalled the previous concern that such overuse could occur with people seeking to use this as part of a 'cleansing diet' alternative therapy. The Member noted that the new indications still alluded to bowel cleansing i.e. 'for the relief of occasional constipation, magnesium sulfate is a naturally occurring mineral that has been used for many centuries for bowel cleansing'.

Several Members therefore asserted that there had been no change to the situation with regard to the concerns of high dose magnesium sulfate. The Committee generally agreed that a case had not been established for allowing general sale of high doses of magnesium sulfate.

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The Committee decided that the current scheduling of magnesium sulfate remained appropriate i.e. Schedule 3 with an exemption for oral preparations containing 1.5 g or less of magnesium sulfate per recommended daily dose.

12.1.8 4-METHYLMETHCATHINONE (MEPHEDRONE)

PURPOSE

The Committee considered the scheduling of 4-methylmethcathinone.

BACKGROUND

Methcathinone, a methyl derivative of cathinone, produces central nervous system stimulant effects similar to those of the amphetamines and is subject to abuse. The methyl derivative 4-methylmethcathinone (mephedrone) is also subject to abuse.

At the November 1998 meeting, the Committee agreed to the inclusion of methcathinone under Schedule 9 due to its potential as a problem drug.

As set out under Part 1, paragraph 1(2)(c) every salt, active principle or derivative of a substance is also captured by the scheduling of that substance unless the contrary intention appears. Therefore 4-methylmethcathinone is currently captured by Schedule 9 due to the scheduling of methcathinone.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested that the Committee consider the inclusion of 4-methylmethcathinone in Schedule 9 for the following reasons:

- XXXXXX have indicated that 4-methylmethcathinone has been detected in seizures in several states and territories.
- Methcathinone is included in Schedule 9. Under the derivative provisions, 4-methylmethcathinone should be captured. However, a specific listing under Schedule 9 will ensure clarity and transparency.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (g) the potential for abuse.

A Member asserted, and the Committee generally agreed, that 4-methylmethcathinone, as a derivative of methcathinone, is captured by the Schedule 9 entry for methcathinone. However, the Committee further agreed that it would be appropriate to create a new entry for 4-methylmethcathinone in Schedule 9 to clarify that this substance is indeed a prohibited substance.

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The Committee decided to create a new entry in Schedule 9 for 4-methylmethcathinone (mephedrone). The Committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 September 2010.

Schedule 9 – New entry

4-METHYLMETHCATHINONE *(MEPHEDRONE).

12.1.9 MONTELUKAST

PURPOSE

The Committee considered the scheduling of montelukast.

BACKGROUND

Montelukast is a selective leukotriene receptor antagonist that blocks the action of leukotriene D4 on the cysteinyl leukotriene receptor CysLT1 in the lungs and bronchial tubes. This reduces the bronchoconstriction otherwise caused by the leukotriene, and results in less inflammation. It is used as the sodium salt with doses being expressed in terms of the base.

In February 1998 the registration of montelukast was recommended for the prophylaxis and treatment of asthma in adults and children over 6 years of age.

At the May 1998 meeting, the Committee considered that Schedule 4 was appropriate for montelukast.

At the October 2009 meeting, the Committee considered a request to reschedule montelukast from Schedule 4 to Schedule 3 for oral preparations containing 10 mg or less of montelukast in packs containing not more than 14 days of supply, when for use in the symptomatic treatment of seasonal allergic rhinitis. The Committee agreed that the risk versus benefit ratio was not high enough to support this request.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested the rescheduling of montelukast from Schedule 4 to Schedule 3 with the following proposed new Schedule 3 entry:

- MONTELUKAST in oral preparations containing 10 mg or less of montelukast for the symptomatic treatment of seasonal allergic rhinitis in packs containing not more than 14 days of supply.

The applicant's overall arguments are summarised below:

- Claimed that additional treatment option of montelukast 10 mg available as Schedule 3 would further equip pharmacists to manage allergic rhinitis and respond to the many people who present to pharmacists with this condition.
- Made reference to a rescheduling application which was rejected at the October 2009 meeting. Asserted that it has reviewed the evaluation report as well as comments noted in the Record of Reasons for the October 2009 meeting. Reiterated its previous position that the risk versus benefit ratio is highly in favor of montelukast for seasonal allergic rhinitis in Schedule 3.

The applicant further claimed that montelukast fulfilled the criteria under Section 52E for listing in Schedule 3. This was discussed below under the Evaluation Report section.

Evaluation Report

The evaluator recommended that the request be rejected. In summary, this was based on the following:

- Argued that the data provided did not remove concerns that montelukast had a slower onset of action in the early days of treatment than loratadine. There was an expectation from users of OTC medicines that they would obtain prompt relief, and montelukast would not meet this expectation.
- Acknowledged that while the authors of two literature reviews may not be totally convinced of the association between montelukast and neuropsychiatric adverse effects, especially suicidality, both advised of the need for careful assessment of the patient's mental state symptoms, including suicidal ideation and past suicide attempts and refer when appropriate. Asserted that it was important to note that this advice was given in the context of the continuing prescription medicine status in the US.
- The application, including the proposed protocol for use by pharmacists, failed to adequately incorporate the above recommendations made by the two authors. The evaluator argued that this was likely due to the implementation of such recommendations being beyond the reasonable expectations of the role of a pharmacist.

Detailed comments were also made by the evaluator on particular data from references provided in the application, as outlined below:

- A cited analysis (Weinstein *et al*, 2005, 'Onset of efficacy of montelukast in seasonal allergic rhinitis', *Allergy and Asthma Proc.*, vol 26, pp.41-6), was XXXXX. Five of the seven authors were XXXXX. The applicant claimed that the analysis in this report of pooled data from four Phase III studies included data on both montelukast

and loratadine (each compared directly with placebo) and demonstrated that both show early efficacy vs placebo. The evaluator argued that the results reported were solely those to do with montelukast versus placebo and no data about or comparisons of the onset of action of loratadine with either placebo or montelukast were provided.

- Argued that the magnitudes of the changes of symptoms scale in the four studies from baseline on Day 1 and Day 2 with montelukast and placebo were quite small. The applicant had chosen not to present a comparison of montelukast and loratadine based on a systematic pooling of the four similar studies, which may have overcome the lack of statistical power.
- Argued that a study provided by the applicant (XXXXXX) included a figure which showed clear differences in mean change from baseline in daytime-nasal symptom score in Days 1 to 3 between montelukast and loratadine. Differences between the two medicines were less marked for nighttime symptoms score and morning-nasal symptoms score.
- In the evaluator's view, there remained reasonable grounds for believing that montelukast had a slower onset of action than loratadine in the early days of treatment.

The evaluator further assessed the application against 52E. Members particularly noted the following:

(b) *Risks and benefits*

- Noted that the applicant reiterated arguments made at the October 2009 meeting on montelukast's fast onset of action. The evaluator argued that the cited references do not include montelukast data supporting superiority of the onset of action compared with loratadine. Argued that the data in a provided study supported the proposition that montelukast had a slower onset of action than loratadine, in days 1 to 3. By week 2, the proportions of responders to montelukast were similar to those for loratadine.
- The evaluator did not accept the applicant's proposition that montelukast had achieved its full effect at week 2. Argued that there was no data demonstrating the efficacy of montelukast after use for 2 or 3 days.
- Noted that the initial evaluation raised the possibility that the treatment effect of montelukast in the early days of a treatment course was inferior to that of loratadine and that it was a factor the Committee might wish to take into account in deciding the product's suitability for inclusion in Schedule 3.

(c) *Potential hazards*

- Agreed with the applicant that the change in the US product monograph concerning neuropsychiatric events involved the inclusion of a "precaution" and not a "black box" warning.

- Two cited analyses of adverse events (AE) in clinical trials were published versions of reports that XXXXX prepared at the request of the USFDA. The conclusion by the USFDA was:
 - Some post-market reports included clinical details consistent with a drug induced neuropsychiatric effect.
 - In the clinical trial data, neuropsychiatric events were not commonly observed. However, the available data was limited because the trials were not designed to look for neuropsychiatric events.
 - Sleep disorders (primarily insomnia) were reported more frequently with all three products (montelukast, zafirlukast and zileuton) compared to placebo.
- A third published review of three clinical trials in asthma did not find evidence of a negative effect of montelukast on emotional well-being in any of the trials. However, the authors acknowledge that despite the strength of having randomized comparison groups, there were certain limitations. A report showed that the study sought particular instances of completed suicides (and not other components of suicidality) and the ages and genders of the population studied were not described.
- Although some papers do not show evidence of an apparent biological basis for why montelukast might cause neuropsychiatric reactions, the evaluator concluded that they do provide evidence of the existence of rodent and human brain receptors sensitive to montelukast, and in rats in early recovery from temporary focal ischaemia, intravenous montelukast entered the central nervous system.
- Two papers gave evidence that asthma (but not allergy as explicitly claimed by the applicant) was associated with increased rates of suicidal ideation and suicide attempts.
- Two other papers gave much more preliminary and less compelling evidence that pollen counts were associated with mood disorders or suicidality.

Neuropsychiatric reactions among current Schedule 3 products

- The applicant noted that several substances recently rescheduled to Schedule 3 were associated with neuropsychiatric reactions i.e. pantoprazole, cimetidine and orlistat. The applicant stated that while this did not in any way downplay the seriousness of such reactions, this did demonstrate the level of confidence the Committee had placed on pharmacists to counsel patients regarding potential psychiatric reactions when recommending such products.
- The evaluator noted, however, that the PIs for Schedule 3 pantoprazole and orlistat state:
 - Pantoprazole: “*Psychiatric disorders* – Rare reports of onset of depression, hallucination, disorientation and confusion, especially in predisposed patients, as well as the aggravation of these symptoms in case of pre-existence. Very rare reports of anxiety.”

- Orlistat: “*Psychiatric Disorder – Uncommon: depression, anxiety.*”
- The evaluator commented that neither PI included contraindications, warnings or precautions concerning suicidal ideation or suicide attempts, and that attempts to draw comparisons with montelukast and suicidality were unreasonable.

(e) Dosage and formulation

- Tablets of XXXXX montelukast in packs of XXXXX, for use in adults aged 15 years and over.

(f) Need for access

- Noted that the applicant had provided information to show that allergic rhinitis (but not seasonal allergic rhinitis) was a very common illness in several age bands in Australia. Contended that this information was not a strong foundation upon which to justify the rescheduling of montelukast.
- Argued that the protocol developed by the applicant was a draft, and had yet to be field-tested. Emphasised that this protocol failed to deal with a current issue of major concern (potential for suicidality) and did not incorporate the sort of advice put forward in several of the submitted references:
 - “Recently, the USFDA started investigating the possibility that montelukast may trigger suicide... clinicians should err on the side of caution, inquiring about past suicide attempts; hopelessness; reasons for living; and suicidal ideation, intent, or plan; and referring the patient to a mental health professional for evaluation if appropriate.”
 - “Before definitive conclusions can be reached, in clinical settings, we strongly recommend that patients with allergy, both treated and untreated with montelukast, be asked about symptoms of depression, suicidal ideations and suicidal behaviours. The patients should be referred for a mental health evaluation when concerns arise.”
- The evaluator had a concern that XXXXX had sought to convey information in a document prepared in collaboration with WHO as a recommendation of WHO, “*The current WHO Allergic Rhinitis guideline recommends the use of leukotriene receptor antagonists as an alternative to the oral antihistamines in the management of intermittent (seasonal) allergic rhinitis...*”.
- The evaluator was not able to locate information in the application to support the claims that prevalence data suggested that there was still an unmet medical need in Australia for additional allergic rhinitis therapies to be available OTC.

Applicant’s Response to the Evaluation Report

The applicant argued that:

- It was generally accepted that medicines currently approved for the symptomatic treatment of seasonal allergic rhinitis have varying degrees of onset of action and efficacy based on their mode of action.
- Their availability on the pharmacy shelves as either Schedule 2 or Schedule 3 provided options for the pharmacist to assist in managing the rhinitis symptoms of patients promptly, without having to wait for a prescription.
- Montelukast as Schedule 3 would give the pharmacist an additional option of treatment for their patients. Hence, the applicant strongly believed that making the product available as Schedule 3, together with the pharmacy protocol, would appropriately equip the pharmacist and potentially lead to better patient outcomes with treatment.

Members also noted the following specific comments from the applicant regarding the onset of action issue:

- Argued that from the Record of Reasons for the October 2009 meeting, the Committee accepted a report from pooled analysis demonstrating the early onset of action of montelukast.
- Conceded that the protocol design of the provided study (XXXXX – onset of action) was not set out to consider a direct comparison between montelukast and loratadine and hence no formal testing was performed. As such, any comparative observation of efficacy between montelukast and loratadine cannot be fully validated.
- Contended that montelukast efficacy had been demonstrated in this study. During the 24 hours after the first intake, when compared with placebo, montelukast demonstrated a borderline significant improvement in Daytime Nasal Symptoms score and significant improvements in night-time symptoms score. The treatment difference between montelukast and placebo in morning-nasal symptoms score did not reach significance 24 hours after the first dose of drug and similarly for loratadine vs. placebo.
- Asserted that the current body of evidence demonstrated that montelukast provided an early onset of action from Day 1, suggesting that it can provide prompt relief from the symptoms of seasonal allergic rhinitis. Claimed that montelukast therefore has a definitive role as a treatment option for pharmacists in managing this condition.

The applicant additionally addressed the comments by the evaluator regarding section 52E matters:

Potential hazards

- Reiterated that the US label change regarding neuropsychiatric reactions was not a black box warning. Also reiterated that psychiatric disorders have been reported in association with the use of pantoprazole and orlistat, both in Schedule 3. Assured that the orlistat PI listed a precaution for patients with chronically treated psychiatric /

neurologic disorders under the section entitled “Use in Patients with Other Disorders”.

- Highlighted that montelukast currently did not have a contraindication regarding suicidal ideation or suicide attempts. Montelukast was only contraindicated in patients who exhibit hypersensitivity to components of the product.
- Asserted that, while the two examples of Schedule 3 products do not belong to the same class of drugs as montelukast and do not have the same indications, they are Schedule 3 products in that they require the involvement of the pharmacist for counselling and dispensing. The applicant believed Schedule 3 montelukast could therefore also be appropriately dispensed by the pharmacist for seasonal allergic rhinitis with the current understanding of the safety profile of the product.
- Claimed that implementation of a proposed protocol would provide further guidance for the pharmacist in ensuring the patient had a realistic expectation of the efficacy and safety of this therapy.

Need for access

- Addressed the evaluator’s comment in relation to a collaboration paper with the WHO. It referred to a cited reference containing a WHO diagram showing that the diagnosis of mild to moderate-severe intermittent (seasonal) allergic rhinitis, and that the treatment options (not in preferred order) included oral antihistamines, intranasal antihistamines and / or decongestant, or leukotriene receptor antagonists.

Potential for misuse

- Acknowledged that the pharmacy protocol was indeed a draft but it was being developed with the relevant bodies to ensure that it would be appropriate. The protocol had been updated to include precautions regarding the potential occurrence of neuropsychiatric effects and how these should be managed.

Pre-meeting Submissions

XXXXXX supported the proposal rescheduling. XXXXXX did not support an Appendix H listing and only supported a Schedule 3 entry if guidelines and training for pharmacists were developed. The pre-meeting submissions also included the following:

XXXXXX

- The limited amount of data contained in the montelukast PI suggest little, if any, benefit of montelukast over loratadine for this indication.
- Montelukast appeared to have a low incidence of adverse events and a low potential for abuse.
- There was a possibility that consumers may seek to purchase montelukast in Schedule 3 for the treatment of asthma rather than seasonal allergic rhinitis, although the probable high cost of an OTC product may reduce this likelihood.

XXXXX

- Believed that montelukast met the Schedule 3 guidelines in relation to its safety profile for the management of seasonal allergic rhinitis by the consumer under the guidance of the pharmacist.
- As montelukast was already available in Schedule 4 for the prophylaxis or treatment of asthma, the packaging and labelling of any Schedule 3 product must be clear that it was for a different indication.
- Advocated activities which would help ensure asthma patients did not inadvertently stop seeing their doctor or rely on the Schedule 3 product for ongoing therapy.

XXXXX

- Raised the following in relation to section 52E:

(a) Toxicity and safety

- Montelukast was well tolerated and provided improvements in daytime and nighttime symptoms, as well as quality of life parameters, for patients with seasonal allergic rhinitis (Phillip G, *et al* 2002, 'Montelukast for treating seasonal allergic rhinitis: a randomised, double-blind, placebo-controlled trial performed in spring', *Clin Exp Allergy*, vol 32, pp 1020-8).
- MIMS Prescribing Information for montelukast stated that the overall incidence of side effects reported were comparable to placebo, usually mild and generally did not require discontinuation of therapy. The most frequently occurring adverse events included abdominal pain, somnolence, thirst, headache, vomiting and psychomotor activity.
- Montelukast has been used concomitantly with a wide range of commonly prescribed drugs in clinical studies without evidence of adverse interactions.

(b) Risks and benefits

- The use of montelukast has been associated with a risk of Churg-Strauss syndrome in patients with severe asthma. A study suggested that montelukast was neither a trigger nor a cause of the syndrome and the association had arisen because the people developing the syndrome had severe asthma which was being treated with several medicines, including montelukast.
- If montelukast were available as a Schedule 3 medicine, there was a risk of off-label use for the treatment of asthma. However, montelukast was not a first line treatment for asthma and the cost would be a disincentive for 'trailing' without initial recommendation by a doctor.

(e) Dosage and formulation

- Montelukast was taken orally, once a day without regard for food intake.

- No dosage adjustment was necessary for the elderly, for patients with renal insufficiency or mild to moderate hepatic impairment, or according to gender.

(f) *Need for access*

- There were a number of different treatments available without prescription that could be recommended for seasonal allergic rhinitis, including:
 - Low-sedating oral antihistamines (e.g., loratadine, fexofenadine, cetirizine).
 - Sedating oral antihistamines (e.g., chlorpheniramine, dexchlorpheniramine).
 - Intranasal antihistamines (e.g., azelastine).
 - Oral nasal decongestants (e.g., pseudoephedrine, phenylephrine).
 - Intranasal decongestants (e.g., oxymetazoline, xylometazoline).
 - Intranasal anticholinergics (e.g., ipratropium bromide).
 - Intranasal mast cell stabilisers (e.g., sodium cromoglycate).
 - Intranasal corticosteroids (e.g., budesonide, beclomethasone).
- Montelukast in Schedule 3 would provide pharmacists with an additional therapy option. This would be particularly useful for patients who find non-sedating antihistamines to be ineffective and / or cannot tolerate intranasal steroids.
- The Therapeutic Guidelines were revised in October 2009 and state that leukotriene receptor antagonists are equivalent to oral antihistamines, but inferior to intranasal corticosteroids for treating seasonal allergic rhinitis.
- The Guidelines for allergic rhinitis include leukotriene receptor antagonists for moderate to severe intermittent symptoms as well as mild and moderate to severe persistent symptoms.
- Proposed collaboration with the Pharmaceutical Society of Australia and other stakeholders, as required, to support the applicant in developing protocols and training for pharmacists.

(h) *Purposes for which a substance is to be used*

- Montelukast in combination with antihistamines such as loratadine or cetirizine has resulted in greater efficacy than when these agents were used alone, and in some studies has produced results comparable with intranasal corticosteroids.

(i) *Other matters*

- Did not support inclusion in Appendix H.
- Pharmacists should be able to consider the appropriateness of a Schedule 3 treatment based on their assessment rather than responding to patient requests based on advertising, particularly when a medicine is initially down-scheduled from Schedule 4 to Schedule 3.

- The selection of any OTC treatment for moderate to severe seasonal allergic rhinitis should be at the pharmacist's professional discretion.

Transitional Considerations

XXXXXX are willing to accept that any decision be considered final even if the decision results in a scheduling change that does not align with its preferred position of Schedule 3. XXXXX also requested that should a Schedule 3 for montelukast be accepted, that an implementation date be later than 1 September 2010.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (c) potential hazards and (f) need for access.

A Member noted the divergence of views between the applicant and the evaluator regarding the interpretation of trial outcomes for the onset of relief and whether this would meet consumer expectations. Several Members argued, however, that although this issue may have some relevance regarding the degree of benefit that could arise from Schedule 3 access to montelukast, it was not the central issue. Regardless of whether or not other preparations have a faster onset of relief, these Members contended that previous considerations were driven by the concerns over the risk of adverse events, of a type which could not be readily monitored by a pharmacist. It was asserted that these concerns still remained.

A Member noted that all pre-meeting submissions supported the proposal. The Member argued that montelukast, while potentially slower acting than some other preparations, should still be available in Schedule 3 as a second line treatment (noting that some other preparations used for the treatment of seasonal allergic rhinitis were currently Schedule 2). The Member asserted that this specific use of montelukast did not need to remain Schedule 4.

Several Members, however, reiterated previous concerns regarding the association of montelukast with reported neuropsychiatric events. It was noted that the change in the US product monograph concerning neuropsychiatric events involved the inclusion of a "precaution" and not a "black box" warning as previously advised. However, Members generally agreed that this remained a serious concern.

A Member also asserted that, in considering down-scheduling, the Committee should keep in mind the limited Australian experience with use of montelukast for the symptomatic treatment of seasonal allergic rhinitis.

A Member asserted that the applicant had not presented a strong case demonstrating that there was a serious unmet need for the treatment of seasonal allergic rhinitis. The Member noted that no evidence had been provided that montelukast would be effective in non responders to antihistamines. The Member asserted that montelukast appeared to be,

at best, no more effective than loratadine, yet had a signal for neuropsychiatric effects, including suicidality, not associated with other antihistamines.

The Committee generally agreed that the risk versus benefit ratio was not sufficient to support down-scheduling of montelukast for seasonal allergic rhinitis to Schedule 3.

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

12.2 SUSDP, PART 5

12.2.1 CHEMISTRY SETS

PURPOSE

The Committee considered the Appendix A entry for chemistry sets.

BACKGROUND

A general exemption for chemistry sets was first considered at the August 1990 meeting, after a Member reported that the WA Department of Consumer Affairs was taking action on the sale of chemistry sets based on a reported poisoning (copper sulfate) which occurred in the UK. Members generally agreed that a national approach needed to be adopted to mitigate problems in terms of labelling uniformity, pending more details of what chemicals were being exempted.

At the November 1990 meeting, the Committee decided to adopt a general exemption from scheduling for chemistry sets ‘when labelled in accordance with Australian Standard (AS) 1647’. Subsequently, at the February 1993 meeting, the Committee decided to include chemistry sets (toy) in Appendix A, General Exemptions, when labelled in accordance with the AS1647.

At the August 1997 meeting, the Committee decided to also exclude chemistry sets ‘for educational use’ through the Appendix A entry. The Committee also decided to amend the entry (toy section) to reflect the new AS updated to 1647-1995.

At the October 2008 meeting, the Committee noted that the referred AS had been superseded. The Committee agreed to update the reference (when used as a toy) to include AS 8124.4-2003 *Safety of toys – Part 4: Experimental sets for chemistry and related activities*. The more general exemption stating “for education use containing Schedule 5 or 6 poisons in containers of 3 mL or less of each liquid preparation or 5 g or less of each solid preparation in a discrete unit.” was maintained.

DISCUSSION - SUBMISSIONS

A request to update the Chemistry sets entry in Appendix A was received from XXXXX. The request identified two issues with the entry.

Firstly, the application recommended replacing the reference to the Australian Standard (AS) 1647-1995 with the new AS 8124.4-2003. Members noted that the AS reference had already been updated.

The second issue identified that section '(b)' of the Appendix A entry (i.e. educational use) implied a more restricted requirement than the AS 8124.4-2003 (specifically with allowed volumes). It was proposed that part (a) could be expanded to include educational use so that it would then include the volume limits from AS 8124.4-2003. Members noted the following:

- The AS 8124.4-2003 permitted list contains a number of substances that could be scheduled, including clove oil, copper compounds, cobalt salts, nickel salts, methylene blue and borax.
- The AS 8124.4-2003 lists quantities in excess of the 3 mL / 5 g limit in the current Appendix A exemption for chemistry sets (e.g. the new AS allows supply of 10 mL of clove oil).
- The proposed inclusion of 'educational use' in (a) would exempt chemistry sets from scheduling with respect to volumes as well as chemicals present, in compliance with the new standard.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards, (f) need for access and (h) purposes of use.

Members generally agreed to expand part (a) of the Appendix A entry for chemistry sets to include educational use, compliant with the AS 8124.4-2003.

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The Committee agreed that it would be appropriate to amend the general exemption in Appendix A for chemistry sets for educational use by requiring such sets to comply with AS 8124.4-2003. The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Appendix A – Amendment

CHEMISTRY SETS – Amend entry to read:

CHEMISTRY SETS for toy and educational use, when complying with the requirements of Australian Standard AS 8124.4-2003 *Safety of toys - Part 4: Experimental sets for chemistry and related activities*.

12.2.2 ENTHEOGENIC SUBSTANCES

PURPOSE

The Committee considered the scheduling of entheogenic substances (psychoactive substances used in a religious, shamanic or spiritual context).

BACKGROUND

An entheogen is a psychoactive substance used in a religious, shamanic or spiritual context. Entheogens are used to supplement various practices for healing and transcendence, including in meditation, psychonautics, art projects, and psychedelic therapy. Historically, entheogens were mostly derived from plant sources, however there now exist many synthetic substances with similar psychoactive properties.

Examples of traditional entheogens include peyote (containing mescaline), iboga and amanita muscaria (both containing ibotenic acid), ayahuasca and acacia (both containing N,N-dimethyltryptamine [DMT]), cannabis, *Salvia divinorum*, opium and kava. Chemically synthesised entheogens can also include psilocine, psilocybine and ibogaine.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested an authorisation for the use of currently prohibited sacramental medicines in the practice, teaching, observance, research and worship of religious beliefs. This request was referred to the Committee, following contact with XXXXX.

Members noted the following points from the application:

- The request was for unrestricted access to all entheogenic substances deemed necessary by the applicant, as dictated by traditional cultural uses, and to all derivative substances resulting from scientific and cultural advances.
- It was asserted that these substances form a vital element in sacramental rituals, central to the applicant's beliefs. In some religions, alcohol is used in sacramental rituals. Noting its dangerous and unpredictable side effects, the applicant has chosen not to utilise alcohol in sacramental rituals.

The application also included reading material outlining the use of the sacrament by Islamic Sects, Tibetan Buddhist Tantric Schools, the Greek Philosophical Initiatory Cult of Eleusis and other recognised systems. Members noted the following points from these attachments:

- Ancient Greek psychoactive sacramental drinks could have contained lysergic acid alkaloids derived from *Claviceps purpurea*, including ergometrine and methylethergometrine. Other possible ingredients could also include psilocybin and opium.
- According to tradition in the Indian subcontinent, psychoactive sacramental drinks may contain substances derived from the *Amanita muscaria* mushroom, *Peganum harmala* or a species of *Stropharia* mushroom. Other possible ingredients also include *Cannabis sativa*, alcohol and camphor.
- Possible traditional Islamic entheogenic substances include ephedra, *Peganum harmala*, acacia and other DMT-producing plants.

Additional information

In a follow up letter, the applicant provided additional information for the Committee's consideration, and requested an immediate nullification of all scheduling of substances deemed to be of entheogenic use by the applicant. Members noted the following from the letter:

- The applicant asserted that as a matter of national and global humanitarian importance, the Australian Constitution denies the right to create law or statute which interferes with the practice of religions.
- The applicant also asserted that the suppression of the use of certain plants and minerals as part of spiritual practices would be considered a contradiction of the right to life.
- The applicant asserted that the Australian Constitution provides for equal rights, which would include the right to practices involving the use of substances as part of sacramental undertaking. The applicant stated that practices involving these substances are integral to human development.

Scheduling precedent

Members recalled the 2007 Hanes v Human Rights and Equal Opportunity Commission (HREOC) and Commonwealth of Australia legal proceedings, where the November 2001 NDPSC decision to include *Salvia divinorum* in Schedule 9 was challenged. The applicant in these proceedings claimed that the Committee's action manifested a restriction on his human rights to access *Salvia divinorum* as part of the practice of his spiritual beliefs.

The judgement upheld the Committee's action, noting that the Schedule 9 decision was based upon considerations of public health and safety and that the manifestation of one's religion or belief may be subject to limitations prescribed by law and which are necessary to protect public health and safety.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (f) the need for access and (g) the potential for abuse.

A Member clarified that the scheduling of substances is used to control, not necessarily prohibit, access to those substances. Although a specific list of substances was not provided by the applicant, Members noted that a majority of substances with potential entheogenic uses were included in Schedules 4, 8 and 9.

It was generally agreed that in scheduling a substance, the Committee gives extensive consideration to the substance's risk profile and potential use patterns prior to making a decision. Members agreed that the use of a substance in an entheogenic context would not diminish a substance's potential associated risk to public health.

The Committee further noted that the 2007 Hanes v HREOC and the Commonwealth decision confirmed that the Committee could schedule entheogenic substances in order to protect public health and safety.

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The Committee agreed that the current scheduling of entheogenic substances remained appropriate.

12.2.3 LENALIDOMIDE

PURPOSE

The Committee considered a proposal to include lenalidomide in Appendix F.

BACKGROUND

At the June 2008 meeting, lenalidomide was included in Schedule 4 and Appendix D, following recommendation from the TGA prescription medicine registration process. At the October 2008 meeting, the Committee decided to include lenalidomide in paragraph 45 under Part 3, Miscellaneous Regulations – Dispensed medicines.

At the February 2009 meeting, Members noted that the New Zealand and Australian entries for lenalidomide were harmonised.

DISCUSSION - SUBMISSIONS

XXXXXX advised that, although lenalidomide was listed in the SUSDP under paragraph 45 of Part 3 as requiring Appendix F, Part 1 warning statements for oral and topical use, lenalidomide was not listed in Appendix F, Part 3. It was noted that this may be due to an

oversight as all other medicines included in paragraph 45 of Part 3 with the potential to cause birth defects are also listed in Appendix F, Part 3.

XXXXXX also advised that if the Committee's decision resulted in a scheduling change, XXXXX would be willing to accept the matter as final with an implementation date of 1 September 2010.

Impact of the proposed changes from SUSDP to SUSMP

As part of the proposed changes to transition the SUSDP into the SUSMP, paragraph 45, under Part 3 has been removed and its intent incorporated into paragraph 14, under Part 2 (see item 1.8.1).

In the new SUSMP, Appendix L lists the requirements for dispensing labels for human and veterinary medicines. As raised at Item 1.8.1, Appendix L, Part 2 lists requirements for each substance previously included in paragraph 45(3) of Part 3 (acitretin, adapalene, bexarotene, etretinate, isotretinoin, lenalidomide, thalidomide and tretinoin), differentiating between the route of administration for each substance, with separate warning statements for oral and topical use:

For oral use:

- 7. WARNING - Causes birth defects.
- 62. Do not use if pregnant.
- 76. Do not become pregnant during use or within (Insert number of months as per approved product information) month(s) of stopping treatment.

For topical use:

- 62. Do not use if pregnant.
- 77. WARNING - May cause birth defects.

In the SUSDP 24, Appendix F, Part 3 contained general entries for acitretin, etretinate and thalidomide, requiring labelling with warning statements 7, 62, and 76. The entries did not specify the route of administration but the warning statements were consistent with oral use as described in paragraph 45(3). The Appendix F entry for adapalene only specified topical use.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (c) potential hazards and (i) other matters including labelling and packaging.

Members discussed the need for an Appendix F entry for lenalidomide. A Member noted that an Appendix F entry may be redundant as appropriate labelling of prescription medicines was a matter for the regulatory authority. Other Members asserted that due to the potential hazards associated with lenalidomide, inclusion of an Appendix F entry would be appropriate to ensure clarity in the interpretation of labelling requirements.

Members discussed the Appendix F and Appendix L entries for the related substance, thalidomide. It was noted that the Appendix L thalidomide entry specified warning statements for both oral and topical uses, whereas the Appendix F entry only listed warnings 7, 62, and 76 (warning associated with oral use). Members noted that, consistent with thalidomide, the lenalidomide Appendix L entry also specified warnings for both oral and topical uses. A Member asserted that consistency should be retained within each Appendix, and that the Appendix F entry for lenalidomide should reflect the thalidomide entry.

Members generally agreed that the Appendix F entry for lenalidomide should list warning statements 7 62 and 76. Members also agreed that the new Appendix F entry was not expected to impact on existing lenalidomide products and agreed that an implementation date of 1 September 2010 would be appropriate.

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The Committee agreed to include an entry for lenalidomide in Appendix F, Part 3, specifying warning statements 7, 62 and 76. The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Appendix F, Part 3 – New entry

POISON

WARNING STATEMENTS

SAFETY DIRECTIONS

Lenalidomide

7,62,76

12.2.4 PSEUDOEPHEDRINE

PURPOSE

The Committee considered the Appendix H entry for pseudoephedrine.

BACKGROUND

Pseudoephedrine is an oral sympathomimetic nasal decongestant that has been available for many years in Australia for the symptomatic treatment of rhinitis associated with colds and flu or hayfever. However, over recent years, the criminal diversion of pseudoephedrine to methamphetamine has resulted in preparations containing smaller quantities of pseudoephedrine being rescheduled from Schedule 2 to Schedule 3 and other preparations from Schedule 3 to Schedule 4.

At the June 2005 Meeting, on the basis of the available information and in the interest of public health and safety, the Committee agreed to reschedule the remaining majority of pseudoephedrine products from Schedule 2 to Schedule 3.

The Committee also agreed to remove pseudoephedrine from Appendix H, considering that such action was in line with the rescheduling of pseudoephedrine because of public health concerns with diversion.

At the October 2005 meeting, the Committee agreed to vary the initial decision from the June 2005 meeting by implementing it in two stages: the first stage being the removal of all remaining Schedule 2 products (slow-release, combination and undivided preparations) to Schedule 3 (implementation date 1 January 2006); and the second stage involving the rescheduling of liquid and other preparations from Schedule 3 to Schedule 4 (implementation date 1 April 2006). The Committee also agreed not to remove pseudoephedrine from Appendix H. The Committee felt that it was reasonable for the advertising *status quo* to remain, at least initially, to allow consumers to be informed of the impact of the scheduling changes.

At the February 2006 meeting, the Committee reviewed the entry for pseudoephedrine in Appendix H, and agreed to retain it in Appendix H at that time, to allow consumers to continue to be informed through advertising of the impact of the scheduling changes and available Schedule 3 pseudoephedrine products.

DISCUSSION - SUBMISSIONS

Applicant's Submission

A proposal to delete pseudoephedrine from Appendix H was referred by XXXXX. In referring this matter, XXXXX noted that the outcome of the February 2006 consideration of pseudoephedrine in Appendix H was that the "... Committee agreed to retain pseudoephedrine in Appendix H of the SUSDP at this stage, to allow consumers to be informed through advertising of the impact of the scheduling changes and available Schedule 3 products". It was noted that no further action on this matter had been taken since then.

Pre-meeting Submissions

XXXXX was not opposed to deleting the Appendix H entry for pseudoephedrine. XXXXX believed, however, that the deletion would have little effect on the illicit use and diversion of pseudoephedrine for the manufacture of illegal drugs.

XXXXX did not support the removal of pseudoephedrine from Appendix H. XXXXX stated that the *status quo* to advertising in Appendix H should remain, so that legitimate users could still find access to pseudoephedrine products. XXXXX also believed that advertising materials were well regulated and that there had not been any inappropriate case of advertising pseudoephedrine.

Specific additional points from XXXXX:

XXXXX

- Stated that pseudoephedrine products were primarily a brand extension of Schedule 2 products containing phenylephrine as the active sympathomimetic agent. Sponsors often rely more on brand extension of Schedule 2 products containing phenylephrine when advertising. Legitimate consumers that do not find phenylephrine effective tend to raise this issue with pharmacy staff, prompting pharmacist intervention. As such, the removal of pseudoephedrine from Appendix H would probably have little impact on sponsor companies.
- Claimed that XXXXX was not aware of any irresponsible advertising relating to pseudoephedrine products, nor was XXXXX aware of any increased demand for pseudoephedrine products that could not be reconciled with seasonal changes.
- Noted that the Advertising Code was available to provide guidance on how medicines could be advertised.
- Argued that it would be inappropriate for the Appendix H entry to be removed unless there were demonstrable, significant clinical or social reasons to do so.
- Asserted that pharmacists have been acquainted for many years with the supply of pseudoephedrine products to treat the symptoms of rhinitis. They were also equipped to respond to those consumers who may find phenylephrine ineffective and were professionally capable of assessing whether pseudoephedrine products provide a more suitable alternative.
- Stated that pharmacists were also aware of the risk for illicit diversion. Asserted that the use of real-time monitoring tools such as Project Stop has had a significant impact on this issue. The criminal elements who want access to pseudoephedrine were aware of which products are needed, and advertising, or lack thereof, would have little impact.

XXXXX

- Argued that the pre-meeting *Gazette* notice did not provide any details on the reasons behind the proposal to delete the Appendix H entry of pseudoephedrine.
- Believed that the ability to advertise pseudoephedrine-containing products had not impacted on the rate or volume of purchases for diversion to illicit manufacture activities.
- Asserted that as pseudoephedrine is contained in many Schedule 3 solid and liquid oral preparations, deletion of the Appendix H pseudoephedrine entry would have a significant impact on sponsors.

Transitional Considerations

XXXXXX requested that should the Committee decide on the deletion of pseudoephedrine from Appendix H, the matter should be considered by the new Advisory Committee on Medicines Scheduling.

XXXXXX advised that they were willing to accept that any decision for pseudoephedrine as final even if the decision resulted in a scheduling change that did not align with their preferred position.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits and (f) need for access.

The Committee considered the need for an Appendix H entry for pseudoephedrine. A Member asserted that five years has passed since the Committee's decision to reschedule pseudoephedrine from Schedule 2 to Schedule 3 and the need for consumers to be informed of the changes is no longer relevant. The Member further stated that the original decision to keep the Appendix H entry was only intended as a means to inform the community of the transition arrangements and was not intended as a long term arrangement.

A Member suggested that as there was no evidence of inappropriate advertising of pseudoephedrine, there was no real harm in maintaining the Appendix H entry. However, another Member asserted that for an Appendix H entry to be maintained there would need to be evidence of a significant public health benefit from allowing the advertising of pseudoephedrine. Members generally agreed that the arguments for maintaining the Appendix H pseudoephedrine entry were not strong and recommended that it be deleted.

A Member noted that the position of several pre-meeting submissions did not align with the removal of the pseudoephedrine Appendix H entry. According to the transitional arrangements detailed under item 1.6.2, Members generally agreed that this matter would not be able to be finalised at this meeting. The Committee agreed that a recommendation to delete the pseudoephedrine entry from Appendix H be provided to the delegate for consideration under the new scheduling arrangements.

RESOLUTION 2010/59 - 32

The Committee agreed that the pseudoephedrine Appendix H entry be removed. The Committee agreed that this recommendation should be provided to the delegate when this matter is considered under the new scheduling arrangements.

12.2.5 RABEPRAZOLE

PURPOSE

The Committee considered a proposal to include rabeprazole in Appendix H.

BACKGROUND

Rabeprazole is a proton pump inhibitor (PPI) indicated for the treatment of peptic ulcer disease and gastro-oesophageal reflux disorder (GORD). PPIs suppress gastric acid secretion by inhibiting the hydrogen potassium ATPase irreversibly, blocking the final step in gastric acid secretion.

At the November 2000 meeting, the Committee considered the scheduling of rabeprazole. The Committee supported Australian Drug Evaluation Committee's (ADEC's) recommendation for the inclusion of rabeprazole in Schedule 4 as it was a new substance, required medical management and to ensure harmonisation with New Zealand's classification of rabeprazole.

At the June 2009 meeting, the Committee decided to down-schedule rabeprazole preparations containing 10 mg or less for the relief of heartburn and other GORD symptoms in packs of up to 14 days supply from Schedule 4 to Schedule 3. The Committee rejected the proposed Appendix H listing on the basis that an insufficient case had been mounted for public benefit from advertising rabeprazole.

At the February 2010 meeting, the Committee rejected an application for Appendix H listing of another PPI, pantoprazole. At the same meeting, two other PPIs, lansoprazole and omeprazole, were scheduled similarly to the current rabeprazole scheduling to harmonise with New Zealand. In both cases it was agreed that a consistent approach for all PPIs should be undertaken in relation to Appendix H listing. Also at the February meeting, the Committee agreed to editorially amend the wording of the Schedule 3 rabeprazole entry for consistency with other PPIs by adding "per dosage unit".

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXXX requested an Appendix H listing for rabeprazole. Members noted the following from the application:

- The applicant asserted that treatment of typical reflux symptoms of acid regurgitation and heartburn by over-the-counter (OTC) PPIs is more efficacious than other OTC therapies, with no evidence of additional risk. The applicant included information from studies indicating that OTC rabeprazole can improve patients' quality of life and psychological wellbeing.

- It was further asserted that although there was no quantitative data available examining the public health benefit of advertising rabeprazole 10 mg, advertising would provide benefits in improving consumer awareness of GORD, reflux and heartburn symptoms and provide a complete picture of available efficacious treatments.
- As a large proportion of consumers self-treat and do not consult their doctor for reflux symptoms, the application asserted that advertising would help encourage people to seek advice and potentially identify serious illness early in the disease state.
- The application noted that potential risks of Appendix H listing include misdiagnosis, potential under-treatment of patients with severe symptoms, and the potential for use of rabeprazole for non-GORD or inappropriate indications. It was asserted that educational material, labelling and pharmacist screening protocols are set in place to minimise these risk factors.
- The applicant asserted that advertising would assist in decreasing medical consultation costs and possible unnecessary investigations, by encouraging sufferers who would not otherwise seek medical treatment to visit the pharmacy, instead of the GP.
- The application noted that rabeprazole is not an addictive substance and therefore there is no abuse potential. Due to its cost, it was unlikely that consumers would continue to use the product if they were not getting satisfactory relief.
- The applicant also noted that as rabeprazole could be considered roughly equivalent in efficacy to pantoprazole, both substances should be viewed similarly in terms of Appendix H approval.

Evaluation Report

The evaluation report recommended rejection of Appendix H listing, specifically stating that:

- The evaluator remained unconvinced that advertising of OTC rabeprazole would lead to greater public health benefits.
- Compared to the failed application one year ago, scant new evidence was provided to support the current resubmission.
- Advertising of any OTC PPI should be precluded until safety concerns surrounding potential pharmacokinetic interactions between PPIs and thienopyridines are disproven.

Members noted the following additional points made by the evaluator:

- The evaluator agreed with the applicant's assertion that the advertising of rabeprazole would provide health benefits by improving consumer awareness of more efficacious treatments. However, as other PPIs are also currently available OTC, the evaluator

asserted that the application could be under-stating community awareness of, and access to, GORD treatments, and hence over-stating the potential benefit of advertising rabeprazole.

- The evaluator did not agree with the applicant's claim that advertising would achieve potential cost benefits by decreasing medical consultation costs and unnecessary investigations, and encouraging sufferers who would not otherwise seek medical treatment to visit the pharmacy. The evaluator asserted that Appendix H listing instead had the potential to increase costs by channelling more people into medical consultations, both directly and via referrals from pharmacists.
- The evaluation further asserted that studies cited by the application suggesting that OTC rabeprazole would be cost effective and increase patients' quality of life, were only of direct relevance to the issue of rabeprazole being OTC, not to the question of whether OTC rabeprazole should be advertised.
- The evaluator noted that while rabeprazole itself was a generally safe and well-tolerated drug, the advertising of rabeprazole had the potential to increase inappropriate medication use, specifically the use of PPIs in combination with thienopyridines. The evaluator noted that this issue was not raised in the application.

Applicant's Response to the Evaluation Report

XXXXXX provided a response to the evaluation report, stating that it should not be used as justification for precluding Appendix H listing of rabeprazole due to errors, inconsistencies and unsubstantiated statements. Members noted the following points from the response:

- In relation to the evaluator's opinion that advertising would not provide public health benefits and that safety issues relating to interactions should preclude approval of Appendix H listing, it was asserted that the report disregarded certain submitted data in its evaluation.
- The response disagreed with the evaluator's opinion that due to the availability of other OTC PPIs there was significant community awareness of this class of medicines. The response asserted that current community awareness is low and also clarified that rabeprazole was not available OTC at this time as it had not yet been launched.
- The response sought to clarify that the benefits in relation to decreasing medical consultation mentioned in the application referred to health benefits not economic benefits.
- The response did not agree with the evaluator's opinion that the studies included in the application were only of direct relevance to the case of rabeprazole being OTC. The response stated that this data should not be discounted as in other countries with similar regulatory standards being OTC included the freedom to advertise and it would be impossible to separate the factors.

- The response disagreed with the opinion that possible interactions with thienopyridines should preclude Appendix H listing. It stated that the evidence suggesting that PPIs reduce the efficacy of certain thienopyridines was inconsistent and was not highlighted as a major drug safety concern. The response also stated that this potential issue could be addressed by labelling.

Pre-meeting Submissions

XXXXXX did not support the proposed inclusion of rabeprazole in Appendix H at this time.

XXXXXX strongly opposed inclusion of rabeprazole in Appendix H. Members noted the following points from the submission:

- The submission asserted that there was no in-use data of this product as a Schedule 3 medicine in the Australian market place. It was noted that this argument was also raised by the Committee in its February 2009 consideration of an Appendix H listing for pantoprazole 20 mg.
- The submission also asserted that rabeprazole was not available as an OTC medicine in any other market and there was no overseas data that could sufficiently inform the Committee to make a decision regarding the Appendix H status of rabeprazole.
- The submission asserted that a “whole of class” approach to Appendix H listing of PPIs should not be applied, as there would be unequal levels of in-market experience for each product.
- It was noted that Appendix H listing for pantoprazole was also rejected at the February 2010 meeting, where one key reason stated that advertising of pantoprazole would potentially impair the ability of pharmacists to adequately carry out their professional responsibilities. The submission did not agree with this reasoning and asserted that there was suitable data to support the public health benefit of advertising.
- The submission also noted the March 2010 European Medicines Agency (EMA) opinion that the interaction between clopidogrel and PPIs was not identical for all PPIs, with warnings only recommended for omeprazole and esomeprazole.

XXXXXX supported the inclusion of rabeprazole in Appendix H, stating that listing would enable further investment in education and training of non-pharmacist pharmacy staff. The submission noted that advertising currently occurs for several Schedule 2 and unscheduled products used to treat uncomplicated GORD and that the availability of rabeprazole could encourage consumers to seek advice from a pharmacist as another potential management option.

XXXXXX supported the inclusion of rabeprazole in Appendix H. The submission stated that rabeprazole’s safety profile, history of safe use, indication for short-term use, pharmacists’ ability to provide professional advice to ensure the quality use of medicines

and the potential public health benefit resulting from increased awareness of available treatments provide sound justification for advertising.

XXXXXX did not object to the inclusion of rabeprazole in Appendix H, noting that such listing should be consistent across the spectrum of PPIs listed in Schedule 3. Members noted the following points from the submission:

- Whilst acknowledging the potential public benefit by prompting health professional intervention through raising consumer awareness, concerns were raised about consumers requesting specific products based solely on an advertisement. It was asserted that this could make it difficult for pharmacists to assess the appropriateness and safety of a product.
- Whilst supporting advertising that advises consumers with specific conditions to consult their pharmacist, the submission was reticent to support inclusion of drugs in Appendix H, particularly newly approved Schedule 3 listings which were down-scheduled from Schedule 4. It was asserted that pharmacists should become accustomed to the protocols and responsibilities associated with the non-prescription supply of these medicines before managing direct product requests resulting from advertising campaigns.
- Potential benefits of Appendix H listing include increased consumer awareness of an effective treatment, where advertising acts as a prompt to patients relying on other treatments to seek pharmacist advice, thereby allowing pharmacists to assess and provide appropriate therapy options.
- It was asserted that due to their indication and interaction profile, there was less concern with the advertising of Schedule 3 PPIs than there was with antacids and H2-Receptor Antagonists (H2RAs). It was believed that there was no significant concern that Schedule 3 PPIs would be irresponsibly advertised or that any advertising would be detrimental to the public.
- It was asserted that pharmacists have had ample time to become accustomed to protocols and responsibilities associated with the supply of Schedule 3 PPIs.
- It was asserted that the concerns surrounding potential interaction between PPIs and certain antiplatelet medicines (e.g. clopidogrel) were only relevant to omeprazole and esomeprazole and that there were no solid grounds to extend any warning to other PPIs. It was also asserted that pharmacists are experienced in managing such interactions, with appropriate support.
- The submission noted that the Committee considered Appendix H listing for pantoprazole at the February 2010 meeting, and asserted that circumstances in relation to risks associated with antiplatelet medication have since changed and were no longer of significant concern. It was further asserted that pharmacists are capable of mitigating any remaining risk in the same manner that they do when dispensing PPIs and clopidogrel as a prescription.

Transition arrangements

XXXXXX requested that any decision not be considered final and that the matter be re-considered under the new arrangements, noting that this could mean no final decision before the end of 2010.

XXXXXX advised that in relation to the consideration of rabeprazole, XXXXXX would be willing to accept the Committee's decision as final even if it resulted in a scheduling change that did not align with XXXXXX preferred position.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits and (f) need for access.

Members discussed the potential risks and benefits associated with rabeprazole. Members agreed that the advertising of rabeprazole would not reduce consultation costs and could facilitate an increase in unnecessary investigations. Although Members noted growing evidence that potential interactions with antiplatelet medication could be limited to omeprazole, it was generally agreed that there was still insufficient evidence of public health benefit of advertising rabeprazole.

Members discussed the level of consumer awareness of the availability of GORD treatments. A Member asserted that due to the general sale and Schedule 2 availability of other products for the same indication, there is limited consumer awareness of PPIs. The Member further asserted that the public would not generally seek advice from a pharmacist for GORD and therefore remain unaware of possible alternative treatments. Another Member asserted that methods other than Appendix H listing could be used to raise public's awareness of GORD and the range of available treatments.

The Committee generally agreed that an Appendix H listing was not appropriate at this time and it would be beneficial for pharmacists to first become accustomed to having rabeprazole available as a Schedule 3 medicine.

RESOLUTION 2010/59 - 33

The Committee agreed that the current scheduling of rabeprazole remained appropriate, i.e. no Appendix H listing.

**13. MATTERS REFERRED BY THE REGISTRATION PROCESS FOR
PRESCRIPTION MEDICINES**

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 CLOFARABINE

PURPOSE

The Committee considered the scheduling of clofarabine.

BACKGROUND

Clofarabine, a purine nucleoside analogue, is used as an antimetabolite antineoplastic in the treatment of relapsed or refractory acute lymphoblastic leukaemia in patients aged 1 to 21 years. Clofarabine is also under investigation for the treatment of acute myeloid leukaemia, myelodysplastic syndrome, and solid tumours.

Clofarabine is related to mercaptopurine, thioguanine, cladribine and fludarabine. The Committee agreed to create new Schedule 4 entries for these substances at the February 1971, May 1987, April 1994 and May 1995 meetings, respectively.

A search of the Australian Register of Therapeutic Goods (ARTG) revealed one entry for 20 mg / 20 mL clofarabine concentrated solution for infusion.

DISCUSSION - SUBMISSIONS

XXXXXX advised that clofarabine XXXXXX had received conditional approval for registration. XXXXXX noted:

- Clofarabine was orphan designated on 2 October 2007 for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens.
- Clofarabine is registered for the proposed indication in the European Union (EU) (May 2006) and USA (December 2004). The EU approval includes the restriction that no other treatment option is anticipated to result in a durable response.
- XXXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

The Committee agreed that the involvement of a medical practitioner should be required for the supply of clofarabine.

Members considered the teratogenicity of clofarabine and whether an Appendix D entry would be appropriate. Members noted that as the indication is limited to acute ALL in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens, it would be probable that treatment would always occur under the direction of a specialist. It was further noted that the related substances mercaptopurine, thioguanine, cladribine and fludarabine were not listed in Appendix D. Members generally agreed that an Appendix D entry for clofarabine would not be necessary.

RESOLUTION 2010/59 - 34

The Committee agreed to include clofarabine in Schedule 4. The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 4 – New entry

CLOFARABINE.

13.1.2 SAXAGLIPTIN

PURPOSE

The Committee considered the scheduling of saxagliptin.

BACKGROUND

Saxagliptin is an oral antidiabetic agent, clinically similar to sitagliptin. Saxagliptin and sitagliptin are dipeptidyl peptidase-4 (DPP-4) enzyme inhibitors, which are presumed to exert their actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones (i.e. glucagon-like peptide-1 and glucose-dependent insulinitropic polypeptide). These agents increase insulin release and decrease glucagon levels in circulation in a glucose-dependent manner.

At the February 2006 meeting, the Committee agreed to include sitagliptin in Schedule 4, following recommendation from the New Zealand Medicines Classification Committee (MCC). Following further recommendation from the MCC, at the June 2007 meeting, the Committee agreed to also include a related agent, vildagliptin, in Schedule 4.

DISCUSSION - SUBMISSIONS

Members noted that as part of the TGA reforms, the Australian Drug Evaluation Committee (ADEC) has changed its name to the Advisory Committee on Prescription Medicines (ACPM).

At its December 2009 meeting, ACPM approved, in part, a submission from XXXXX for saxagliptin XXXXX indicated for the improvement of glycaemic control in patients with type 2 diabetes mellitus as:

- add-on combination therapy in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control; or
- initial combination therapy with metformin, as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).

XXXXX.

In July 2009, saxagliptin was approved for monotherapy in the USA. In October 2009, saxagliptin was also approved in the EU and Canada as combination therapy.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

The Committee agreed that the involvement of a medical practitioner should be required for the supply of saxagliptin.

Members also noted that neither the ACPM minutes nor the Poisindex monograph specified any effects in pregnancy or sedation which would warrant an Appendix D or Appendix K entry.

RESOLUTION 2010/59 - 35

The Committee agreed to include saxagliptin in Schedule 4. The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 4 – New entry

SAXAGLIPTIN.

13.1.3 VORINOSTAT

PURPOSE

The Committee considered the scheduling of vorinostat.

BACKGROUND

Vorinostat is a member of a class of anti-neoplastic agents called histone deacetylase inhibitors, used for the treatment of cutaneous T-cell lymphoma (CTCL). Vorinostat is also under investigation for the treatment of multiple myeloma and mesothelioma.

A search of the Australian Register of Therapeutic Goods (ARTG) revealed one entry for vorinostat 100 mg capsules.

DISCUSSION - SUBMISSIONS

XXXXXX advised that vorinostat XXXXX 100 mg capsules had received registration approval as an orphan drug. Members noted the following from the XXXXX:

- Vorinostat is indicated for the treatment of cutaneous manifestations in patients with CTCL who have progressive, persistent or recurrent disease subsequent to prior systemic therapies. The recommended dose is 400 mg orally once daily with food.
- The mechanisms of action for the antineoplastic effect of vorinostat have not been fully characterised.
- One study assessing the impact of vorinostat on ventricular repolarisation indicated that administration of a single supratherapeutic dose did not prolong the QTc interval in patients with advanced cancer. However, results from other clinical studies indicated prolonged QTc measurements in some patients exposed to daily doses of vorinostat.
- Vorinostat was not evaluated in patients under 18 years of age.
- Vorinostat is contraindicated in patients with severe hepatic impairment and is not recommended in patients with moderate hepatic impairment. Vorinostat was not evaluated in patients with renal impairment.
- Efficacy studies indicated clinical benefit both in patients with CTCL and advanced CTCL treated with vorinostat.
- Reported adverse events include pulmonary embolism, deep vein thrombosis, nausea, vomiting, diarrhoea, fatigue, chills, thrombocytopenia, anaemia, hyperglycaemia, hepatic ischaemia, hypotension, skin lesion and taste disorders.
- Effects on the female reproductive system were observed in XXXXX, with male fertility remaining unaffected. Testicular degeneration was observed in XXXXX.

- Vorinostat crossed the placenta in XXXXX, where treatment-related developmental effects were observed. Use of vorinostat in pregnant women has not been adequately evaluated, and women are advised to avoid pregnancy during treatment. Due to the potential for serious adverse reactions in nursing infants, breast feeding is also advised against.
- Carcinogenicity studies were not performed. Vorinostat was evaluated as a weakly genotoxic compound, except for chromosome damaging effects in some cells.
- No formal clinical studies have been conducted to evaluate drug interactions with vorinostat.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

The Committee agreed that the involvement of a medical practitioner should be required for the supply of vorinostat.

Members considered the teratogenicity of vorinostat and whether an Appendix D entry would be appropriate. Members noted that as the indication is limited to the treatment of cutaneous manifestations in patients with progressive, persistent or recurrent CTCL, it would be probable that treatment would always occur under the direction of a specialist. Members generally agreed that an Appendix D entry for vorinostat was not required.

RESOLUTION 2010/59 - 36

The Committee agreed to include vorinostat in Schedule 4. The Committee agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 4 – New entry

VORINOSTAT.

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

13.2.1 HUMAN PROTHROMBIN COMPLEX

PURPOSE

The Committee noted the December 2009 Advisory Committee on Prescription Medicines (ACPM) consideration of human prothrombin complex.

BACKGROUND

The December 2009 ACPM meeting recommended approval of a submission from XXXXX to register XXXXX powder for injection containing the new chemical entity human prothrombin complex 250 IU and 500 IU for the indication:

- Treatment and perioperative prophylaxis of bleedings in acquired deficiency of the prothrombin complex coagulation factors, such as deficiency caused by treatment with vitamin K antagonists, or in case of overdose of vitamin K antagonists, when rapid correction of the deficiency is required.

XXXXX is a plasma-derived human prothrombin complex concentrate (PCC) containing coagulation factors II, VII, IX, X, Protein C and Protein S. Excipients include human albumin, human antithrombin III and heparin.

The October 2007 NDPSC meeting decided to include fractionated blood products and equivalent recombinant products in Appendix A to exempt such products from the requirements of scheduling. Human prothrombin complex is exempt from scheduling under (c)(vi) of the human blood products entry in Appendix A.

RESOLUTION 2010/59 - 37

The Committee noted the December 2009 ACPM consideration of human prothrombin complex.

13.2.2 VILDAGLIPTIN

PURPOSE

The Committee noted the December 2009 Advisory Committee on Prescription Medicines (ACPM) consideration of vildagliptin.

BACKGROUND

Vildagliptin is an oral antidiabetic agent from a new class of drugs which is claimed to selectively and reversibly inhibit an enzyme, dipeptidyl peptidase-4 (DPP-4) involved in glucose homeostasis.

The June 2007 NDPSC meeting included vildagliptin in Schedule 4 to harmonise with New Zealand.

The December 2007 ACPM (formerly the Australian Drug Evaluation Committee) meeting recommended rejection of vildagliptin on the grounds of lack of demonstrated safety and inadequate data. ACPM's rejection was noted by the June 2008 NDPSC meeting.

The December 2009 ACPM meeting considered a submission from XXXXX and recommended approval for registration of vildagliptin XXXXX tablet 50 mg for the indication:

- Treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

RESOLUTION 2010/59 - 38

The Committee noted the December 2009 ACPM consideration of vildagliptin.

13.2.3 C1 ESTERASE INHIBITORS

PURPOSE

The Committee considered the scheduling of C1 esterase inhibitors.

BACKGROUND

C1 esterase inhibitors (C1-INH) are serine protease inhibitors affecting complement components C1r and C1s. They are also inhibitors of other serine esterases involved in the coagulation (factor XI and thrombin), fibrinolysis (plasminogen activator) and contact (factor XII and kallikrein) systems. They are prepared from human plasma and given as replacement therapy in hereditary angioedema (HAE). HAE is an autosomal dominant disorder caused by deficiency or abnormal function of the C1-INH. C1-INH are administered for both short-term prophylaxis and treatment of acute life-threatening attacks by slow intravenous injection or infusion.

At the October 2007 meeting, 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. As a plasma-derived product, C1-INH would be covered under the Appendix A exemption for human blood products.

To ensure that there is no inadvertent exemption of a substance which should be scheduled, the Committee also decided to consider all new blood product substances not previously approved for use in Australia.

DISCUSSION - SUBMISSIONS

At its December 2009 meeting, ACPM approved a submission from XXXXX, subject to PI changes, to register XXXXX powder containing C1-INH for injection, for the treatment of acute attacks in patients with hereditary angioedema (HAE). The minutes also noted that:

- C1-INH is a soluble single chain glycoprotein containing 478 amino acid residues organised into three beta sheets and 8 or 9 alpha sheets. Each vial contains 500 U C1-INH, 50 to 80 mg total protein, and glycine, sodium citrate and sodium chloride as excipients.
- A human C1-INH product has been registered in Germany since 1979.

C1-INH has marketing approval in Europe, USA, Japan, Argentina, Switzerland, Cyprus, with applications pending in Canada and Israel, where the approved indication was usually for treatment of acute episodes of HAE types I and II. C1-INH was also approved for pre-operative prophylaxis in Argentina and Switzerland, and in the US for abdominal or facial attacks in adults and adolescents only.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

Members noted that many blood-based products which qualify for the Appendix A exemption are indicated for the treatment of serious disorders and in practice it is common for these products to be treated as Schedule 4 substances. A Member noted that as C1-INH was indicated for the treatment of HAE, supply would usually occur with the involvement of a medical practitioner. The Committee agreed that access to C1-INH should be consistent with other blood-based products (i.e. that it should be covered by the Appendix A general exemption for human blood products).

The Committee noted the human blood products Appendix A entry, specifically sub-paragraph (c), which lists specific plasma-derived therapeutic proteins. A Member asserted that due to the phrasing of sub-paragraph (c), there was potential for confusion as to whether C1-INH would be covered by the existing entry. Members generally agreed that to ensure clarity, C1-INH be specifically listed in the Appendix A general exemption for blood products.

RESOLUTION 2010/59 - 39

The Committee agreed to include C1 esterase inhibitors in the Appendix A general exemption for blood products. The Committee agreed that this decision would be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Appendix A – Amendment

HUMAN BLOOD PRODUCTS – Amend entry to read:

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) C1 esterase inhibitors;
 - (iv) clotting factors;
 - (v) fibrinogen;
 - (vi) protein C;
 - (vii) prothrombin complex concentrate (PCC); and
 - (viii) thrombin.

14. OTHER MATTERS FOR CONSIDERATION

14.1 XXXXX

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

15.1 AMBROXOL

This item was withdrawn prior to the meeting.

15.2 ASPIRIN

PURPOSE

The Committee considered the scheduling of aspirin.

BACKGROUND

Low dose aspirin (up to 150 mg daily) has been recommended for the prevention of serious vascular events, including myocardial infarction (MI) and stroke, in patients at

high risk (e.g. acute and post MI, angina, peripheral arterial disease, stroke or atrial fibrillation).

Aspirin was first included in Schedule 2 in May 1977. Preparations containing 325 mg or less per tablet or capsule in pack sizes of up to 20 dosage units, and 500 mg or less of aspirin in powder preparations in pack sizes of up to 10 powder sachets were exempted from scheduling.

At the May 1987 meeting, the Committee discussed a proposal to reschedule aspirin when used for the inhibition of platelet aggregation (blood clotting) from Schedule 2 to Schedule 3. The proposal originated from a lack of scheduling uniformity as in some states aspirin was listed in Schedule 3 when used for inhibition of platelet aggregation. The Committee agreed that there was insufficient evidence of risks and benefits to upschedule to Schedule 3 for this use and reconfirmed its Schedule 2 position.

At the June 2003 meeting, the Committee considered recommendations by the Trans Tasman Harmonisation Working Party (TTHWP) with respect to harmonisation of the scheduling of aspirin. The TTHWP recommended as a first step a partial harmonisation of Schedule 2 entries, to be followed by final harmonisation when the warning statements were transferred to the new Medicines Labelling Order (MLO). Members noted that according to the MLO, it was mandatory for medicine labels to include any label advisory statements specified in *Required Advisory Statements for Medicines Labels* (RASML). On this basis, the Committee endorsed the TTHWP's recommendation and foreshadowed an amendment to the Schedule 2 aspirin entry to exempt low dose aspirin from scheduling requirements in order to harmonise with NZ.

At the October 2003 meeting, the Committee agreed to adopt the foreshadowed Schedule 2 entry to exempt from scheduling packets of 100 tablets or less of low dose aspirin (100 mg or less) for prevention of cardiovascular (CV) disease or inhibition of platelet aggregation. Any single active aspirin for prevention of CV disease or for the inhibition of platelet aggregation, which does not qualify for exemption would be caught by the Schedule 2 entry.

Aspirin is also available as an analgesic in strengths of 300 to 500 mg per dosage unit, in which small quantities are unscheduled (24 or less), and larger packs are Schedule 2 (200 or less).

DISCUSSION - SUBMISSIONS

At its meeting on 17 September 2009, the Medicines Evaluation Committee (MEC) (now replaced by the Advisory Committee on Mon Prescription Medicines – ACNM) considered issues relating to low dose aspirin products being available unscheduled. The MEC agreed that the current exemption from scheduling of low dose aspirin products was inconsistent with its recommendation that these products should not be available for self-selection by consumers. MEC requested that the Committee consider including low dose aspirin in Schedule 3 (without inclusion in Appendix H) when indicated for

inhibition of blood clotting and to reduce the risk of heart attack and stroke in patients with CV / cerebrovascular disorders. [Members noted that MEC subsequently clarified its position, requesting that all OTC or general sale aspirin for prevention of CV disease or inhibition of platelet aggregation be rescheduled to Schedule 3, not just low dose.]

Members noted the following background provided by MEC:

- Noted the label statements required by RASML for products containing low dose aspirin, particularly statement 63: “For use under medical supervision only. - Note. This warning is only required for products that are indicated for the prevention of cardiovascular disease or for the inhibition of platelet aggregation.”
- Stated that low dose 100 mg aspirin products were approved specifically for secondary prevention of CV / cerebrovascular conditions, and not for primary prevention, e.g. the majority of approved indications refer to “patients with blood vessel disorders” or “patients with known CV or cerebrovascular disease”. Asserted that consumers may lack the knowledge to distinguish between primary and secondary prevention.
- Asserted that CV / cerebrovascular disease was a serious condition not amenable to self-diagnosis or treatment. Asserted that low dose aspirin should not be available for self-selection by consumers, as any decision to use low dose aspirin should be made by a medical practitioner on the basis of the risk-benefit profile for the individual, including the risk of adverse effects.
- XXXXX. The MEC concluded that, while the risk-benefit profile for low dose aspirin was favourable in patients with confirmed CV disease and previous myocardial infarction or occlusive stroke, the overall risk-benefit profile was unfavourable in those who were not at moderate to high risk of CV disease, due to the risks of harm from an increase in significant adverse events related to bleeding.
- Asserted that concurrent use of aspirin and anticoagulants may increase the risk of bleeding (e.g. gastrointestinal [GI] bleeding or haemorrhagic stroke), and patients taking other anticoagulant medication may not be aware that they should tell a doctor or dentist if they were taking aspirin. In addition, many consumers were unaware that there was an increased risk of bleeding if low dose aspirin was taken prior to surgical procedures or dental extractions. The MEC had considered the latter to be of particular concern, given that most low dose aspirin products were not scheduled.
- Asserted that the existing exemption from scheduling of these products was inconsistent with the requirement for unscheduled products, which were generally intended for short-term use for the relief of symptoms of minor ailments. Asserted that low dose aspirin products were instead intended to be used long-term for the prevention of a serious medical condition.
- In addition to the above concerns, there were ongoing concerns about risks to the non-target population with use of low dose aspirin, specifically in light of recent studies which have concluded that aspirin should not be made more widely available for primary prevention.

- Asserted that if low dose aspirin was included in Schedule 3, it should not be included in Appendix H, stating that advertising of low dose aspirin products for the requested restricted representation would not be appropriate.

Members recalled the discussion resulting from the consideration of the scheduling of aspirin at the June and October 2003 meetings. At these meetings, Members agreed that was no public health impediment to prevent the exemption from scheduling of tablets and capsules each containing 100 mg or less of aspirin, in packs containing 100 or less such tablets and capsules, when labelled for the prevention of CV disease or inhibition of platelet aggregation.

Pre-meeting Submissions

XXXXXX supported the proposal of low dose aspirin to be scheduled in Schedule 3 (XXXXXX supported Schedule 2 or Schedule 3) when indicated to reduce the risk of CV disease. XXXXX agreed with the proposal stating that the initial recommendation to take aspirin every day should be medically initiated and the advice about its use reinforced by a pharmacist. The inclusion of aspirin in Appendix H was supported by XXXXX and opposed by XXXXX.

XXXXXX supported a more restrictive schedule for low dose aspirin. It was stated that the rationale behind the proposed rescheduling was not made available. XXXXX was concerned that a rescheduling of low dose aspirin to Schedule 3 would create the peculiar circumstance where low strength formulations were more restricted than high strength. [Members noted that MEC subsequently clarified its position, requesting that all OTC or general sale aspirin for prevention of CV disease or inhibition of platelet aggregation be rescheduled to Schedule 3, not just low dose.] XXXXX also argued that XXXXX could not support Schedule 3 without further information. Both suggested that a move to Schedule 2 may be more appropriate than Schedule 3.

XXXXXX did not support the proposal to reschedule low dose aspirin medicines to Schedule 3, asserting that aspirin has a long history of safe and effective use. XXXXX regarded the proposal to restrict the access of any aspirin containing medicines as unjustified, since analgesic preparations of aspirin at higher concentration were exempted. XXXXX also noted that MEC proposed a rescheduling of low dose aspirin from unscheduled to Schedule 3, however, it did not address a change to the current Schedule 2 of low dose aspirin (packs greater than 100 dosage units), inferring that the proposed rescheduling would not apply to this pack size. [Members again noted that MEC had subsequently clarified its position.]

XXXXXX

- Commented that use of low dose aspirin for the prevention of thromboembolic vascular events should be instigated under advice from a health professional who can ascertain the appropriateness of the therapy and advice on its safe use.

- Stated that should Schedule 3 be determined, listing it within Appendix H would provide a greater opportunity for responsible promotion to encourage people to seek advice from the pharmacist, reducing the risk of people inadvertently resorting to higher dosed aspirin products.
- XXXXX made particular reference to the following sections under 52E (1):

(a) Toxicity and Safety

- Asserted that low dose aspirin is one of the main agents used for the prevention of thromboembolic vascular events, having the advantage of low cost and a prolonged duration of antiplatelet action. However, it was associated with a doubling of the risk of GI bleeding, even at doses as low as 75 mg daily.
- Noted that in a European study, the odds ratios for patients who presented with acute upper GI bleeding increased from 2.3 for 75 mg per day to 3.9 for 300 mg per day. Additionally, alterations in dose formulation (e.g. buffered or enteric coated) did not lower the risk of related gastric / duodenal ulcer bleeding.
- Stated that aspirin is also associated with an increased risk of intracranial haemorrhage in about one per 1000 patients treated for three years, with no clear variation in risk with the dose of aspirin used.

(b) Risks and Benefits

- Asserted that the safety of the most vulnerable of the population should be considered before allowing a substance to be unscheduled. The vulnerable groups that were more likely to suffer upper GI complications from low dose aspirin included those over 60 years old, with prior ulcer history or ulcer complications, concomitant steroid or anticoagulant use and multiple or highdose non-steroidal anti-inflammatory drug (NSAID) use.
- Claimed that facilitating access to health professional support was in line with quality use of medicines principles, ensuring that the choice and subsequent use of low dose aspirin was appropriate and safe.

(c) Potential Hazards

- Asserted that it would not be appropriate to rely solely on information from a medicine pack if there was any risk of misuse. Such risk could instead be ameliorated by facilitating access to advice from a pharmacist.

(f) Need for Access

- Noted that public awareness of the use of aspirin to prevent thromboembolic vascular events has increased. However, asserted that this was a treatment which should not be instigated without consultation with a health professional.
- Asserted that other antiplatelet medicines available on prescription (such as clopidogrel, dipyridamole and prasugrel) may be more suitable than low dose aspirin for people at risk of thromboembolic vascular events; particularly for those at risk of

GI bleeding or intracranial bleeding. The pharmacist would be able to assess the patient's risk status and refer them to a doctor accordingly.

- Asserted that people using low dose aspirin were likely to be on other prescription medicines for chronic conditions and pharmacy personnel were experienced in maintaining continuity of supply. Questioned whether a need for access to low dose aspirin from outside a pharmacy could be justifiably demonstrated.

Consideration of Appendix H listing

- Stated that should the Committee support the inclusion of low dose aspirin in Schedule 3, XXXXX would not object to its inclusion in Appendix H.
- Claimed that the public was aware of the benefits of aspirin for such use, but not necessarily aware of any dose differentiation according to indication.
- Asserted that responsible advertising would encourage consumers to consult a pharmacist to discuss the matter, rather than thinking that any aspirin product would be suitable and potentially taking higher dose products.

XXXXX

- Argued that low dose aspirin medicines and preparations containing less than 325 mg of aspirin have been available in Australia as unscheduled medicines for at least 26 years, and there did not appear to be any evidence of adverse effects on public health and safety. XXXXX also presented the same argument.
- Referred to the June 2003 meeting, noting that the Schedule 2 entry was amended to specifically refer to cardiovascular medicines as part of the trans-Tasman scheduling harmonisation process. XXXXX also presented the same argument.
- Asserted that XXXXX was not aware of any public health and safety issues that have arisen from low dose aspirin being available unscheduled.
- Asserted that the current labelling of low dose aspirin products informs the consumer that ongoing medical supervision is required. Reiterated that although low dose aspirin was unscheduled, inclusion of the restricted representation relating to CV disease on labelling and in advertising to consumers was not permitted without the TGA's prior approval.
- Claimed that responsible advertising of a low-dose aspirin product to consumers has been carried out since 2006 with no adverse effects to public health.
- Asserted that there are sufficient controls on low dose aspirin products through legislative and regulatory controls.

XXXXX.

- Contended that there was no new data negating the risk-benefit profile of low dose aspirin for secondary prevention of CV disease, and there were no safety signals to suggest that the current scheduling of low dose aspirin was inadequate. Contended that without supportive data the current schedule should be retained.

- Argued that the concerns raised by MEC would be better addressed by changes to the RAMSL of low dose aspirin rather than via scheduling changes.
- Asserted that changing the current scheduling of low dose aspirin did not seem justifiable, given that:
 - The proposal of rescheduling low dose aspirin for Schedule 3 covered those products that were currently unscheduled and not products which are currently Schedule 2 i.e. not logical. [Members again noted that MEC subsequently clarified its position.]
 - Low dose aspirin is indicated only for use in people with known CV disease.
 - The labelling of low dose aspirin products contained clear instruction as to the need for ongoing medical supervision.

XXXXX also addressed other points summarised as follows:

Scheduling background

- Asserted that aspirin is classified as an OTC product in all European Union (EU) countries and in 10 non-EU countries. Aspirin is a general sale product in NZ and the UK. The OTC status in the US indicated that it is able to be purchased in an unsupervised environment.
- Claimed that there was no apparent concern regarding the unscheduled availability or advertising of low dose aspirin in any of these international markets, all of which were comparable to Australia.
- Argued that it was common practice for some consumers to divide aspirin tablets in half, or quarter and take them in place of specific low dose aspirin products. Any change in the availability of specific low dose aspirin may push consumers to access unscheduled or Schedule 2 products, where compliance with required dosage would be more difficult.
- Argued that it was not logical to contemplate a change to the scheduling of low dose aspirin without addressing divisible 325 mg and 500 mg aspirin tablets.

Use of low dose aspirin for primary prevention

- Argued that any concerns regarding the use of low dose aspirin for primary prevention was premature considering that the label did not communicate its use for primary prevention. Argued that there was no data showing that the use of low dose aspirin in the primary prevention of a CV event (i.e. off label use) was a public health concern in Australia.

Initiation and long-term use of low dose aspirin use

- Stated that any decision to use low dose aspirin should be made by a medical practitioner on the basis of the risk-benefit profile for the individual patient, and that two implications should be considered:

- Despite the current exemption from scheduling, the use of low dose aspirin for the secondary prevention of CV disease was recommended to a patient after an initial CV event during which time they were under the care of a healthcare professional. Given the predisposing medical condition, consumers would continue to remain under professional supervision over the long-term allowing for continual monitoring of the individual risks and benefits.
- The RASML warning stated that the product must only be used under medical supervision. This warning statement indicated that consumers should discuss the use of this product with a healthcare professional.
- XXXXX.
- Contended that MEC did not present any data to suggest that the current unscheduled availability resulted in inappropriate use of low dose aspirin. Asserted that XXXXX was not aware of any data which indicated low dose aspirin had adversely impacted public health and safety.
- Also contended that while unscheduled products are generally intended for short-term use, this was not the case for all OTC products, for example:
 - Psyllium fibre indicated for the management of constipation, was being advertised as a product that can help to maintain healthy cholesterol levels. Rare side effects include hypersensitivity reactions, including anaphylactic shock, intestinal obstruction and oesophageal obstruction.
 - Calcium supplements are indicated for calcium deficiency and used by many over the long-term to aid in the prevention of osteoporosis. Rare side effects include renal calculi and milk-alkali syndrome.
- Argued that there was no evidence that long-term use of low dose aspirin had caused adverse events. The MEC's concerns regarding duration of treatment were of limited relevance (given this did not apply to low dose aspirin alone) and there was no data demonstrating a negative public health outcome.

Consumer confusion over primary vs. secondary prevention

- Contended that clarification of any perceived confusion between primary and secondary prevention would not be afforded through a change in scheduling as it would not change the permitted indication of the drug. Asserted that the wording permissible in labelling statements and advertisements should instead be reconsidered.

Concerns regarding risks of inappropriate use

- Reiterated that from 2000 to 2010, there have been a total of only 69 deaths associated with aspirin, including both analgesic and low dose aspirin use.
- Contended that while there have been 69 aspirin-related deaths, thousands of lives have been saved by using low dose aspirin to prevent a secondary cardiovascular event.

Concurrent use of aspirin and other anticoagulants may increase bleeding

- Argued that no data had been provided to support that consumers might not divulge their use of low dose aspirin to a doctor or other healthcare professional.
- Reiterated that 89 per cent of consumers using low dose aspirin were doing so on their doctor's advice.

Appendix H

- Contended that the proposal only requested a scheduling change for low dose aspirin from unscheduled to Schedule 3. The proposal did not address the current Schedule 2 availability of low dose aspirin which would remain. As Schedule 2 medicines could be advertised, there was confusion surrounding the proposal to not include an Appendix H entry.
- Asserted that the current advertising of low dose aspirin encouraged the appropriate use of low dose aspirin in the secondary prevention of a CV event. In addition this advertising strongly communicated the need to discuss the use of low dose aspirin with a doctor, consistent with current labelling.

XXXXX

- Asserted that aspirin had a long history of safe and effective use in Australia in the adult population and products in the marketplace have been available and used safely for decades. The safety profile of aspirin was well known and well described.
- Contended that there was no evidence in the Australian market suggesting patterns of misuse, either intentional or accidental. This included both aspirin for analgesic use and low dose aspirin for blood clotting and CV risk reduction indications.

XXXXX

- Claimed that the proposal was unwarranted and a change to the current scheduling may impose an unnecessary burden on health care resources.
- Stated that about 3.7 million Australians have CV disease, which accounts for 50,000 deaths in Australia every year.
- Asserted that the benefit of low dose aspirin therapy was that it could reduce the risk of CV morbidity and / or mortality from ischemic heart disease by 25 per cent and stroke by 27 per cent. The National Prescribing Service advocated the use of low dose aspirin as the antiplatelet drug of first choice.
- Asserted that CV patients require long term therapy and it was necessary that they have easy access. Noted that low dose aspirin for the prevention of CV disease has been exempt from scheduling since June 2004.
- Argued that a change from unscheduled to Schedule 3 would be an impediment for people who are already on low dose aspirin therapy. Noted that the burden of CV disease increases in remote areas, being 15 per cent higher in remote areas than in

major cities. Asserted that there was a need for access to this cost-effective therapy for people living in the remote areas.

- Asserted that pharmacovigilance data from the UK has not revealed any new or unexpected AEs, or record of misuse / abuse. Argued that the Appendix H status should remain, so that people with CV disorders could be made aware of its availability.

Transitional comments

Members noted the following comments on transitional arrangements:

- XXXXX requested that if a decision was made to upschedule low dose aspirin, such a decision should not be considered final, and instead should be referred to the new Advisory Committee on Medicines Scheduling.
- XXXXX willing to accept any decision for low dose aspirin as final even if the decision resulted in a scheduling change that did not align with XXXXX preferred position.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (c) potential hazards and (h) purpose for which the substance is to be used.

Members noted the Committee's 2003 consideration of the scheduling of aspirin. A Member argued that there has been no change in circumstances surrounding the use of aspirin since that consideration and asserted that the existing scheduling remains appropriate.

Members considered the risk of inappropriate use of aspirin by people with CV disorders. It was asserted that this risk was mitigated, as consumers with CV disorders would most probably already be under medical supervision. Another Member also asserted that labelling for this indication is reasonable and mandates that patients consult with their doctor. The Member further noted that there would be more risk associated with rescheduling aspirin indicated for prevention of CV disease to Schedule 3, as patients may switch to off label use of general sale analgesic aspirin products.

A Member asserted that there was an issue with aspirin being promoted as a primary treatment for serious health problems like CV disorder. A Member asserted, however, that this was not an issue that should be addressed by scheduling. Members generally agreed that this matter would be best addressed through the regulatory system.

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The Committee agreed that the current scheduling of aspirin remained appropriate.

15.3 COUGH AND COLD MEDICATION

PURPOSE

The Committee considered the scheduling of over-the-counter cough and cold medicines containing the following:

- *Antihistamines*: brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine.
- *Antitussives*: codeine, carbetapentane (pentoxyverine), dihydrocodeine, dextromethorphan and pholcodine.
- *Mucolytics/expectorants*: ammonium chloride (or carbonate), bromhexine, guaiphenesin, ipecacuanha and senega.
- *Decongestants*: phenylephrine, pseudoephedrine, oxymetazoline and xylometazoline.

BACKGROUND

The scheduling of the substances currently used in approximately 645 cough and cold medicines registered in Australia was complex, with most of these preparations containing two or more active ingredients. Most of these substances were included in Schedule 2, while a few were in Schedule 3, 4 or 8 depending on the strength or dosage and whether they were in single-active products or in combinations with certain other substances.

At the February 2008 meeting the Committee considered a TGA review of the safety, efficacy and scheduling of antihistamines for their use in the treatment of children aged less than 2 years, and decided to no longer allow Schedule 2 access for this age group. This decision was confirmed at the June 2008 meeting.

From October to December 2009, the TGA, through its Cough and Cold Medicines Review Panel (the TGA Panel) with the assistance of external medical experts and the Medicines Evaluation Committee – MEC (now replaced by the Advisory Committee on Non Prescription Medicines – ACNM), reviewed the safety, efficacy, availability and packaging of all OTC cough and cold medicines registered in Australia for use in the symptomatic treatment of children aged 2 to 12 years (www.tga.gov.au/nprm/consult/drlp-ccmedicines.htm). The TGA concluded that there was a lack of evidence of efficacy and potential safety concerns associated with use in children, especially those aged less than 6 years.

DISCUSSION - SUBMISSIONS

Applicant's Submission

XXXXX requested that the Committee consider the following recommendations from the TGA Panel regarding the scheduling of substances in cough and cold medicines:

- Schedule 2: if labelled with a warning stating that it not be used in children under 12 years of age. This would ensure that professional advice would be available but would not restrict supply for use in adults and older children and not unduly burden pharmacists with the need to deal personally with every sale of an OTC cough and cold medicine.
- Schedule 3: if labelled with warnings stating that it not be used in children aged under 6 years and should only be used in children aged 6 to 11 years on the advice of a doctor, pharmacist or nurse practitioner. This would ensure that professional health advice was provided, including referral to medical practitioners.
- Schedule 4: in preparations for the treatment of children under 6 years of age. This would greatly reduce the usage of these medicines in young children but would allow medical practitioners to prescribe them if necessary, particularly as treatment for an ailment other than common cough and cold.

Members also noted that XXXXX sought to further clarify XXXXX position subsequent to the pre-meeting *Gazette* Notice. The Secretariat therefore circulated an email notification prior to the June 2010 meeting (through the online self-subscribing service for stakeholders wishing to receive news updates about scheduling matters), advising that, in addition to the highlighted proposals for children, the body of the TGA Panel's review also made recommendations for additional controls for adults and / or for those aged 12 and above which may also form part of the June 2010 considerations.

There are 22 active substances currently used in cough and cold medicines as follows:

ANTIHISTAMINES	ANTITUSSIVES	MUCOLYTICS/ EXPECTORANTS	DECONGESTANTS
Brompheniramine	Codeine	Ammonium chloride	Phenylephrine
Chlorpheniramine	Dihydrocodeine	Ammonium carbonate	Pseudoephedrine
Dexchlorpheniramine	Dextromethorphan	Bromhexine	Oxymetazoline
Diphenhydramine	Pentoxyverine*	Guaiphenesin	Xylometazoline
Doxylamine	(also known as	Ipecacuanha (also	
Pheniramine	carbetapentane)	known as Cephaelis	
Promethazine	Pholcodine	ipeacacuanha and C.	
Tripolidine		acuminata)	
		Senega	

*Members noted that although the application mentioned that pentoxyverine was not scheduled, the synonym 'carbetapentane' was Schedule 2.

XXXXX proposed the rescheduling of these substances (except codeine, dihydrocodeine and pseudoephedrine, for which the current scheduling was considered appropriate), in

line with the TGA Panel recommendations. Members noted the following particular points from the XXXXX application:

- There was no robust evidence of efficacy for the above 22 active substances for the symptomatic treatment of cough and cold, and that use of these substances constituted a safety risk to children, especially those aged under 6 years.
- Public and stakeholder consultation was undertaken and responses considered.
- While the numbers of adverse events reported to the TGA may not be high, safety data from other countries with regulatory systems comparable to that of Australia (UK, USA, Canada and New Zealand) demonstrated a high rate of adverse events. Reviews by these regulators reached similar conclusions to those of the TGA Panel i.e. when these substances were used in cough and cold medicines they constituted a safety hazard to children.
- Argued that while the current scheduling (mostly Schedule 2) ensured that advice about these products was available at pharmacies it did not guarantee that advice was actually given or that the advice was necessarily appropriate.
- Also asserted that both the labelling and scheduling needs to ensure that parents and caregivers were made fully aware of the lack of efficacy for the treatment of cough and cold and the risks involved in administering these medicines to young children.
- The TGA Panel recommended changes to labelling requirements for these products to ensure that they carry clear warnings that they are not to be used in children aged under 6 years (rather than under 2 years as at present) and that they should only be used in children aged 6-12 years on the advice of a doctor, pharmacist or nurse practitioner.
- It was the TGA Panel's view that the scheduling of the substances concerned needed to reflect these proposed changes to the indications and labelling.

Ammonium salts

- Advised that ammonium salts could remain unscheduled since, when used in cough and cold medicines, they were normally compounded with other substances that would be scheduled.

Codeine, dihydrocodeine and pseudoephedrine

- Stated that the current scheduling of codeine, dihydrocodeine and pseudoephedrine was appropriate.

Members particularly noted the following from the public consultation feedback submitted to the TGA Panel:

Safety, efficacy and availability

- Submissions from the medical profession concurred with the TGA's conclusions about the lack of proven efficacy and the potential risks associated with these medicines for the treatment of children. However, they considered that in relation to

oxymetazoline and xylometazoline nasal drops and oral dextromethorphan that it was not the lack of efficacy, but the potential risk, which was of concern.

- However, it was argued that the need for the new restrictions should be reviewed if and when efficacy data became available. Several submissions also argued that implementation of these changes by mid-2010 was impractical, contending that May 2011, at the earliest, would be more feasible as changes to packaging would require a longer phase-in period.

Packaging

- Generally, the public submissions supported the proposal that all OTC cough and cold medicines be marketed in containers with child-resistant closures. However, a professional association noted that in their opinion this should not be applied to topical preparations such as nasal sprays as it believed this to be unjustified and unwarranted.

Scheduling and TGA labelling requirements

- In addition to the proposed scheduling changes discussed above, the review also recommended that:
 - labelling should not include dosage instructions for children under 6 years of age;
 - if doses were included for children aged 6-11 years, the labelling must include:
 - a. a statement advising that the product should only be administered on the advice of a doctor or pharmacist; and
 - b. a warning statement advising against use in children under the lowest specified age.
 - labelling for use in adults and / or children above 12 years old should contain a warning statement against use in children under 12 years of age.
- Pharmacy professionals did not support the rescheduling of cough and cold medicines to Schedule 4 for children under 6 years. They suggested that Schedule 3 was a sufficient restriction for children aged 2-12 years.
- XXXXX and individual pharmaceutical companies were opposed to any upscheduling of cough and cold medicines to Schedule 3 for use in children aged 2-5 or 6-12 years. General comments included:
 - Any upscheduling would be excessive, place unnecessary additional burdens on physicians and pharmacists, be impractical and could easily be circumvented by consumers.
 - The current Schedule 2 classification was still appropriate.
 - Changes to the labelling would be adequate and more practical and effective in achieving the desired improvement in the proper use of these medicines for children.

- Generally accepted the current lack of robust evidence of efficacy and the potential for harm from the use of these drugs (with the exception of single-active bromhexine) in the treatment of children.
- Also accepted the need to label cough and cold medicines with a warning that they should not be used in children aged less than 6 years.

The application additionally addressed matters under section 52E(1), summarised as follows:

(a) Toxicity and safety, (c) Potential hazards

- Since 1981 there have been 99 adverse drug reactions (ADRs) reported in children under the age of 12 (promethazine and codeine were excluded when clearly not used for the symptomatic relief of coughs and colds). Of these:
 - 86 occurred in children under the age of 9.
 - 71 occurred in children under the age of 6.
 - 14 of the ADRs were serious, with 12 (86 per cent) under 6. Two deaths were included, as follows: a 1 year old infant administered oxymetazoline and morphine and a 2 year old child administered ipecacuanha (unclear whether ipecacuanha was used for its expectorant or emetic properties) in combination with other medications.
 - 2 intentional and 2 accidental overdoses were also reported.
- The following table summarised the ADRs for children 12 and under between 1981 and 2009 for each therapeutic agent. Serious and non-serious ADRs were reported for all classes of cough and cold medications. Pseudoephedrine followed by dexchlorpheniramine had the highest events of ADRs. Numbers in brackets refer to ADR when used in combination with another cough and cold medication.

Drug available in Australia	Nº ADR (Total)	Nº ADR (Serious)	Child-Resistant Closure Required
ANTI-HISTAMINES:			
Brompheniramine maleate	0	0	Yes
Chlorpheniramine maleate	1	1 (1)	Yes
Dexchlorpheniramine maleate	13	3	Yes
Diphenhydramine hydrochloride	(1)	0	Yes
Doxylamine succinate	0	0	Yes
Pheniramine maleate	0	1	Yes
Promethazine hydrochloride	3 (5)	0	Yes
Triprolidine hydrochloride	0	0	Yes
ANTI-TUSSIVES:			
Codeine phosphate	(1)	0	Yes
Dihydrocodeine tartrate	0 (1)	0	Yes
Dextromethorphan hydrobromide	10 (2)	2	No
Pentoxyverine citrate	0	0	No

Pholcodine	15	1	No
MUCOLYTICS/EXPECTORANTS:			
Ammonium chloride	0	0	No
Bromhexine hydrochloride	10 (2)	1	No
Guaifenesin (guaiphenesin)	3	0	No
Ipecacuanha	3	1	No
Senega & ammonia (as bicarbonate)	0	0	No
DECONGESTANTS:			
Phenylephrine hydrochloride	(1)	(1)	Yes
Pseudoephedrine hydrochloride	18 (4)	2	Yes
Oxymetazoline hydrochloride	9	2	No
Xylometazoline hydrochloride	1	0	No
TOTAL	86 (17)	13 (2)	

(b) Risks and benefits

- There was a lack of robust evidence of efficacy, whereas there was extensive evidence of actual and potential harm to children treated with cough and cold medicines. There was therefore an adverse risk / benefit balance.

(d) Extend and patterns of use

- Cough and cold medicines have been used for many years for both children and adults, available mostly through pharmacies but in some cases through retail outlets.

(e) Dosage and formulation

- In view of the very large number of oral liquid OTC cough and cold medicines and the wide range of drug combinations it was not practical to provide detailed dosages.

(f) Need for access

- Coughs and colds are generally self-limiting conditions and there were more effective non-medical treatments available for relief of symptoms in children. The concern was over children being given OTC cough and cold medicines for treating disorders such as asthma and bronchitis when, in fact, the child should be assessed by a medical practitioner to ensure that appropriate treatment(s) were provided.
- There did not appear to be a significant safety risk in children aged over 12 years and adults and a comprehensive review of the clinical data was necessary to evaluate the efficacy of cough and cold medicines for that age group. Therefore, it would be inappropriate to restrict the availability of these medicines for that age group.

(g) Potential for misuse / abuse

- Age distribution has shown a consistent pattern of poison frequency, morbidity and mortality seen in very young children in Western countries over decades. Data from the NSW Poisons Information Centre demonstrated this typical pattern, where childhood poisoning was most evident in children aged less than 2 years.

- The higher poisoning (as ‘non-intentional’ poisoning) seen in the 1-3 year old age group, resulted from a combination of behavioural characteristics of the very young child and unsupervised access to potentially very high doses of drugs.
- In Australia, although the same pattern of high incidence was seen in young children, there had been a much lower morbidity, and close to zero mortality, since child-resistant closures came into widespread use.

(h) Purpose for which the substance is to be used

- Symptomatic treatment of cough and cold.

Pre-meeting Submissions

Pre-meeting submissions were received from XXXXX.

XXXXX noted that the TGA have reviewed a selection of registered over-the-counter (OTC) cough and cold medicines, and requested that any proposed rescheduling for these products should not unintentionally capture complementary cough and cold medicines not included in the TGA Panel’s review where there was no identified safety concern.

Many of the remaining pre-meeting submissions made reference to a review on pharmacokinetic and efficacy studies in children, conducted in the US under the watch of the FDA, with results expected to be available in 2011. The general view was that any consideration of scheduling changes would seem premature in light of this pending review and a decision should be deferred until robust data became available. Additional general conclusions from the pre-meeting submissions included:

- XXXXX suggested an alternative, less restrictive rescheduling cascade – Schedule 4 for children less than 2, Schedule 3 between 2 and 6 and Schedule 2 for children greater than 6. XXXXX also requested that the current schedule status be maintained for oxymetazoline and xylometazoline (topical decongestants) and bromhexine.
- XXXXX accepted the proposal that Schedule 4 capture cough and cold medicines for children under 6. XXXXX reiterated XXXXX request that bromhexine and the topical nasal decongestants oxymetazoline and xylometazoline be excluded from any rescheduling.
- XXXXX also asserted that, given the long history of safe use, they did not support the proposal to restrict all cough and cold medicines to Schedule 3 when intended for use in children aged 6-12 years. Asserted that the scheduling for this age group remained appropriate.
- XXXXX specifically opposed rescheduling bromhexine and argued instead that the current Schedule 2 entry for bromhexine be maintained for children between 2 and 12 years of age.
- XXXXX did not support the proposed scheduling cascade. XXXXX asserted that this was a matter for the registration process.

Members also noted a number of specific additional points from the pre-meeting submissions, including:

XXXXX

- Contended that, currently, individual OTC products are not listed in separate medicine schedules according to the intended patient age but rather according to the presence and / or strength of particular active ingredients and / or pack size.
- Asserted that although evidence regarding the efficacy of cough and cold products was significantly lacking, this did not mean that these products were ineffective.
- As an alternative, proposed mandating products for children to have dosage set by weight rather than age. If this was supported, then dosage information for children aged 2 to 6 years would still be readily available. In addition, the pack should include directions that 'use in children less than 6 years of age should only be on the advice of a health professional'.

XXXXX

- Considered that the enhanced labelling proposed for products for use in children between 6 and 12 years, i.e. to consult with a health care professional before use (except for bromhexine and topical nasal decongestants), would provide sufficient additional safeguards.
- Contended that the proposed rescheduling would result in more serious restrictions than those of other comparable jurisdictions, i.e. Canada and the UK, and believed there was no evidence to justify these restrictions.

XXXXX *additional arguments against Section 52E*

(a) Toxicity and safety

- Believed that the proposed schedule changes were premature and excessive, particularly for children aged 6 to 12, and for the topical decongestants oxymetazoline and xylometazoline and the mucolytic bromhexine.
- Claimed that safety concerns regarding topical nasal decongestants related to large overdoses and that this risk would remain with adult products, irrespective of restrictions to paediatric formulations.
- The safety profile of bromhexine was more favourable than that of the other ingredients being considered for rescheduling. Asserted that out of 18,575 enquiries to the Maryland Poisons Centre (US) involving exposure of children under six to any substance, none involved mucolytics or topical nasal decongestants.
- Argued that safety concerns for either topical decongestants or bromhexine were better addressed by appropriate packaging, labelling and counselling by pharmacy personnel rather than through the proposed schedule changes.
- Contended that rather than the proposed schedule changes, safety concerns could be better addressed with:

- Dose instructions according to weight rather than age.
- Appropriate child-resistant packaging (already in place).
- Mandating the inclusion of a suitable graduated measure in medicines licensed for use in children.
- Limiting access according to risk so that products (or dosage instructions) for children under six were available only after consultation with a pharmacist or other health professional.
- Training and empowering pharmacy personnel to more effectively provide advice and support.

(b) Risks and benefits

- Asserted that there was significant demand for these products for children from the community. The conditions were usually self-limiting and not serious in nature and capable of self-management for adults, or management by a parent or guardian for children, particularly with access to a community pharmacist.
- XXXXX was concerned that, should cough and cold medicines for children under six only be available on prescription, there would be a risk that parents may not consult a doctor, and instead preferentially use adult preparations, guessing the dose for their child.
- Alternatively, parents may resort to using complementary products such as herbal or homeopathic remedies which may have greater efficacy and / or safety issues.
- Much of the more damning data presented in the TGA review related to drugs with little clinical significance for OTC products in Australia.
- It would appear that some trials suggested efficacy with dextromethorphan and that there have been limited or no trials for products such as pholcodine, ammonium chloride, bromhexine and guaiphenesin and therefore it was inappropriate to make such momentous changes based on so little information.
- While it was appropriate that safety concerns be addressed through scheduling, it was asserted that the efficacy concerns were not relevant to scheduling. Asserted instead that this was a matter better dealt with as part of the product registration process.
- Reiterated that the proposed changes were not justified by the information presented to date in the TGA's review.

(d) Extent and patterns of use

- XXXXX contended that, in considering the proposal to restrict cough and cold products for children under six to Schedule 4, the following issues should be considered:
 - Reiterated the above concerns about the consequential potential for off label use of adult products for children. Additionally argued that doctors are less familiar

with cough and cold medicines than pharmacists. There would be a greater risk of incorrect dosing, particularly if this information was not as readily available and doctors were not supported or sufficiently informed.

- There would be significant pressure on doctors to provide a prescription – this may result in inappropriate prescribing of antibiotics or bronchodilators.
- A more appropriate action would be to wait until further research data was available.
- In addition to this, the following should be considered:
 - The capacity of general practice to treat children under six in a timely manner, particularly in rural and remote areas.
 - Potential delays in the treatment of children because of long waiting lists to see a doctor and the increased need for parents to take carer's leave for their child's doctor appointments.
 - Potential delays in treating patients with more serious health complaints as waiting lists grow due to demand for treating minor cough and cold ailments in children.
 - Delays and costs associated with additional pathology tests for upper respiratory tract infections.

(i) Additional matters

- If the proposed changes proceed, there will be considerable impact on community pharmacy, including:
 - Confusion on the schedule status of the medicines, which could affect labelling, supply and storage requirements.
 - Concern that parents may provide misleading information about their child in order to obtain the medicine they want, which may result in many childhood overdoses.
 - Concern that parents may resort to requesting inappropriate products as an alternative (e.g. promethazine syrup).
 - Capacity of community pharmacy to professionally manage the significant increase in Schedule 3 medicines.

XXXXX

- Was concerned that consumers would be confused should products they have used for years become prescription only, noting that this would also incur additional costs.
- Asserted that the incidence of adverse events (AE) in children and adults was very rare.

- The ADRAC report for some cough and cold medicines (from 1 June 1998 to 31 May 2008) documented only 30 cases of AEs for children and adults. For children aged 2 – 12 years, AEs were reported at a rate of 0.0004 per cent.
- Argued that there was no evidence of significant problems with accidental or intentional misuse within the Australian market, and that this was supported by ADRAC.
- Also argued that the US data raised in the TGA Panel's review was not reflective of Australian use since regulation differed substantially between the two countries. The US had a wider access to these products, with a larger variety of combination products, often in larger pack sizes with no child-resistant closures. Labelling was also not as strictly controlled.
- Contended that with the adoption of the measures outlined in the TGA Panel's review, it should not be necessary to include cough and cold medicines in Schedule 3. Asserted that the following measures recommended by TGA Panel's review would work towards consumers seeking more advice:
 - Removal of dosage information for children aged less than 6 years.
 - Requirement for an additional warning when dosage information for children aged 6-12 years was included.
 - Child-resistant closures.
 - Public awareness campaign.

XXXXX

- Made reference to an External Report provided previously to the TGA in December 2009. The report acknowledged that these active substances were all unlikely to be harmful at label dosages, and that the substances were all relatively safe in overdose.
- Much of the concern from the US had been over reports of deaths in infants and young children which have been isolated and simply reflect gross overdose.
- While unintentional overdose was most typical in the 1-2 year age group, serious poisoning was rarely seen.
- Topical decongestants are currently all Schedule 2 medicines, except for topical phenylephrine 1 per cent or less. This provides parents and caregivers access to medical advice within the pharmacy setting should it be required.
- Most topical nasal decongestants are marketed in pack sizes of 20 mL or less and usually fitted with a restricted flow spray insert or dropper insert. The nature of the packaging would minimise the risk of accidental gross overdose and severe AEs.
- The most common report of misuse or abuse of topical nasal decongestants was inappropriate use with regards to frequency or duration of use, while the most frequently reported adverse events were usually non-serious.

- XXXXX. Between the period of 1996 and 2008, over XXXXX units were sold in the UK, with only 3 reported cases of AEs in children under 12 years of age.
- The best outcome from any changes would be one that added further protection to the public, and any decision made prior to the availability of the US study results would be in haste, as these studies were aimed to address the concerns surrounding the risk benefit ratio of these substances.

XX

- Asserted that most of the substances in cough and cold medicines do not appear to have safety issues according to the data analysed by the External Reviewers for the TGA Panel's review.
- Asserted that the evidence of risks outweighing benefits for the substances below was not substantiated in the data presented to date, and these substances should not be rescheduled. This position could then be reviewed once the results of the efficacy studies being conducted in the US were available:
 - Brompheniramine, doxylamine, triprolidine, pentoxyverine, ammonium, diphenhydramine, codeine, dihydrocodeine, guaiphenesin, senega, ammonia, xylometazoline and phenylephrine.
- Analysis of safety data from Australia, NZ, UK, US and Canada showed that the substances responsible for most reports of AEs were the sedating antihistamines and pseudoephedrine, which were already scheduled as Schedule 2 or higher.
- Argued that upscheduling any other substance in cough and cold medicines would be of little benefit in preventing adverse drug reactions given it has not stopped these events with use of medicines already in Schedule 2.

XXXXX

- Single active bromhexine has been marketed in Australia for approximately 30 years. It has been marketed worldwide since 1962.
- The efficacy of bromhexine in children and adults was well supported by clinical studies, and the favourable safety profile was well supported by both ADRAC and worldwide safety data.
- Taking into consideration the totality of all efficacy and safety in both adults and children, a clear positive risk-benefit profile of single active bromhexine has been established.
- Enhanced labelling for bromhexine products 'for use in children 2-12 years' to 'consult with a health care professional before use in children of this age', would provide sufficient additional warning in relation to the use of these products in this age group.
- Claimed that the TGA's review was still ongoing. Advised that, in response to TGA's consultation document (October 2009), it opposed restricting the minimum

age of use from 2 to 6 years for products containing bromhexine. Asserted that they were still awaiting the outcome of the consultation.

- Noted that Medsafe considered the efficacy and safety of bromhexine through its Cough and Cold Review Group Meeting of 18 August 2009, and overall concluded that bromhexine was safe and appropriate for use in children 2 years and above.
- Health Authorities in the UK, Canada and the US also conducted reviews on cough and cold medicines in children, however, none of them reviewed bromhexine, as it was not available in these countries. Therefore, the conclusions reached by each of these Health Authorities could not be applied to bromhexine.
- Contended that there were many unscheduled, listed complementary medicines indicated for use in cough and cold that would continue to be allowed for dosing in children 2 years and above. Argued that these medicines should, therefore, also be considered for the proposed age restrictions.

XXXXX

- Contended that the scheduling system should not be used for transient problems or as a substitute for the registration process.
- Asserted that problems with children's cough and cold medicines were acknowledged as being rare in Australia. Too much weight, therefore, should not be placed on experience in other countries, especially when Australian conditions were different and where there was very little evidence concerning toxicity in these age groups.
- Agreed that evidence for the efficacy of the cough and cold medicines in question was unconvincing. Argued that this suggested that the products should be removed from the Australian Register of Therapeutic Goods (ARTG) on the grounds of not meeting the efficacy criterion set out in section 4 of the *Therapeutic Goods Act 1989*.
- Proposed as an alternative, that these products be relabelled to exclude children's doses and include a statement that 'this medicine is not effective for children under 2 years of age and should not be given to them'. Contended that to have cough and cold medicines available only on prescription does not make them efficacious or confer legitimacy on them.
- Emphasised that when a substance was placed in Schedule 4, unauthorised supply and possession attracted criminal penalties which in this case were unjustified given the virtual absence of evidence of toxicity. This approach could lead to the scheduling system falling into disrepute.

XXXXX

- Was opposed to age-based scheduling due to the difficulties it presented to pharmacists, and found the proposal to schedule substances in cough and cold medicines differently when used in children aged 6 to 12 years to be unreasonable.

- Topical decongestants oxymetazoline and xylometazoline should be excluded from the Committee's considerations. The hazards posed by these medicines to children are best minimised by enforcing packaging requirements.
- Was aware of the potential toxicity of imidazoline decongestants intended for ocular and intranasal administration if ingested, particularly by children.
- Was also aware that these products were intended only for short-term use and that these products, particularly decongestant nasal sprays, were available in refill presentations, which promoted the inappropriate long-term use of such products. These refill packs represented the greatest risk of poisoning to children.
- Was of the opinion that the marketing of refill packs of products containing imidazoline decongestants should be discontinued, and that eye drops and nasal spray formulations should be marketed only in sealed units.

XXXXX

- Requested a more evolutionary approach given the long history of use of cough and cold medicines, the low incidence of serious adverse reactions in Australia, the reasonably large number of products that could be affected by any proposed amendments, and the complexity of social issues surrounding the use of these medicines.

Transitional considerations

XXXXX requested that any decision not be considered final. Also requested consideration of an implementation date of, at a minimum, one year following finalisation of any scheduling decision, noting:

- For currently marketed products sourced overseas, a lead time of 9 – 12 months would be required for implementing labelling changes.
- There would be a need to allow time for educating representatives, pharmacists and the community of any scheduling changes that will directly impact on consumer access – this can only be done post a scheduling decision.

XXXXX requested that, if a decision would result in a scheduling change that does not align with XXXXX position, such a decision should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (b) risks and benefits, (d) extent and patterns of use, (f) need for access, (g) the potential for abuse / misuse and (h) purpose of use.

Members discussed the main concerns driving this proposal. The key concern identified was that current scheduling allowed certain substances to be administered to children to treat cough and colds which may not be effective and for which there were indications of hazard. It was noted that these substances were mostly Schedule 2 (with some being

unscheduled and a few already more restricted due to other concerns e.g. pseudoephedrine) although many did have some restrictions regarding use in children under two (such as the antihistamines).

Risk versus benefit

Members noted that a principal concern identified in the TGA Panel's review was the lack of efficacy of these substances in treating cough and colds. The Committee was further advised that there was also some positive evidence of no efficacy in any age group, especially children, including results from a number of clinical trials.

A Member noted, however, that the cited efficacy studies appeared to be mostly poor, with low numbers and little statistical power, and that this undermined to a degree the basis of the TGA Panel's conclusions. Another Member contested that the external report (which formed part of the basis of the TGA's review) drew on a Cochrane assessment which found no evidence "for or against" efficacy rather than "positive evidence of no efficacy".

A Member, while conceding that there was little evidence of efficacy, asserted that this should not be surprising as these were mostly old products where there had been no regulatory requirement or commercial reason to date to drive companies to undertake new studies. The Member asserted that, while acknowledging the lack of robust efficacy data, this should not be the basis for rescheduling. The Member observed that in recent considerations of codeine it was agreed that the issue of efficacy was best left to the regulator (as part of any product approval process) and that rescheduling was instead due to codeine misuse concerns. Other Members asserted that the codeine issue was a different situation (where efficacy was less central to the concerns given the clear risks of abuse). The Committee agreed that each issue needed to be assessed on its own merits with regard to the relevance of efficacy to scheduling considerations.

Some Members reiterated the query from one pre-meeting submission that, if there was no evidence that these products were efficacious, why were these products registered at all. Other Members argued, however, that deregistering would be an extreme response given the quality of the data and the low likelihood of serious AEs, and that a more reasonable compromise might be to consider more restrictive access through scheduling in the first instance, until better information became available.

Several Members highlighted the low number of reported serious AEs (less than 3 per annum for children under 6 years of age in Australia). Other Members noted that AEs for OTC medicines were always strongly under-reported. A Member asserted that, while it is assumed that under reporting occurs, this was the conventional way to collect this data, at this time, and therefore this information should be considered.

A Member questioned this data and noted that the reported AE numbers did not identify how many of these occurred before the mandated child-resistant closure (CRC) requirements took effect for cough and cold preparations. Recent PIC data seemed to

indicate that less severe AEs were being reported, with serious AEs becoming increasingly rare since the introduction of the CRC requirement. The Member therefore suggested that the data presented in the TGA Panel's review may not reflect the current situation.

While a number of Members contended that there appeared to be insufficient data for considering tighter access restrictions for these medicines, the Committee generally agreed that the regulator (and the Committee) could only make a decision based on the available evidence and that this evidence indicated that while the risk signal may not be strong, this was being balanced against no, or little, evidence of efficacy.

A Member also asserted that, in addition to AE concerns, the current use of these products in children could mask symptoms and delay medical intervention. The Member argued that, especially for the very young, consultation with a doctor was often necessary to determine if a child was suffering from a more serious condition e.g. asthma.

Possible scheduling

The Members then debated what actions might be appropriate to mitigate the concerns discussed above.

Members again discussed the TGA Panel's recommended approach to cough and cold medicines for children – the proposed scheduling cascade, together with proposed regulatory action through changes to indications, labelling and packaging. Members particularly focussed the discussions on the proposed cut-offs based on age.

A Member reiterated the likely off-label misuse of these products, as raised in a number of pre-meeting submissions, should access be differentiated on the basis of age. Other Members argued that, while perhaps likely (at least initially), such a risk should not prevent scheduling action. Members generally agreed that a cascade of controls based on age cut-offs would communicate what was considered appropriate, would send a strong message that medicating children for cough and colds was a serious matter, and would improve awareness that cough and cold medication may not be the best option for treating these symptoms in children.

The Committee noted that many suggestions and views on possible cut-offs had been presented, as broadly summarised in the following table. Additionally, there were suggestions that the concerns could be addressed solely through application of contraindications and other regulatory mechanisms i.e. no scheduling change.

	TGA review Cascade 1	Cascade 2	Cascade 3	Cascade 4	Cascade 5
Schedule 2	≥ 12	≥ 6	> 6	≥ 12 current scheduling	≥ 2 current scheduling (extra labelling <6)

Schedule 3	6 to < 12	-	2 to ≤ 6	2 to <12	-
Schedule 4	< 6	< 6	< 2	< 2	< 2

Members also recalled the tabled advice regarding international controls, noting that the UK, NZ (pharmacist only) and Canada require cough and cold medicines for children over 6 (to 12) to be sold through pharmacies. A Member additionally advised that the UK controls were effectively Schedule 3 for children 6-12 as involvement of a health professional was required for supply (and the UK did not allow use in children under 6).

It was also clarified that in NZ, use in children under 6 was controlled largely through contraindications for this use, rather than by classification as a prescription only medicine. A Member suggested that this may be an appropriate approach for Australia to consider, noting that use in under 2 years was already precluded, though not necessarily through scheduling (while this was the case for antihistamines, some other actives did not have current scheduling age cut-offs for OTC use). Members generally agreed, however, that it would be clearer for such controls to be reflected by a scheduling cascade.

Under 2 years of age

Several Members supported the proposal that cough and cold medicines for children under 6 should be Schedule 4, arguing that the minimal benefit did not outweigh the risks to this age group.

A Member noted that certain international regulatory systems set a prescription only cut-off for children under 6. The Member argued, however, that this approach seemed arbitrary, and there was little basis for this cut-off as the risks were different for children aged 2 to 6 and those aged 6 to 12. The Member conceded that some of the AE data seemed to indicate a differentiation, but questioned whether increasing controls on this basis would address the concerns. The Member asserted that, while there was good public acceptance that babies were different to children over 2 years of age, it was not generally accepted by the public that children aged 4 or 5 had different responses to medicines compared to children aged 6 or 7.

The Committee generally agreed that the current scheduling restriction for sedating antihistamines (Schedule 4 when for use in children under 2) should be extended to medicines for cough and colds. The proposal to extend this up to children aged 6 or less was not supported.

The Committee also noted that this only applied to those substances identified in the TGA review, apart from the exemptions discussed below. In particular, this did not extend to complementary preparations not included in the TGA Panel's review.

From 2 up to, and including, 6 years of age

Members then considered whether additional scheduling controls were also necessary for children aged 2 or above.

One Member advocated the XXXXX proposal, i.e. Schedule 2 for children 2-12 (largely status quo except for those few substances which were currently unscheduled), arguing that any concerns for these children could be addressed through enhanced labelling requirements through the regulator, emphasising the need to consult with a healthcare provider before use.

Other Members maintained, however, that the various concerns discussed in detail above (AEs, lack of efficacy, misuse), which led to agreement that these products be Schedule 4 for children under 2, would also apply to children aged 2 and over, although not to the same extent. It was argued that these concerns could be sufficiently mitigated through the mandatory involvement of a pharmacist in the supply of these medicines, when coupled with other regulatory actions by the TGA.

The Committee generally agreed that those substances identified in the TGA review, apart from the exemptions discussed below, should be captured by Schedule 3 when used in children aged 2 to 6 in preparations to treat cough and cold. A proposal to extend this more broadly to those aged 2 to 12 was not supported.

Above 6 years of age

Members discussed whether the scheduling of the use in the remaining age group (i.e. all use above 6 years of age) should be maintained (mostly Schedule 2 with some others currently unscheduled). Members generally agreed that it was appropriate that all cough and cold medicines for use in those above 6 years of age be captured by Schedule 2.

Exceptions

Members noted that, of the 22 substances identified in the TGA Panel's review, a number were recommended for exemption from the proposed cascade as it was considered that either existing controls were sufficient (codeine, dihydrocodeine and pseudoephedrine) or that scheduling was not necessary (ammonia). Members also noted that various pre-meeting submissions proposed that certain other substances (including bromhexine, guaiphenesin, oxymetazoline and xylometazoline) also be excluded from any rescheduling decision.

A Member advised that in NZ, tightening of controls on cough and cold medicines did not include bromhexine as there was little reported risk from use of this substance. Another Member argued that, from the AE data in the TGA review, there seemed to be no justification for treating bromhexine as any safer than the other substances of concern. Other Members agreed, however, that there were no significant concerns, based on available data, regarding bromhexine cough and cold medicines.

A Member also advised that in NZ, while the use of guaiphenesin in children under six was contraindicated, a change to the scheduling of cough and cold medicines that contained guaiphenesin only was not warranted as there was little reported risk from use

of this substance in children aged six years and older. Additionally, there appeared to be better evidence of efficacy for guaiphenesin with no real safety issues.

The Committee therefore agreed that bromhexine and guaiphenesin should not be included in the rescheduling action set out above. Additionally, the Committee agreed to the TGA Panel's proposal that rescheduling of ammonia was not necessary.

Members also noted the various arguments tabled regarding the scheduling of oxymetazoline and xylometazoline. Members noted that, in this case, there was decent data regarding efficacy, but that this was balanced in part by a higher risk profile. Members noted the arguments that this risk was mitigated by the current method of use (nasal spray). The Committee generally agreed that oxymetazoline and xylometazoline, when used in cough and cold medicines as nasal sprays, should be excluded from the rescheduling action set out above. However, any other presentation of oxymetazoline or xylometazoline for treating cough and cold should be captured.

No down scheduling

Several Members noted that for some substances the current scheduling may in fact be more restrictive than the proposed cascade (e.g., pseudoephedrine). Indeed, this was the basis for the TGA Panel recommending that existing controls were sufficient for codeine, dihydrocodeine and pseudoephedrine and did not need to be rescheduled. Members agreed that the rescheduling action set out above should apply to codeine, dihydrocodeine and pseudoephedrine (and indeed all the other substances identified in the TGA Panel's review unless excluded), but only where it would not result in less restrictive scheduling.

Implementation / referral to delegate

Members agreed that this was a complex issue that could not be finalised at this meeting, as per the transition arrangements discussed under item 1.6.2. The Committee decided, however, that its agreed position, as above, should be referred as a recommendation to a delegate under the new scheduling arrangements commencing from 1 July 2010, noting that this process would provide for additional public consultation on this issue.

Other matters - labelling

Members also considered recommending to the delegate potential inclusion in Appendix L. The Committee considered, however, that this was a matter best left for the delegate to consider following public consultation on the Committee's scheduling recommendations.

Other matters – education and training

Several Members reiterated the concern identified in some pre-meeting submissions that the implementation of such significant changes to a long established and widely used product range would require practical public awareness through an appropriate education

campaign and pharmacy staff training. A Member asserted that such communications should also emphasise that there were alternative non drug approaches for managing cough and cold symptoms in children.

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The Committee agreed:

- That the use of certain substances in preparations for treating cough and cold be rescheduled to:
 - Schedule 4 for use in children less than 2 years of age.
 - Schedule 3 for use in children aged from 2 to 6 years of age.
 - Schedule 2 for use in children and adults above 6 years of age.
- That this rescheduling apply to brompheniramine, carbapentane, chlorpheniramine, codeine, dexchlorpheniramine, dextromethorphan, dihydrocodeine, diphenhydramine, doxylamine, ipecacuanha, pheniramine, phenylephrine, pholcodine, promethazine, pseudoephedrine, senega and triprolidine.
- That the rescheduling should apply only where it will not result in less restrictive scheduling.
- That the rescheduling not apply to oxymetazoline and xylometazoline when for nasal spray use for treating cough and cold, but would apply for any other preparation for treating cough and cold.
- That use of ammonia, bromhexine, and guaiphenesin in preparations for treating cough and cold did not need to be rescheduled.

The Committee agreed that these recommendations be referred to a delegate under the new scheduling arrangements commencing from 1 July 2010.

15.4 IBUPROFEN COMBINED WITH PARACETAMOL

PURPOSE

The Committee considered the scheduling of ibuprofen when combined with paracetamol.

BACKGROUND

Ibuprofen

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used in the management of mild to moderate pain and inflammation. It is also used to reduce fever. Ibuprofen was first included in Schedule 4 in February 1973.

At the October 2003 meeting, the Committee agreed to exempt certain divided preparations of ibuprofen from scheduling: 200 mg or less, in packs of 25 or less, when labelled with a recommended maximum daily dose of 1200 mg and compliant with the mandatory label requirements.

At the February 2006 meeting, the Committee considered a requested rescheduling, from Schedule 4 to Schedule 2, of divided oral preparations of 400 mg or less of ibuprofen. The Committee, however, agreed to include 400 mg or less ibuprofen, in packs of 50 or less when labelled not for the treatment of children aged less than 12 years, in Schedule 3.

The current ibuprofen Schedule 2 entry includes oral preparations when labelled with a recommended daily dose of 1200 mg or less, in divided preparations with 200 mg or less per dose in packs of 100 or less **except** when it is the only therapeutically active constituent, in which case it became unscheduled.

Paracetamol

Paracetamol is a p-aminophenol derivative that inhibits analgesic and antipyretic effects without anti-inflammatory activity.

Paracetamol preparations containing 500 mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine, effervescent agents or, since February 2010 meeting, guaiphenesin) in packs of 25 or less are currently exempt from scheduling (when compliant with labelling, packaging and age restrictions). However, these preparations become Schedule 2 if combined with another therapeutic active ingredient such as ibuprofen.

DISCUSSION - SUBMISSIONS

XXXXXX considered a XXXXX combination XXXXX containing ibuprofen XXXXX and paracetamol XXXXX (ibuprofen+paracetamol) XXXXX.

XXXXXX noted that while ibuprofen+paracetamol in packs of up to 100 tablets meets current requirements for Schedule 2, it was likely that the Committee had not specifically considered a combination of ibuprofen and paracetamol. XXXXX therefore requested clarification from the NDPSC regarding the scheduling of ibuprofen+paracetamol and whether it was appropriate that such combinations remain in Schedule 2.

XXXXXX was provided, and the relevant points for the scheduling consideration of ibuprofen+paracetamol are summarised below:

- XXXXX.
- No products containing this combination of active ingredients have been registered in Australia.

- Ibuprofen+paracetamol products are marketed in a number of Central and South American, African, Asian and Eastern European countries, XXXXX. This combination was not currently approved in the USA, UK, Canada or Western European countries, XXXXX.
- XXXXX.
- XXXXX was advised that this combination claimed to provide an additive analgesic and antipyretic effect with no reduction in safety, through the complementary mechanisms of action of ibuprofen and paracetamol, and that it delivers both peripherally and centrally mediated analgesia providing a dual approach to pain management which is claimed to be superior to that of ibuprofen or paracetamol monotherapy.
- XXXXX also contended that concomitant use of these substances is currently widespread in both self-medication and prescription settings. XXXXX.

XXXXX

- XXXXX.
- XXXXX was advised that published papers dealt mostly with the individual effects and toxicity of either ibuprofen or paracetamol, and not with the proposed ibuprofen+paracetamol combination.
- XXXXX. Any significant interactions of ibuprofen and paracetamol would be unlikely, due to separate mechanisms for their primary pharmacological actions.
- XXXXX did not demonstrate that ibuprofen+paracetamol would offer any therapeutic advantage over use of either ingredient alone as an analgesic, anti-inflammatory or antipyretic agent.
- XXXXX.
- While the different metabolite profiles suggested there may be no metabolic interactions between ibuprofen and paracetamol, a metabolite of paracetamol, N-acetyl-p-benzoquinoneimine (NAPQI), can cause severe, and potentially fatal, hepatotoxicity following an overdose.
- There was no information to indicate whether the presence of ibuprofen may increase the formation of NAPQI and potentiate paracetamol toxicity.
- Renal impairment or failure had been reported with paracetamol overdose. XXXXX did not address whether ibuprofen enhanced the potential renal toxicity of paracetamol.
- There were concerns that ibuprofen+paracetamol could potentially increase gastrointestinal (GI) toxicity, since both ibuprofen and paracetamol are non-selective COX inhibitors, and inhibition of COX-1 is reportedly linked to GI toxicity. XXXXX.

XXXXX

- XXXXX.
- XXXXX were concerned that patients might be unnecessarily exposed to the combination product, where their condition might be more appropriately managed by monotherapy with ibuprofen or paracetamol.
- Noted again that while it appears that the mechanism of action is different between ibuprofen and paracetamol, there was a potential for interactions, as both ibuprofen and paracetamol are non-selective COX-1 and COX-2 inhibitors.
- XXXXX.
- XXXXX was advised that there did not appear to be any significant cardiovascular (CV) effects with ibuprofen+paracetamol. However, given the potential for overuse of analgesics, their widespread availability, and the proposed pack sizes, this safety issue should be considered.

Pre-meeting Submissions

XXXXX.

XXXXX requested that the current scheduling (Schedule 2) be retained XXXXX. Asserted that the risk versus benefit profile of ibuprofen+paracetamol was well-defined and was consistent with the Schedule 2 status. Submissions from XXXXX also supported retaining the current scheduling of ibuprofen+paracetamol i.e. Schedule 2 when in accordance with existing criteria.

XXXXX supported a Schedule 2 entry only for small pack sizes.

XXXXX considered a Schedule 3 entry to be appropriate for ibuprofen+paracetamol in a maximum pack size of 100 dosage units. It was argued, however, that the proposed maximum pack size of 100 dosage units or less did not correlate logically with the proposed limits of a maximum recommended daily dose of six dosage units and 3 days supply i.e. 18 tablets.

XXXXX commented that many of the issues regarding the risks and benefits associated with a fixed dose combination of ibuprofen+paracetamol remained unanswered. XXXXX opinion was that until such data was available it would be pertinent to err on the side of caution when determining the appropriate schedule of ibuprofen+paracetamol.

Specific additional points from a number of pre-meeting submissions are also summarised below:

XXXXX

- Asserted that the quality use of ibuprofen+paracetamol could be achieved by labelling. Access to advice from a pharmacist as Schedule 2 would still be available to maximise the safe and effective use of this combination.

- Ibuprofen+paracetamol was substantially safe for short term treatment and the potential for harm from inappropriate use was low.
- XXXXX.
- Claimed that there was no evidence to suggest that either paracetamol or ibuprofen was associated with dependency, abuse or illicit use. It was expected that ibuprofen+paracetamol would not produce dependency or abuse, misuse or illicit use.
- Asserted that ibuprofen+paracetamol offered benefits over combination analgesics containing codeine (CACC). Considered that availability of ibuprofen+paracetamol as Schedule 2 would potentially decrease the supply of products that may have some dependence potential.
- Asserted that consumers were accustomed to self-medicating with paracetamol and ibuprofen and the contra-indications and warnings were familiar to them. The packaging and labelling of combination products would utilise the same warnings.
- Ibuprofen+paracetamol at established dosage levels was unlikely to mask the symptoms or delay diagnosis of a serious condition. As with single actives in OTC use, the combination was not intended for treatment of a chronic condition.
- Asserted that the combination provided improved efficacy as analgesics compared with maximal OTC doses of ibuprofen and paracetamol individually, and had a tolerability profile consistent with the individual actives.
- The indications listed for ibuprofen+paracetamol could be easily recognised and managed by the consumer without the need for medical intervention.
- There was a low and well-characterised incidence of adverse effects for both substances and this was shared by ibuprofen+paracetamol at the proposed dose.

UK and NZ scheduling status

- Asserted that this combination was under review by the UK and was being considered as a pharmacy only medicine, consistent with the proposed scheduling for Australia.
- In NZ, ibuprofen 150 mg and paracetamol 500 mg combinations have been scheduled for general sale in pack sizes of 8 and 16 tablets and as Pharmacy only for pack sizes of 50 and 100.

Other combination analgesics

- Noted that paracetamol+aspirin was currently classified as Schedule 4. Believed that this scheduling was based on the concern for nephrotoxicity associated with aspirin. Claimed that there was no association with nephrotoxicity with either paracetamol or ibuprofen at the proposed OTC doses. Asserted that Schedule 4 would be inappropriate for ibuprofen+paracetamol.

XXXXX also addressed matters under section 52E, including:

(a) Toxicity and safety

- The non-prescription daily dose for the short-term treatment of pain and fever is up to 1.2 g ibuprofen and up to 4 g paracetamol, which have demonstrated similar tolerability profiles.
- Claimed that ibuprofen had an excellent safety profile, with rare cases of gastrointestinal (GI) bleeding, ulceration or perforation.
- Also claimed that paracetamol has an excellent safety profile similar to ibuprofen, for short-term use. Haematological reactions include thrombocytopenia, leucopenia, pancytopenia, neutropenia and agranulocytosis. Skin rashes and other hypersensitivity reactions occur more rarely. The greatest concern with paracetamol was toxicity in overdose.
- Asserted that the overall conclusion of a bibliographic review of safety of the combination was:
 - No additional safety issues were identified with ibuprofen+paracetamol, and the safety profile was comparable to ibuprofen and paracetamol alone.
 - XXXXX.

UK General Practicing Research Database (GPRD)

- Claimed that it was aware of the practice of co-prescribing ibuprofen and paracetamol in the UK. Therefore, XXXXX commissioned a pharmacoepidemiology study utilising data from the UK GPRD. The study population included 1.2 million patients. The safety outcomes evaluated were upper GI effects, myocardial infarction, stroke, heart failure, renal failure, suicidal behaviour and mortality.
- Acknowledged that there were a number of limitations to the data, however, the data showed that the relative risk was generally lowest with ibuprofen, followed by co-prescribed ibuprofen and paracetamol and then paracetamol alone.
- The hazard rate patterns for co-prescribed ibuprofen and paracetamol in renal failure were proportional or lower than the single substances.
- Concluded that the results suggested that concomitant use of ibuprofen and paracetamol did not increase the risk of the various safety outcomes examined over use of these substances alone.

(b) Risk and benefits

- Stated that the clinical efficacy data on the use of ibuprofen and paracetamol as a combination (or on an alternating treatment regime) in the public domain, was limited.
- Claimed that, from available data, ibuprofen+paracetamol was more effective than paracetamol alone or placebo in acute pain; acknowledged that there was no clear difference with ibuprofen alone.
- XXXXX.

- Asserted that for those patients currently co-dosing with ibuprofen and paracetamol, a fixed combination would simplify dosing, thus improving compliance, reducing the risk of medication errors and potential unintentional overdose.

(c) *Potential hazards*

- Acknowledged that it was critical that consumers and healthcare professionals were aware of products containing paracetamol because of the wide range of OTC medications available containing paracetamol. XXXXX.
- Asserted that counselling and verification by a pharmacist was recommended before use of ibuprofen+paracetamol to ensure that the consumer recognised that the combination contained both ibuprofen and paracetamol, and to counsel against concurrent intake with other ibuprofen and / or paracetamol-containing analgesics.
- Was aware that the USFDA had reviewed issues of overdosage of paracetamol and recommended reducing the dosage of paracetamol available OTC. However, the TGA also reviewed this issue and decided not to reduce the tablet dosage of paracetamol.
- Hepatotoxicity in overdose: Claimed that pack size restrictions in the UK have reduced the number of deliberate overdoses with paracetamol and salicylates, which were down by 22 per cent in the year following the legislation, and in the following 4 years liver unit admissions and liver transplants for paracetamol-induced hepatotoxicity were reduced by 30 per cent (Hawton, K *et al*, 2004, 'Legislation on Analgesic Pack: Before and After Study of Long Term Effect on Poisonings,' *British Medical Journal* doi:10.1136).

(d) *Extent and patterns of use*

- Ibuprofen+paracetamol is licensed in NZ, India, Russia, Poland and South Africa and in Asia and South America. The products contain various dose ratios of ibuprofen and paracetamol and the posology varies with maximum daily doses ranging from 1.2 – 2.4 g for ibuprofen and 1.3 – 2.6 g for paracetamol. XXXXX.

(e) *Need for access*

- Asserted that ibuprofen+paracetamol offered an alternative to CACC for the short-term relief of pain, particularly for patients who are poor metabolisers of codeine.

XXXXX

Argued that ibuprofen+paracetamol provided more effective analgesia than ibuprofen or paracetamol alone, with no deterioration of the safety or tolerability profile. Also asserted that:

- A clinical program has established that ibuprofen+paracetamol was bioavailable with a comparable pharmacokinetic (PK) profile to each alone. A repeat dose PK study showed that there was no accumulation of ibuprofen or paracetamol, and that a 3

times daily dosing strategy provided more consistent plasma levels than a twice daily dosing regimen.

- Ibuprofen and paracetamol act at different sites, and hence the possibility of an adverse pharmacodynamic interaction between the two substances was unlikely.
- Reiterated the above arguments on efficacy and safety. Also asserted that 1 tablet of ibuprofen+paracetamol provided clinically meaningful efficacy benefits over currently marketed OTC analgesics.

XXXXX

Included a compilation of data from published clinical trials and a review paper, and concluded the following:

- The relevance of the data from these studies was restricted because of limitations in the study design and/or the dose of study medications used. Only one study used a combination of ibuprofen 150 mg and paracetamol 500 mg, and this was limited to adults and children aged 16 or more. This study was composed of post-surgical analgesia which was not reflective of an OTC indication for the temporary relief of moderate to strong pain and/or inflammation, and fever reduction. Emphasised that authors of the study were also of the view that confirmation of the paracetamol+ibuprofen combination's efficacy required confirmation in other pain states.
- Discouraged ibuprofen+paracetamol use in fever management. Argued that despite accumulating efficacy data for the practice of combined or alternating dosing, it has been suggested that increased education to decrease fever phobia in parents may ultimately be of more value than (complicated) drug alternation regimens that have little or no clinically significant difference in fever control.
- The UK's National Institute for Health and Clinical Excellence (NICE) guidelines recommended that paracetamol and ibuprofen should not routinely be given together or used in an alternating schedule.
- There was limited safety data on ibuprofen+paracetamol therapy.
- Made reference to a report that concluded that, based on current evidence, the combination of paracetamol and an NSAID may offer superior analgesia compared with either drug alone, for post-operative pain. Contended, however, that this report also cautions that there were some potential disadvantages in combining paracetamol with NSAIDs. The disadvantages cited were:
 - A combination may be disadvantageous when individual drugs are specifically suited to a patient's symptoms.
 - Combining analgesics may increase the incidence of adverse effects.

- The use of a fixed-dose combination may reduce dosing flexibility in dose titration or may expose patients to unnecessarily large doses of NSAIDs with consequent adverse effects, particularly in susceptible individuals.
- Combinations may not be suitable for patients with contraindications to either drug alone.

XXXXX

- Asserted that the current policy to determine the appropriate schedule of products containing more than one substance is set out in the SUSDP as follows:
 - *If a preparation contains two or more poisons, the provisions relating to each of the Schedules in which those poisons are included apply.*
 - *Where it is not possible to comply both with a provision relating to one of those Schedules and with a provision relating to another of those Schedules, the provision of the more restrictive Schedule applies, unless a contrary intention is indicated in the Schedules or relevant legislation.*
- Supported maintaining the Schedule 2 listing consistent with current policy guidelines.

XXXXX

- Argued that larger pack sizes would be more appropriately managed in consultation with the pharmacist to ensure safe and appropriate use and to minimise any risk of misadventure due to misuse or unintentional paracetamol overdosage.
- The use of a fixed dose ibuprofen+paracetamol product would provide an alternative therapeutic agent for the short-term relief of pain or fever.
- Believed that the safety profile is such that listing in an OTC schedule would be appropriate.

XXXXX also made reference to section 52E as follows:

(a) Toxicity and Safety

- Reiterated the above observation about the proposed posology.
- Hepatotoxicity is the greatest risk following paracetamol overdosage. A trial has found that paracetamol 4 g daily for four or more days commonly caused elevated aminotransferase levels, however the clinical significance of this was unclear.
- Paracetamol has a low incidence of AEs when compared to other drugs.
- The more common AEs of ibuprofen relate to upper GI effects. Other common AEs include raised liver enzymes, diarrhoea, headache, dizziness, salt and fluid retention and hypertension.

- Both paracetamol and ibuprofen were safe to use for breastfeeding mothers. Paracetamol was safe to use in pregnancy, being Category A. NSAIDs such as ibuprofen were Category C and are cautioned to only to be used in the second half of pregnancy, on specialist advice, and should be avoided during the last few days of pregnancy.

Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed.

Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible.

- The relative risk of these medicines, particularly in combination, warrants consumer access to advice and support from a pharmacist or other appropriate health professional.

(b) Risks and benefits

- Considered that the greatest risk with a fixed dose of ibuprofen+paracetamol was that consumers may inadvertently overdose on paracetamol by taking this product in combination with other paracetamol products.
- This risk could be ameliorated through appropriate warnings on the pack, and having the product appropriately scheduled to facilitate access to the advice and support of a pharmacist or other health professional.
- Asserted that combination analgesics of proven efficacy could have a number of benefits including improved adherence, simplified dosage, improved efficacy without increasing AEs, and decreasing AEs without loss of efficacy.
- Clinical studies on patients with musculoskeletal conditions, dental pain or post-operative pain have shown that combinations of paracetamol and NSAIDs may provide additive pain-relief (www.elsevier.com/locate/pain).
- Asserted that the use of NSAIDs combined with paracetamol was recommended for extra pain relief using the lowest effective dose for the shortest period of time and that the use of paracetamol enabled the use of lower doses of NSAIDs (Australian Medicines Handbook 2010).

(e) Dosage and formulation

- Claimed that in a controlled trial, superior pain relief was demonstrated for an ibuprofen 150 mg / paracetamol 500 mg combination (for up to 48 hours following oral surgery), as compared to paracetamol or ibuprofen alone.
- There was also evidence for the efficacy at the recommended dose of one dosage unit (200 mg ibuprofen / 500 mg paracetamol) three times a day.
- A recent trial has demonstrated that ibuprofen 400 mg / paracetamol 1000 mg was significantly better than ibuprofen 200 mg / paracetamol 500 mg. However, the

lower-dose combination was often more effective and had a better safety profile than both ibuprofen 400 mg alone and paracetamol 1000 mg alone (Mehlish, D R *et al*, 2010, 'Comparison of the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults').

- There was a risk with combination products in which active ingredients have significantly different half-lives, for accumulation of the drug with the longer half-life. This should not be an issue for ibuprofen+paracetamol as the elimination half-life for both active ingredients was similar.

(f) Need for access

- Reiterated the above arguments regarding ibuprofen+paracetamol as an alternative to other OTC medicines such as CACC.
- Argued that, with appropriate training of pharmacy assistants, the availability of small packs of ibuprofen+paracetamol in Schedule 2 could also have a positive impact on pharmacy workflow by having alternative therapies available without the need to always consult a pharmacist.
- Asserted that XXXXX would collaborate with XXXXX to assist in developing and implementing appropriate training modules for pharmacy assistants to adequately triage patients and refer to the pharmacist when appropriate.

(g) Potential for abuse

- Neither paracetamol nor ibuprofen have any significant abuse potential, and the availability of a combination analgesic in Schedule 2 may also assist in reducing the reliance many patients have had to date on CACC.

XXXXX

- Argued that this appeared to be more a matter for registration.
- There was some superficial evidence that combinations of paracetamol and NSAIDs provided superior analgesia than either component administered singly (Ong CK *et al.*, 2010 *Anesthesia & Analgesia*, vol 110, pp 1170-9)]. This paper, however, needed to be read carefully, taking into account the particular NSAIDs studied and the doses of the active ingredients.
- Patients with arthritis commonly take paracetamol with one of the prescription NSAIDs and there would be concern about consumers taking excessive quantities of NSAIDs.
- Concerned that industry would market this combination as a substitute for the CACC.
- Reiterated that it would be prudent to place ibuprofen+paracetamol in Schedule 3 (but exclude from Appendix H) until more experience of its safety and efficacy was obtained.

XXXXX

- Argued that the inclusion of two substances in one analgesic product, both of which are readily available in a multitude of other products not necessarily intended for analgesia creates a significant risk of therapeutic duplication and overdose for both ingredients.
- Concerned that paracetamol was predominantly metabolised by the liver while ibuprofen was predominantly cleared by the kidney, which could be of significance, particularly to those with a degree of either renal or hepatic impairment.

Transitional Considerations

XXXXX requested that if Schedule 2 was not retained, the matter should be referred to the new scheduling process. XXXXX requested that, if a decision would result in a scheduling change that did not align with XXXXX position such a decision should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (b) the risks and benefits, (d) the extent and pattern of use, (e) dosage and formulation and (h) the purpose for which a substance is to be used.

XXXXX.

A Member felt some concern about this new combination given the lack of Australian experience and suggested that perhaps some initial access restrictions, such as through a Schedule 3 listing, might be appropriate. Several other Members responded, however, that the individual actives had a long history of use in Australia with well known risk profiles and that there was little, if any, evidence that the combination would behave any differently. A Member also noted that there was nothing currently to stop consumers from concurrent use of single active paracetamol and ibuprofen products.

Several Members asserted that this matter appeared to an issue best addressed by the regulator, particularly with regard to the disputed efficacy. There appeared to be little data on risks from use of ibuprofen+paracetamol over and above those expected for single active paracetamol and ibuprofen. The Committee generally agreed that no strong argument had been presented for changing the current scheduling.

XXXXX.

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The Committee agreed that the current scheduling of ibuprofen and paracetamol remained appropriate i.e. 200 mg or less of ibuprofen in combination with 500 mg or less of paracetamol, in packs of not more than 100 dosage units, remained Schedule 2.

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 NEW MEDICINES FOR HARMONISATION

16.1.1 BETA-CAROTENE

PURPOSE

The Committee considered the scheduling of beta-carotene.

BACKGROUND

Carotene exists in 3 isomeric forms, all of which are converted to some extent into vitamin A in the livers of man and animals. Of the 3 isomers of carotene, the beta form is more active than the alpha- or gamma-isomers.

At the November 1986 meeting, the Committee determined that the Schedule 4 vitamin A entry did not capture beta-carotene. Members considered that as beta-carotene is present in much of the food one eats and that the body only converts it to vitamin A if required, its inclusion in the vitamin A entry would be unnecessary.

At the November 1993 meeting, the Committee again considered a query as to whether vitamin A precursors, such as beta-carotene, were scheduled the same as vitamin A. The Committee confirmed that such precursors were not covered by the vitamin A entry.

At the February 2000 meeting, the vitamin A entry was harmonised with New Zealand (NZ). Neither beta-carotene, nor any other pre-cursors were mentioned in the record. Subsequently, the Committee further amended the vitamin A entry.

At the October 2005 meeting, the Committee considered recommendations from the Trans-Tasman Harmonisation Working Party. The meeting record noted that the NZ position on the scheduling of vitamin A and beta-carotene remained unchanged and that NZ would not support harmonisation with the Australian scheduling for these substances due to differences in the dietary intakes between two countries. It was further noted that this issue should be reviewed again at a future meeting.

At the February 2007 meeting, harmonisation of the vitamin A entry was again considered. The Committee decided that the scheduling of vitamin A for internal use would be harmonised and recommended that NZ harmonise with Australia on topical preparations. At the meeting there was discussion on whether beta-carotene supplements were to be included or excluded from the Schedule 4 entry for vitamin A, given that beta-carotene supplements are readily available in pharmacy outlets. Members noted a submission asserting that beta-carotene had no upper level of intake as excess intake had not been associated with vitamin A toxicity. The Committee did not comment further on the status of the scheduling of beta-carotene.

DISCUSSION - SUBMISSIONS

XXXXXX queried whether the Committee had ever considered the scheduling of beta-carotene, noting that NZ currently classifies the substance as a prescription medicine, except in preparations containing 18 mg or less of beta-carotene.

The query noted that the difference in scheduling between Australia and NZ may have been inadvertently overlooked. It was also noted that beta-carotene is included in the list of substances that may be used in Australian Listed Medicines (with no restrictions).

The query further noted that there was no record of the NZ classification of beta-carotene being discussed in any Medicines Classification Committee minutes over the past 10 years (extent of online records).

Pre-meeting Submissions

XXXXXX did not support the scheduling of beta-carotene, stating that it would not result in a benefit to public safety. Members noted the following from this submission:

(a) Toxicity and safety

- According to the Nutrient Reference Values for Australia and New Zealand, an Upper Level for beta-carotene could not be established for supplemental use and does not need to be established for food use. Excess intake had not been associated with vitamin A toxicity in humans, and beta-carotene is of low toxicity in animals and humans. Human studies indicated that an intake of 20 mg / day and above by smokers and subjects exposed to asbestos was associated with an increased risk of lung cancer. However, there was insufficient scientific basis to set an Upper Level as no dose-response relationship was available.
- According to the Physicians' Desk Reference for Nutritional Supplements (PDR), beta-carotene is used in the treatment of erythropoietic protoporphyria at doses of up to 180 mg per day. No toxic effects were seen in these subjects at this dose, though carotenodermia may occur. This condition is considered harmless and reversible.

(b) Risks and benefits

- Although excessive intake of vitamin A is associated with liver abnormalities and teratogenicity, the metabolic conversion of beta-carotene to vitamin A is regulated by the body's vitamin A status, so that excess intake of carotene does not lead to vitamin A toxicity.
- According to the PDR, beta-carotene has a number of positive effects on immune function.

(d) Extent and patterns of use

- Beta-carotene has been included in the Australian Register of Therapeutic Goods as an ingredient suitable for use in listed and registered medicines. It has been approved for use as both an active ingredient and as an excipient.
- Oral medicines containing beta-carotene as an active ingredient are available with maximum recommended daily dosage levels ranging from 0.6 to 2.4 mg per day. As an excipient in oral medicines, beta-carotene is also available in dosages well below 18 mg per day (highest noted was 7 mg).
- As beta-carotene is used as an ingredient in cosmetics, it may be reasonable to assume that it is used as an excipient in some medicines for topical use.

(h) Purposes for use

- Beta-carotene demonstrates antioxidant activity *in vitro* and many manufacturers prefer to add beta-carotene to vitamin supplements rather than preformed vitamin A, due to its greater safety.
- Beta-carotene is frequently used as a colouring agent in therapeutic goods, in preference to synthetic additives.
- The submission further noted that the Food Standards Code permits beta-carotene in foods without restriction or maximum level set. It was asserted that scheduling a substance as a prescription medicine when it is also permitted as a food ingredient without any restrictions would be inconsistent. [Members noted that Schedule 4 lists several substances which also occur naturally in food – i.e. red yeast rice.]

XXXXXX noted that the purpose of the proposed Schedule 4 entry was to harmonise with NZ with respect to medicines. The submission asserted that beta-carotene is widely and safely used in cosmetic products and potentially topical therapeutic products and recommended that the NDPSC consider limiting the scheduling of beta-carotene to non-topical therapeutic use only.

XXXXXX noted that a number of listed complementary medicine products in Australia contain 25 mg of beta-carotene and that the proposed scheduling amendment would capture these products, consequently impacting the industry.

Other considerations

According to the Martindale monograph for beta-carotene:

- Adverse effects included effects on the skin, loose stools with rare reports of bruising, dizziness and arthralgia. It was noted that excessive intake of beta-carotene would not result in hypervitaminosis A.
- Yellow pigmentation of the skin may result from an unusually high consumption of carrots or other source of carotene, or from a defect in the enzyme that normally metabolises beta-carotene to vitamin A. Although it has been stated that the

condition is harmless, as the body converts carotene to retinol only as required, others consider that long-standing hypercarotenaemia can have clinical sequelae: neutropenia and amenorrhoea have been reported to be associated with the condition.

- A systematic review of the effect of antioxidant supplements on mortality found that beta-carotene, used either singly or with other antioxidants, significantly increased all-cause mortality. In other studies, beta-carotene supplementation showed a trend towards increased cancer mortality.
- There was no UK dietary reference value for beta-carotene, and in the USA recommended dietary allowances or dietary reference intakes have not been set. However, the UK-based Expert Group on Vitamins and Minerals established a safe upper level for beta-carotene of 7 mg daily, or about 0.11 mg / kg daily for a 60 kg adult.

Transitional considerations

XXXXXX requested that if the decision made at the June 2010 meeting did not align with their preferred position, it should not be considered final.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits, (d) extent and patterns of use and (h) purpose for use.

Members noted the NZ scheduling of beta-carotene. A Member asserted that there was no evidence at this time that Australia should also include beta-carotene in Schedule 4.

Members considered listing beta-carotene in Appendix B, noting its low toxicity. Members noted that an Appendix B entry would ensure greater clarity of the scheduling status of beta-carotene, specifically with regard to its relationship as a precursor to vitamin A. However, it was asserted that an Appendix B entry would infer that the Committee had considered evidence confirming that beta-carotene was a safe substance. It was asserted that there was insufficient data at this time to make this claim.

Members generally agreed that beta-carotene would remain unscheduled, as there was no information to suggest that scheduling was required at this time. Members noted that Australia was not harmonised with New Zealand with respect to beta-carotene.

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The Committee agreed that beta-carotene would remain unscheduled.

16.2 MEDICINES HARMONISED – FOR INFORMATION

No items.

16.3 MEDICINES NOT HARMONISED – FOR INFORMATION

No items.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC)

No items.

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

No items.

19. INFORMATION ITEMS (PHARMACEUTICALS)

19.1 XXXXX

20. GAZETTAL NOTICES

20.1 PRE-MEETING GAZETTE NOTICE

The Committee noted the pre-June 2010 meeting Gazette Notice dated 28 April 2010.

20.2 POST-MEETING GAZETTE NOTICE

The Committee noted the post-February 2010 meeting Gazette Notice dated 7 April 2010.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

PURPOSE

The Committee considered editorially amending the Schedule 4 sulfonamides entry.

BACKGROUND

Oryzalin is a selective pre-emergent dinitroaniline herbicide used on a wide variety of crops for the control of annual grasses and broadleaf weeds. Dinitroaniline herbicides are of very low order toxicity to mammals. PUBCRIS contains 16 registered herbicide products containing oryzalin, as well as five approvals for the active constituent.

Oryzalin is also a dinitroaniline sulfonamide of the ‘sulfanilamide’ family. Sulfonamides are currently listed in Schedule 4 as a class entry, except where specifically listed in Schedules 3, 4, 5 or 6.

At the August 1977 meeting, the Committee agreed to specifically exempt oryzalin from the Schedule 4 entry for “sulphanilamide”. At the May 1986 meeting, it was agreed to add oryzalin to Appendix B for substances specifically exempt from scheduling.

At the February 1989 meeting, the Committee agreed to amend the entry for sulphanilamide and its derivatives to read “sulfonamides”.

In 1990, oryzalin was removed from Appendix B and a specific exemption for oryzalin was added to the Schedule 4 entry for sulfonamides. At the December 1993 meeting, the Committee agreed to broaden this specific exemption for oryzalin to exempt all sulfonamides ‘(d) when packed and labelled solely for use as a herbicide’.

At the June 2004 meeting, the Committee noted advice from the Expert Advisory Group on Antimicrobial Resistance (EAGAR) which recommended that, as the potential for and realisation of resistance to agents in the same class as sulfonamides and the development of cross resistance to other antibiotics, all sulfonamides currently registered for use in humans and food animals should be included in Schedule 4 for all uses. The Committee were also provided with documentation to suggest that no sulfonamides, packed and labelled solely for use as a herbicide, were registered with the APVMA. There was no mention of oryzalin in the documents. The Committee agreed to remove the use in herbicides exemption (d).

Due to the removal of exemption (d), oryzalin is currently captured by the Schedule 4 class entry for sulfonamides. Oryzalin does not appear to be used for therapeutic use (human or veterinary) in Australia.

DISCUSSION - SUBMISSIONS

Applicant’s Submission

XXXXXX has requested that the Committee consider whether the June 2004 decision to remove exemption ‘(d) when packed and labelled solely for use as a herbicide’ from the sulfonamides class entry was an erratum that should be amended for the following reasons:

- The papers provided to the Committee at the June 2004 meeting stated that no sulfonamides, packed and labelled for use as a herbicide, were registered with the AVPMA (i.e. that the exemption was redundant). The document made no specific mention of oryzalin. No concerns in regard to the use of sulfonamides in agricultural (herbicidal) applications were mentioned in the considerations of the Committee’s decision.
- Although information was found on the use of oryzalin as an antibiotic, antifungal and anti-malarial in animal studies, oryzalin does not appear to be used for therapeutic use (human or veterinary) in Australia.

- Currently, oryzalin is captured by the Schedule 4 sulfonamides class entry. The existing requirements for prescription medicines are considered inappropriate for herbicides.
- The decision to remove exemption (d) appears to have been based on advice provided to the Committee which did not accurately reflect the registration status of sulfonamides for herbicidal use. Therefore, the removal of the herbicide use exemption appears to be an erratum.

Members also noted that another reason for the June 2004 decision to remove exemption (d) was to limit the use of sulfonamides outside Schedule 4 due to the potential risk of promoting resistance to sulfonamide antibiotics. The Committee specifically agreed to include sulfonamides (except sulfacetamide pending advice) when used in humans and food animals in Schedule 4 of the SUSDP.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the relevant matters under section 52E(1) included (c) potential hazards, (f) the need for access to a substance, and (h) the purposes for which a substance is to be used.

Members generally agreed that the June 2004 decision to remove exemption (d) was informed by incorrect advice and not based on any perception of risk.

A Member suggested that an Appendix B entry for oryzalin could be appropriate. However, another Member asserted that there was insufficient toxicological data to support an Appendix B entry. Additionally, Appendix B entries are universal, and it would not be appropriate to suggest that other uses besides herbicidal use were considered safe e.g. therapeutic use or use in food animals.

Members generally agreed that the June 2004 decision to remove the exemption for sulfonamides ‘when packed and labelled solely for use as a herbicide’ was an erratum and to editorially correct the erratum by again including this exemption in the Schedule 4 class entry for sulfonamides.

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The Committee agreed that the June 2004 decision included an erratum which removed exemption ‘(d) when packed and labelled solely for use as a herbicide’ from the Schedule 4 sulfonamides class entry, inadvertently capturing oryzalin as Schedule 4 under the class entry. The Committee decided to editorially correct the erratum by amending the Schedule 4 entry for sulfonamides to again exclude sulfonamides ‘when packed or labelled solely for use as a herbicide’.

The Committee further agreed that this decision be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

Schedule 4 – Amend entry to read:

SULFONAMIDES **except:**

- (a) when separately specified in this Schedule;
- (b) when included in Schedule 3, 5 or 6; or
- (c) when packed and labelled solely for use as a herbicide.

21.2 AMENDMENTS TO POISON STANDARD FROM FEBRUARY 2010 MEETING – NOT YET IMPLEMENTED

PURPOSE

The Committee considered the implementation of the amendments to the Poisons Standard resulting from decisions of the February 2010 meeting.

BACKGROUND

Under current arrangements (i.e. prior to 1 July 2010), the decisions of the February 2010 meeting would be included in an amendment to the current Poisons Standard with an implementation date of 1 September 2010.

However, as discussed in detail under item 1.6.2, new scheduling arrangements to be implemented from 1 July 2010, will prevent this from occurring. Transition arrangements will instead apply in relation to the decisions of the February and June 2010 meetings.

Decisions made at the February 2010 meeting, which would normally have resulted in an amendment to the current Poisons Standard (including any changes from reconsideration of some of these decisions at the June 2010 NDPSC meeting), would be referred to the Secretary or her delegate for inclusion in the first Poisons Standard legislative instrument under the new arrangements (the ‘first instrument’).

The first instrument is expected to be registered in the Federal Register of Legislative Instruments (FRLI) prior to September 2010 so as to allow the decisions of the February 2010 meeting to be implemented on 1 September 2010.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that the amendments to the Poisons Standard resulting from February 2010 decisions should be referred to the delegate for inclusion in the first instrument without any additional changes, noting the consideration of post-meeting submissions under items 10.1 and 10.2.

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The Committee noted the amendments to the Poisons Standard which resulted from the decisions of the February 2010 meeting. The Committee agreed to refer these amendments to the delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument with an implementation date of 1 September 2010.

22. CLOSURE AND NEXT MEETING

The Chair closed the Meeting at 4.00 pm, 23 June 2010 and advised that this was the last Meeting of the NDPSC.