Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

55th Meeting
17-18 February 2009

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACCC	Australian Competition and Consumer Commission
ADEC	Australian Drug Evaluation Committee
ADI	Acceptable Daily Intake
ADR	Adverse Drug Reactions
ADRAC	Adverse Drug Reactions Advisory Committee
AGRD	Australian Guidelines for the Registration of Drugs
AHMAC	Australian Health Ministers' Advisory Council
APMF	Australian Paint Manufacturers Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods
BAN	British Approved Name
CACC	Combination analgesic containing codeine
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia

CMEC	Complementary Medicine Evaluation Committee
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-Resistant Closure
CRIH	Chemical Review and International Harmonisation
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party (NDPSC)
DAP	Drafting Advisory Panel (NDPSC)
DPSC	Drugs and Poisons Schedule Committee (now NDPSC)
DPSSC	Drugs and Poisons Schedule Standing Committee (now NDPSC)
DSEB	Drug Safety and Evaluation Branch (now OPM)
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program
EPA	Environment Protection Authority
ERMA	Environmental Risk Management Authority
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
FWP	Fluorides Working Party
GHS	Globally Harmonised System for Classification and Labelling of Chemicals.
GIT	Gastro-intestinal tract

GP	General Practitioner
HCN	Health Communication Network
INCB	International Narcotics Control Board
INN	International Non-proprietary Name
ISO	International Standards Organization
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
LC_{50}	The concentration of a substance that produces death in 50 per cent 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 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
MCC	Medicines Classification Committee
MEC	Medicines Evaluation Committee
MOH	Ministry of Health (NZ)
NCCTG	National Coordinating Committee of Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOEL	No Observable Effect Level
NOHSC	National Occupational Health & Safety Commission
NPMB	Non-Prescription Medicines Branch
NZ	New Zealand
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety

OTC	Over the Counter (medicines)
ODBT	Office of Devices, Blood and Tissues
OLSS	Office of Laboratories and Scientific Services
OPM	Office of Prescription Medicines
OOS	Out of Session
OTC	Over the Counter
PACIA	Plastics And Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
PSC	Poisons Schedule (Standing) Committee (now NDPSC)
PSSC	Poisons Schedule Sub-Committee (now NDPSC)
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

SSRI	Selective serotonin reuptake inhibitor
STANZHA	NDPSC Members representing Australian 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
UK	United Kingdom
USFDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1. PRELIMINARY MATTERS

1.5 ADMINISTRATION

1.5.1 ELIMINATION OF THE 16 WEEK SUBMISSION CUT-OFF

PURPOSE

The Committee considered the current scheduling/rescheduling submission cut-off including a proposal to remove the 16 week cut-off in favour of the 20 week cut-off which allows the applicant the opportunity to provide a pre-meeting response on evaluations.

BACKGROUND

The February 2004 NDPSC Meeting considered a proposal seeking the release of medicine evaluation reports to the applicant so that comment could be submitted prior to Committee consideration. Members requested that the Secretariat review the proposal and identify implications for consideration by the Committee.

The February 2005 NDPSC Meeting noted that the cut-off for scheduling applications was 16 weeks prior to a meeting to allow time for the submission to be despatched and assessed, and for the evaluation report to be forwarded to Members. The Secretariat advised that additional pre-meeting applicant comment on an evaluation report would require medicine submissions to be made at least 20 weeks prior to a meeting. This extra time would be required to obtain reports from the evaluators, distribute these to the applicant and allow them reasonable time to comment. The Committee was of the view that the provision of medicine evaluation reports to applicants would be beneficial to the scheduling process and prepared the following model:

- Medicine rescheduling submissions must be made 20 weeks before an NDPSC meeting to allow for applicant comment.
- Medicine evaluation reports (prepared following assessment of an application) would be sent to the applicant with personal information, e.g. the evaluator's name, deleted.
- The applicant would have a maximum of 10 working days to comment. Responses would be limited to six single sided A4 pages and in a font no smaller than 12 point. The response must only address those issues raised in the evaluation report and not contain any new or additional data.

The June 2005 NDPSC Meeting agreed to proceed with the proposed model for applicant access to medicine evaluation reports to allow implementation for the February 2006 NDPSC Meeting. The October 2005 NDPSC Meeting confirmed the decision of the June 2005 NDPSC Meeting and also considered broadening the process to apply to scheduling and rescheduling applications for domestic or other chemicals where an evaluation report was produced (excepting agvet chemicals where there was an existing

APVMA process). The Committee agreed to defer consideration of this proposal to allow time for consultation with peak industry groups. The February 2006 NDPSC Meeting subsequently agreed:

- to broaden the process for applicant access to evaluation reports to also apply to the scheduling and rescheduling of domestic chemicals where an evaluation report had been produced following assessment of a scheduling application (excepting agvet chemicals where there is an existing APVMA process); and
- that the proposed amendment to the *Interim Guidelines for the National Drugs and Poisons Schedule Committee* (the NDPSC Guidelines) for the provision of medicine and domestic chemical evaluation reports to applicants be referred to NCCTG for support and approval.

The June 2006 NDPSC Meeting noted that NCCTG supported the amendment of the NDPSC Guidelines to allow the release of evaluation reports to applicants. The Committee therefore agreed to implement the changes to the NDPSC Guidelines.

The October 2008 NDPSC Meeting noted a proposal to eliminate the 16 week cut-off submission process to give a mandate only for the 20 week cut-off process to ensure procedural fairness. The Committee agreed to consider this proposal at the February 2009 NDPSC Meeting.

DISCUSSION - SUBMISSIONS

Members noted that the pre-meeting gazette notice on this issue included a reference to "see item 1.5.1 of the October 2008 Record of Reasons". However, item 1.5.1 was not included in the October 2008 Record of Reasons.

Members noted the following from pre-meeting comments:

XXXXX

- Has consulted its members and there was general support for the proposal.
- Some members, particularly multi-nationals, requested that the proposed change be implemented in 2010 as they were working to agreed timeframes which had been put in place around NDPSC dates previously published.
- There was also a query as to whether (strictly on a case by case basis) submissions would be allowed after 20 weeks but before 16 weeks if the applicant was willing to forego the opportunity to comment on the evaluator's report.

XXXXX

- As a XXXXX, had no particular problem with only having the 20 week cut-off.
- However, was able to see some merit in also retaining the 16 week cut-off (without access to any evaluation report) as currently occurs. The 16 week cut-off can be of benefit when either data is delayed to complete an application or a sponsor requests

assistance with their submission too close to the 20 week cut-off to adequately prepare the application. Without the 16 week cut-off option a sponsor missing the 20 week cut-off will have a delay of approximately four months.

- Additionally, if the Committee considers an application and the outcome is not favourable, an applicant may wish to resubmit information as soon as possible addressing the Committee's concerns. The 20 week cut-off only allows a little over one month to prepare a new submission or wait for 20 weeks until the next cut-off by which time nearly a year will have passed before the Committee would reconsider the matter.
- An alternative option might be to remove the 16 week cut-off and instead allow a sponsor to provide a written justification to the NDPSC Secretariat to accept an application within the 16-20 week timeline.

XXXXX

- Was not aware of the background to this consideration.
- Has not received any objections from members on the proposal to date.

Members noted that the NDPSC Guidelines did not stipulate cut-offs for submissions (apart from a passing reference to 20 weeks under the section dealing with applicants commenting on evaluation reports). Instead, this detail is provided in the Committee workplan on the NDPSC webpage (which currently sets both a 20 and 16 week cut-off).

Other issues with the current process for applicant's commenting on evaluations

XXXXX advised the Committee of two common situations which have arisen following the introduction of the right of an applicant to comment on an evaluation report prior to NDPSC Meeting consideration. These were:

- Applicants withdrawing submissions after being provided the evaluation report. This almost always occurred where the recommendation from the evaluation did not support the rescheduling proposal.
- Applicants introducing new data with their evaluation report comment. It was suggested that the introduction of new data should trigger automatic roll over of the item to the following meeting, so that the new data could be evaluated. Members recalled that the current Guidelines for commenting on evaluations stipulated that 'Inclusion of new or additional data is likely to be grounds for consideration of the rescheduling application by the NDPSC to be deferred to a later meeting to allow assessment of this information'.

XXXXX were simply seeking a discussion of these issues.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Several Members noted that while this proposal was in part to reduce administrative complexity, it was mainly being driven by fairness considerations. In particular, all evaluation reports should be open to applicant comment prior to the NDPSC Meeting and a 20 week cut-off was required to accommodate this.

A Member, however, contended that there was no fairness issue as the consequences of missing the 20 week submission cut-off were clearly spelt out in the current NDPSC Guidelines, template and workplan.

A Member advised that, from industry's perspective, there needed to be consistency and certainty regarding deadlines for submissions. If the Committee was minded to remove the 16 week deadline then the Member requested a deferred implementation until the February 2010 NDPSC Meeting as industry already had near term timelines. Another Member asserted that implementation for the October 2009 NDPSC Meeting would be reasonable.

A Member also advocated retaining the 16 week cut-off on a case-by-case basis, asserting that circumstances may arise where applicants just miss the 20 week cut-off. Other Members noted, however, that a proper consideration of an issue required that applicants have the opportunity to comment on any evaluation. Additionally, it would be very difficult to develop criteria for allowing case-by-case access to the 16 week cut-off that would be consistent and fair to all parties.

The Committee generally agreed to move to a single submission cut-off of 20 weeks before a Meeting with an applicant having the opportunity to comment on an evaluation prior to the Meeting. Members agreed that this change should be in effect for submissions going to the February 2010 NDPSC Meeting, noting that the 20 week cut-off for this Meeting is 25 September 2009. Members noted, however, that this decision was pending approval by the NCCTG, including endorsement of proposed amendments to the NDPSC Guidelines.

Withdrawal of items due to a negative evaluation report

Members noted that a number of items had been withdrawn at recent Meetings, including twice for this Meeting, due to a negative recommendation in the evaluation report. Members were advised that:

- A not insignificant allocation of resources was required in performing these evaluations.
- There were already difficulties in retaining sufficient evaluators for those applications (mostly medicines rescheduling) deemed to require an external evaluation.
- Evaluators may be reluctant to undertake such work in future if they considered their efforts wasted.

A Member suggested that any such item could still be considered by the Committee as it will have been mentioned in the pre-meeting Gazette Notice. The Committee was advised, however, that companies have in the past argued that any information in a submission withdrawn by the applicant was confidential and owned by the company.

Several Members noted that the issue would likely be resolved with the introduction of a cost-recovery process, as flagged in the AHMC agreed scheduling reforms which are currently in train.

RESOLUTION 2009/55 - 1

The Committee decided to eliminate the 16 week submission cut-off for the February 2010 NDPSC Meeting, pending NCCTG approval, by amending the Committee workplan on the NDPSC website and amending the NDPSC Guidelines as follows:

Chapter 2 – Application and information requirements – Amendments

Commenting on Evaluation Reports for Rescheduling of Medicines – Amend entry to read:

The NDPSC can, where warranted, have an application for rescheduling evaluated. The evaluation report can be distributed to the sponsor/applicant for comment prior to consideration by the NDPSC. Personal information, such as the evaluator's name, and confidential information not belonging to the applicant, will be deleted. Distribution will, where possible, be either by fax or email. The applicant will have a maximum of 10 working days to comment, with comments to be sent by email to the NDPSC mailbox NDPSC@health.gov.au. Comments are to be limited to six single sided A4 pages and in a font no smaller than 12 point. The response may only address issues raised in the evaluation report and must not contain any new or additional data. Inclusion of new or additional data is likely to be grounds for consideration of the rescheduling application by the NDPSC to be deferred to a later meeting to allow assessment of this information. Evaluation reports are confidential and are released to the sponsor/applicant on the understanding that they are not to be released to third parties without permission.

Commenting on Evaluation Reports for Rescheduling of Domestic or Other Chemicals – Amend entry to read:

The NDPSC can, where warranted, have an application for the scheduling or rescheduling of domestic or other chemicals, evaluated. The evaluation report can be distributed to the sponsor/applicant for comment prior to consideration by the NDPSC. Personal information, such as the evaluator's name, and confidential information not belonging to the applicant, will be deleted. Distribution will, where possible, be either fax or email. The applicant will have a maximum of 10 working days to comment, with comments to be sent by email to the NDPSC mailbox NDPSC@health.gov.au. Comments are to be limited to six single sided A4 pages and in a font no smaller than 12 point. The response may only address issues raised in the evaluation report and must not

contain any new or additional data. Inclusion of new or additional data is likely to be grounds for consideration of the rescheduling application by the NDPSC to be deferred to a later meeting to allow assessment of this information. Evaluation reports are confidential and are released to the sponsor/applicant on the understanding that they are not to be released to third parties without permission.

1.5.2 ELECTRONIC SUSDP

BACKGROUND

The October 2008 NDPSC Meeting agreed to include a link on the NDPSC webpage to the Federal Register of Legislative Instruments (FRLI) on the ComLaw website which contains the current *Poisons Standard (*SUSDP No.23 and Amendments No.1 and 2). The Committee also agreed that a suitable explanation be included on the NDPSC webpage regarding the naming convention used for the SUSDP and its Amendments on FRLI.

DISCUSSION - SUBMISSIONS

The Committee noted that links to the SUSDP No.23 and each Amendment No.1, 2 and 3, as published on FRLI, were included on the NDPSC webpage in December 2008. The Committee noted the following explanation regarding the legislative naming convention was also included on the NDPSC webpage:

> **Electronic version**
>
> The SUSDP is now available in electronic form on the ComLaw website at the Federal Register of Legislative Instruments (FRLI). The FRLI is a repository and authoritative source of Commonwealth legislative instruments, explanatory statements and compilations of legislative instruments in electronic form.
>
> Please note that the naming conventions used on FRLI are slightly different to common usage naming for the SUSDP. Rather than referring to the edition number, the publications are named according to the year of publishing (the year the publication is published on FRLI). The naming convention used on FRLI and how it correlates to SUSDP publications is explained in the table below:

Title used/to be used on the Federal Register of Legislative Instruments (FRLI)	**SUSDP Title**
Poisons Standard 2008	SUSDP No.23
Poisons Standard Amendment No.2 of 2008	SUSDP No.23 Amendment No.1
Poisons Standard Amendment No.3 of 2008	SUSDP No.23 Amendment No.2
Poisons Standard Amendment No.1 of 2009	SUSDP No.23 Amendment No.3

The Committee noted that the November 2008 NCCTG Meeting had been informed of the NDPSC's intention to include this link on its webpage.

RESOLUTION 2009/55 - 2

The Committee noted that the NDPSC webpage includes links to the electronic versions of the SUSDP and its Amendments, being the *Poisons Standard* and *Poisons Standard Amendments*, as published on the FRLI (ComLaw website) and that a suitable explanation regarding the legislative naming convention of the publications on FRLI has also been included on the website.

1.5.3 SCHEDULING/RESCHEDULING TEMPLATE

PURPOSE

The Committee noted proposed changes to the *NDPSC Scheduling/Rescheduling Template* (the submission template).

BACKGROUND

The February 2006 NDPSC Meeting agreed to develop a submission template. The June 2006 NDPSC Meeting considered a draft and foreshadowed adoption, posting a draft on the web for comment. The October 2006 NDPSC Meeting considered feedback and agreed:

- That the template, as amended, provided suitable guidance to industry and would improve the efficiency with which the Committee could consider applications.
- To amend the NDPSC guidelines to allow electronic submission as an alternative to the mandatory submission of 25 hard copies of an application. These amendments were forwarded to the November 2006 NCCTG Meeting for consideration.

The February 2007 NDPSC Meeting noted NCCTG endorsement of the draft template and of amendments to the NDPSC guidelines to allow electronic submissions. The Committee agreed to consider finalising the template at the June 2007 NDPSC Meeting.

The June 2007 NDPSC Meeting adopted the template (as amended at the Meeting). Members noted that, while a final template was endorsed, it would still be open for comment/improvement, particularly given the wide range of applicants. The Secretariat was directed to maintain the template with only major template changes expected to come through to the Committee for consideration.

DISCUSSION - SUBMISSIONS

Members were advised that XXXXX had forwarded comment from XXXXX on the submission template.

- The comment suggested that it would be helpful if guidelines to the template were provided in a separate document and not in the template itself.

  - Members noted advice that including the Guidance Notes within the template was a deliberate move supported by the Committee at the time to allow the submission template to be a reasonably stand-alone aid to those wishing to make applications. There were multiple references back to the full NDPSC Guidelines (noting that this document had not been fully reviewed for some years). This suggestion was therefore not pursued.

- The comment suggested that the formatting was prescriptive and did not easily permit changes, particularly the table of contents. If there was a preference for certain font sizes, styles and formatting it should be covered in the guideline document, rather than embedded into the template as it is at present.

  - Members noted advice that the template does not mandate any particular formatting. It does recommend a certain format for narrative text and footnotes. A note to clarify that the applicant was not required to use a particular format had been added. The table of contents in the template was a standard format for a word document, but again was not mandated.

- Regarding confidentiality, the comment noted that most submissions contain sales data, in-house adverse reaction or PSUR reports and market research information. These were always commercial-in-confidence and there should be no need to always provide a written justification. It was also not clear what form the written justification should take or whether it is sufficient to mark it as 'market research data – commercial-in-confidence'.

  - Members noted advice that the template addresses this issue specifically in the Guidance Notes under the confidentiality heading. This advice was deliberately crafted by the Committee to address precisely the concern raised by XXXXX. This advice remains sufficient.

- The comment put forward that as Part A Overview required a critical evaluation of the schedule proposed, this was often the same information as contained in Part B when addressing the scheduling criteria. If it was intended that the Overview only contain a brief summary of the data it should be clearly stated. A critical evaluation could in effect contain the same information as provided in both Part A and Part B. This Overview should provide an overall summary of the entire application while the other parts should contain the more robust information.

  - The Committee noted advice that the current wording may imply an unnecessary duplication of arguments. The guidance for the Overview section has therefore been amended to more clearly reflect the intent of this section.

- The comment further suggested that Part B 'Background' was duplicative regarding critical evaluation of the scheduling criteria.

  - Members noted that the background section was not intended for presenting arguments regarding the application. It was where basic background could be presented e.g., previous scheduling status, historical context, and basic chemistry facts. A sentence was added to clarify this intent.

- The comment further suggested that Sections A, B and C in Part B were often already covered in addressing the 'Overview' in Part A and the 'Background' in Part B.
  - Members noted that new wording for 'Overview' and 'Background' have clarified that the "detailed claims against the scheduling criteria" was where the detailed arguments should be presented.
- The comment noted that the current Sections D and E work well. The comment put forward, however, that Section F was duplicative as this was often already covered by the other sections on toxicity. It was also suggested that Section G and H would already be covered by other Sections and should not necessarily be duplicated.
  - Members noted that the criteria under Section 52E of the Act can be duplicative, but the Committee was required to consider these criteria. Hence the Committee's clear direction that each criteria be responded to. A clarifying point has been added advising applicants that where an argument applies under more than one criteria it was acceptable to reference (e.g., see criteria X) rather that duplicate.
- The comment asserted that the Part C 'Supporting Data' section was convoluted and repetitious. Point 17 required bibliography details already included in point 16.
  - Clarifying text has been added to the submission template.
- The comment suggested that Point 18 should be headed 'Additional Data', although a clinical expert report would probably already be included in the bibliography and would not need to be separated out into 'Additional Supporting material'.
  - Members noted that 'Supporting Data' rather than 'Additional Data' was used to avoid confusion with the 'Additional Matters' criteria under Part B and to reinforce that only data relevant to supporting the consideration should be supplied, rather than any additional data. This suggestion was therefore not pursued.
- The comment, with regard to supplying copies of papers referenced (Part C), noted that often these were in PDF format and could comprise a very large section of the application. The guidelines could offer sponsors the option of providing any references via CD disc as sometimes these difficult to embed into the application and need to be attachments.
  - Text has been added to this effect.

Members also recalled the following from previous considerations:

- The template was intended for scheduling/rescheduling applications made directly to the Committee, not for those coming via a regulatory agency. It was not intended to be used for general communications from stakeholders such as pre- and post-meeting comments.
- A Member asserted that specific guidance would become possible following the proposed splitting of the NDPSC into medicines and chemicals committees as the

focus of these committees would be different. However, a template would currently need to remain generic because of the different types of submissions considered at this time.

- A Member noted that although industry should be strongly encouraged to use the template, it could not be mandated as this may not allow equitable access by a range of stakeholders. The Committee confirmed this position, but would be seeking an industry commitment to electronic submissions using the template.

DISCUSSION – RELEVANT MATTERS UNDER 52E

A Member queried whether there may be benefit in having the template guidance notes separate to the template itself. Other Members, however, endorsed the previous Committee intent that the template remain a reasonably stand-alone document, and that any need for a separate guidance document should be addressed through the current NDPSC guidelines document. It was noted that the NDPSC guidelines had not been reviewed for a number of years (although individual sections in the document had been) and was not as up to date as the template. Members noted that the guidelines will be reviewed as part of the implementation of the new scheduling framework. It was additionally noted that any such review would include public consultation.

The Committee confirmed that these changes come under the mandate provided by the June 2007 NDPSC Meeting for the Secretariat to maintain the template (with only major template changes expected to come through to the Committee for consideration). These changes therefore did not need to be referred to NCCTG for sign-off.

Members agreed that the template would also be dated so that industry could be confident that they were using the current version.

A Member also advised that XXXXX intended to provide some additional small editorial suggestions to the Secretariat following the Meeting. The Committee agreed that the Secretariat could use its judgment in whether these were suitable as part of the Secretariat's mandate to maintain the template.

The Committee additionally agreed to include this item in the Record of Reasons as it may prompt further feedback from industry regarding the template, and endorsed the Secretariat's efforts to date in seeking industry's views on the template.

The edited scheduling/rescheduling template will be available at http://www.tga.gov.au/ndpsc/schedule-template.htm (dated April 2009).

RESOLUTION 2009/55 - 3

The Committee noted the changes to the NDPSC template for scheduling/rescheduling submissions.

1.7 PROCEDURAL MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.1 ENDORSEMENT OF REFERENCES IN THE NEW POISONS STANDARD (SUSDP NO.24)

BACKGROUND

New editions of and amendments to the Poisons Standard (the SUSDP and its Amendments) are Legislative Instruments and as such are required to be registered on the Federal Register of Legislative Instruments (FRLI). Section 52EA of the *Therapeutic Goods Act 1989* sets out requirements for validation of the Poisons Standard, including disallowance under the *Legislative Instruments Act 2003*.

References in a Legislative Instrument must be up-to-date and, in regard to any tertiary, legislative or quasi-legal documents, must fully reference the title and year of publication of such documents before registering on the FRLI. Wording to the effect "as specified or amended from time to time" is not appropriate for references in a Legislative Instrument and are to be excluded.

The October 2008 NDPSC Meeting noted that a number of references would be updated to include the current version and/or correct nomenclature following a review of all the references contained in the SUSDP No.23. That Meeting also noted that a number of references would be deferred to the February 2009 NDPSC Meeting for consideration

DISCUSSION - SUBMISSIONS

The Committee noted that the following references would be separately considered under separate agenda items:

Item 2.1.1 Part 1, Interpretation - "approved name"
Item 21.1.3 Appendix E - Poisons Information Centre – consideration of post-meeting comment
Item 21.2.1 Appendix A - chemistry sets
Item 21.2.2 Part 1, Interpretation – "Australian Code for the Transport of Dangerous Goods by Road and Rail"

RESOLUTION 2009/55 - 4

The Committee endorsed the references in the SUSDP No.24, excluding those listed above which were considered separately.

1.7.1.2 ENDORSEMENT OF THE NEW POISONS STANDARD (SUSDP NO.24)

BACKGROUND

Pursuant to subsection 52D(2)(b) of the *Therapeutic Goods Act 1989*, the NDPSC is required to prepare a new Poisons Standard (being the SUSDP No.24) in substitution of the current Poisons Standard (being SUSDP No.23).

If the NDPSC agrees to endorse the new Poisons Standard described above:

- a notice will be published in the Commonwealth Gazette to the effect that a new Poisons Standard has been prepared by the Committee, in substitution for the current Poisons Standard; and

- the new Poisons Standard will also be published on the Federal Register of Legislative Instruments (FRLI).

The Committee previously endorsed a new Poisons Standard in December 2007 (SUSDP No.22) and in June 2008 (SUSDP No.23).

RESOLUTION 2009/55 - 5

The Committee endorsed the new Poisons Standard (SUSDP No.24).

1.8 NDPSC WORKING PARTIES

1.8.1 CODEINE WORKING PARTY

PURPOSE

The Committee considered the Codeine Working Party's (CWP) progress on the consideration of the scheduling of OTC codeine.

BACKGROUND

The June and October 2005 NDPSC Meetings noted concerns with a codeine+ibuprofen bi-layer tablet reportedly being cut in half to access the codeine. Given that the product was withdrawn by the sponsor and replaced with a single layer formulation the Committee agreed that concerns of abuse had been resolved.

The June 2007 NDPSC Meeting noted claims of apparent increasing incidence of codeine+ibuprofen abuse where the codeine was being easily separated by simple dissolution in water. The Committee asked the TGA to investigate dissolution rates of the products in question. The February 2008 NDPSC Meeting noted that the results of

the dissolution investigation were not yet available and agreed to foreshadow consideration at the June 2008 NDPSC Meeting.

The June 2008 NDPSC Meeting decided to form a working party (the CWP) to review the availability of all OTC combination analgesics containing codeine (CACC) and the definition of 'compounded' (as discussed in item 2.1.2). The Committee also agreed to foreshadow consideration for the October 2008 NDPSC Meeting of a reduction in the Schedule 2 codeine+ibuprofen pack size limit and to include a Schedule 3 pack size limit.

The October 2008 NDPSC Meeting:

- noted the CWP's progress on the definition of 'compounded', including the likelihood of recommendations being tabled at the February 2009 NDPSC Meeting on that issue;
- deferred consideration of codeine+ibuprofen pack sizes until the CWP had progressed further while noting the importance of resolving this issue without undue delay; and
- endorsed the CWP's recommendation to pursue the services of a consultant to assist its investigations. This last point was not released in the October 2008 Record of Reasons.

This item was related to 2 other considerations at the February 2009 NDPSC Meeting: 2.1.2 *Definition of compounded* and 11.3 *Codeine combined with menthol & ammonium citrate*.

DISCUSSION - SUBMISSIONS

Codeine Working Party

Members noted the following from the minutes of the 3rd CWP teleconference (held on 16 December 2008):

Efficacy

- TGA advised that efficacy data had not been evaluated by the regulator for any OTC product containing codeine. All such products had been approved on the basis of established use rather than demonstrated efficacy.
- It was noted that while efficacy data was critical to an assessment of overall risk-benefit balance, efficacy was not a primary issue for consideration under 52E. It was suggested that this might more appropriately be referred to the regulator and that the CWP could instead focus on the key issues of access and safety. A Member, however, disagreed that the issue of efficacy should be set aside, noting that without proof of efficacy (at doses < 30 mg) there was no basis for allowing OTC supply of codeine.

- There was general agreement that the efficacy questions should not be dismissed. However, it was noted that CWP had made a strenuous effort to obtain efficacy data without success.
- Several Members queried whether TGA was contemplating an investigation into the efficacy of OTC codeine. XXXXX was unaware of any such moves and advised that such a move was unlikely to be welcomed, as it was not in line with the usual TGA risk-based regulatory approach for monitoring of OTC products. XXXXX suggested that perhaps industry should be approached directly by NDPSC rather than through the regulator.
- Other Members felt that the regulator was in a much better position to pursue this issue, noting that the TGA made final decisions on product availability. The CWP generally agreed therefore, that a recommendation to the February 2009 NDPSC Meeting should be that NDPSC write to TGA strongly advocating the need for TGA to pursue the question of codeine efficacy in OTC products, including suitability of the combinations and amounts/strengths/daily doses, noting that there appeared to be reasonable evidence that at least some harm was already being caused by these products.

Literature Review

- A literature search failed to locate any scientifically rigorous data on efficacy beyond what had already been considered by the CWP and NDPSC. Reports on cases of misuse/abuse were found, but were largely similar to reports already considered. A copy of a Coroner's report was provided. This gave further insight into one case which had been tabled at June 2008 NDPSC Meeting. A Member also advised that XXXXX had located a number of papers on abuse and forwarded these to the CWP after the teleconference. These papers were provided to the external evaluator.

External Evaluation

- The possibility of employing the services of an external party to garner raw data on the various issues was investigated. However, this approach was not feasible given available resources of the CWP and NDPSC Secretariat.
- Members agreed that an evaluation would be valuable in advancing this issue. The evaluator could review data so far presented to NDPSC, together with additional papers identified by Members, a summary of New Zealand's position and XXXXX. The evaluator should comment on:
  - Whether the individual case reports and other evidence of abuse could be extrapolated to allow a discussion of the risk to the general population. What was the evaluator's opinion of such risk, and are the current access restrictions sufficient to address any such risk?
  - Where possible, focus on Australian data, particularly given the wide diversity of OTC codeine products available internationally which may not be meaningful in the Australian context. In order to do this the evaluator may engagement with Australian Addiction Treatment and Emergency Medicine clinicians.

- Whether it is possible to reasonably conclude that OTC CACCs were unsafe given the data available, or instead, given the evidence presented to date, that there was sufficient evidence that OTC CACCs are safe i.e. the current access arrangements remain appropriate.
- Noting that OTC analgesics are approved only for short-term treatment of acute pain, might the evaluator have a position on what duration of time might qualify as 'short-term'.

- There was discussion on whether work by the CWP should be put on hold until the evaluation had been finalised. However, this issue had been under consideration for some time, and it was reasonable for the CWP to develop a number of options for NDPSC, prior to the evaluation being received, as any such options could be refined/amended at that time. It was also noted that the evaluator was likely to produce high level broad recommendations only and that it would be appropriate for the CWP to draft some specific options in parallel to the evaluator's work. NDPSC public consultation to date on this issue had already established a degree of support for some scheduling changes.
- The CWP agreed that regardless of whether the evaluation report was available for the February 2009 NDPSC Meeting, there should be a CWP recommendation to NDPSC to foreshadow some options so that public consultation could be progressed for a June 2009 NDPSC consideration.

Comment on New Zealand's position

- The November 2008 MCC Meeting:
  - Confirmed that >15 mg codeine base per dose should be prescription only.
  - Decided to seek further advice from addiction specialists about the local experience with codeine abuse before making any recommendations.
  - Considered that pack size limitations may be the only way to minimise this risk.
- The New Zealand Representative supported limiting pack size stating XXXXX felt that this was sound risk management if it was concluded that there was sufficient evidence that prolonged exposure was associated with an increased risk of habituation leading to abuse. If risk is not influenced by the codeine dose, as long as the treatment period is short, then a possible option for Schedule 2 would be a recommended daily dose (RDD) of 90-120 mg, a pack size ≤ 20 tablets or 5 days total treatment, with a 10 day total pack size being available at up to this dose as Schedule 3. This would allow a consumer to obtain both products containing higher (and in the Member's opinion, more effective doses) of codeine OTC but for a minimum period before having to obtain further pharmacy advice. In effect, this approach would limit OTC availability to treatment of acute pain (which, in the Member's view, was appropriate) with larger pack sizes (possibly anything above 36 or 40 tablets) being prescription medicines.

- Restricting the time of exposure to codeine was the key and therefore the Member did not support limiting pack sizes by total codeine content. Total codeine content was only relevant if the codeine was being diverted for illicit use.
- The Member stated that his fall back position would be to allow total codeine per dose to be different for Schedule 2 (≤ 10 mg, ≤ 80 mg RDD for ≤ 5 days) and Schedule 3 (≤ 15 mg, ≤ 120 mg RDD for either ≤ 5 days or ≤ 10 days). This approach would allow some existing products to remain the same schedule, as long as they were in small pack sizes.
- The Member would favour taking a harm minimisation approach of limiting both dose and pack size, and would seek advice from addiction specialists on whether this is the correct approach.
- The CWP noted the above views. A Member noted that NZ's position seemed somewhat more generous than was likely to be supported by NDPSC.

XXXXX

Proposed Changes to Current Codeine Scheduling

- Several CWP Members agreed to a suggestion that, given the substantial number of case reports that have been drawn to the attention of the NDPSC (and further, put into the public domain through the Record of Reasons), there would appear to be a *prima facie* case of abuse/misuse of OTC CACCs. A number of CWP Members agreed that, for public health reasons, this issue should be addressed. Another CWP Member asserted that, while this consideration could be advanced, a final position should not be locked in until the evaluation had been received.
- The CWP noted the suggestion that while case reports of abuse or misuse related mainly to codeine+ibuprofen, the CWP may wish to consider whether it is reasonable to extrapolate that, should substantial restrictions be placed on access to OTC codeine+ibuprofen, this could give rise to codeine seeking behaviour becoming directed to codeine+paracetamol or codeine+aspirin.
- A number of CWP Members agreed that all codeine combinations should be scheduled the same (noting that currently there are non-opioid analgesic combinations and, separately, other therapeutically active combinations – mostly for cough suppressant activity). It was agreed that as the issue was codeine abuse, all codeine combinations should be similarly scheduled.
- Another CWP Member, while agreeing in general to the principle of consistency, was not keen to broaden the consideration beyond OTC analgesic use until CWP had received the evaluation report. The Member suggested that perhaps potentially broadening the consideration was a decision for the NDPSC to make, rather than the CWP.
- The CWP discussed and generally agreed that, as the codeine scheduling is not currently indication specific, it was appropriate for the consideration to continue to stay at the level of reviewing the current OTC codeine scheduling. Indication-

specific concerns could be pursued later, if this was deemed warranted by the NDPSC.

- It was suggested that, pragmatically, the CWP may wish to consider whether current access arrangements were consistent with the approved indications. OTC CACCs were only TGA-approved for short term treatment of acute pain. Thus it may be argued that the OTC availability of larger pack sizes was inconsistent with the approved indications for these products. It may be argued that a more reasonable quantity might be calculated based on the recommended (OTC) maximum daily doses for each particular substance, multiplied by an appropriate duration of therapy. Several draft options, on the premise of limiting supply of OTC CACC as per approved indications for short term use of acute pain, were considered:
  - One option suggested that instead of stipulating pack size, scheduling could instead stipulate period of supply. The quantity would then be determined by what the regulator determines as appropriate (i.e. maximum recommended daily doses). This reasoning was in line with recent decisions such as the Schedule 3 entry for pantoprazole and the recently amended Schedule 3 entry for levonorgestrel.
  - A second option proposed cut-offs by number of doses per pack.
- The CWP considered the proposals and generally agreed that there was merit in limiting supply of OTC codeine combinations to a duration, as the abuse risk appeared to be directly linked to longer term use. However, it was generally felt that the proposed amendments to the existing wording would perpetuate the current confusing nature of the codeine schedule entries. The CWP instead proposed starting from scratch.
- A CWP Member suggested that the NZ Member's proposals appeared to have merit, particularly that the need to restrict the time of exposure to codeine was key to addressing the habituation risk. The CWP generally agreed with the NZ Member's view that setting a total codeine content limit was not relevant to the habituation risk, only to diversion (which should be separately addressed by the 'compounded' requirement as such need not be part of the OTC codeine consideration). One Member did note, however, that those actively misusing/abusing OTC codeine products did seem to be attracted to high total codeine content products.
- The CWP considered what constituted an appropriate maximum duration limit. A Member noted that these products were often used on an 'as required' basis and that a duration limit was therefore not easily determined in contrast to a pack size limit. Other Members disagreed, noting that it was the ongoing use by some that put them at risk of becoming addicted to the codeine, and that the risk of addiction needed to be the driver of setting a duration limit.
- A CWP Member argued that a pack size limit would provide for more consistency across the various combinations/products available e.g. a limit of 24 tablets, regardless of strength per unit dosage. The CWP in general, however, felt that consistency by number of tablets was not necessarily a useful outcome.

- The CWP did agree that while number of tablets a day need not be stipulated, it would be important to have a maximum Recommended Daily Dose (RDD) limit for OTC supply, as this was also a habituation risk, in addition to duration of use.
- A CWP Member noted, but did not necessarily support, XXXXX view that there was no justification for including codeine in OTC preparations. Several Members did, however, strongly support removing codeine from Schedule 2 entirely (Option 1 below). Others supported maintaining both Schedule 2 and Schedule 3 availability (Option 2 below). The CWP therefore generally supported considering both these as options.

Option 1

- A CWP Member proposed that all OTC codeine be Schedule 3, with a 5 day duration limit, but allowing the RDD to be increased to 100 mg to allow more efficacious use of codeine (i.e. 2x 12 mg tablets, 4x day = 96 mg). This would be appropriate for most patients, particularly those using products intermittently, while the requirement of pharmacist involvement would assist in limiting multiple purchases and identifying those misusing and at risk of habituation. A maximum pack size limit was not necessary (noting that RDD and duration limit in effect set such a limit). There was to be no differentiation regarding the various combinations (except that CACCs would continue to be restricted to 'single non-opiate').
- Another CWP Member asserted that a 6 day duration limit might be more appropriate but agreed that this detail (5 or 6 days) could be debated once presented at NDPSC. The Member queried where the 5 day limit in relation to the subjective term 'short term use' came from. Another Member indicated that this would be in line with some international guidelines such as the American Hospital Formulary System (AHFS). The CWP generally agreed to use 5 days at this time, but also agreed that the question of an appropriate duration limit, in line with 'short term use', was an additional point that the evaluator was asked to comment on.
- The CWP also looked at replicating the current Schedule 2 limit for undivided preparations (≤ 0.25 per cent) into the proposed new Schedule 3 entry. It was agreed that this was appropriate and would prevent the current Schedule 2 undivided preparations becoming Schedule 4 when the Schedule 2 entry was deleted. It was noted that while this was an upscheduling there was also a loosening of the RDD limit (in Schedule 3 this would be ≤ 100 mg while currently undivided preparations with RDD > 60 mg jump from Schedule 2 to Schedule 4).
- A CWP Member mentioned that packaging requirements such as CRC/blister/strip was best left to the regulator.

Option 2

- A CWP Member supported retaining both Schedule 2 and Schedule 3 for OTC combination codeine products. The Member suggested that a duration limit be incorporated as for the previous option. Again, the CWP debated the question of most appropriate quantity for this limit, and whether the Schedule 3 entry should have

a longer limit than the Schedule 2 entry. The CWP generally agreed, however, that both Schedule 2 and Schedule 3 products were indicated for short term use, and both had risks of habituation from longer use. The CWP therefore agreed that the differentiation between these Schedules should only be by RDD and amount per dose.

- The CWP agreed that the limits suggested for Option 1 remained appropriate for the Schedule 3 entry under Option 2. Additionally, the current Schedule 2 limit of 10 mg per dosage unit was supported. There was debate, however, whether the RDD should be increased to 80 mg as suggested by NZ, or maintained at 60 mg. The CWP generally supported maintaining the current 60 mg RDD in Schedule 2. There was to be no differentiation regarding the various combinations (except that CACCs would continue to be restricted to 'single non-opiate').
- The CWP also agreed to maintain the current Schedule 2 ≤ 0.25 per cent limit for undivided preparations with RDD ≤ 60 mg in Schedule 2, and allowing ≤ 0.25 per cent with 60 < RDD ≤ 100 mg in Schedule 3.
- The proposals are summarised in the following table:

	Schedule 2 (compounded)	**Schedule 3 (compounded)**	**Schedule 4 (compounded)**
Current	Tablets/individual powders, single non-opiate analgesic: • ≤ 10 mg/dose, ≤ 25/pk, CRC etc Other therapeutic active: • Divided ≤ 10mg/dose, ≤ 25/pk • Undivided ≤ 0.25 per cent (CRC packaging etc left to TGA) RDD ≤ 60 mg	Single non-opiate analgesic • Divided, ≤ 10 mg/dose, RDD ≤ 60 mg, no pack limit (packaging etc left to TGA) With paracetamol • Divided ≤ 12 mg/dose, ≤ 12/pk, 60 < RDD ≤ 100 mg CRC No Schedule 3 undivided	With therapeutically active substance • Divided ≤ 30 mg/dose, ≤ 25/pk • Undivided ≤ 1 per cent
Option 1 (S3 only)	DELETED	≥1 therapeutic actives (or single non-opiate analgesic) RDD ≤ 100 mg, ≤ 5 days • Divided ≤ 12 mg/dose, • Undivided ≤ 0.25 per cent (CRC packaging etc left to TGA)	NO CHANGE
Option 2	≥1 therapeutic actives (or single non-opiate analgesic) RDD ≤ 60 mg, ≤ 5 days • Divided ≤ 10 mg/dose, • Undivided ≤ 0.25 per cent (CRC packaging etc left to TGA)	≥1 therapeutic actives (or single non-opiate analgesic) RDD ≤ 100 mg, ≤ 5 days • Divided ≤ 12 mg/dose, • Undivided ≤ 0.25 per cent 60 < RDD ≤ 100 mg (CRC packaging etc left to TGA)	NO CHANGE

- A CWP Member suggested adding a 3rd option – amending Option 2 so that the duration limit was 10 days rather than 5. The CWP generally agreed, however, that

only the 2 basic options above should go to NDPSC at this time, noting that this did not limit the NDPSC raising any case for variations, such as to the duration limit, at its February 2009 NDPSC Meeting.

The two options from the 3rd CWP teleconference were subsequently discussed at a follow-up CWP teleconference held on 3 February 2009. Members noted the following from these discussions:

Recommendations

- The CWP confirmed the two options from the 3rd CWP teleconference for tabling at the February 2009 NDPSC Meeting.
- The CWP also agreed that it was putting forward the two options without a preference for one or the other, as it had been unable to reach agreement on which of these proposed changes was more appropriate.

Discussion

- A CWP Member was concerned that the removal of the pack size restriction from the Schedule 2 entry proposed under Option 2 could actually result in increased pack sizes – suggesting that up to 40 tablets of a current paracetamol product could be allowed. Manufactures may deliberately reduce the codeine content in a tablet so that more tablets could be allowed per day while remaining compliant with the RDD ≤ 60 mg of codeine condition. The Member suggested that perhaps the Schedule 2 entry in Option 2 should have a shorter duration limit.
- Another CWP Member asserted, however, that the possibility of any significantly increased pack size achieved through reduced codeine content would also lead to efficacy questions, and that the appropriateness of such product presentations was best left to the regulator. A Member noted that the number of tablets for a 5 day duration would also by limited by the required dosing interval, not just the RDD.
- A CWP Member additionally noted that while slight increases for some current products may be possible, this proposal would allow a consistent approach for all combinations. It was also agreed that 5 days duration was in line with the indications of these products and reinforced that these were only intended for short term relief of acute pain.
- XXXXX noted that setting a five day duration limit potentially will have a regulatory impact given that certain CACCs have separate dosage instructions for adults and for children aged 7 to 12 years of age (i.e. a product containing 5 days supply for an adult would exceed a 5 day supply at the child dose rate).
- A CWP Member suggested increasing the RDD limit for Schedule 2 under Option 2 from 60 mg to 80 mg, as this would mean no impact on current Schedule 2 paracetamol products (which can be indicated for 2 tablets 4 x / day (i.e. RDD of 80 mg), compared to two tablets 3 times a day for ibuprofen combinations (i.e. RDD of 60 mg). Other CWP Members strongly disagreed and felt that a 60 mg RDD was more appropriate. A CWP Member noted that there would always be some issue

given the different dosing rates but noted that RDD > 60 mg (and ≤ 100 mg) combinations would still be available to the public under Option 2, but as Schedule 3. A CWP Member also noted that there appeared to be no literature establishing whether an 8 mg codeine+paracetamol formulation was any more or less efficacious than a 10 mg codeine product.

- Several CWP Members also noted that if there is a strong desire to tighten Schedule 2 availability of codeine combinations, then Option 1 may address this (deleting Schedule 2 entirely).
- A CWP Member noted that a 2007 UK report provided to the CWP "*An inquiry into Physical Dependence and Addiction to Prescription and Over-the-Counter Medication*" (http://www.mhra.gov.uk/home/groups/l-cs-el/documents/committeedocument/con028602.pdf) gave, in the Member's opinion, the best summary to date of this issue, and included a number of case reports highlighting the various routes to codeine habituation. The Member felt that this report supported the view that restricting by duration was the best approach to take. The CWP also noted that:
  - This report was authored by the All-Party Parliamentary Drugs Misuse Group (APPDMG) which holds regular meetings to inform Members of Parliament on current issues involving the misuse of controlled drugs – it was not created especially to consider the issue of combination codeine.
  - The APPDMG Chair was persuaded to conduct this inquiry after noting that the 2006 International Narcotics Control Board Annual Report concluded that "the abuse and trafficking of prescription drugs is set to exceed illicit drug abuse".
  - The report noted (in the section on Over-the-Counter Medication) that, while there were no reliable figures which would allow APPDMG to put a precise figure on the scale of addiction to OTC medicines, the inquiry did receive a range of evidence from various sources relating to products containing codeine which allowed it to conclude that the problem does exist and affects enough people for action to be required to address and combat it.
  - Recommendation 3.4 was that access should be restricted for CACCs by reducing pack sizes (to 18) and making them only available after consultation with a pharmacist.
- A CWP Member queried why the proposed options no longer stipulated packaging controls such as blister/strip packaging. The CWP recalled advice to the 3rd CWP teleconference that TGA now sets such requirements for medicines. The TGA CWP Representative confirmed that TGA requires any OTC codeine combination to have child-resistant packaging.
- A CWP Member also noted that there was some ambiguity regarding the need to combine with a single non-opiate analgesic or other therapeutic active. While this was based on the UN Single Convention requirements, it was noted that the Single Convention did not appear to intend that if codeine was combined with a non-opiate

analgesic, then no other therapeutic active could be present. Indeed, it was noted that several such products were currently on the market. The CWP agreed that the schedule wording drafted for Options 1 and 2 should make clear that OTC codeine:

- must not be combined with any other opiate; and
- must by compounded with one or more therapeutic substances, only one of which may be another analgesic substance.

- The CWP also noted a brief update from the evaluator which advised that:
  - the report would be tabled at the February 2009 NDPSC Meeting.
  - the data available was not great, but there was clear evidence that harm was occurring and there were enough grounds for imposing further restrictions to OTC codeine combinations.

Unsolicited Public Comment (there was no pre-meeting gazette notice for this issue)

The Committee noted correspondence from XXXXX which:

- Asserted that if people need large amounts of Nurofen Plus®, they need to see a doctor. This drug should be banned from OTC sale.
- Asserted that Nurofen Plus® was being inappropriately advertised on television (particularly with some members of the public with a mental illness). Also asserted that a pharmacist was promoting this drug with a large window display and competition whereby an overseas trip could be won if the drug was purchased.
- Asserted that this was banned from OTC sale in the UK and Ireland due to deaths.

Members also noted the following from XXXXX:

- Noted a comment in the October 2008 Record of Reasons that Schedule 2 use of codeine+ibuprofen was only valid for short term pain. Asserted that if self treatment of pain is only suitable in the short term, then the same criteria should apply to all analgesics.
- Asserted that this conflicts with a previous discussion of paracetamol, where an OTC pack size of 100 was endorsed to enable people to purchase a 2 week supply for chronic painful conditions.
- Suggested that pack size limitations should be applied to all analgesics equally.

Members were additionally advised that XXXXX provided a copy of comments XXXXX submitted XXXXX regarding the October 2008 NDPSC consideration, including:

- It was disturbing that jurisdictional controls were not harmonised. On the other hand, if greater controls were required in NSW for Schedule 2 supply, they should be enforced.

- Noted a new warning statement requiring OTC NSAIDs to be labelled with "Do not use for more than a few days at a time unless a doctor has told you. Keep to the recommended dose. Excessive use can be harmful." Asserted that this will add to an already overcrowded panel of warnings which may be easily overlooked or ignored. Also asserted that "a few days at a time" was an ambiguous statement.
- Noted a comment that pharmacists have a duty of care role and are ideally placed to detect purchasing which may imply inappropriate medicine use. XXXXX asserted that this depends on accessible written records and supports the case for limiting non-prescription supplies to three to five days.

Cases of OTC Codeine Abuse

XXXXX has advised that:

- Recently requested that local addiction medicine specialists refer details of any clients they were aware of who had a history of abuse of codeine+paracetamol. A number of the subsequently referred reports instead related to codeine+ibuprofen.
- 4 cases seen by one addiction medicine specialist "over recent months" were detailed. This specialist commented that XXXXX had "at least as many more". The cases arose from high intake of Nurofen Plus® or Panadeine 15®.
- 3 cases reported by another addiction medicine specialist over a 3 month period were detailed. The cases arose from high intake of Nurofen Plus®, Panadeine Extra® or Panadeine Forte®.
- The Member asserted that, whilst this was somewhat anecdotal information, it did add to the data available that may help with the Committee's deliberations about OTC codeine.
- The Member particularly noted that all these patients needed active detoxification and/or the prescribing of maintenance opioid pharmacotherapy. There may obviously be other cases where such clinical intervention to treat the addiction was not necessary or had not occurred and where the consumer had not sought help from or been referred to an addiction medicine specialist.

Review of October 2008 Discussion

At the October 2008 NDPSC Meeting a Member asserted that there was evidence (the primarily case reports) that OTC products were currently causing real harm. The Member felt that the Committee needed to consider whether this constituted a public health risk requiring immediate action, rather than an issue that could reasonably be delayed, pending further data collection and analysis by the CWP. Another Member, however, raised a concern that if codeine+ibuprofen pack sizes were restricted in isolation, abuse might shift to other codeine combination products.

The Committee agreed that the case reports already provided to it (and, through the Record of Reasons, to the public) were valuable and should not be dismissed as either insubstantial or inconclusive. Furthermore, randomised controlled trials are used to evaluate efficacy and safety, but are not appropriate for determining abuse potential.

The Committee generally agreed, however, that any changes to the scheduling of codeine+ibuprofen could have significant impact on the Australian market and that it would be more appropriate to await completion of the CWP's review before coming to a decision. A Member asserted that it needed to be made very clear that the Committee had not necessarily determined that the current scheduling was appropriate, but rather, that the Committee needed to attempt to obtain further data in order to inform any decision it might make on this issue.

A Member supported the CWP's intent to seek further data but noted that there may be little additional data to be found. Should the CWP find this to be the case, then the Committee would need to proceed on the basis of the currently available data.

A Member asserted that the issue of consistency across the jurisdictions on supply controls was not a matter for NDPSC but should be noted by the Jurisdictional Members.

Review of October 2008 Pre-meeting Comments

Members recalled the following points from the many comments considered at the October 2008 NDPSC Meeting:

Discussion

- Advice was noted that all available OTC products containing ibuprofen are now required to be labelled with "Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.".
- Several comments noted that codeine misuse potential was not limited to ibuprofen combinations and asserted that all codeine products should be examined as a class.
- A comment asserted that there was less concern regarding OTC codeine+paracetamol (compared to codeine+ibuprofen) than had sometimes been implied. Another comment, however, contended that codeine+paracetamol preparations were identified as being most commonly used (in an illicit sense).
- A comment asserted that while the potential risk of misuse/abuse of OTC codeine existed, available data indicated that levels of misuse/abuse were low and there was no convincing evidence that it was increasing. It was asserted that in the absence of data demonstrating that more than a small minority were at risk of the potential side-effects of very large quantities of ibuprofen it would be inappropriate to deny the majority of the community the opportunity to decide on the level of pain relief most appropriate for them.

- Several comments asserted that codeine combinations must remain available as OTC. It was claimed that these were safe and effective when used appropriately and pharmacists are both suitably trained and best placed to manage their supply.
- A comment accepted that there was data that abuse/misuse was occurring but asserted that the Record of Reasons did not disclose if the various reports were in any way tested in regard to validity, integrity, robustness or ability to be extrapolated to population levels. It was asserted that the information did not amount to a *prima facie* case justifying further consideration.
- A number of pharmacists relayed their own experiences with abuse/misuse of larger pack sizes of codeine combinations and the measures they undertook in response.
- A comment asserted that public education initiatives were key to improving consumer behaviour and that work was underway to develop a national program regarding appropriate analgesic use, including potential risks associated with using OTC analgesics (particularly codeine) for longer than recommended periods.
- A comment asserted that pharmacists come under considerable pressure to supply codeine+ibuprofen and at the moment there was little to back up pharmacists' advice that use should be short term only.

Specific recommendations

- Several comments supported no change to the current pack size limits or scheduling of OTC codeine+ibuprofen. Several comments recommended that if any changes were made these should apply equally to all other OTC CACCs, while others asserted the opposite.
- A number of comments suggested uniformity across all jurisdictions was required, noting in particular there was a NSW variation which allowed packs of 72 codeine+ibuprofen to be sold as Schedule 2.
- Several comments suggested a limit for large pack sizes and revision of the codeine content for Schedule 2. Another comment noted that limiting pack sizes will change little as long as Schedule 2 products remain accessible for self-selection. The comment recommended a system where a pharmacist must have a serious patient interview and record all sales, i.e. Schedule 3 with sales recording for all OTC codeine combinations.
- A comment recommended making packs of ≤ 12 Schedule 2, ≤ 24 Schedule 3 and bigger packs Schedule 4 (if stocked at all). If a person was getting these products on a regular basis they should see their doctor for a script.
- A comment recommended, given that all ibuprofen products were only intended for short term use, pack size restrictions for Schedule 3 codeine+ibuprofen (48 doses was suggested, enough for a patient to be treated for eight days at the recommended maximum dose). Imposing a Schedule 3 pack size limit in the order of 24 dosage units would be too restrictive at this point in time.

- A comment suggested that new sub-entries to be created in the Schedule 3 codeine entry specifying each "single non-opiate analgesic substance" with which codeine is currently compounded (i.e. aspirin, ibuprofen and paracetamol). In this case the Schedule 3 pack size limit for codeine+paracetamol and codeine+aspirin should initially be 100 doses.
- A comment asserted that the safety of the public would be better served by excluding codeine+ibuprofen from Schedule 2 i.e. paracetamol and aspirin to be the only single non-opiate analgesic substance which may be compounded with codeine in Schedule 2 entry.
- A comment recommended that all Schedule 2 codeine combinations be stored behind the counter and that all Schedule 3 codeine supplies be recorded as a prescription if, after discussion between patient and pharmacist, safety and therapeutic need were established.

Additional Information

Members recalled the following points from Members' discussion at the June 2008 NDPSC Meeting:

General

- A Member noted that many people who abuse combination codeine products did not attempt to separate the codeine from the other analgesic. It was agreed that a review of the availability of all codeine combinations was warranted to look at the broader issues relating to the supply of codeine, rather than focussing on codeine+ibuprofen alone.

Codeine+ibuprofen

- The Committee agreed that the issue of misuse/abuse of codeine+ibuprofen was only a segment of the overall issue. The Committee agreed that, in the interim, there was evidence that abuse/misuse was occurring with codeine+ibuprofen and that, pending the full review of the scheduling of codeine, consideration of limiting Schedule 2 and 3 pack sizes of codeine+ibuprofen combinations be foreshadowed for consideration at the October 2008 NDPSC Meeting.
- A Member stated that the data provided to the Committee by medical practitioners working in the field of addiction medicine suggested that the problem was real and causing significant harm.
- It was noted that industry submissions had shown that ADR monitoring data did not appear to show significant problems or an increase in reports for codeine+ibuprofen despite widespread use and increase in sales. However, a Member noted that this may be due to reporting mechanisms for ADRs not being routinely used for OTC products.
- A Member noted that the number of tablets taken (from case reports) seemed to correlate with available pack sizes. Considering the combination was indicated for

temporary relief of pain, the maximum allowable pack size could be reduced without inconvenience.

- The Committee also noted jurisdictional advice on the abuse/misuse of codeine, including a suggestion that, as the problem was with the codeine causing dependence and, thus, overuse, the Committee really should look at the inappropriate use of all codeine combinations rather than focusing on codeine+ibuprofen alone.

Members also recalled the following from June 2008 comments:

Abuse/misuse risk

- Several comments agreed that there was likely to be at least low levels of misuse of all codeine analgesics. A number of comments asserted that anecdotes of misuse were infrequent and unverifiable and that it had proven difficult to quantify the extent of the problem.
- Several comments reported cases of codeine+ibuprofen misuse causing serious GI injuries or electrolyte disturbances, including one detailed review of 23 serious cases attributed to exposure to high doses of ibuprofen. A comment asserted the profile and behaviour in these cases was unlike other illicit drug users in that most patients started taking the combination for its approved indications and then, once habituated, took chronically at doses far exceeding recommended units.

Benefit

- Several comments asserted that codeine+ibuprofen was an important part of the OTC range of analgesia options. Availability as OTC was appropriate to the management of a range of short-term conditions which may otherwise require unnecessary medical intervention.

Role of Pharmacist

- A comment asserted that pharmacists have a duty of care role and are ideally placed to monitor purchasing patterns which may suggest inappropriate use. If detected, pharmacists (and staff) should refuse sale and refer the patient to a medical practitioner.
- A comment discussed whether it was fair to expect pharmacists to have to identify drug seeking behaviour and thus deny access to such persons. Many of these patients did not fit the stereotypical profile of a drug dependant person.

Opposing scheduling changes

- Several comments asserted that making codeine+ibuprofen prescription-only would inconvenience the great majority of consumers who use this combination as recommended while 'protecting' only a small number from potentially causing themselves harm.

Support for scheduling change

- Several comments asserted that the current controls on codeine+ibuprofen combinations had failed to control misuse/abuse.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (b) risks and benefits, (d) extent and patterns of use, (f) dosage and formulation and (g) potential for abuse.

The Committee was advised that the evaluator's report had been completed. Members noted the following from this report:

- At present, there was no firm published evidence that codeine in doses ≤ 30 mg produced significant analgesia. As with all opioids, use of codeine is associated with the potential for dependence.
- The evidence of potential harm associated with OTC CACC has hitherto been drawn from case reports. With the exception of a case reported by a Coroner, cases were anecdotal, depth of available information was variable, and presumably very few, if any, were independently verified. Nevertheless, they collectively paint a compelling picture of the potential harm associated with OTC CACC.
- Although some of this harm arose from codeine, the focus of most cases was on ibuprofen-mediated adverse effects. The assumption was that most of the affected patients developed dependence on codeine, and excessive consumption of the compounded ibuprofen led to toxicity. Common adverse effects of ibuprofen reported in the series were typical for non-steroidal anti-inflammatory drugs (NSAIDs): namely gastrointestinal ulceration and/or bleeding and renal impairment. Hypokalaemia was also observed. The mechanism for ibuprofen-induced hypokalaemia was believed to be renal tubular acidosis.
- At present, there appears to be very little published epidemiological evidence regarding the risk or likelihood of harm arising from OTC CACC in Australia. Evidence from other countries also appears scarce. Based on currently available data, it was not possible to accurately quantify the risk of harm associated with OTC CACC in Australia. However, a discussion about risks could still be held around what is known or suspected.
- The case reports, while comprising many incidents of harm arising from OTC CACC, in themselves provide no indication of the extent of the problem in Australia. Such is the situation with all case reports. Nevertheless, it was highly likely that many more cases of adverse reactions occurred than was captured from these case reports.
- Although data regarding the frequency of use of OTC CACC in Australia were not precisely known, it can reasonably be assumed that use is commonplace. Therefore,

despite the fact that there may be many cases of harm arising from OTC CACC, these would be small relative to the large number of users, meaning the risk of harm from OTC CACC among all users of these drugs is likely to be low, and probably even rare.

- The presumption that the risk of harm associated with OTC CACC among the wider population (the majority of whom probably would have taken OTC CACC at some time) is likely to be low was a view shared by three emergency physicians working at three separate emergency departments across Melbourne. All based their opinions on having encountered the problem only rarely in their careers. It was noted that these health professionals were conveniently rather than randomly contacted by the evaluator. Combined with the fact that the group was few in number, this means that their views were not necessarily representative.
- As recommended by the CWP, the evaluator also sought the opinion of XXXXX. XXXXX also expressed the view that the risk of harm arising from OTC CACC use among the general public was probably small. Her own experience was limited to the combination of codeine+ibuprofen and not codeine+paracetamol. Nevertheless, XXXXX highlighted that the risk of harm needed to be balanced against the fact that there was currently no published evidence of the analgesic efficacy of codeine at ≤ 30 mg.
- The evaluator thought it reasonable to conclude that number of patients who abuse OTC CACC, relative to all users of these products, is likely to be low. This notion was supported by an addiction medicine specialist contacted by the evaluator. The specialist based his opinion on over 20 years' experience in Sydney and Melbourne.
- Nonetheless, the risk of harm among abusers of OTC CACC is likely to be high. Depending on patient factors, such as age and co-morbidities, the risks of gastrointestinal and renal adverse effects with even therapeutic use of ibuprofen were not insignificant, and at least sufficient to warrant precaution. Because the risks of these adverse effects are dose-related, it follows then that prolonged, high-dose exposure to ibuprofen was likely to be associated with a high potential for harm.
- Other than abuse of OTCC CACC, risk factors for harm from OTC CACC have not conclusively been identified. However, many of the reported cases involved patients who were also abusing, or had abused, other substances, especially other opioids. Many patients were also noted to have psychiatric disorders. These were intuitive risk factors for abuse of OTC CACC and hence also risk factors for harm.
- Indeed, the addiction medicine specialist suspected that the majority of abuse of OTC CACC would be occurring among patients with background abuse of other, stronger opioids. XXXXX felt that such patients would be only using OTC products to supplement their use of other substances, and that only a minority of patients would be primarily abusing OTC CACC.
- Of note, the addiction medicine specialist was also of the opinion that most abusers of CACC, whether OTC or not and 'supplemental' or 'primary', would be unaware of

the potential toxicity of compounded agents like ibuprofen and paracetamol. If accurate, this would be a compelling fact.

- The evaluator advised that the addiction medicine specialist cautioned about upscheduling, as the harm reduction may be offset by the impact on the much larger population of non-abusing patients. It was also asserted that the strategy would not reduce the problem of opioid abuse specifically, as users would just then seek alternative sources.

Conclusions and Recommendations

- Based on the currently available information from Australia, the evaluator concluded that there was potential for significant harm from OTC CACC and even death, and it was not possible to accurately estimate the associated risk, although the following were reasonably assumed:
  - the proportion of all users that abuse OTC CACC is low.
  - the risk of harm among all users of OTC CACC is low.
  - the risk of harm among abusers of OTC CACC is high.
- At the very least, the appropriateness of OTC CACC as a Schedule 2 product might certainly be called into question. Therefore, in the interests of harm minimisation, the evaluator felt that it would be justified to upschedule OTC CACC from its current listing. The key intention of upscheduling should be the restriction of free (without pharmacist intervention) access to large quantities of OTC CACC.
- Importantly, and notwithstanding that the evidence base for the analgesic efficacy of codeine in doses of ≤ 30 mg was weak, the evaluator felt that upscheduling of OTC CACC could occur without affecting the use of these products by 'genuine' (non-abusing) patients for the 'short-term treatment of acute pain' (the currently approved indication). In this context, and to address a question posed by the CWP, the evaluator felt that 'short term' would constitute a few days, and no more than one week.

The Committee discussed the issue of efficacy of codeine in OTC doses. A Member noted that a central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to any case justifying OTC supply of codeine, the Committee noted the CWP advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at ≤ 30 mg. The Committee therefore agreed that it would have to proceed with the scheduling consideration of codeine with this concern duly noted.

A Member brought to the Committee's attention that the amounts of codeine present in currently available OTC products (whether efficacious or otherwise) have not been arbitrarily included by companies but rather have been restricted by the scheduling cut-

offs that this Committee has set. Further, given the length of time these products have been on the market, it would be unlikely that companies would commit resources to undertaking efficacy studies.

Members generally agreed that it was important that the Committee's concerns relating to efficacy of doses < 30 mg of codeine be brought to the TGA's attention, regardless of what regulatory action might ensue. A Member asserted that the promotion of products containing an addictive opiate substance at potentially sub-therapeutic doses with known cases of harm should be of concern to the regulator.

One Member suggested that the majority of incidents appeared to be from codeine+ibuprofen and that there should therefore be no change to the scheduling of codeine+paracetamol. Other Members reiterated the Committee's previous concern that any restriction of codeine+ibuprofen alone would just see a shift of the abuse/misuse to codeine+paracetamol. The Committee again concluded that the consideration should apply to all OTC CACCs.

The Committee noted the two CWP options. While there was majority support for Option 1 (to no longer allow Schedule 2 supply), the Members were unable to reach a clear consensus on all facets of this proposal. Members therefore agreed that while the Committee would foreshadow deleting the Schedule 2 entry, it would welcome pre-meeting comments to the June 2009 NDPSC Meeting on both of the CWP options. In particular, the Members identified the following as areas where public consultation may assist the June 2009 NDPSC Meeting's consideration:

- The current provision requiring that codeine be compounded with at least one 'other therapeutically active substances'. This current wording was potentially ambiguous. Members therefore agreed that the wording may need to be modified to clearly reflect the intent that the presence of an 'other therapeutically active' was to circumvent diversion or abuse. Further, this requires a therapeutic quantity of the active(s).
- There was some ambiguity regarding the requirement to combine codeine with a single non-opiate analgesic **or** other therapeutic active. There was no intention that codeine, in combination with a non-opiate analgesic, could not also be combined with another therapeutic active. Indeed, it was noted that several such products were currently on the market. Members noted that the wording should make clear that OTC codeine:
  - must not be combined with any other opiate; and
  - must be compounded with one or more therapeutic substances, only one of which may be another analgesic substance.
- The foreshadowed proposal would limit supply to 5 days or less at maximum daily dose for adults. However, the Committee noted that this would exceed 5 days supply at a paediatric dose. The Committee noted that this may could be resolved by stipulating in the scheduling entry that the limit was based on adult dosage, noting

that this would also be consistent with other schedule entries for substances used in both adults and children.

- There was concern over the scope of the June 2009 consideration:
  - The current Schedule 2 entry makes no distinction between analgesic and non-analgesic indications and a Member aired concern that the foreshadowed proposal might have regulatory impact on non-analgesic codeine products currently in Schedule 2 (such as some decongestants and cough suppressants).
  - A Member proposed limiting the proposal to analgesic indications. Other Members noted that codeine remained an abuse risk, regardless of the indication.
  - A Member also asserted that it was important that any scheduling change did not impact on the codeine+phenylephrine combinations being promoted as a substitute for pseudoephedrine products. In this specific case, the public health benefit of reducing the OTC pseudoephedrine supply clearly outweighed the low risk of abuse of codeine+phenylephrine. It was suggested that the June 2009 NDPSC Meeting consider a specific Schedule 2 entry for codeine+phenylephrine while the general entry would be upscheduled to Schedule 3. Members therefore agreed that the June 2009 pre-meeting Gazette Notice should clearly indicate that the foreshadowed proposal would affect all OTC codeine, not just analgesics, as this may encourage relevant public comment to assist the Committee in developing an appropriate way forward regarding this concern.

RESOLUTION 2009/55 - 6

The Committee decided to foreshadow amendments to the scheduling of codeine, including a proposal to delete the Schedule 2 codeine entry and amend the Schedule 3 codeine entry by:

- Limiting the recommended daily dose to a maximum of 100 mg codeine base;
- Limiting pack size to a maximum of 5 days supply;
- Restricting divided preparations to a maximum of 12 mg codeine base per dosage unit; and
- Restricting undivided preparations to a maximum concentration of 0.25 per cent codeine base.

The Committee also decided to seek advice from the TGA regarding the efficacy of codeine in OTC combination products intended for pain relief, and the appropriateness of the fixed dose combinations currently registered.

1.8.2 GLOBALLY HARMONISED SYSTEM (GHS) FOR CLASSIFICATION AND LABELLING OF CHEMICALS (STANDING ITEM)

Nil.

1.9 PROPOSED ROUTINE CHANGES TO THE SUSDP

Nil.

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

2.1 SUSDP, PART 1

2.1.1 PART 1, INTERPRETATION – "APPROVED NAME"

BACKGROUND

Following a review of the references in the SUSDP, the October 2008 NDPSC Meeting was asked to consider whether or not all reference sources listed under the "approved name" entry in Part 1, Interpretation, were still warranted. The Committee agreed to defer consideration to the February 2009 NDPSC Meeting pending advice from the TGA, APVMA and NICNAS.

DISCUSSION - SUBMISSIONS

The Meeting was informed that due to the delay in receiving advice from TGA, APVMA and NICNAS, Members were not afforded the opportunity of due consideration of this item prior to the Meeting. Therefore, it was suggested that this item be passed to the Committee's Drafting Advisory Panel (DAP) for initial consideration prior to referral to the June 2008 NDPSC Meeting.

The Committee agreed that the matter be referred to DAP, noting that the references currently listed under "approved name" will be transferred to SUSDP No.24 and, therefore, the new Poisons Standard.

RESOLUTION 2009/55 - 7

The Committee decided to refer this item to its Drafting Advisory Panel to determine the authoritative references to be included under the "approved name" entry in Part 1, Interpretation for consideration at the June 2008 NDPSC Meeting.

2.1.2 DEFINITION OF COMPOUNDED

PURPOSE

The Committee considered the SUSDP definition of 'compounded'.

BACKGROUND

At the May 1987 Meeting, the following definition was proposed: "*Compounded preparation means a preparation compounded with one or more other poisons in such a way that the poison, restricted substance or drug of addiction contained therein cannot be readily extracted*". It was not recorded where this definition was derived form. From July 1987 to February 1991 this definition was subject to considerable consultation and review.

At the August 1991 Meeting, the proposal was amended and the current wording agreed to "*Compounded in relation to a substance means combined with one or more other therapeutically active substances in such a way that it cannot be separated from them by simple dissolution or other simple physical means*". It was also agreed that use of 'compounded' would be confined to narcotic schedule entries and other drugs which may be subject to abuse. The schedule entries for sedating antihistamines were therefore amended to replace 'compounded' with the phrase 'when combined with'.

The June and October 2005 NDPSC Meetings noted concerns with a codeine+ibuprofen bi-layer tablet formulation and whether this particular product met the definition of compounded, although this was not pursued as the bi-layer formulation was withdrawn by the sponsor and replaced with a single layer formulation.

The June 2007 NDPSC Meeting noted claims of apparent increasing incidence of codeine+ibuprofen abuse where the codeine was being easily separated by simple dissolution in water. The Committee asked the TGA to investigate dissolution rates of the products in question. The February 2008 NDPSC Meeting noted that the results of the dissolution investigation were not yet available and agreed to foreshadow consideration at the June 2008 NDPSC Meeting. The June 2008 NDPSC Meeting decided to form a working party (the Codeine Working Party – CWP) to review the availability of all OTC codeine combination analgesics and the definition of 'compounded'.

The October 2008 NDPSC Meeting noted the CWP's progress on the definition of 'compounded', including the likelihood of recommendations being tabled for consideration at the February 2009 NDPSC Meeting on that issue.

This item is closely related to 2 other items under consideration by the February 2009 NDPSC Meeting: 1.8.1 *Codeine Working Party* and 11.3 *Codeine in combination with menthol & ammonium citrate.*

DISCUSSION - SUBMISSIONS

The Committee noted the following from pre-meeting comments:

XXXXX

- On the basis of the present definition, there is a case for asserting that XXXXX is in Schedule 4 because the product, as presently formulated, allows separation of the codeine phosphate "by simple dissolution". Member's noted that any possible up-

scheduling due to not meeting the definition of 'compounded' would actually be to Schedule 8.

- In respect of this combination of drugs, any departures from Schedule 4 could be limited to codeine phosphate being formulated with ibuprofen lysine or other water soluble salt or complex of ibuprofen. This would then make amateur separation more difficult because of the high solubility of both drugs.

XXXXX

- Concurred entirely with the comment above.

XXXXX

- Asserted that there was no universally agreed definition of compounded.
- Particularly noted two widely recognised definitions 1) derived from Article 3 of the *International Convention on Psychotropic Substances* (discussed below) and 2) the current SUSDP definition.
- Noted that the CWP was to provide a recommendation on the proposed definition. Asserted that any further proposed definitions should be made available for comment before a final decision was made.

XXXXX

- Supported an amended definition of 'compounded', whereby combination products are evaluated in the context of a range of issues relating to the possible separation of active substances. These issues should include ease of separation, whether there was evidence of separation and whether such separation posed significant risk to public health. Most importantly, the definition should aim to avoid inflexibility that could lead to combination products inadvertently falling into different schedules based on technicalities, contrary to the (asserted) intent of scheduling criteria set out under 52E.

Member's recalled the following from the September 2008 CWP teleconference:

CWP Recommendations

- The CWP considered the following options but, while generally in favour of Option 2, was not in a position to make a recommendation at that time.
  - **Option 1**: Retention of current definition (noting that the CWP had already agreed that XXXXX did not meet this definition).
  - **Option 2**: Replace the definition of 'compounded' in Part 1 with the following (i.e. adopt parts of the *UN Convention on Psychotropic Substances 1971*):

    "Compounded" in relation to a substance means combined with one or more other therapeutically active substances in such a way that it ~~cannot be separated from them by simple dissolution or other simple physical means~~ presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily

applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem.

CWP discussion

- The CWP discussed whether this should be set-aside until the overall matter of the scheduling of codeine (see item 1.8.1) had been resolved, particularly as the issue of abuse related to people taking excessive amounts of whole product rather than people extracting the codeine. However, it was noted that if the current definition were not amended (in light of recent dissolution testing), at least one (and possibly several) major OTC products must be considered Schedule 8.
- A CWP Member suggested removing 'compounded' from the SUSDP and instead have TGA pick up a definition. Several CWP Members asserted, however, that the definition should remain in the SUSDP as it was the justification for allowing codeine combinations out of Schedule 8 in compliance with Australia's obligations to the *Single Convention on Narcotic Drugs 1961* (the Single Convention). It was further asserted that if the risk of codeine abuse of a product was found to be more than negligible, then there was no choice but to consider the product Schedule 8 if Australia was to comply with the Single Convention.
- The CWP noted that the intent of the 'compounded' definition was to address public health risk arising from extraction of actives such as codeine from formulations. The CWP therefore considered recommending replacing the current definition (with its strict requirement for the therapeutically active substance to not be separable by simple dissolution or other simple physical means) with a more outcomes-based wording that would allow the regulator to consider the broader goal of protecting public health.
- Several CWP Members supported the increased flexibility that this new wording would allow the TGA, noting that it would be up to a sponsor to convince the regulator that it was complying with "no, or negligible, risk of abuse". XXXXX, however, was concerned that the regulator might have problems with the very subjectivity of the proposed definition which other CWP Members favoured due to the increased flexibility. The CWP agreed, therefore, that it should not proceed with this proposal without first seeking the views of XXXXX.

Members also recalled the following from the October 2008 NDPSC Meeting's discussion of the definition of 'compounded':

- The Members noted that the current definition of 'compounded' was problematic. While no uniform definition had been adopted internationally, the general intent of the Single Convention (and thus the definition of 'compounded') was management of diversion, rather than individual overuse. Members therefore supported the CWP's 'Option 2', as this replaced the current, inflexible criteria with a more outcomes based standard, in line with the original intent of the Single Convention.

Members also noted the following from the December 2008 CWP teleconference:

- The CWP noted some advice regarding possible codeine+ibuprofen combinations which might comply with the current SUSDP 'compounded' definition based on solubility data from the British and United States Pharmacopoeias (BP and USP):

	Aspirin	**Ibuprofen**	**Lysine ibuprofen**	**Paracetamol**	**Codeine phosphate**	**Codeine**
Water	1 in 300	Insoluble	1 in 2	Sparingly	1 in 2.5	1 in 120
Boiling Water	-	Insoluble	?	1 in 20	1 in 0.5 (80°)	Soluble
Alcohol	1 in 5	Freely soluble	?	1 in 10	1 in 325	1 in 2

  - The combination that most lends itself to water extraction is codeine phosphate+ibuprofen because it contains a relatively high dose of codeine per tablet, codeine phosphate is very soluble in water, and ibuprofen is insoluble.
  - Because of the high aqueous solubility of codeine phosphate and the relatively low solubility of all three non-opioids, separation by pulverising, dissolution and filtration appeared straightforward. An exception would be dispersible and soluble aspirin combinations.
  - If codeine hemihydrate or sesquihydrate were used instead of codeine phosphate, aqueous separation would be less productive in amateur hands but by using boiling water, the separation could be effected. In any case, the availability and costs of an alkaloid base hydrate would be higher and sponsors would have to submit stability and perhaps efficacy data on each product that was reformulated. Even if codeine hydrate and ibuprofen were combined, the small number of milligrams of codeine in a tablet would not require much water (at room temperature) to dissolve it.
  - Therefore, it was asserted that codeine phosphate would have to be formulated with a non-opioid analgesic that was also very soluble in the same solvents that dissolve codeine phosphate readily. A possibility would be to formulate with lysine ibuprofen. Lysine ibuprofen is commercially available and is used in XXXXX. While separation could be effected, it would rely on more sophisticated means than simple filtration. There are products on the ARTG containing ibuprofen sodium dehydrate, which is freely soluble in water. There are other water soluble variants of ibuprofen such as salts, esters and complexes.
  - Even if ibuprofen with codeine phosphate tablets were reformulated as above, the effects of overdose of the whole tablet and gastrointestinal toxicity would be unchanged; i.e. there are two separate problems being overdose and extraction.

- The CWP agreed that while the above advice indicated that it may be possible to come up with an codeine+ibuprofen combination that met the current SUSDP 'compounded' requirement, this current definition was still not very practical. It was generally felt that this information merely reinforced the need to consider a more outcomes-based definition of 'compounded' at the February 2009 NDPSC Meeting.

Additional Information

'Compounded' is a term used in the SUSDP in reference to narcotic substances when combined with a non-opiate analgesic or other therapeutically active substance. This allows, under Schedule III of the Single Convention, for certain preparations of narcotics to require less stringent reporting obligations (interpreted in Australia, to date, to mean other than Schedule 8). When first adopted, the Single Convention set down the following for substances included in Schedule III:

(a) compounded with one or more other ingredients in such a way that the preparation has no, or negligible, risk of abuse, and in such a way that the drug cannot be recovered by readily applicable means or in a yield which would constitute a risk to public health; and

(b) containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more that 2.5 per cent in undivided preparations.

In 1966, sub-paragraphs (a) and (b) were deleted and replaced by "*When compounded with one or more other ingredients and containing not more than 100 milligrams of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations*". That is to say, the public health qualifications of negligible risk, recovery by readily applicable means and yields constituting a public health risk were all removed. While this may have been because none of these terms were defined in Article 1, such an amendment did not exclude a signatory from applying its own interpretation of 'compounded', as it deemed appropriate.

Article 3 of the *Convention on Psychotropic Substances 1971* states the following in relation to exempted substances: "*If a preparation containing a psychotropic substance other than a substance in Schedule I is compounded in such a way that it presents no, or a negligible, risk of abuse and the substance cannot be recovered by readily applicable means in a quantity liable to abuse, so that the preparation does not give rise to a public health and social problem, the preparation may be exempted from certain of the measures of control provided in this Convention in accordance with paragraph 3*." This was adopted five years after similar wording was removed from the Single Convention.

The following definitions of 'compounded' are in use by various jurisdictions:

- New Zealand: *Misuse of Drugs Act, Third Schedule, Class C, Part VI* "Compounded with one or more other pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health."
- Queensland: *Health (Drugs and Poisons) Regulation 1996* "Compounded, for a substance combined with a therapeutically active substance, means the way the substances are combined prevents their separation by simple dissolution or in another simple physical way".

- Victoria: *Drugs, Poisons and Controlled Substances Act 1981* "Compound in relation to a poison or controlled substance means a medicament prepared in accordance with a formula and being a combination of -
  - a poison or controlled substance; and
  - any other substance or substances - in such a way that the poison or controlled substance cannot be readily separated from the other substance or substances, and to compound and derivative expressions have corresponding meanings;".
- No other States or Territories define 'compounded' in relevant Acts or associated regulations. However, these jurisdictions may pick up the SUSDP definition through adoption by reference to Part 1.
- USFDA legislation does not define 'compounded', except in relation to positron emission tomography drugs. The UK's Medicines and Healthcare products Regulatory Agency and the European Medicines Agency do not define the term "compounded" in legislation. However, definitions may be contained in tertiary documents, as it is in Australia (i.e., the SUSDP).

Members also recalled the following from discussion at the June 2008 NDPSC Meeting:

- Australia is a signatory to the Single Convention and, unless in a 'compounded' preparation, codeine falls into Schedule II of the Single Convention (interpreted in Australia, to date, to require classification as Schedule 8).
- The original concern brought to the Members' attention regarding codeine+ibuprofen combinations was whether or not they fit the SUSDP definition, particularly in relation to 'simple dissolution'. The Committee agreed that there was an issue of formulation and compliance with the SUSDP definition.
- A Member stated that, given the dissolution testing results, there was now reasonable evidence that currently available codeine+ibuprofen formulations might not comply with the conditions for non-Schedule 8 classification. Another Member stated, however, that the Committee scheduled substances, not products, and the issue of whether a product was compliant with a particular schedule was a matter for the sponsor and the registration authority.

Members also noted the following points from comments to the June 2008 NDPSC Meeting:

- Several comments asserted that, as codeine was more soluble than aspirin, paracetamol or ibuprofen, it was possible that all codeine combinations might be considered Schedule 8. A comment asserted that further restricting these combination analgesics was not in the best interest of the Australian public and it was a matter of public health that these combinations remain available OTC. Another comment asserted that a better approach to address the issue of appropriateness of the physical properties of a particular formulation was an issue for the regulator to address.

- A comment noted that using methods to reduce the solubility of codeine may affect a product's ability to meet the TGA's dissolution requirements.
- A comment put forward that developing an objective definition for the term 'compounded' was not an effective way of discouraging illicit diversion. Criminals were likely to just find more sophisticated ways of extracting.
- Another comment asserted that a clear and unambiguous statement regarding the definition of 'compounded' was required.
- Several comments asserted that the issue of 'compounded' was a secondary consideration to the concerns surrounding potential abuse as it did not appear that extraction of codeine was the preferred means by which the reported abuse was occurring.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (f) dosage and formulation and (g) potential for abuse.

A Member, noting that the Single Convention did not require the use of a definition for 'compounded', suggested dropping the definition and instead stipulating the requirements (combined other therapeutically actives in a way that cannot be separated by simple physical means) specifically in each entry. Other Members noted that this would require consistency in all relevant opiate entries and, over time, the wording throughout the Schedules may not remain consistent. The Committee generally agreed, therefore, that there was a need to maintain a specific definition of 'compounded' in the SUSDP.

Members considered the two options put forward by the CWP. The Committee noted the following regarding the CWP's alternative definition:

- There was some discussion about the practicality of the subjective language in this proposal. A Member asserted that the subjective clauses would be difficult for a regulator to enforce. Other Members agreed that terms such as "negligible" and "social problem" were open to interpretation.
- A Member reiterated, however, that subjective flexibility was the point of the proposed amended wording. The Member asserted that this flexibility would allow the regulator to interpret compliance with the definition in an outcomes based manner, rather than the prescriptive nature of the current definition. The Member also recalled that this whole issue first arose because certain products currently available OTC appeared to be readily separable by simple dissolution i.e. not compliant with the current definition.
- Another Member asserted that the use of a subjective term could require the Committee to be involved in determining whether a product meets the definition on a case-by-case basis. The Member asserted that the current (less subjective) definition

allowed the regulator to make this determination as part of the product approval process.

- The Committee generally agreed that the CWP's proposed amended definition was not supported.

Given the lack of support for the proposed amendment, a Member recalled that the main issue that the definition of 'compounded' was originally intended to address was related to diversion for heroin production. The Member therefore suggested that the current definition remained appropriate in addressing this concern and that the issue of individual abuse/misuse of codeine would need to be addressed through scheduling rather than by the definition of 'compounded'.

A Member noted, however, that there were problems in retaining the current definition given that, while some ibuprofen salts can be formulated to have a similar solubility to codeine, this did not appear to be the case for paracetamol. The Member therefore asserted that the current definition's requirement "cannot be separated …. by simple dissolution" meant that it may not be possible to have a non Schedule 8 codeine+paracetamol product, and that many current ibuprofen products would also have to be considered Schedule 8.

It was reiterated that the current definition relies on the term 'simple dissolution', and that separating of many current formulations required more complex manipulation (various solvents/temperatures/pH) than may be considered "simple". Additionally, the ease with which an opiate may be separated out is not just a question of the solubility of the individual actives, it is also influenced by the properties of the other, non-active, ingredients. A Member advised that in at least one codeine+paracetamol product known to the Member, the action of a binding agent in that product would not allow separation by simple dissolution, despite the disparate solubilities of the actives. That is to say that appropriate product formulation could overcome such issues with differences in solubilities of actives.

The Committee therefore agreed that the current definition of compounded remained appropriate to address the risk of diversion, and that the concerns regarding misuse/abuse were better addressed by the specific conditions of individual schedule entries. The Committee then considered whether to propose changes to the OTC codeine schedule entries to convey the intent of minimising the potential for misuse or abuse. The Committee decided, however, that this could be addressed as part of the codeine scheduling review (detailed under item 1.8.1).

Several Members, while supportive of retaining the current definition of 'compounded', asserted that there seemed to be a disconnect between the SUSDP's requirement for compliance with the definition of 'compounded' and the regulator's enforcement of this when approving products. A number of Members asserted that there were some current products for which it did not appear that the current definition had been uniformly applied. In light of the Committee's agreement to retain the current definition, a Member

suggested that the regulator should be advised of the outcome, as this definition is relevant to the approval process for combination analgesic products to be classified outside of Schedule 8.

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The Committee decided that the current SUSDP definition for "compounded" remains appropriate.

2.2 SUSDP, PART 2

Nil.

2.3 SUSDP, PART 3

2.3.1 SCHEDULE 5 AND SCHEDULE 6 STORAGE STATEMENTS

PURPOSE

The Committee considered the jurisdictional responses to questions raised at the October 2008 NDPSC Meeting and progress by the working group.

BACKGROUND

Having agreed with a STANZHA (Australian States and Territories and New Zealand Health Authorities) recommendation to include a paragraph in Part 3 of the SUSDP relating to retail storage of Schedule 5 and Schedule 6 poisons, the October 2005 NDPSC Meeting deemed that further consultation with stakeholders was necessary. Schedule 5 and Schedule 6 storage statements were also discussed at the February, June and October 2006 NDPSC Meetings. The Committee also agreed to establish a working group to develop a guidance document on minimising access by children to Schedule 5 and Schedule 6 products in the retail setting for consideration. The Guidance document was to be referred to as the "Draft Code of Practice for National Retail Storage of Schedule 5 and Schedule 6 Products" (the 'draft Code').

The February 2007 NDPSC Meeting considered the progress of the working group. The Committee agreed that the working group would continue developing the draft Code in consultation with States/Territories and that industry were encouraged to move forward on this issue.

At the October 2007 NDPSC Meeting, the draft Code was subsequently tabled. The Members agreed that the draft Code should be focused on the specific issue of retail storage of Schedule 5 and Schedule 6 products. Members also agreed to a number of changes to the draft Code, including a preamble that explains that it is not a hierarchy of control but rather that each option is equal in its effectiveness. The Committee also agreed to an extended public consultation on the amended draft until late March 2008.

At the June 2008 NDPSC Meeting, the Committee noted that while some editorial comments on the draft Code were received from Members, there were no comments from major industry stakeholders from the extended public consultation. The Committee discussed the way forward on this matter, particularly considering the fact that there was no agreement with States and Territories yet regarding acceptance of the draft Code and whether compliance with the draft Code meant compliance with State and Territory legislation. The working group was charged with developing a discussion paper with a series of questions on implementation aspects for States and Territories to respond to before further consideration by the Committee.

At the October 2008 NDPSC Meeting, the Committee noted that the working group had held a teleconference on 8 October 2008:

- It was inappropriate to make recommendations on the outstanding issue of whether the draft Code should include Schedule 5 products at this stage (pending response from the jurisdictions).

- One of two possible situations exists in each of the jurisdictions: That the draft Code goes beyond current jurisdictional legislation or that the draft Code does not meet current requirements of jurisdictional legislation.

The working group also formulated the following set of questions for consideration by jurisdictions:

i. Does the draft Code go beyond your current jurisdictional legislative requirements?
ii. Could the draft Code be introduced without a regulatory impact statement?
iii. If not, would you be willing to undertake such consultation, and how long would that take?
iv. Would you also require a legislative change?
v. Are you willing to undertake legislative change and how long would that take?
vi. How could it be otherwise referenced in your jurisdiction?
vii. If it was referenced in SUSDP only, could it be used as a compliance tool in your jurisdiction?
viii. If the draft Code does not meet the prescribed requirements of your current legislation, could it be used as a compliance tool in your jurisdiction?
ix. If so, would reference in the SUSDP be sufficient?
x. If not, could it be otherwise referenced?
xi. If not, would you require a legislative change, and if so, would you be willing to undertake such a change and how long would that take?

The following broadly summarises the jurisdictional responses:

- Western Australia does not propose to adopt the draft Code of practice for the retail storage of Schedule 5 and Schedule 6 poisons.
- Victoria states that the Code is more stringent than current legislations and does not support the draft Code becoming part of the SUSDP if the effect is to make the code a statutory requirement in that jurisdiction. Victoria could promote the draft Code administratively as a code of practice or guideline.
- Queensland has not yet reached a decision about adoption of the draft Code. If it were not made a part of the SUSDP it would be difficult to reference it in legislation.
- New South Wales states that the draft Code is more stringent for Schedule 5 poisons, but less stringent for Schedule 6 poisons and that it is unwilling to undertake legislative change. NSW suggests adding the draft Code into the SUSDP as guidance only.
- South Australia would be willing to put a proposal to the Controlled Substances Advisory Council for amendment of their poisons regulations. If supported, amendment of the legislation would take up to six months.
- Tasmania supports regulation of Schedule 5 and Schedule 6 storage and such a regulation could be put in place without a regulatory impact statement. However, action by other jurisdictions to support the draft Code would strengthen their case for regulation.
- Northern Territory states that the draft Code goes beyond current legislative requirements, but that their poisons legislation has a provision for the Minister to adopt a new Appendix of the SUSDP.
- Australian Capital Territory would be willing to adopt the draft Code if there was a nationally agreed approach and if was included as an Appendix to the SUSDP.

DISCUSSION

The Committee noted the range of responses from the jurisdictions and that several jurisdictions were comfortable with the current arrangements. Further it was noted that the Productivity Commission Research Report 'Chemicals and Plastics Regulation' focussed on ensuring uniformity and this aspect of the report had been endorsed by COAG in its interim response.

In the absence of a uniform approach, the Committee was of the opinion that it would be best to refer the matter to the NCCTG for policy direction.

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The Committee noted the responses from the jurisdictions.

2.4 SUSDP, PART 5

Nil.

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))

Nil.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 LIQUID HYDROCARBONS – FOOD & PHARMACEUTICAL GRADE WHITE MINERAL OIL

PURPOSE

The Committee considered the scheduling exemption for food grade and pharmaceutical grade white mineral oils (WMOs) following concerns regarding risk from aspiration of WMOs.

BACKGROUND

WMO is a hydrocarbon mixture derived from either naphthenic or paraffinic base oils. Composition and properties vary depending on the source and the degree of refinement. WMO, often referred to as white oil, is crystal clear, odourless and can be found in a variety of different viscosities. WMOs are among the most versatile of petroleum products and, because of their high purity, may be employed where less highly refined products would be unsuitable. WMOs are used in cosmetics, pharmaceuticals, food, paints, animal feeds, plastics, adhesives and household cleaners. Certain WMOs can be classified into food, pharmaceutical and technical grade categories, depending on factors such as the degree of refinement, certain handling procedures, and the addition and/or removal of certain substances.

WMOs are currently captured in the liquid hydrocarbons Schedule 5 group entry, with a specific exemption for “food grade and pharmaceutical grade white mineral oils”. This exemption was introduced at the November 1996 Meeting in order to clarify the Committee’s position that such oils are exempt from scheduling. It was unclear from the record of that Meeting what prompted the WMO exemption.

In February 2002, XXXXX received a letter highlighting concern about US reports of deaths in children due to aspiration of baby oil which could occur when low viscosity oil or liquid hydrocarbon was accidentally ingested. The letter proposed that Australia adopt the US requirement for child-resistant closures (CRCs) on baby oil containers. A Secretariat response noted that the concerns had been referred to a June 2003 meeting of the States, Territories & New Zealand Health Authorities (STANZHA), along with data provided by various Australian Poison Information Centres (PICs). The PIC reports suggested that child accidental ingestion of baby oil was not a significant health concern. On the basis of available information, STANZHA agreed that in the absence of evidence to justify regulation of baby oil, its unrestricted status remained appropriate at that time. Furthermore, it was noted that baby oil was specifically exempted from scheduling. STANZHA concluded that substances not controlled in their poisons legislation or equivalent were outside their jurisdiction and that it would be appropriate to refer the matter to the relevant fair trading authority for consideration. The February 2009 NDPSC Meeting noted that no record was found of this matter coming before NDPSC, or indeed confirming whether STANZHA had in fact referred this to fair trading authorities as indicated.

The October 2008 NDPSC Meeting noted that a recent episode of "Today/Tonight" focused on the dangers of infants ingesting (and aspirating) WMO, and noted that in the US, all baby oils have CRCs. Members also noted that in September 2008, Johnson & Johnson Pacific released a media statement which stated that it had decided to move to CRC caps for all baby oil products sold by Johnson & Johnson companies worldwide, and would implement this decision as soon as possible in Australia. Interim advice from NICNAS was that a Priority Existing Chemical (PEC) Review would not be warranted at this time. The Committee therefore agreed to revisit this issue at the February 2009 NDPSC Meeting.

Baby oils are generally considered to be simple consumer goods i.e. not regulated as therapeutic or cosmetic goods.

DISCUSSION - SUBMISSIONS

Members noted the following regarding the classification of WMOs:

- These classifications do not appear to be separately specified in Australia. References to food, pharmaceutical and technical grades by Australian manufactures largely appear to mean compliant with the following US requirements.

Food Grade WMO

- Food grade WMO meets specifications set forth by the USFDA's *Code of Federal Regulations (CFR) 21 (Food and Drugs) for approving WMOs for direct and indirect food contact*. These are:

  21 CFR 172.878 *Food additives permitted for direct addition to food for human consumption*.

- This requires compliance with the US Pharmacopeia (USP) tests for carbonizable substances and sulfur compounds.
- Requires that the WMOs meet the specifications prescribed in the *Journal of the Association of Analytical Chemists* (1962 Volume 45, page 66).
- Allows the WMO to contain any antioxidant permitted in food by regulation, in an amount not greater than that needed to reproduce its intended effect.
- Sets limits for particular use patterns, largely restricting to < 1 per cent WMO.

21 CFR 178.3620(a) *Indirect Food additives: adjuvants, production aids and sanitizers*

- WMO meeting the specifications in 172.878 (above) may be used as a component of non-food articles provided such use complies with any applicable limitations.

- Additionally food grade WMO must be processed and repackaged through a white room environment.

Pharmaceutical Grade WMO

- This grade appears to be very similar to food grade WMO.
- In the US WMOs used in cosmetic/medical applications meet purity tests in the USP/ National Formulary (NF) as well as 21 CFR 172.878. The tests prescribed in these standards assure the absence of polynuclear aromatic compounds so that these materials can be used in medical and direct food applications.
- Grades meeting NF standards range in viscosity from 55 to 174 Saybolt Universal Seconds (SUS); grades meeting USP standards range in viscosity from 178 to 550 SUS. [Members noted advice that SUS is a measure of kinematic viscosity used in classical mechanics. It is the time that 60 cm^3 of oil takes to flow through a calibrated tube at a controlled temperature].

Technical Grade WMO

- Technical white mineral oil meets specifications set forth also by the FDA, 21 CFR 178.3620(b) for only indirect food contact and a white room is not necessary.

The Committee noted the following from the liquid paraffin (WMO) Martindale monograph:

Adverse effects/precautions

- Absorbed to a slight extent and may give rise to foreign-body granulomatous reactions.
- Lipoid pneumonia has been reported after aspiration of liquid paraffin. Because of the risk of aspiration, oral liquid paraffin should not be given to patients who have difficulty swallowing, or to those with impaired neurodevelopment.

- Liquid paraffin should not be used when abdominal pain, nausea, or vomiting is present.

Uses and Administration

- Taken orally, liquid paraffin acts as a lubricant and, since it keeps the stools soft, it has been used in the symptomatic treatment of constipation, although it should be used with caution because of its adverse effects. The recommended daily oral dose is 10 to 30 mL in divided doses.
- Externally, liquid paraffin may be used as an ingredient of ointment bases, as an emollient and cleanser in certain skin conditions, and as an ophthalmic lubricant in the management of dry eye.

The Committee also noted the following from a PubMed search for "lipoid pneumonia" relating to WMO aspiration:

- A large proportion of case reports of lipoid pneumonia caused by WMO aspiration arise from its use as a laxative (including the use of baby oil as a laxative).
- Frequently WMO aspiration is as a result of swallowing dysfunction/immature or otherwise compromised gag reflex. It was suggested that WMO may not elicit a normal protective cough reflex and may impair mucociliary transport.
- Symptoms may range from none to respiratory failure and the degree of inflammation can range from little to none up to sudden severe necrosis and haemorrhage. The clinical presentation is often totally asymptomatic but can present as acute or chronic symptoms attributable to pneumonia, pulmonary fibrosis.
- A case report of lipoid pneumonia secondary to baby oil aspiration, including a review of the literature, noted that the paucity of information regarding this subject points to the need for increased public and physician awareness of the problem (Bandla, HP, Davis, SH & Hopkins, NE 1999 Feb, 'Lipoid pneumonia: a silent complication of mineral oil aspiration', *Pediatrics,* 103(2):E19).

A transcript of the Today Tonight program broadcast on the 23 September 2008 asserted that baby oil, massage, hair and bath oils, essential oils, and eucalyptus and camphor oils are responsible for at least 3000 reported ingestion accidents in young children every year in Australia. In addition it was claimed that:

- In the US, 20 children a year die from breathing in household oils and 5 of these deaths are from baby oil. In total, around 80,000 household oil ingestion accidents are reported to the US Poisons Centre yearly.
- Seven years ago, the US Consumer Product Safety Commission (CPSC) made child-resistant packaging (CRP) mandatory for oily liquids containing hydrocarbons - like baby oils, bath, body, hair and massage oils, and sunscreens.

Members noted the following from a 2001 US CPSC media release:

- The CPSC had voted unanimously to require CRP for some common household products and cosmetics containing hydrocarbons that can poison children. This safety standard will help prevent injuries and deaths to children < 5 who swallow and aspirate certain oily liquids containing hydrocarbons. When these products enter the lungs, chemical pneumonia can develop and cause death.
- If products contain ≥ 10 per cent hydrocarbons by weight and have a low viscosity they will have to be in CRP. Thicker products are less likely to be aspirated.
- The CPSC was aware of five fatalities of children < 5 years old from 1993 to 2001 involving aspiration of hydrocarbon products. The most recent fatality occurred after a 16-month-old aspirated a baby oil product.

Members were advised that this CRP requirement came into effect from October 2002 in the US through 16 CFR 1700 *Household Products Containing Hydrocarbons; Final Rules*. Members noted:

- These rules, in addition to the above, stipulate that the CRP requirement applies to certain pre-packaged non emulsion-type liquid household chemical products, including drugs and cosmetics, that contain ≥ 10 per cent hydrocarbons by weight and have a viscosity of < 100 SUS at 100°F (38.6°C).
- Direct aspiration into the lung, or aspiration during vomiting, of small amounts of petroleum distillates and other similar hydrocarbon solvents can result in chemical pneumonia, pulmonary damage, and death. These chemicals are the primary ingredients in a multitude of consumer products to which children have access.
- The viscosity of a hydrocarbon-containing product contributes to its potential toxicity. Products with low viscosity pose a greater risk of aspiration into the lungs. Details of an additional death resulting from aspiration of baby oil were also noted. A 16 month-old who had a history of respiratory problems ingested baby oil. The child was admitted to the hospital on the following day with breathing problems and died 29 days after the exposure.
- The final rules exclude aerosols, products packaged in mechanical pumps and trigger sprayers (provided that the spray mechanism is either permanently attached to the product or has a child-resistant attachment). Writing markers and ballpoint pens were also exempt due to the difficulty a child would have in obtaining a toxic amount of fluid from these types of products. For the same reason, products that were packaged so their contents were not free-flowing, such as some battery terminal cleaners, paint markers, and make-up removal pads, were also excluded.

The Committee also noted the following from comments to the CPSC when consulting on the proposed 16 CFR 1700 (http://www.cpsc.gov/library/foia/foia00/pubcom/hydroc2.pdf):

- There are two types of pathology reported after hydrocarbon aspiration, namely the acute diffuse chemical pneumonitis due to low viscosity hydrocarbons and the chronic lipoid pneumonia associated with high viscosity hydrocarbons.

- The less viscous hydrocarbons are likely to get into the lungs. Due to their physical properties they "creep" along mucosal surfaces and produce a significant pneumonia due to their irritant effects. Children exhibit shortness of breath, hypoxemia and significant changes in chest X-rays.
- When the more viscous hydrocarbons get into the lung, they produce a more localised inflammatory process which results in a less devastating problem. Typically mineral oil aspirations have been reported in humans taking it for constipation on a long-term basis. Most cases have occurred in patients with neurologic impairment who perhaps may also have some abnormalities with their swallowing mechanism. These pneumonias are localized and the diagnosis can only be confirmed by demonstrating fat laden lung macrophages.
- A comment from a Medical Director of a Drug and Poison Information Center (who was a paediatrician, medical toxicologist and clinical pharmacologist) asserted that he had seen hundreds of children with hydrocarbon pneumonia secondary to aspiration of low viscosity straight chain hydrocarbon products such as mineral spirits, lighter fluid, gasoline, furniture polish, etc. Most recover but there had been at least one fatality due to low viscosity hydrocarbon aspiration. On the other hand, the Director had not encountered a single case of accidental ingestion of WMO resulting in pneumonia but had seen 3 or 4 cases of lipoid pneumonia secondary to chronic usage of mineral oil [as a laxative], none of which were fatal.
- A comment from the Cosmetic, Toiletry and Fragrance Association (CTFA) noted that the term hydrocarbon can be misleading because the differences in the chemical and physio-chemical properties (which affect things like viscosity, volatility, surface tension etc.) of hydrocarbons will result in differences with regard to the relative risk of aspiration leading to some degree of toxicity. In this context, WMO is very different from other "hydrocarbons". The CTFA asserted that the child fatality risk from purchase and storage an individual bottle of baby oil is less than 1 in 100,000,000.

The Committee also noted the following from 2 issues papers considered by the January 2002 Meeting of the OECD Task Force on Harmonisation of Classification and Labelling:

US Issue paper on Aspiration Toxicity
(http://ecb.jrc.it/classlab/2703a1_OECD_aspiration_toxicity.doc)

Justification for the use of 100 SUS as viscosity cut off
(http://ecb.jrc.it/classlab/2703a2_IND_aspiration_cutoff.doc):

- Depending on the nature of the material aspirated into the lung, pathological consequences such as pneumonitis, chemical pneumonia or lipoid pneumonia can be severe and life-threatening.
- A variety of hydrocarbons have been implicated in human poisoning incidents, with ancillary data compiled in various animal studies. Although human experience identifies an association between chemical pneumonia and various aliphatic and

aromatic hydrocarbon mixtures, p-dichlorobenzene, and certain detergents, no reported human incident identifies primary alcohols or ketones. The potential for aspiration hazard in ketones and alcohols is based solely on animal data.

- Low viscosity and low surface tension determine the potential of a substance to constitute an aspiration hazard to the lung; low viscosity leads to flow and low surface tension leads to spread of a liquid through the respiratory tract. In addition, low solubility appears to be correlated with the ability of substances to penetrate the lungs. The characteristic of low solubility points to nonpolar organic compounds. Substances associated with chemical pneumonia do not include those with extremely high volatility or low boiling point.
- Based on toxicological considerations, several classes of chemicals pose a risk of aspiration toxicity, namely aliphatic hydrocarbons such as kerosene and gasoline, fat-like materials such as mineral oils, and certain halogenated and aromatic hydrocarbons.
- The EU sets an upper limit (for use in consumer products) of viscosity of 48.8 SUS at 40^{o} C unless surface tension exceeds a cut off value of 33 mN/m at 25^{o} C. US regulations set a viscosity cut off value of 100 SUS at 38.6 ^{o} C and surface tension is not considered (only hydrocarbons are classified, whereas the EU include ketones and alcohols as well). The US further articulates that viscosities of $\leq$ 35 SUS pose severe aspiration hazard and products with viscosities in the range of 35 to 100 SUS pose moderate aspiration hazard.
- Hydrocarbon mixtures can have extremely wide ranging viscosity values, while the surface tension is confined to a narrow range.
- Human incident data used to support the US hydrocarbon regulation was based upon cases involving deaths and hospitalizations due to ingestion of hydrocarbons from a number of consumer products including; paint thinners, lamp oil, baby oil, kerosene, mineral seal oil, gasoline, turpentine, and other hydrocarbons. Some of these other hydrocarbons include; trumpet valve oil, degreaser, mineral spirits, chain saw oil, spot remover, automatic transmission fluid, automotive cleaning compound, pine oil, and motor oil.
- In addition to human data, animal data also supports regulation using a viscosity value of up to 100 SUS. Based on deaths at 24 hours post exposure, the aspiration hazard potential in the rat model appeared to be the greatest for hydrocarbons with a viscosity in the range of 32 - 59 SUS. However, changes in the lung weights were noted at 24 hours post exposure following exposure to hydrocarbons having a viscosity up to 100 SUS. These changes are consistent with pulmonary changes seen in humans. It was important to note that not all human fatalities due to hydrocarbon exposure occur within 24 hours. Many cases of aspiration of hydrocarbon results first in chemical pneumonia; death occurs only after a lingering period of illness.

Pre-meeting Comments

Members noted the following from pre-meeting comments:

XXXXX

- XXXXX
- Asserted that the risk of aspiration of WMO from the typical use of toothpastes, sunscreens and cosmetic creams and lotions would be negligible and therefore contended that the current scheduling exemption should remain for such products.
- Where there were products presented to the consumer in a form that may increase the risk of aspiration, then the usage characteristics (how often used, where used, particle size, etc.) need to be carefully considered so that unreasonable scheduling of low risk products is not introduced.
- In many cases, an additional labelling statement instructing that the product only be used in well ventilated areas could be sufficient to mitigate health hazards rather than removing the scheduling exemption. [Members noted that aspiration of aerosolised WMO produced by products such as furniture polish, smoke detector tester or sunscreen spray may not present the same hazard as that of neat low viscosity WMO, and also noted that there was currently an exemption from the Schedule 5 entry for liquid hydrocarbons for preparations packed in pressurised spray packs.]

XXXXX

- Markets personal care and other household products which contain liquid hydrocarbons as an ingredient, including products containing pharmaceutical grade WMO. They were not aware of any adverse events involving ingestion of their products which contain pharmaceutical grade WMO.

XXXXX

- Has a pharmaceutical grade WMO-based product which is currently exempt from scheduling.
- Supports meaningful and realistic restrictions for use of chemicals in personal care products and supports scheduling where this is done in accordance with risk.

XXXXX

- Asserted that these grades of WMO have been used safely in personal care products for many years. Advised that, based on the experience and advice of XXXXX, there has only been one recent incidence of aspiration of food grade or pharmaceutical grade WMO in Australia.
- Although the theoretical aspiration hazard may be real, experience demonstrates that the risk associated with the use of these products is extremely small. Therefore asserted that changes to scheduling of these products will have an enormous impact on the industry without adequate justification.

- Further asserted that food grade and pharmaceutical grade WMO that undergo a deep refining process should not be treated in the same manner as other hydrocarbon liquids that do not go through the extensive refining process. The current scheduling exemption for food grade and pharmaceutical grade WMO should be maintained.

XXXXX

- Noted an interest in this matter. Members noted that these comments had not addressed a matter under Section 52E and were therefore not valid pre-meeting submissions as defined by legislation.

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

A Member noted that children and the elderly were the most at-risk groups from WMO aspiration, but even amongst these groups, the incidence of aspiration was low. However, the hazard was well established and if aspiration occurred, the consequences could be serious. Members agreed that this was a hazard with a very low but foreseeable risk.

A Member suggested that if the Committee was minded to take action then this should be restricted to WMO baby oil products, noting that infants have a strong sucking reflex. Another Member noted that out of 2261 ingestions of baby oils in US (figures from 2007 across 61 poisons centres), there were no deaths recorded. The Member also noted that the US CRC requirements have been in place since 2002, yet there seems to have been little change in the incidence of ingestions. The Member suggested that it was entirely possible that, given the at risk groups involved, a CRC may actually increase the risk of aspiration i.e. use by the elderly who may have difficulty with opening a CRC, or by parents of infants who need to keep one hand on their child, may mean that a CRC merely encourages leaving the lid off entirely.

A Member noted that the children in the Australian cases of WMO ingestion all appeared to recover quite well and that no deaths had been recorded in Australia. Another Member asserted that the extent of the risk had been somewhat sensationalised by the media. Members also noted that the risk from aspiration of WMO was a result of the physical properties (i.e. viscosity) rather than any purity issue arising from the refinement of the WMO. A Member asserted that aspiration of any liquid with similar viscosity runs similar risks, such as vegetable oils or even gastric acids.

Another Member observed that the risk of chemical pneumonitis is greater for some other liquid hydrocarbons, such as kerosene, petrol or turpentine, than for WMO, which is why these currently have CRC requirements (when in containers of ≤ 5 L capacity). In the US there were around 20 deaths a year from chemical pneumonitis by aspiration of liquid hydrocarbons out of a population of around 300 million. A Member asserted that if the

Committee wished to pursue mandating CRC controls on WMO products then there would be an obligation to look at all oils.

A Member advised that there were 69 calls in 2008 to the Victorian PIC regarding baby oils (out of a total of 40,230 calls), but as usual for PIC data, no outcome information was available.

A Member also advised that the recent announcement by Johnson & Johnson Pacific to voluntarily add CRCs to all its baby oil products may not reflect an actual concern in Australia, but rather that the company may be globally sourcing its products from the US (which mandates CRCs for these products). A Member observed that manufacturers with fast-moving consumer goods may respond rapidly to perceptions of risk, irrespective of their substance.

A Member suggested making the current WMO exemption conditional on displaying the label "Keep Out Of Reach Of Children", noting that such labelling already appears on many products intended for use on children. Other Members maintained, however, that such a label seemed incompatible with the use pattern of baby oils.

The Members considered a proposal that preparations with > 10 per cent food or pharmaceutical grade WMO and a viscosity ≤ 100 SUS would need a CRC and label "Keep Out Of Reach Of Children" to qualify for exemption from the Schedule 5 liquid hydrocarbons entry, in line with the USFDA restrictions for hydrocarbons. The Committee generally agreed, however, that this was not appropriate, noting that the most potentially dangerous liquid hydrocarbons already had CRC requirements. Instead, it was agreed that the current scheduling of WMO remained appropriate.

The Members also considered specific SUSDP definitions for food and pharmaceutical grade WMO, noting that there do not appear to be current Australian specifications for these grades. However, it was noted that there did not appear to be any issue currently and that industry was comfortable with adhering to international specifications, such as the US specifications. The Committee therefore agreed that specific definitions in the SUSDP were not warranted at this time.

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The Committee confirmed that the current scheduling exemption of food grade and pharmaceutical grade white mineral oils remains appropriate.

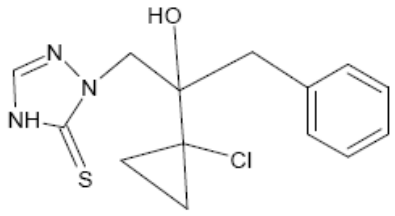
4.2 PROTHIOCONAZOLE-DESCHLORO & PROTHIOCONAZOLE-TRIAZOLIDINETHIONE

PURPOSE

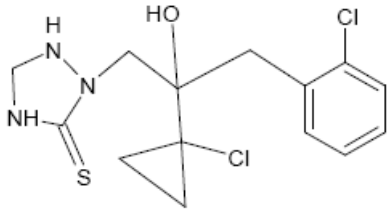
The Committee considered scheduling prothioconazole-deschloro and prothioconazole-triazolidinethione.

BACKGROUND

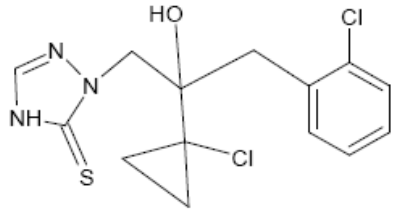
Prothioconazole-deschloro (IUPAC name 2-[2-(1-chlorocyclopropyl)-2-hydroxy-3-phenylpropyl]-2,4-dihydro-3H-1,2,4-triazole-3-thione) and prothioconazole-triazolidinethione (IUPAC name 2-[2-(1-chlorocyclopropyl)-3-(2-chlorophenyl)-2-hydroxypropyl]-1,2,4-triazolidine-3-thione) are two by-products produced during the manufacturing of prothioconazole, with the following structures:



Prothioconazole deschloro



Prothioconazole triazolidinethione



Prothioconazole

Prothioconazole-deschloro and prothioconazole-triazolidinethione do not currently have specific schedule entries. They are likely to currently fall into Appendix B as salts/derivatives of prothioconazole.

The June 2008 NDPSC Meeting was advised that XXXXX had provided data to amend the particulars and conditions of the APVMA approved active constituent prothioconazole. XXXXX had modified its manufacturing process in order to eliminate a by-product, prothioconazole-desthio, which had been identified as a significantly more potent developmental toxin than prothioconazole itself. However the new manufacturing process resulted in the generation of two new by-products, prothioconazole-triazolidinethione (at < XXXXX per cent), prothioconazole-asymmetric disulfide (at < XXXXX per cent), together with an increased amount of the by-product prothioconazole-deschloro, which was also present in the technical grade active constituent (TGAC) produced by the old manufacturing process, from < XXXXX to < XXXXX per cent. An evaluation report on the new TGAC prothioconazole highlighted that two of the by-products, prothioconazole-deschloro and prothioconazole-triazolidinethione, were skin sensitizers in XXXXX. No additional skin sensitization studies were provided on the new-TGAC produced by the modified manufacturing process which may contain up to XXXXX per cent of these two by-products. Due to concerns that the by-products had the potential to cause skin sensitisation, the Committee agreed that prothioconazole would need to be upscheduled to Schedule 5 unless sensitisation data on the TGAC (such as a Local Lymph Node Assay) was provided by the applicant which supported an Appendix B listing. Members agreed to foreshadow inclusion of prothioconazole in Schedule 5 for the October 2008 NDPSC Meeting.

At the October 2008 NDPSC Meeting, a Member maintained that the current Appendix B scheduling of prothioconazole *per se* was appropriate based on its low toxicity and that the deschloro and triazolidinethione by products responsible for the skin sensitisation should be separately listed in Schedule 5 with a cut-off to unscheduled in amounts of less than about 0.5 per cent. The Committee was of the opinion that there was sufficient data to support the deschloro and triazolidinethione by-products being captured by Schedule 5.

DISCUSSION - SUBMISSIONS

The Committee recalled the following toxicity data for the deschloro and triazolidinethione by products from the evaluation report:

XXXXX

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included included (a) toxicity and safety, (c) potential hazards and (e) dosage and formulation.

A Member noted that after all the previous work by the Committee in establishing prothioconazole as suitable for Appendix B listing, it would not be ideal to reschedule

prothioconazole itself. The sensitisation concerns were only in relation to two impurities arising from a specific manufacturing process and different methods may be developed in the future which may not produce these particular impurities. The Member therefore supported the foreshadowed intent of specifically scheduling prothioconazole-deschloro and prothioconazole-triazolidinethione. A Member asserted that it was important to remember that the new TGAC prothioconazole no longer included a strong developmental toxicant impurity.

A Member noted that there was little toxicological data for the deschloro and triazolidinethione impurities and there was a risk that this unknown toxicology may actually require more restrictive scheduling than the proposed Schedule 5 entries. A Member agreed that there was little data but noted that these impurities would only be present at low levels. Only the sensitisation risk was likely, noting that the impurities were unlikely to be reproductive toxicants at these low levels. Another Member queried whether specific schedule entries for prothioconazole-deschloro and prothioconazole-triazolidinethione might lead to products including these substances as major ingredients rather than at impurity levels (i.e. may possibly have insecticidal activity), in which case the other unknown toxicity data would be important. The Committee generally agreed, however, that this was unlikely and that it would be appropriate at this time to consider scheduling in light of these substances only being present in products at impurity levels.

The Committee also recalled that the foreshadowed Schedule 5 entries for the deschloro and triazolidinethione impurities included ≤ 0.5 per cent exemptions from scheduling. This cut-off value appeared to have been a pragmatic value for the purposes of public consultation on the foreshadowed proposals. A Member noted that the sensitisation tests were only done at XXXXX and XXXXX per cent concentrations for the deschloro and triazolidinethione impurities respectively, so there was no real basis for setting an exemption cut-off. The Committee agreed that it was unfortunate that skin sensitisation testing had not been undertaken for the new TGAC. The Committee generally agreed that the exemption cut-off foreshadowed at 0.5 per cent could not be increased, XXXXX.

A Member queried why impurity concerns were being addressed by scheduling, mechanisms, rather than GMP (good manufacturing practice) compliance through the regulator. The Member noted that paragraph 1(2)(k) in the SUSDP exempted substances present as an impurity in a pesticide at a level set by the APVMA. The Committee noted advice that scheduling was needed for where the impurities exceeded the APVMA's limits. Members were advised that impurities dealt with through the registration process were usually present at much lower levels.

Members also noted that the names prothioconazole-deschloro and prothioconazole-triazolidinethione did not appear to be common names and could not be used to derive the exact structures of these compounds. However, these names were those recognised by the industry producing these by-products. The Committee therefore agreed to include a cross reference from the IUPAC names in the SUSDP index.

RESOLUTION 2009/55 - 11

The Committee decided to schedule both prothioconazole-deschloro and prothioconazole-triazolidinthione into Schedule 5 with a cut off to unscheduled of ≤ 0.5 per cent and to include a cross reference from the IUPAC names.

Schedule 5 – New entries

PROTHIOCONAZOLE-DESCHLORO **except** in preparations containing 0.5 per cent or less of prothioconazole-deschloro.

PROTHIOCONAZOLE-TRIAZOLIDINETHIONE **except** in preparations containing 0.5 per cent or less of prothioconazole-triazolidinethione.

SUSDP index – New entry in the SUSDP 25 index

2-[2-(1-CHLOROCYCLOPROPYL)-2-HYDROXY-3-PHENYLPROPYL]-2,4-DIHYDRO-3H-1,2,4-TRIAZOLE-3-THIONE
See PROTHIOCONAZOLE-DESCHLORO

2-[2-(1-CHLOROCYCLOPROPYL)-3-(2-CHLOROPHENYL)-2-HYDROXYPROPYL]-1,2,4-TRIAZOLIDINE-3-THIONE
See PROTHIOCONAZOLE-TRIAZOLIDINETHIONE

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

5.1 SUSDP, PART 4

5.1.1 ETHYLENE GLYCOL AND DIETHYLENE GLYCOL

PURPOSE

The Committee considered the scheduling of ethylene glycol and diethylene glycol (DEG) in light of a number of recent incidents where these substances were substituted for non-toxic propylene glycol.

BACKGROUND

Ethylene glycol

The May 1978 Meeting agreed that ethylene glycol in antifreeze should be Schedule 6. The May 1979 Meeting allowed down-scheduling to Schedule 5 for ethylene glycol boiling point/freezing point modifiers containing ≥ 10 mg/kg of the bittering agent benzyldiethyl (2,6-xylylcarbamoyl methyl ammonium benzoate). The bittering agent designation was simplified at the November 1988 Meeting to “denatonium benzoate”.

The April 1994 NDPSC Meeting discussed the presence of ethylene glycol in many products and the lack of appropriate labelling (noting the human single lethal dose was ~1.4 mL/kg) and agreed to undertake a review. The August 1995 NDPSC Meeting reviewed the toxicology of ethylene glycol and agreed to foreshadow more restrictive scheduling as the risk of accidental poisoning, leading to serious morbidity with renal and liver impairment or death, particularly in children, was high. Further discussion was subsequently deferred until May 1996.

The May 1996 NDPSC Meeting reconsidered the August 1995 review in light of new information, particularly a report that bittering agents may not decrease the initial ingestion volume. The Committee recommended that ethylene glycol products at any concentration which contained a bittering agent should be Schedule 5, with a 2.5 per cent exemption and a requirement for a child resistant closure (CRC) when ≥ 50 per cent and in containers of ≤ 5 L. All other ethylene glycol products should be in Schedule 6 with a CRC when in containers of ≤ 5 L. This decision was foreshadowed in view of the many products affected which had not previously been scheduled. The August 1996 NDPSC Meeting agreed to the foreshadowed decision, with a deferred implementation of September 1998.

The May 1996 NDPSC Meeting also considered the potential for inadvertent scheduling of ethylene glycol derivatives. It was agreed that ethylene glycol (or its derivatives) as a component of pharmaceuticals or ag/vet chemicals did not warrant special attention for scheduling. If ethylene glycol contributed significantly to the overall toxicity of the product, then its toxicity should be taken into account. However, it was considered that auto products and other household products based on ethylene glycol as the major active ingredient should be scheduled because of known exposure potential. The February 2009 NDPSC Meeting noted that the 'known exposure potential' was not explained further, but presumably referred to ethylene glycol's sweet taste and presence in liquid domestic products. The Committee therefore agreed to exclude derivatives from any proposed schedule entry.

The February 1998 NDPSC Meeting noted that ethylene glycol was used in paints/tinters in concentrations which would be captured by the Schedule 6 entry. The Committee noted that there was little potential for children to gain access to tinters. Furthermore, the finished paints would be 'unattractive' to young children, who for other reasons would not be given free access to them. The February 2009 NDPSC Meeting noted that 'other reasons' was not explained further, but presumably assumed that young children were not usually allowed unsupervised access to paints. It was therefore agreed that an exemption was appropriate.

The May 1998 NDPSC Meeting noted information from several Poisons Information Centres on poisonings with ethylene glycol products. No significant morbidity had resulted from any of the exposures detailed. Members noted that this may be as a result of the effectiveness of the bittering agent in preventing consumption of any more than the first mouthful.

DEG

DEG is used worldwide as an intermediate in the production of polyester resins, polyurethanes, explosives and other glycols. It is used in cement grinding, as an anti-freeze, in brake fluids and as a plasticiser. It is also used as a solvent for paints, lacquers and cosmetics.

The May 1974 Meeting, in considering a number of chemicals used in insecticides, agreed that DEG should be exempted from the requirement of scheduling.

The June 2007 NDPSC Meeting was advised that Queensland had taken action on toothpaste products adulterated with DEG. This followed the recall of product from stores in New South Wales and a number of media articles. The October 2007 NDPSC Meeting noted that NICNAS had undertaken a call for information on DEG in oral cosmetic products (e.g. toothpaste and mouthwash) to determine the extent of use. The June 2008 NDPSC Meeting considered a NICNAS assessment on DEG and decided to ban use in toothpastes and mouthwashes through inclusion in Appendix C, with a ≤ 0.25 per cent cut-off.

DISCUSSION - SUBMISSIONS

In September 2008, the TGA released a media statement advising that it was recalling Thermoskin brand gel hot/cold packs after testing revealed the presence of ethylene glycol, rather than the non-toxic ingredient propylene glycol. The TGA's investigation was prompted by the accidental poisoning of a young child following the ingestion of the contents of a hot/cold pack. Following this incident, the TGA wrote to all sponsors of gel hot/cold packs to obtain samples for testing. It was confirmed that some of these products also contained ethylene glycol (which were also recalled). The TGA subsequently has advised that some of the recalled products also contained DEG.

XXXXX therefore referred both ethylene glycol and DEG to the Committee for review. In particular, it was suggested that the Committee:

- Consider reviewing the ≤ 2.5 per cent exemption cut-off for ethylene glycol.
- Consider aligning DEG scheduling with that of ethylene glycol.

Additionally, it was suggested that the Committee may wish to consider adopting the current Appendix C entry for DEG in toothpastes or mouthwashes at > 0.25 per cent. While propylene glycol substitution in toothpastes or mouthwashes has previously only been identified by the Committee as an issue with DEG, ethylene glycol appears to have similar attributes that led to the DEG substitution risk (sweet tasting and cheaper than propylene glycol), noting that ethylene glycol is also more acutely toxic that DEG.

Pre-meeting comments

XXXXX advised that it supplies XXXXX products containing ethylene glycol and DEG to resellers for retail sale within Australia, and is engaged in the formulation of these products. They wished to nominate as an interested party in case there were wider ramifications. Members noted that this comment had not addressed a matter under Section 52E and was therefore not a valid pre-meeting submission as defined by legislation.

XXXXX (a manufacturer and supplier of both ethylene glycol and DEG to industrial users) recommended, given the similarity of the toxicological profile of DEG to ethylene glycol, that any scheduling of DEG be aligned with that of ethylene glycol. Also included in the comment were summaries of the ethylene glycol and DEG toxicology monographs from Patty's Toxicology, 5th edition (Bingham, E; Cohrssen, B; Powell, C: Wiley US, 2001) (discussed below).

XXXXX:

Ethylene glycol

- This consideration was prompted by the recall of hot/cold packs containing ethylene glycol rather than propylene glycol. However, this was caused by mis-use of ethylene glycol and could not have been prevented by tighter control through scheduling.
- Noted that all ethylene glycol scheduling exemptions currently in place had been previously risk assessed and asserted that this remained valid. Specifically:
  - Asserted that ethylene glycol had low acute oral toxicity and that the major ingestion risk relates to its sweet taste. Addition of a bittering agent reduces this risk and warrants lower scheduling requirements for these products (Schedule 5 rather than Schedule 6).
  - Asserted that preparations with low concentrations of ethylene glycol posed little ingestion risk. Asserted that due to its low toxicity a large quantity of low concentration preparations need to be ingested before producing any harmful effect and that maintenance of current scheduling exemption for products containing ≤ 2.5 per cent was warranted.

Diethylene Glycol

- As far as XXXXX was aware, DEG was not involved in the incident resulting in the recall of medical devices. Members recalled the advice above that DEG was in some of these products according to TGA.

Recommendation

- On the basis that this review has been prompted by mis-use of ethylene glycol, supports maintaining scheduling status quo for ethylene glycol and DEG.

Ethylene glycol

Members recalled that NICNAS referred DEG for consideration at the June 2008 NDPSC Meeting. The NICNAS DEG hazard assessment included information from a 2004 OECD SIDS Initial Assessment Report on the Ethylene Glycols Category. Members may wish to note the following from the OECD report regarding the toxicity of ethylene glycol:

- The evaluated ethylene glycol category included ethylene glycol, DEG, triethylene glycol, tetraethylene glycol and pentaethylene glycol. The report was prepared from information identified prior to October 2002. The Ethylene Glycols Consortium, an international industry group, reviewed the report and provided unpublished data.

Use

- In 1999, 78 per cent was used in the manufacture of polyethylene terephthalate (PET) to make bottles, film and fibers. 13 per cent was used to make antifreeze. The remaining 9 per cent was in other, smaller uses, including de-icing/anti-icing of planes; in surface coatings, paints, inks, waxes, adhesives; as a component of electrical boards and electronic condensers; as a component in heat transfer fluids; as a reacted ingredient in unsaturated polyester resins; and in industrial hydraulic fluids and surfactants.
- The February 2009 NDPSC Meeting noted that ethylene glycol is also used as a solvent in a large number of APVMA registered products.

Exposure

- Human exposure in commercial products can occur through dermal contact and dietary intake and can also occur through inhalation of air near point sources. Even using conservative assumptions the estimates were very low – in the ug/kg bw/day range.
- Dermal contact may occur, infrequently and for short periods, when topping off vehicle radiator antifreeze. There are low concentrations in windshield deicers; automotive and household waxes/polishes; caulking, glazing and drywall compounds; and latex paints.
- One study has demonstrated the presence of ethylene glycol (ppb range) in food packaged under extreme storage conditions (high heat) in PET. In Europe, Directives 93/10/EEC. 1993 O.J. (L.93) and 2002/72/EC set a migration limit of ≤ 30 mg per kg of food.
- Ophthalmic solutions may contain ethylene glycol at low levels. It is not an intentional ingredient, but is formed by reaction with water when the solutions are sterilized with ethylene oxide.
- The February 2009 NDPSC Meeting noted that exposure from deliberate substitution to replace non-toxic (but more expensive) propylene glycol was not addressed.

Absorption

- Oral – essentially completely absorbed by laboratory animals.
- Inhalation – rats exposed to 32 mg/m^3 vapour, or 184 mg/m^3 condensation aerosol on particles, absorbed ~ 60 per cent of the ethylene glycol. Using a minute volume of 0.7935 mL/min/g bw for rats, the absorption estimate increased to ~100 per cent.
- Dermal – variability and potential methodological problems in the various human and rodent studies (both *in vivo* and *in vitro*) preclude drawing meaningful quantitative data on absorption. Rather, it could only be concluded that dermal exposure will yield plasma concentrations of ethylene glycol and metabolites far below an equivalent oral dose.

Distribution, Metabolism and Elimination

- Ethylene glycol is completely soluble in water and was expected to be well distributed throughout the aqueous tissues of the body with lower concentrations in adipose tissue.
- The main metabolic pathway of ethylene glycol is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases (ADH/ALD). The main metabolites are carbon dioxide (in exhaled air), oxalic acid and glycolic acid (in blood, kidneys and urine). It may be directly eliminated by urinary excretion. Acid metabolites are also eliminated in urine and may also be metabolized to CO_2 and eliminated in exhaled breath.

Mode of Action

- Therapy for acute human poisoning relies on inhibition of metabolism using fomepizole or ethanol. Acute toxicity is related to the presence of metabolite(s) and/or metabolic acidosis which develops concurrently with ethylene glycol metabolism. The renal toxicity upon repeated dosing in rats is due to crystal nephropathy caused by calcium oxalate crystals, indicating that kidney oxalic acid concentrations are key to understanding susceptibility to renal effects of ethylene glycol.
- A rat whole-embryo culture system was used to compare the effects of ethylene glycol and glycolic acid. No developmental toxicity was detected with ethylene glycol, while glycolic acid produced malformations similar to those observed *in vivo* at glycolic acid concentrations that correspond to blood levels following developmentally toxic doses of ethylene glycol. Hence the mode of action of ethylene glycol in developmental toxicity is presumed to involve glycolic acid. Mechanistic data indicate that ethylene glycol developmental toxicity requires saturation of an intermediary step in ethylene glycol's metabolism leading to accumulation of the proximate toxicant, glycolic acid. This saturation event occurs following administration of large oral bolus doses of ethylene glycol but does not occur when the same mg/kg/day dose is given at a slower rate.

Acute Toxicity

- Animal – The results of rat acute mortality studies indicate that ethylene glycol generally produces low acute toxicity by the oral, inhalation and dermal routes of exposure (LD_{50} ~10 g/kg). Acute oral toxicity studies conducted in mouse, guinea pig, and rabbit generally indicate that toxicity does not vary greatly among these species. The acute toxic effects can include narcotic effects, metabolic acidosis, and renal toxicity.
- Human – The effects of acute oral exposure have been documented in case reports. While dose is typically poorly characterized, these reports provide qualitative information on the toxicity in humans. Human toxicity has three recognized stages:
  - Stage 1 (0.5 - 12 hrs post-ingestion); primarily neurological effects and may include transient inebriation and euphoria, nausea and vomiting, metabolic acidosis and CNS depression. At very high doses, coma may result.
  - Stage 2 (12 - 24 hrs post-ingestion); primarily cardiopulmonary effects. Most deaths are reported in Stage 2. Specific observed effects include tachycardia, hypertension, severe metabolic acidosis with compensatory hyperventilation, hypoxia, congestive heart failure and adult respiratory distress syndrome.
  - Stage 3 (typically 24 - 72 hrs post-ingestion); renal effects. Renal failure progressing to anuria may occur earlier in severe poisoning. Oliguria, hematuria, proteinuria, acute tubular necrosis, and renal failure are also associated with Stage 3. Calcium oxalate crystals may be present in the urine. In survivors, renal function usually returns to normal but in some cases permanent renal damage has occurred.
- Oral toxicity is expected to be moderate even though tests with animals show a lower degree of toxicity. Because actual dose is not known and because first aid treatment can affect the outcome, the information from case reports was generally insufficient for meaningful characterization of the dose-response relationship. However, it was estimated that the minimum lethal human dose is 100 mL for a 70 kg adult (1.6 g/kg).

Irritation and sensitisation

- Some skin irritation and minor eye irritation. Is not a skin sensitiser in guinea pig.

Repeated Dose Toxicity

- Inhalation toxicity to rats was generally low. Repeated dose inhalation toxicity testing at high levels was difficult because even nose-only exposure was noted to result in nose deposition of quantities of ethylene glycol that could be toxic by the oral route. Studies of repeated dermal exposure were limited but also indicated low toxicity.
- Repeated oral exposure was studied in rats and mice, with rats showing renal effects at substantially lower doses than mice. Differences in strains were also noted. In a 16-week study NOAELs and LOAELs of 150 mg/kg/d and 500 mg/kg/d, respectively,

were established for both Wistar and F344 rats with a critical effect of crystal nephropathy.

- Small studies of adult male workers and volunteers have not identified any significant effects. Working in the presence of ethylene glycol did not produce demonstrable kidney damage in 33 adult male Canadian airport deicing workers. Urinary ethylene glycol was significantly elevated and glycosaminoglycan excretions were significantly decreased in a group of 10 male Finnish mechanics, relative to age-matched male office workers, but oxalic acid, ammonia, calcium, and succinate dehydrogenase activity did not significantly differ between groups. No serious signs of toxicity were attributed to one month of 20-22 hrs daily exposure to 3 to 67 mg/m^3 ethylene glycol by 19 adult male volunteers.

Genotoxicity and carcinogenicity

- Mutagenicity studies in bacteria and *in vitro* mutagenicity studies in mammalian cells were negative in the presence or absence of activation. *In vitro* assays for chromosomal aberrations (CHO chromosomal aberration and sister chromatid exchange assays) have been negative. When tested in an *in vivo* mouse bone marrow micronucleus study the results were equivocal. There were some findings of statistically significant increases in micronuclei but no dose-related trends and potential confounding due to toxicity at high doses. There was no increase in incidence of chromosomal aberrations in mice *in vivo*. An *in vivo* rodent dominant lethal mutagenesis assay at doses up to 1000 mg/kg/d in rats was negative as were good quality cancer bioassays in rats and mice. These studies added to the weight of evidence that ethylene glycol was not genotoxic *in vivo*.
- Several two-year studies in mice (up to 12000 mg/kg/d in feed) and rats (up to 1000 mg/kg/d in feed) gave no evidence of carcinogenic activity.

Reproductive Toxicity

- Reproductive toxicity was assessed by the Reproductive Assessment by Continuous Breeding protocol in which parental mice received chemical via drinking water during pre-mating exposure, cohabitation, pregnancy, and lactation. The F1 generation received prenatal exposure via maternal exposure during gestation, with the exposure continuing during lactation, weaning, and mating of F1 animals and production of an F2 litter. Very large doses produced decreased numbers of litters per fertile pair and numbers of live pups per litter. Additional reproductive toxicity testing in rats indicated no reproductive effects following dietary exposure of up to 1000 mg/kg/day.
- The NOAEL was 840 mg/kg/day, the LOAEL was 1640 mg/kg/day (decreased number of litters per fertile pair). Furthermore, the NOELs for reproductive toxicity by the oral route were no less than the developmental toxicity NOELs. Therefore, estimated NOELs greater than or equal to 2000 mg/kg/d for repeated dose and reproductive toxicity are likely to be conservative (health protective) approximations.

Developmental Toxicity

- Oral developmental toxicity was tested in rats, mice, and rabbits and demonstrated in rats and mice. Effects include reduced foetal body weights and malformations. Developmental toxicity was seen in studies where animals were exposed to high aerosol concentrations but the significant ethylene glycol ingestion from postexposure grooming clouds the interpretation of the results in terms of inhalation concentration versus response.
- The National Toxicology Program's Centre for Evaluation of Risks to Human Reproduction (NTP-CERHR) 2003 report on ethylene glycol concluded: "the lack of reproductive toxicity in experimental animal studies indicates there is negligible concern for reproductive effects in humans".

Members noted the following from the August 1995 NDPSC Meeting:

- Ethylene glycol is sweet-tasting and for this reason a bittering agent had been recommended for most products to be included in Schedule 5.
- The human toxicity is greater than that observed in animals, the lethal oral dose of a 30 per cent solution for an adult human would be approximately 100 mL (42 mL for a 10 kg child, with serious morbidity being reached with only 10 mL of a 30 per cent solution). Dermal and eye toxicity was not considered to be a severe hazard and inhalational exposure was only a hazard at high temperatures or if it was atomised.
- Ethylene glycol was not genotoxic, but in reproduction and developmental studies teratogenic effects including cranio-facial fusions was evidenced. These effects were not found in dietary studies but only in water-based or gavage treatments. Whilst the reproductive toxicity was significant, given the use of the compound this hazard was not considered to be of serious concern.
- The major concern was its high acute toxicity, with treatment requiring IV infusion of ethyl alcohol which also carried risks. The risk of accidental poisoning with ethylene glycol, leading to serious morbidity with renal and liver impairment, or death, particularly in children, was considered to be high.

Members also noted the following from the May 1996 NDPSC Meeting:

- Members agreed that an oral dose of 1400 mg/kg should be taken to be a reasonable estimate of lethal dose in humans who are the most sensitive species. In relation to ingestion by a 10 kg child, the standard 5 mL volume of a swallow was used in assessing potential risk. It was also suggested that a safety factor be applied.
- Ethylene glycol is known to be palatable. Therefore, it could be assumed that a young child could drink quantities of the liquid consistent with what would be required to relieve thirst - 150 mL would seem reasonable and conservative for a 10 kg child.
- Using a fatal dose of 1.4 mL/kg, 14 mL would be expected to be fatal to a 10 kg child and morbidity could be expected to occur at 3.5 mL ethylene glycol in 150 mL of

product (2.33 per cent). At this concentration and greater, products should have a CRC if they are in Schedule 6 (no bittering agent).

- A level of 2.5 per cent (i.e. the morbidity level) (approx 2.33 per cent) was recommended as a cut-off for not requiring CRCs in either Schedule 5 or Schedule 6.
- Although Schedule 5 would be dependent on inclusion of a bittering agent, it was proposed that there should be no CRC below the concentration (70 per cent) which would yield the morbidity dose (3.5 mL) to a 10 kg child in the estimated swallow volume (5 mL), given that a study has shown that when a bittering agent is included, the first mouthful is still swallowed. It was agreed to amend this concentration to 50 per cent in order to introduce a safety margin.

Members also noted the following from the May 1998 NDPSC Meeting:

- Poisons Information Centres (PIC) were requested to collect data on poisonings with ethylene glycol products. A Victorian PIC report (March 1997 - April 1998) described 11 calls involving 12 people. Only three cases involved children < 5, which appeared to be a lower incidence of exposure than reported previously. In only one case did the poisoning occur from ethylene glycol stored in its original container. Eight cases resulted from the substance being contained in a soft drink bottle or drinking glass. The data provided from Queensland involved a total of 57 calls relating to preparations containing glycols. Data on the storage containers in which these glycols were contained was not available.
- The Committee noted with some concern the number of exposures which had arisen from the poison being placed in drinking containers. A Member noted that although in all States it is an offence to sell a poison in drinking containers, in SA it was an offence to place certain poisons in drink containers. Members also noted that under hazardous substances legislation, it was illegal to re-package poisons in the workplace without proper labelling being applied.
- Nevertheless, the Committee noted that no significant morbidity had resulted from any of the exposures detailed, and this may be a reflection of the effectiveness of the bittering agent in preventing consumption of any more than the first mouthful.
- The NDPSC considered whether the information received should prompt encouragement being given to other bodies to initiate appropriate education campaigns. These could be aimed at pointing out the dangers not only of ethylene glycol but the general issue of decanting poisons into drinking containers. XXXXX.

Members additionally noted the following points in the ethylene glycol monograph from Patty's Toxicology 5th Edition:

- Reiterated many of the above points regarding toxicology (particularly acute oral), use pattern, exposure risks, kinetics and mechanism of action.
- The principal health hazard of ethylene glycol is from ingesting large quantities in single doses. Lesser quantities ingested, inhaled, or absorbed through the skin

repeatedly over a prolonged period of time can also present a significant health hazard.

Human cases

- The American Association of Poison Control Centers reported six and five deaths due to ethylene glycol ingestion in 1989 and 1990, respectively.
- A review of 18 human cases stressed effects on the brain. Possible permanent cerebral injury from acute poisoning was also noted in one report.
- Another report described a fatal case in which 1/4 to 1/2 pint of an antifreeze solution was ingested; acute meningoencephalitis followed by anuria and death from renal failure resulted after 12 days.
- A report indicated that acute renal failure occurred after an 18-year old male inadvertently ingested antifreeze. When admitted, the patient exhibited nausea, vomiting, and convulsions, but recovered in 8 days.
- The single oral dose lethal for humans has been estimated at 1.56 g/kg. It is apparent that ethylene glycol is more acutely toxic for humans than for the laboratory animals studied.

Diethylene glycol

Members recalled the following from the June 2008 NDPSC Meeting:

- Chemicals in toothpastes are regulated as either cosmetics by NICNAS or therapeutic goods by TGA, depending on their characteristics and performance claims.
- NICNAS undertook a hazard assessment for DEG in oral cosmetic products which included a recommendation to include DEG in Appendix C for intentional oral cosmetic use because of the potential for toxic effects following a single high oral dose or repeated lower oral doses.
- NICNAS made no recommendation regarding scheduling of DEG to address the risk of inadvertent ingestion for use patterns other than intentional oral cosmetic use. A Member suggested that the estimated acute oral toxicity (~LD_{50} 1490 mg/kg bw) from a case report of paracetamol syrup contaminated with DEG could provide a basis for consideration of a general DEG schedule entry (i.e. Schedule 6). The Committee did not support this approach.
- Instead, the Committee agreed that consideration should be restricted, at this time, to use in toothpastes and mouthwashes since there was clear evidence of misuse in these products and this had been the focus of the NICNAS assessment. Members generally felt that it was appropriate to ban DEG in toothpastes and mouthwashes through Appendix C as there was a clear risk to health, especially for children, from DEG in these products. The Committee agreed, however, that the wording suggested by NICNAS “intentional oral cosmetic use” could create problems with interpretation.

A Member suggest the Appendix C entry could ban "oral use" but the Committee instead supported the specific wording "toothpastes and mouthwashes".

- Members also noted that the "for intentional oral cosmetic use" in the NICNAS recommendation appeared to be trying to make allowance for unavoidable trace levels of DEG in polyethylene glycol (PEG), an allowable ingredient for food and medicines which may also be used in toothpastes or mouthwashes. Members therefore agreed that an Appendix C exemption at ≤ 0.25 per cent, in line with an ACCC's Consumer Protection Notice, would be appropriate.

Members also recalled the following from the NICNAS assessment:

- In 2007, DEG was found in certain brands of imported toothpaste. In conjunction with advice from NICNAS, the ACCC issued recall notices for some toothpaste brands, while others were withdrawn from sale. Subsequently, the ACCC issued a Consumer Protection Notice banning the supply of toothpaste containing > 0.25 per cent, effective 3 August 2007 for a period of 18 months.
- Several countries have imposed restrictions/bans on DEG in toothpaste. Chinese authorities announced in July 2007 that it had banned the use of DEG in toothpaste. The Italian and Spanish authorities have ordered the precautionary seizure of toothpastes including counterfeited well-known Western branded products and toothpaste samples.
- There are currently no medicines, including toothpastes, or foods containing DEG as an allowable ingredient approved for general sale in Australia. [The June 2008 NDPSC Meeting noted advice that a search of the ARTG located a hospital grade disinfectant registered as a device for use in Australia which contained ~10 per cent DEG.]
- In cosmetic products (including toothpastes), the presence of DEG is required to be disclosed through labelling (disclosure of the concentration, however, was not mandated) (cosmetics requirements under the *Trade Practices Act 1974*).

Absorption and Metabolism

- In animals, absorption of oral DEG is rapid and distribution occurs to all organs and tissues. Dermally administered DEG is slowly and incompletely absorbed. DEG and metabolites are readily cleared from the blood and excreted in the urine. Saturation of metabolism occurs at high doses.

Acute Toxicity

- In animals, DEG has low acute toxicity. The oral LD_{50} for mice and rats were in the range of 13-30 g/kg bw, and the dermal LD_{50} for rabbits was 12-13 g/kg bw. However, humans appear to be 10 times more susceptible to oral toxic effects of DEG.

- Toxicokinetic studies in rats report narcosis, metabolic acidosis, increased urine volumes, anuria and hydropic degeneration of renal tubules following oral administration of DEG.

Irritation and Sensitisation

- DEG produces no or only minimal eye and skin irritation. DEG causes respiratory depression in mice, but the characteristics were reported not to be typical of a pure airways irritant. No other information on respiratory irritation was available.
- DEG does not cause skin sensitisation in animals. A single case of skin sensitisation to DEG was identified in a man who had been smoking cigarettes containing DEG.

Repeat Dose Toxicity

- In animals, repeated DEG exposure was mainly associated with kidney effects (increased urine volumes, hydropic degeneration and tubular necrosis) and to a lesser extent the liver (vacuolar degeneration). From 98-day and 225-day studies in Wistar rats, a LOAEL for increases in urine volume was established at 230 mg/kg bw/d with the NOAEL at 100 mg/kg bw/d. A LOAEL based on renal hydropic degeneration was established at 1.6 g/kg bw/day with the NOAEL at 300 mg/kg bw/d.

Genotoxicity and Carcinogenicity

- Available data indicated that DEG was negative in *in vitro* genotoxicity tests. Some positive results were obtained in *in vivo* genotoxicity studies, however, only at high toxic doses. Taken together, DEG was considered non-genotoxic.
- Urinary bladder calculus and tumour response were recorded in some long-term oral rat studies. These were considered to result from chronic irritation of the bladder wall by DEG-induced stones. No information was found in the literature concerning the occurrence of bladder stones in humans after DEG ingestion. Human data was insufficient to evaluate the carcinogenic potential of DEG.

Reproduction

- Several animal reproduction toxicity studies indicated that DEG induced adverse effects on fertility and development, but only at doses higher than those associated with repeat dose effects and in the presence of biologically relevant maternal toxicity. From these studies, the LOAEL for fertility/developmental effects was established at 6.1 g/kg bw/d based on reductions in litters/pair, live pups/litter and live pup weight. The NOAEL was 3.1 g/kg bw/d. Maternal toxicity (decrease in body weight) was noted at 6.1 g/kg bw/d.

Human Oral Exposure to DEG

- A number of poisonings in humans involving substitution of DEG for more expensive, non-toxic glycols in medicinal preparations have been documented over the last 70 years. Typical features of toxicity include neurological impairment, metabolic acidosis and acute renal failure. Early mortality and morbidity are high, with most deaths occurring within the first 2 weeks post exposure.

- Large overlaps in ranges of lethal and non-lethal doses have been observed for adults and children. A median lethal oral dose of 1.49 g/kg bw DEG (range 0.25-4.9 g/kg bw) was estimated from large-scale intoxication of Haitian children with a paracetamol syrup contaminated with DEG.
- Previously, DEG has been improperly used as counterfeit glycerin in overseas consumer products based on its pleasant smell, sweet taste and lower cost. In 2007, DEG was detected in Australia as a component of some imported toothpastes.
- NICNAS sought information on the Australian use of DEG in oral cosmetic products (e.g. toothpaste and mouthwash) from industry in August 2007. No manufacture or importation of oral cosmetic products containing DEG was reported by Australian companies. No information on Australian uses of DEG in other types of cosmetics was available, although information overseas indicates use in specific brands of foundations, facial powders and concealers.
- NICNAS also made the following points regarding the data above:
  - Although DEG was not an allowable ingredient in foods or medicines, it is a known impurity in PEG, an allowable ingredient for these applications. PEG is also used in cosmetics. Therefore, there was potential for very low levels of DEG to be present in cosmetics, including oral cosmetics.
  - Given its rapid absorption following ingestion and documented oral toxicity in animals and humans, there was concern about potential risks of adverse effects from exposures to DEG in oral cosmetic products such as toothpaste and mouthwash. Toothpastes and mouthwashes are not intended to be swallowed, but unintentional swallowing or ingestion of products containing DEG has a meaningful risk to certain populations, such as children or individuals with kidney or liver disease.

Members additionally noted the following points in the DEG monograph from *Patty's Toxicology Fifth Edition* (Bingham, Cohrssen & Powell (ed) 2000 Wiley-Interscience, USA)

- Reiterated many of the above points regarding toxicology, use pattern, exposure risks, kinetics and mechanism of action.

Human experience

- Human experience in industrial handling and use of DEG has been excellent except for an incident in 1937 when more than 100 deaths were caused by the ingestion of an elixir consisting of sulfanilamide and DEG as one of the major solvents.
- In general, pathology observed in human victims resembles closely that which has been described for laboratory animals and consists primarily of degeneration of the kidney and fewer lesions in the liver. Death in practically all cases was due to renal insufficiency.

- As a result of the "elixir of sulfanilamide" episode, the acute lethal dose for humans has been estimated at about 1 mL/kg.

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

A Member asserted that in the recent incidents, discussed above, the risk arose from non-compliant and inappropriate use i.e. substitution. While industry had no issue with treating the scheduling of ethylene glycol and DEG the same, the Member asserted that it was important to recognise that scheduling was unlikely to prevent similar substitutions happening in the future.

A Member noted that humans are very susceptible to the toxic effects of both ethylene glycol and DEG. The degree and mechanism of toxicity was similar with these two compounds. The Committee therefore decided that these substances should have similar scheduling, consistent with the existing ethylene glycol scheduling. For the same reasons, any risk posed by ethylene glycol in mouthwashes or toothpastes would be similar to that posed by DEG. Members therefore agreed that the DEG Appendix C entry should also be applied to ethylene glycol.

The cut-off of ≤ 0.25 per cent in Appendix C was raised as a concern due to the risk of chronic exposure from daily oral use. However, as other products containing ethylene glycol or DEG were unlikely to involve chronic exposure, a Member asserted that the general ≤ 2.5 per cent exemption, based on sporadic exposure, was sufficient and that there was no need to reduce this. Another Member noted that the 2.5 per cent exemptions in the current Schedule 5 and 6 ethylene glycol entries were based on an approximation of the toxicity from 1 cup (0.35 g/kg bw = 3.5 g for 10 kg child; 150 mL at 2.33 per cent = 3.5 g), with an apparently small safety margin (noting that the lethal dose for ethylene glycol is 1.4 g/kg bw). Another Member asserted that the general ≤ 2.5 per cent exemption was important to industry and any change could result in significant regulatory impact for many products which did not pose any apparent risk to the public. The Committee agreed that the 2.5 per cent exemption remained appropriate.

The Committee also confirmed that the specified bittering agent (not less than 10 mg/kg of denatonium benzoate) should remain a condition for Schedule 5 listing as this was a very strong bittering agent with a toxicological profile suitable for the purpose of limiting the risk of ingestion, particularly accidental ingestion by a child.

RESOLUTION 2009/55 - 12

The Committee decided to:

Ethylene glycol

- Include ethylene glycol for use in toothpastes and mouthwashes in Appendix C, with an exemption cut-off of 0.25 per cent, with corresponding amendments to Schedule 5 and 6 ethylene glycol entries.

Diethylene glycol

- Create a new parent entry in Schedule 6 for diethylene glycol (excluding its salts and derivatives).
- Create a new entry in Schedule 5 for diethylene glycol (excluding its salts and derivatives) in preparations containing not less than 10 mg/kg of denatonium benzoate as a bittering agent.
- Confirm that diethylene glycol for use in toothpastes and mouthwashes should be captured in Appendix C, with an exemption cut-off of 0.25 per cent.
- Exempt other preparations containing 2.5 per cent or less of diethylene glycol.

Schedule 5 – New Entry

DIETHYLENE GLYCOL (excluding its salts and derivatives) in preparations containing not less than 10 mg/kg of denatonium benzoate as a bittering agent **except**:

(a) in paints or paint tinters;

(b) in toothpastes or mouthwashes containing more than 0.25 per cent of diethylene glycol; or

(c) in other preparations containing 2.5 per cent or less of diethylene glycol.

Schedule 5 – Amendment

ETHYLENE GLYCOL – Amend entry to read:

ETHYLENE GLYCOL (excluding its salts and derivatives) in preparations containing not less than 10 mg/kg of denatonium benzoate as a bittering agent **except**:

(a) in paints or paint tinters;

(b) in toothpastes or mouthwashes containing more than 0.25 per cent of ethylene glycol; or

(c) in other preparations containing 2.5 per cent or less of ethylene glycol.

Schedule 6 – New Entry

DIETHYLENE GLYCOL (excluding its salts and derivatives) **except**:

(a) when included in Schedule 5;

(b) in paints or paint tinters;

(c) in toothpastes or mouthwashes containing more than 0.25 per cent of diethylene glycol; or

(d) in other preparations containing 2.5 per cent or less of diethylene glycol.

Schedule 6 – Amendment

ETHYLENE GLYCOL – Amend entry to read:

ETHYLENE GLYCOL (excluding its salts and derivatives) **except**:

(a) when included in Schedule 5;

(b) in paints or paint tinters;

(c) in toothpastes or mouthwashes containing more than 0.25 per cent of ethylene glycol; or

(d) in other preparations containing 2.5 per cent or less of ethylene glycol.

Appendix C – New entry

ETHYLENE GLYCOL for use in toothpastes or mouthwashes **except** in preparations containing 0.25 per cent or less of ethylene glycol.

5.1.2 GUANIDINE

PURPOSE

The Committee considered the scheduling of guanidine including a proposal to exempt its use in hair care products from Schedule 4.

BACKGROUND

Guanidine carbonate ($[H_2NC(=NH)NH_2]_2 \cdot H_2CO_3$) is a white crystalline solid with a solubility of up to 45 g/100 g water, with a saturated aqueous solution having a pH of 11-11.5. Guanidine carbonate is the precursor for preparing guanidine hydroxide, the active ingredient in some chemical hair relaxing treatments.

Chemical hair relaxing is a method for permanently straightening curly hair. It is a non-reversible one-step chemical process involving the application of strong alkali to convert the disulfide bond of cystine in hair to the ether bond of lanthionine. In the late 1950s hair relaxing kits using 1.5-2.5 per cent sodium hydroxide (or "lye") were introduced. In 1978 a "no-lye" treatment based on guanidine hydroxide was introduced, claiming to be less irritating to the scalp than "lye" relaxers. A guanidine hydroxide hair relaxer has a pH in the same range as that of a sodium or potassium hydroxide based relaxer (pH 12-14). Guanidine hydroxide is unstable and hydrolyses to form urea and ammonia and must therefore be generated *in situ* immediately prior to use by reaction of guanidine carbonate and calcium hydroxide.

Guanidine carbonate and guanidine hydroxide are currently not specifically scheduled but are instead captured as salts of guanidine in Schedule 4. The August 1999 NDPSC Meeting first included guanidine in Schedule 4 following a recommendation from the Trans-Tasman Harmonisation Working Party. It was seen as more appropriate that both countries should adopt "prescription only" status for the drug based on its history and toxicity. This was in line with the generally applied harmonisation policy that substances for human therapeutic use be placed in Schedule 4 if there was no marketed product in either country.

DISCUSSION - SUBMISSIONS

The Committee considered a request from XXXXX to exempt guanidine carbonate from scheduling when:

- ≤ 25 per cent in an aqueous solution;
- packed in volumes ≤ 50 mL; and
- sold as part of a hair relaxer kit.

Members noted the following points from this submission:

- While preparing an XXXXX for a hair relaxing kit, it was discovered that the core ingredient, guanidine carbonate, was in Schedule 4.
- Guanidine carbonate has been used in hair relaxing kits for many years worldwide. These kits have also been widely available in Australia for many years.
- It is asserted that the SUSDP entry should be changed to allow Australian companies to compete both against imported product and in the world market. The February 2009 NDPSC Meeting noted that there appeared to be a mistaken impression that

scheduling applied differently to Australian manufactured guanidine hair product compared with similar imported product.

The submission included detailed claims against the provisions of 52E(1). Members noted the following:

(a) Toxicity and Safety

- Referred to a toxicity discussion in a USFDA policy paper by Henshel (http://classwebs.spea.indiana.edu/dhenshel/toxicology/Policy%cent20Briefs%20Consumer%20Products/Guanidine%20monohydrate%20%20in%20hair%20productsTanaisha%20Lee%20PolicyBrief.pdf). Members noted the following:
  - Hair relaxer ingestion can cause moderate to severe chemical burns on the lips, face, oral cavity and occasionally on the pharynx.
  - Guanidine carbonate is an irritant to skin, eyes, and mucous membranes and also has an irritating effect on lungs upon inhalation. There are no known allergic or sensitization effects.
  - The acute and chronic toxicity of guanidine carbonate is not fully known. It is known to be very hazardous if ingested, as summarised in the following table:

Organism	Test Type	Route	Reported Dose
Mouse	LD_{50}	Oral	350 mg/kg
Mouse	LD_{Lo}	Not Reported	500 mg/kg
Rabbit	LD_{Lo}	Subcutaneous	500 mg/kg

Note: LD_{Lo} (Lethal Dose Low) is the minimum amount of a chemical which tests have shown will be lethal to a specified type of animal.

  - No data on the carcinogenic properties of guanidine carbonate was available.

Henshel's Recommendations

  - Recommended initiatives to alleviate the public health risks associated with exposure to guanidine carbonate and its two precursors (guanidine carbonate and calcium hydroxide) in hair relaxers.
  - Mandatory warning labels on children's relaxers should be required. Children's relaxers should also be packaged to look less like toys. This could be a contributing factor to relatively high incidents of relaxer ingestion, when compared to ingestion of other caustic agents, most of which are packaged in a less alluring manner.
  - More research is needed on the long term health effects and toxicology associated with the use of caustic agents in hair relaxers.
  - Noted that "all of the Material Safety Data Sheets (MSDSs) for hair relaxers are incorrect and/or incomplete". Often only considered the calcium hydroxide parent of guanidine carbonate, with no consideration given to synergistic effects that may be observed from the relaxer mixture.

- The applicant also noted that MSDSs exist for guanidine carbonate. The Committee, however, noted that the MSDSs referenced by the submission (published by Sigma Aldrich and Science Lab.com) appeared to have been designed for research and development situations, not for cosmetic/domestic products, and would have limited relevance to topical cosmetic applications.

(b) Risks and Benefits

- Referred to the information in (c) Potential Hazards and (f) Need for Access.

(c) Potential Hazards

- Asserted that it was well accepted by consumers who use these products that irritation may occur due to the caustic nature of the products. This risk did not deter their use.
- The applicant backed this claim with reference to the following articles where the continued use of guanidine based hair relaxer products, despite the known irritation potential, was discussed:
  - Syed, A; Naqvi, A., *Comparing the Irritation Potential of Lye and No-Lye Relaxers*, February 2000, Allured's Cosmetics & Toiletries magazine, Vol. 115(2) pages 47-52.
  - Meadows, M., *Heading Off Hair-Care Disasters: Use Caution With Relaxers and Dyes*, January-February 2001, FDA Consumer magazine. (http://www.fda.gov/fdac/features/2001/101_hair.html)
  - Henshel policy paper discussed above.
  - Rosenberg, L., et al., *Hair Relaxers Not Associated with Breast Cancer Risk: Evidence from the Black Women's Health Study*, May 2007, Cancer Epidemiology Biomarkers Preview, Vol. 16 (5), pages 1035-1037.
  - Ruetsch, S., et al., *Cuticular Damage to African-American Hair During Relaxer Treatments – A Microfluorometric and SEM Study*, 2008, IFSCC Magazine, Vol. 11(2), pages 131-137.
- Members noted that it was unclear how public acceptance of a risk to achieve a cosmetic result should in any way reduce the Committee's concern of this risk i.e. irritation due to the caustic nature of the product

(d) Extent and Patterns of Use

- Advised that the use of guanidine carbonate, as part of a no-lye hair relaxing kit, was wide spread worldwide. Further asserted that it was also presently freely available in Australia, with several products detailed.
- Extensive patterns of use and product market in the US were described.

(e) Dosage and formulation

- Guanidine carbonate is presented as a 25 per cent aqueous solution as part of a relaxing kit. As a minimum, a no-lye relaxing kit would generally contain the following:
  - A protective paraffin product to apply to bare skin to protect from the caustic nature of the relaxer.
  - A cream containing an appropriate amount of calcium hydroxide, packed such that there is void space in the container to receive the guanidine carbonate solution and allow user mixing of the two parts (generally a pack of around 180g).
  - A 25 per cent aqueous solution of guanidine carbonate (generally a pack of around 50mL).
  - A shampoo to neutralise the caustic cream and rinse the product from the hair.

(f) Need for Access, Taking into Account Its Toxicity Compared with Other Substances Available for Similar Purpose

- The applicant reported that sodium hydroxide or lye-based no-mix hair relaxers were easier to use since they did not require mixing, but were less accepted by consumers because they were skin irritants. Guanidine hydroxide works well as a relaxer giving a pH range of 12-14 but was unstable and decomposes to form urea and ammonia within a short time.

(g) Potential for Misuse/Abuse of the Substance

- Asserted that the accidental ingestion of the guanidine carbonate solution was the most likely incidence of misuse. Advised that the ingestion of caustic hair relaxers had been examined by the following articles:
  - Syed, A., et al., *Absence of Esophageal Injury in Paediatric Patients After Hair Relaxer Ingestion,* September 1999, Arch Otolaryngol Head Neck Surg, Vol 125, pages 953-955.
  - Abstract – Cox, Artemus J. III MD; Eisenbeis, John F. MD., *Ingestion of Caustic Hair Relaxer – Is Endoscopy Necessary?* Laryngoscope. 107(7):897-902, July 1997.
  - AHSAN, S. and HAUPERT, M., Absence of Esophageal Injury in Pediatric Patients After Hair Relaxer Ingestion, Arch. Otolaryngol. Head Neck Sur. (1999), Vol. 125, pages 953-955.
- Members noted that the conclusion reached by the Syed article was that the accidental ingestion of the guanidine carbonate solution was the most likely incidence of misuse. The ingestion of caustic hair relaxers has made up a major proportion of all children admitted to hospital in the US for caustic ingestion. However, no significant oesophageal injuries have been associated hair relaxer ingestion. The problem of ingestion of hair relaxing products was more pronounced in the US where these

products exist for young children, and are often in child-attracting packaging, without adequate child-resistance closures, an issue which is being addressed in that country.

- The applicant reports that the potential for abuse of this substance was not known.

(h) Purpose for Use

- Guanidine carbonate was used as part of a hair straightening kit as described previously.

The applicant also included a list of references relating to this issue. The Members may wish to note the following points from relevant references which where not discussed above:

- Ertell., K., *A Review of Toxicity and Use and Handling Considerations for Guanidine, Guanidine Hydrochloride and Urea*, March 2006, Battelle Memorial Institute, Pacific Northwest National Laboratory for the United States Department of Energy:
  - Highlights a dearth of toxicity data for guanidine and hence the need to include toxicity data for guanidine hydrochloride.
  - Guanidine hydrochloride does not appear to be absorbed through the skin, and the only information on human exposure comes from the US pharmaceutical industry, where it is used as an orally administered drug, which has significant effects on the gastrointestinal and nervous system and on the neuromuscular systems.
  - There are no published studies of the effect of guanidine on humans, however the Buehler and Draize test have been performed on rabbits and guinea pigs, which concluded that guanidine applied topically was a mild skin irritant.
  - Guanidine should be considered a toxic compound by oral ingestion.
  - Guanidine is a significant irritant to the eyes, skin and lungs. In solution the pH may approach corrosivity, depending on the concentration.
  - Guanidine does not appear to be absorbed through the skin.
- McNamara, D., *Study explores hair care practices and alopecia among black women*, 17 December 2007, MD Consult, Elsevier Global Medical News:
  - This study explores hair care practices and alopecia among black women and indicated that there was no significant correlation between development of central centrifugal cicatricial alopecia and the use of relaxers or a history of burns or raw spots after use of relaxers but that some doctors were informing patients that relaxers were implicated.

Members also noted the following from XXXXX pre-meeting comment:

- Welcomed the proposal to exempt use of guanidine in hair care products. Suggested, however, that the exemption be extended to all cosmetic products.

- Advised that in Europe, various guanidine salts/derivatives were used safely in a number of different cosmetic products without limitation. Some examples include guanidine carbonate and guanidine phosphate that were used as skin conditioning and buffering agents, and lauramidobutyl guanidine acetate used as a hair conditioner.
- Asserted that guanidine salts/derivatives that are used safely and effectively in cosmetics preparations in other parts of the world should be excluded from scheduling.
- Asserted that the current schedule entry for guanidine relates to oral therapeutic applications of guanidine only and proposed that the Schedule 4 entry of guanidine be amended to read "GUANIDINE for oral therapeutic use".

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits, (c) potential hazards, (d) extent and patterns of use and (f) dosage and formulation.

Several Members noted that the key factors in considering separate scheduling controls for non-therapeutic use of guanidine were the caustic nature of some guanidine salts/derivatives and the inherent toxicity of guanidine itself. Guanidine hydroxide preparations (often generated *in situ* from guanidine carbonate and calcium hydroxide) could be very caustic and highly irritant to eyes, lungs and skin, and could pose a serious risk, especially for children. Members in particular noted a number of US reports of harm in children from ingestion of guanidine hair straighteners. Similar risks, although probably less severe, were likely to exist for some other salts/derivatives of guanidine. Additionally, there appeared to be little in the way of human toxicity data available, beyond oral toxicity for some guanidine salts (significant effects on the gastrointestinal and nervous system and on the neuromuscular systems) which several Members asserted were also grounds for a conservative scheduling approach.

Members considered a pre-meeting proposal to limit the current Schedule 4 entry to internal therapeutic use. However, it was noted that there may in future be non-oral therapeutic uses and these should not be exempted from scheduling without proper supportive data being presented to the Committee.

The Committee also considered limiting the current Schedule 4 guanidine parent entry to "therapeutic use", and capturing all other uses of guanidine in Schedule 6 (together with appropriate first aid instructions). Members generally felt this was appropriate, given the information at hand. The Committee therefore agreed that the following standard statements be required for guanidine through an Appendix E entry:

- A "For advice, contact a Poisons Information Centre (Phone eg Australia 13 1126; New Zealand 0800 764 766) or a doctor (at once)".
- G3 "If swallowed, do NOT induce vomiting".

- E2 "If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes."
- S1 "If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water".

Members noted however, that while supportive of requiring the Appendix E S1 standard statement, to address the concerns raised by the US reports of skin burns from using guanidine hair straighteners, it would be reasonable to reword this warning statement, given that products containing guanidine are intended for use on the hair. Such rewording is in keeping with the intention of the statement in the Appendix E introduction that "Standard statements specified in this appendix may be varied provided that the intent is not changed".

The Committee also considered an exemption cut-off from the Schedule 6 parent entry for non-therapeutic use of guanidine. Members noted that while an exemption was requested for ≤ 25 per cent guanidine carbonate, no evidence was provided to show that this would prevent the *in situ* generated guanidine hydroxide from having a high pH. Indeed, a Member noted that a high pH had to be reached at some point for the hair straightening chemical reaction to work, and that the guanidine hair straightener involved in a reported incident in Victoria causing skin burns had < 25 per cent guanidine carbonate. Members generally agreed that the requested exemption for ≤ 25 per cent was not appropriate. An alternative suggestion of an exemption based on a pH limit, in line with the current sodium hydroxide scheduling, was also not supported, given a lack of data. The Committee therefore agreed that an exemption from the Schedule 6 parent entry could not be set at this time. However, Members were not opposed to a cut-off, should appropriate data supporting the proposed cut-off be brought to the Committee.

A Member also noted that in Europe, guanidine salts/derivatives were allowed for broad cosmetic use and as such any discussion of exemptions may also need to consider other possible cosmetic use patterns i.e. beyond hair straightening. A Member noted that cosmetics may involve prolonged dermal contact on a daily basis, which differed significantly from the exposure pattern for hair straighteners. Another Member noted, however, that guanidine was not dermally absorbed which may mitigated this risk.

Noting the possible broad impact of a Schedule 6 parent entry for non-therapeutic guanidine and the uncertain status of possible exemption cut-offs, the Committee agreed that it would be appropriate to foreshadow a decision for consideration at June 2008, in order to allow time for further public consultation. The Committee would particularly welcome submissions providing arguments or data that may allow an exemption cut-off from Schedule 6 to be established.

Members also wished to confirm, in relation to the applicant's assertion that imported guanidine based hair straightening products were available in Australia at this time, that these products would currently be captured by the guanidine Schedule 4 entry and

therefore would not to be compliant with scheduling requirements. A Member advised that any importers of these non-compliant products were unlikely to be large scale companies (who would be conversant with scheduling requirements) but more likely to be smaller scale businesses such as hair salons, selling products from overseas via the internet.

RESOLUTION 2009/55 - 13

The Committee decided:

- To restrict the Schedule 4 entry for guanidine to therapeutic use only.
- To include a new parent entry in Schedule 6 for guanidine.
- To include a new entry in Appendix E, Part 2 with the following standard statements to apply:
  - A "For advice, contact a Poisons Information Centre (Phone eg Australia 13 1126; New Zealand 0800 764 766) or a doctor (at once)".
  - G3 "If swallowed, do NOT induce vomiting".
  - E2 "If in eyes, hold eyelids apart and flush the eye continuously with running water. Continue flushing until advised to stop by the Poisons Information Centre or a doctor, or for at least 15 minutes."
  - S1 "If skin or hair contact occurs, remove contaminated clothing and flush skin and hair with running water".

FORESHADOWED DECISION (for consideration at the June 2009 Meeting)

Schedule 4 – Amendment

GUANIDINE – Amend entry to read:

GUANIDINE for therapeutic use.

Schedule 6 – New Entry

GUANIDINE **except** when included in Schedule 4.

Appendix E, Part 2 – New Entry

POISON .....**STANDARD STATEMENT**

Guanidine.....A,G3,E2,S1

5.2 SUSDP, PART 5

Nil.

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

6.1 TRALOPYRIL

This item was withdrawn XXXXX prior to the Meeting.

6.2 DIQUAT

This item was withdrawn XXXXX prior to the Meeting.

6.3 EUBACTERIUM SPP. STRAIN DSM 11798

PURPOSE

The Committee considered the scheduling of *Eubacterium* spp. strain DSM 11798.

BACKGROUND

Eubacteria are obligate anaerobic bacilli which produce various combinations of butyric, lactic, acetic and formic acids. They are slow growing, fastidious and generally unreactive in biochemical tests. As a consequence, cultivation and identification are difficult and the taxonomy of the group remains indifferent. The genus *Eubacterium* spp. is one of the major groups of bacteria in the digestive tract of livestock and humans. In humans it is also found in dental plaque.

Eubacterium spp. strain DSM 11789 is a gram-positive, nonmotile, non-sporing, irregular rod shaped bacterium occurring singly, in pairs and long-branched chains up to 100 μm. It is strictly anaerobic; experiences growth promotion with yeast extract or L-arginine; does not experience growth inhibition by nalidixic acid, polymyxin-B-sulfate or 2-bromo-ethanesulfonic acid; is non-saccharoclastic; produces neither acid-nor H2-production on PYG-medium; has cytochrome b and c; is arginine dihydrolase and arginine arylamidase positive; is glutamic acid decarboxylase positive; is urease negative; does not produce indol and reduces nitrates.

Eubacterium spp. strain DSM 11798 biotransforms the epoxide ring in trichothecenes, including mycotoxins, by enzymatic (epoxidase) reduction of the 12,13-epoxide group. The de-epoxy metabolites have been shown to be significantly less toxic than their epoxy parents in a variety of cytotoxicity tests.

DISCUSSION - SUBMISSIONS

XXXXX sought APVMA registration for a XXXXX containing *Eubacterium* spp. strain DSM 11798 XXXXX. XXXXX undertook an evaluation and recommended:

XXXXX

Public Health Standards

- No ADI has been previously set for *Eubacterium* sp. strain DSM 11798, XXXXX. There was no data on the capacity of any of the constituents to leave harmful residues in the organs or tissues of its target food animal species or any data which enable a determination of a safe daily intake of such residues.
- No ARfD has been set for *Eubacterium* sp. strain DSM 11798, XXXXX. There was no data as to whether any of constituents has a capacity to cause acute systemic effects in humans following oral exposure.
- Given the lack of knowledge of the pathogenicity in humans of *Eubacterium* sp. strain DSM 11798 and the limited availability of acute toxicity data for the remaining constituents, a recommendation for scheduling cannot be made. XXXXX.

Members particularly noted the following from the evaluation report:

- *Eubacterium* spp. has not been previously scheduled by the Committee. The toxicological profile of strain DSM 11798 was evaluated by XXXXX in 2007 and was not referred for scheduling consideration because the following data deficiencies were identified:

  1) The acute oral toxicity.

  2) The acute dermal toxicity.

  3) The acute inhalational toxicity.

  4) The skin and eye irritancy.

  5) The skin sensitising potential.

  6) The strain cannot be assigned to an existing species, and as a result there is no historical information on its prevalence within the digestive tract of livestock or humans.

  7) The potential for human pathogenicity/infectivity (particularly via inhalation).

  8) The transmissibility and persistence of the organism under Australian climatic conditions.

  9) The specificity, host range and indication of whether the agent is closely related to a pathogen of vertebrate species.

  10) The potential transmissibility from the target species to humans.

- The applicant has provided several acute toxicity studies. These studies indicate that strain DSM 11798 has low acute dermal toxicity in XXXXX, is not a skin or eye irritant in XXXXX and is not a skin sensitiser in XXXXX. The evaluator advised that these studies resolved the previous data deficiencies 2, 4 and 5 above.
- The applicant also submitted a XXXXX -day sub-chronic oral study in XXXXX, but no acute oral study nor a scientific argument as to why one was not provided. The submitted study showed that strain DSM 11798 showed no evidence of toxicity or adverse effects up to XXXXX, equivalent to XXXXX, via repeated oral administration. The NOEL was therefore XXXXX.

Evaluator's Request

- The evaluator considered that the available data and information were not adequate for hazard characterisation. However, since this was the second time that an application had been submitted for scheduling of *Eubacterium* sp. strain DSM 11798, the evaluator has requested advice from the Committee on which of the outstanding data requirements below are essential for consideration of scheduling:
  - The acute oral toxicity (from a study compliant with OECD guideline 401).
  - The acute inhalational toxicity (from a study complaint with OECD guideline 403).
  - Identification with an existing species, which could necessitate scheduling as *Eubacterium* spp. strain DSM 11798.
  - Data on the potential for human pathogenicity/infectivity particularly via inhalation (the OCS has identified suitable overseas guidelines, such as the EPA microbial pesticide test guideline (OPPTS 885.3150) for assessing the acute pulmonary toxicity/pathogenicity of microbial actives (EPA, 1996b)).
  - Data relevant to the persistence and potential transmissibility of the organism from the target species to humans under Australian climatic conditions.

Members additionally noted the following from the evaluation report:

Strain identification

- Based on morphological, physiological and genetic investigations, the applicant has determined that the live constituent organism marketed as XXXXX belonged taxonomically to the genus *Eubacterium*. It originated from XXXXX content and was identified as isolate DSM 11798. The strain has not been previously isolated. The strain was not able to be assigned to an existing species and as a result there was no historical information on its prevalence within the digestive tract of livestock or humans.
- A search of databases of European culture collections did not reveal any strain of the genus *Eubacterium* spp. that produced antibiotics. Literature studies did not give any indication that *Eubacterium* spp. has any antibiotic capabilities.

- There is no data as to the pathogenicity of *Eubacterium* spp. strain DSM 11798 in humans.

Applicant's Argument

- The following characteristics of *Eubacterium* spp. strain DSM 11798 were used to support the applicant's claim that the strain may be safely used in the product:
  - *Eubacterium* spp. is one of the major groups of bacteria in the digestive tract of livestock and humans.
  - There are no morphological or biochemical data for *Eubacterium* spp. strain DSM 11798 suggesting any similarity with data of already known pathogenic bacteria species.
  - The strain is viable only under strictly anaerobic conditions. Contact with oxygen immediately terminates the reproductive process.
  - The strain does not show metabolic activity under environmental conditions.
- Laboratory personnel, working with *Eubacterium* sp. *in vitro* and *in vivo* since XXXXX, had not experienced or observed any injurious effects to humans or animals.
- XXXXX is currently being used in approved feed additives in several countries and there have been no detrimental effects reported.

Additional Evaluator's Comments

- The acute inhalation toxicity of *Eubacterium* spp. strain DSM 11798 is unknown, as are a number of risk factors related to the possible inhalational risk posed by the product. The available data did not allow determination of the capacity of the product to form a dust, the proportions of respirable and inhalable particles and the capacity of dust formed by the product to cause pneumoconiosis or silicosis with repeated inhalation.
- The species of *Eubacterium* to which the strain belongs is not known. Studies indicating the potential pathogenicity of *Eubacterium* spp. strain DSM 11798 to humans or the potential transmissibility to humans from target species were not available. From a public health perspective, data on the pathogenicity of bacterial strains are required, and can be readily obtained via acute injection and inhalation pathogenicity/toxicity studies in mice.

XXXXX

Tolerance studies with XXXXX

- XXXXX has previously evaluated five studies designed to establish whether XXXXX tolerated a concentration of *Eubacterium* sp. strain DSM 11798 in feed XXXXX -fold higher than the recommended concentration.

- The lack of adverse effects reported was based on the lack of clinical signs in the subject animals and did not utilise blood chemical or haematological or whole body pathological examinations.
- Although these studies did not elicit adverse effects, the design of the studies did not provide the capacity or the power to detect all such effects. The tolerance studies did not therefore have the capacity to allow a conclusion as to the biological effects on target species, or by inference, on humans.

Use Pattern and Exposure

- XXXXX
- The likely routes of exposure for the professional user are dermal, inhalational and ocular. The likely pattern of exposure for the professional user is expected to be brief, intermittent exposure when used on-farm and long-term exposure when used in the preparation of pre mixed feeds.
- The product is not intended for home veterinary use. The exposure of bystanders during mixing or after the treated feed has been distributed is unlikely to occur. Cleanings from the sheds are likely to be the subject of specific disposal systems that do not provide access to bystanders.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (b) risks and benefits, (c) potential hazards, (d) extent and patterns of use and (f) dosage and formulation.

A Member advised that the applicant had provided XXXXX with a response to the evaluation report. The Member noted the following in relation to this response:

- Regarding the lack of an acute oral study, the applicant argued that, given the nature of the product constituents, the chronic study should be sufficient. A Member asserted, however, that the chronic study was itself not particularly well designed. The applicant argued that an acute study on the *Eubacterium* spp. DSM 11798 would require an unrealistic quantity of the product to be introduced into the test animal's stomachs, and that, as a result, effects of the product would be due to physical problems, not toxicological. Several Members noted that this assertion seemed to arise from a misunderstanding of the evaluation report's request for data on the active *Eubacterium* spp. strain DSM 11798 with data for the product.
- Regarding inhalation toxicity, the applicant argued that as XXXXX of particles in the product were larger than XXXXX and the application rate was XXXXX, the degree of exposure would be very small and could be eliminated by simple precautions. The applicant advised that the product's proposed safety directions have been revised to this effect. Members again noted that this seemed to represent a misunderstanding regarding the need for data on the active *Eubacterium* spp. strain DSM 11798 with

data for the product. Several Members felt that the applicant's particle size argument did not seem valid.

- Similarly the applicant responded to the evaluation report's criticism of the acute inhalation study (where the organism was introduced directly to the trachea instead of the more usual protocol of either having the animals in a chamber containing dust or a "nose only" study) by arguing that the particle size of the organism was too large to inhale. Several Members disputed this position, noting as above that this seemed to reflect confusion between the active and the product.
- The applicant advised that further studies were being commissioned to establish the particle size spectrum of the product and that this data would be provided to XXXXX in the near future.

The Committee noted that the applicant's response had only addressed two of the issues of concern identified by the evaluator, and even these were not considered to have been addressed sufficiently. A Member noted that the eye irritancy test had been done with a liquid preparation, not with a dry powder form as was usually required for determining irritancy from microbial preparations. In the absence of such studies, the Member asserted that *Eubacterium* spp. DSM 11798 should be considered a possible eye irritant.

Another Member noted that *Eubacterium* species were not well known and not many species had been isolated or studied. The bacterium appeared to be present as part of the mixed flora of the mouth/gut and does not appear to have been isolated as a single organism in a single culture. Nothing was known about the virulence potential. Given its ubiquitous nature, it seemed difficult to determine whether the *Eubacterium* was indeed pathogenic. The Member also queried under what conditions these organisms could do what is claimed by the applicant, given that so little is known about the species. The Member asserted that this reinforced that the data provided were far from adequate.

It was concluded that this matter appeared to have come before the Committee prematurely and it would therefore not be reasonable to schedule this substance. The Committee agreed that there were too many outstanding questions on *Eubacterium* spp. strain DSM 11798 to allow a scheduling decision to be made at this time.

With regard to the evaluator's request (that the Committee set some specific data requirements for further scheduling consideration), the Members agreed that it was not appropriate for the Committee to mandate specific data requirements and that this was more appropriately determined by the regulator.

RESOLUTION 2009/55 - 14

The Committee decided to defer a scheduling decision for *Eubacterium* spp. strain DSM 11798.

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

Nil.

8. OTHER MATTERS FOR CONSIDERATION

8.1 N-PHENETHYL-4-PIPERIDONE

PURPOSE

The Committee considered the scheduling of N-phenethyl-4-piperidone (NPP), a precursor to fentanyl, including a proposal to include in Schedule 9.

BACKGROUND

N-Phenethyl-4-piperidone (NPP) is a precursor for the opioid analgesics fentanyl and carfentanyl. Fentanyl has potency approximately 81 times that of morphine and is currently widely used as intravenous anaesthetic, lozenges and in long acting transdermal patches. Carfentanyl has potency approximately 10,000 times that of morphine and 100 times that of fentanyl and is one of the most potent opioids known and the most potent opioid used commercially. It was suggested by Wax et al ("Unexpected "gas" casualties in Moscow: a medical toxicology perspective" Annals of Emergency Medicine 2003 May; 41(5):700-5.) that carfentanyl was the most likely substance used by the Russian military to incapacitate Chechen rebels in the 2002 Moscow theatre hostage crisis.

Fentanyl may be synthesised from NPP in three steps using simple reagents. In the first step, NPP is reacted with aniline to form an imine intermediate. In a second step, the carbon nitrogen double bond of the imine is reduced with sodium borohydride affording 4-anilino-N-phenethyl-piperidine (ANPP). Finally, ANPP is reacted with propionic anhydride or propionyl chloride to form fentanyl. That is to say, there are a number of "intermediates" and the inclusion of NPP in Schedule 8 or 9 may not capture the ANPP intermediate. Further, NPP itself can be easily synthesized from piperidone and phenethyl-tosylate or phenethyl-bromide. The synthesis of carfentanyl is slightly more complex, requiring introduction of a carboxymethyl group.

DISCUSSION - SUBMISSIONS

A submission from XXXXX highlighted a report from the United States on an epidemic in non-pharmaceutical fentanyl-related deaths. As a result, the United States Drug Enforcement Agency (DEA) began regulating access to NPP. Fentanyl is widely used in medical practice around Australia in the form of transdermal patches, lozenges, or injectable solutions. XXXXX, had informed the XXXXX that their products are imported as finished products.

XXXXX.

The Committee noted the Morbidity and Mortality Weekly Review published by the Centre for Disease Control and Prevention (CDC) on 25 July 2008 included in XXXXX submission. Points noted from the review:

- The CDC Epidemic Information Exchange (Epi-X) reported on 21 April 2006 increases in overdoses among illicit drug uses which then brought to light other reports of similar overdoses in other parts of the US;
- These increases had been attributed to heroin overdoses until illicitly manufactured non-pharmaceutical fentanyl (NPF) was found at the scene of some overdoses;
- In May 2006, the CDC implemented an *ad hoc* case finding and surveillance system which identified 1,013 NPF-related deaths that occurred from 4 April 2005 to 28 March 2007;
- As a result, the Drug Enforcement Administration (DEA) regulated access to NPP from 23 April 2007;
- Since the 1970s, non-pharmaceutical fentanyl and various fentanyl analogues (e.g., alphamethylfentanyl) have been produced illicitly and used for their heroin-like effect;
- According to the DEA, manufacture of fentanyl requires minimal technical knowledge and methods for making it can be found on the Internet;
- Henderson suggests in 'Designer Drugs: Past History and future Prospects'(*Journal of Forensic Science* 1988;33:569-75 that with the relative ease of illicit production and low cost of fentanyl compared with heroin, future epidemics of non-pharmaceutical fentanyl are likely to occur.

XXXXX, noted that NPP was not included in Schedule 8 or 9 either as a named substance or as a derivative, and requested that NPP be considered for inclusion in either Schedule 8 or 9 with a view to trying to avoid the situation that has arisen in the United States.

The Committee noted that currently Schedule 9 includes only three "intermediates" (lysergic acid, 4-cyano-2-dimethylamino-4,4-diphenylbutane (a methadone intermediate) and 2-methyl-3-morpholino-1,1-diphenylpropane carboxylic acid (a dextromoramide intermediate)). Further, the Plastics and Chemicals Industries Association (PACIA) and Science Industry Australia (SIA) in consultation with Government and Law Enforcement Agencies have jointly prepared a Code of Practice for Supply Diversion into Illicit Drug Manufacture which was designed to protect against the diversion of [precursor] chemicals and scientific apparatus into illicit production of drugs. The Code contains a list of illicit drug precursors/reagents which could be extended and is also reviewed on an annual basis by a joint committee from PACIA and SIA.

The Committee also noted that NPP is not a precursor/intermediate for a large number of other fentanyl analogues such as alphamethylfentanyl, alphamethylacetylfentanyl, 3-methylfentanyl, betahydroxyfentanyl, ohmefentanyl, and betahydroxythiofentanyl.

The Secretariat advised that it had only been able to uncover a single acute toxicity value for NPP

Test type	**Route of exposure**	**Species**	**Dose**	**Toxic effects**	**Reference**
LD_{50}	Oral	Mammal (species unspecified)	350 mg/kg	Behavioural alteration of classical conditioning	J. Medicinal Chemistry (1965) Vol. 8, page 619.

XXXXX.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The members noted that as there is no legitimate use of NPP other than as an opioid precursor restricting through Schedule 9 would not be an imposition to industry.

Members also considered that it would not be inappropriate to also refer this issue to the PACIA for inclusion of related precursors and intermediates of NPP on the list of substances in its *Code of Practice for Supply Diversion into Illicit Drug Manufacture* and also refer to The National Working Group on the Prevention of the Diversion of Precursor Chemicals (National Precursor Working Group).

One Member noted that NPP was already included in the *Drugs of Misuse Act 1983* in Queensland which gave the police powers to act on possession of this substance whereas XXXXX did not have this ability at present without the inclusion of NPP in Schedule 9.

RESOLUTION 2009/55 - 15

The Committee decided to include N-phenethyl-4-piperidone in Schedule 9.

Schedule 9 – New entry

N-PHENETHYL-4-PIPERIDONE.

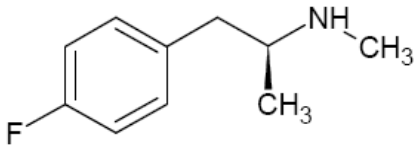
8.2 4-FLUORO-N-METHYLAMPHETAMINE

PURPOSE

The Committee considered the scheduling of 4-fluoro-N-methylamphetamine including a proposal to include it in either Schedule 8 or Schedule 9 rather than rely on the current Schedule 8 entry for methylamphetamine.

BACKGROUND

4-Fluoro-N-methylamphetamine (4-FMP-M), also known as 4-fluoromethamphetamine, is a derivative of methamphetamine in which the hydrogen in the 4-postion has been replaced by a fluorine atom.



The name 4-fluoromethylamphetamine is perhaps ambiguous since it could be interpreted as signifying a (4-fluoromethyl) substituted derivative of amphetamine and hence the unambiguous name 4-fluoro-N-methylamphetamine may be preferred. This also reflects the naming convention followed for the current Schedule 8 methylamphetamine entry. Alternatively, the name methamphetamine appears to be far more common than methylamphetamine, so Members also considered the name 4-fluoromethamphetamine. The IUPAC name for 4-FMP-M is 1-(4-fluorophenyl)-N-methylpropan-2-amine.

DISCUSSION - SUBMISSIONS

XXXXX requested that the Committee consider the inclusion of 4-FMP-M in either Schedule 8 or Schedule 9 for the following reasons:

- This substance had been found in illicit drugs seized in Victoria in March 2008.
- XXXXX had made an enquiry regarding the scheduling of this substance.
- XXXXX had been advised by XXXXX, a forensic scientist XXXXX, that this substance appeared to have no legitimate use and that, XXXXX opinion, even though the molecule looked very similar to methylamphetamine (fluorine replacing hydrogen), 4-FMP-M cannot be made by adding fluorine to methylamphetamine. Rather, XXXXX stated that it has to be made using a fluorinated precursor and processed to the final product and it could be therefore argued that it is not covered under the meaning of ‘derivative’.
- There appeared to be some doubt as to whether 4-FMP-M was captured by the Schedule 8 entry for methylamphetamine and because the schedules are used by persons with a limited understanding of chemistry and derivatives, inclusion in

Schedule 8 should be made unambiguous if indeed there was an intention that it be captured as a derivative of methylamphetamine.

The Secretariat advised that an internet search for "4-fluoro methamphetamine" failed to uncover any information other than that it became a controlled drug in Japan in 2006. Substitution of hydrogen by fluorine is one of the most common monovalent isosteric replacements. Since hydrogen and fluorine are quite similar in size, replacement of hydrogen with fluorine is said to lead to similar binding of the fluoro and non-fluoro analogues at the receptor site hence 4-fluoro substituted methamphetamine could be expected to have similar pharmacological properties to that of the parent methamphetamine.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (d) the extent and patterns of use of a substances, (g) the potential for abuse and (h) the purposes for which a substances is to be used.

The Committee noted that there is seemingly no legitimate use of 4-fluoro-N-methylamphetamine and so for clarity it would be reasonable to include it in Schedule 9. The Committee agreed that the current scheduling of methylamphetamine unambiguously captured 4-fluoro-N-methlyamphetamine but a separate entry would be useful.

The Committee also agreed to cross-reference methylamphetamine with methamphetamine in the SUSDP index to assist those not necessarily familiar with chemical nomenclature. The Committee further agreed to do the same for 4-fluoro-N-methlyamphetamine.

RESOLUTION 2009/55 - 16

The Committee decided to create a new entry in Schedule 9 for 4-fluoro-N-methylamphetamine.

Schedule 9 – New entry

4-FLUORO-N-METHYLAMPHETAMINE.

8.3 1-(8-BROMOBENZO[1,2-b;4,5-b']DIFURAN-4-YL)-2-AMINOPROPANE (BROMODRAGONFLY)

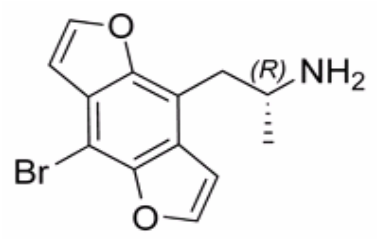
PURPOSE

The Committee considered a proposal to ban 1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane through its inclusion in Schedule 9.

BACKGROUND

1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane is a psychedelic hallucinogenic drug first synthesised in 1998. It is approximately one fifth the potency of lysergic acid diethylamide (LSD). According to the US Drug Enforcement Administration's (DEA) Microgram Bulletin, August 2007, the dosage unit is allegedly 0.5 mg. DrugScope, the UK's leading independent centre of expertise on drugs and policy development issued the following statement regarding the dosage for this drug: "The drug is a liquid and taken in similar ways to LSD - but as it is relatively rare, little is known about its effects or what may or may not be a 'safe' dose."

This drug is said to have an effective duration of action of up to 2-3 days. This compound contains an asymmetric carbon atom with the R-isomer, depicted below, being the more pharmacologically active isomer.



The International Union of Pure and Applied Chemistry (IUPAC) name of this compound is 1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane. It is also known by the trivial or unofficial name Bromo-Dragonfly by people involved in the policing/drug/youth culture and in international scientific papers.

The hallucinogenic effect of Bromo-Dragonfly is mediated by its agonist activity at the 5-HT2A serotonin receptor with this compound being the most potent ligand (i.e. binder) of both the 5-HT2A and 5-HT2C serotonin receptors yet known. The affinity of ligands for either the 5-HT2A or 5-HT2C agonist binding sites are enhanced by modification of the 2, 5-oxygen substituents that are found in typical hallucinogenic amphetamines. Restriction of the conformationally flexible 2, 5-dimethoxy substituents into fused dihydrofuran rings generally resulted in increased potency relative to the parent 2, 5-dimethoxy compounds.

Bromo-Dragonfly is fairly similar in structure to the Schedule 9 substance 2, 5-dimethoxy-4-bromoamphetamine, and could possibly be considered to be captured by the Schedule 9 group entry "ALKOXYAMPHETAMINES and substituted alkoxyamphetamines".

DISCUSSION - SUBMISSIONS

A submission was received from XXXXX requesting that this substance be considered for inclusion in Schedule 9. XXXXX was advised XXXXX that Bromo-Dragonfly is an hallucinogenic drug from the phenethylamine family with a similar effect to LSD.

An amount of 750 grams of Bromo-Dragonfly (disguised in paint containers) was seized in Queensland and sent to the US DEA for testing. This information appeared in the February 2008 edition of US DEA publication Microgram Bulletin.

There was no regulation of the substance in Australia [XXXXX it was not captured by any of the Schedule 9 entries]. However, the drug was subject to regulatory action in Sweden, Denmark and Norway and was linked to the death of an 18 year old woman in Denmark. The action of the drug in the death of this person was proved at autopsy. This case lead to the classification of the substance as illegal in Denmark on 5 December 2007.

Further, cases of severe peripheral vasoconstriction following an overdose with Bromo-Dragonfly were reported. At the XXVIII International Congress of the European Association of Poisons Centres and Clinical Toxicologists in May 2008, Hulten P and Personne M presented a paper "Bromo-Dragonfly, a Life Threatening Designer Drug", which reported pronounced and previously unknown, severe vasoconstrictor effects of this new dangerous drug of abuse. The paper described two cases of ingestion of the substance in which a 20 year old male experienced necrosis and a 34 year old male lost digits. The paper reported that another person had been found dead in Sweden, as a result of Bromo-Dragonfly and one person in Norway had also died after using the drug.

There are a large number of analogue compounds related to Bromo-Dragonfly. Although most of these analogues have not been made and tested, many are predicted to be active hallucinogens. The analogue 2C-B-FLY was synthesised and has produced hallucinogenic effects lasting from 6 to12 hours, following an oral dose of between 1 mg to 10 mg of Bromo-Dragonfly. Therefore, Members considered not excluding salts or derivatives from any scheduling entry for Bromo-Dragonfly.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that due to the potential for abuse of this substance, its manufacture, possession, sale and use be prohibited by law through inclusion in Schedule 9. It was also agreed to cross-reference the IUPAC name with 'Bromo-Dragonfly' in the SUSDP index.

RESOLUTION 2009/55 - 17

The Committee decided to create a new entry in Schedule 9 for 1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane and also to include a cross-reference from Bromo-

Dragonfly to 1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane in the SUSDP 24 index.

Schedule 9 - New entry

1-(8-BROMOBENZO[1,2-B;4,5-B]DIFURAN-4-YL)-2-AMINOPROPANE
*(Bromo-Dragonfly)

SUSDP 25 index – New entry

BROMO-DRAGONFLY
See 1-(8-bromobenzo[1,2-b;4,5-b]difuran-4-yl)-2-aminopropane

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

Nil.

PHARMACEUTICALS

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

Nil.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 PHOSPHODIESTERASE TYPE 5 INHIBITORS

PURPOSE

The Committee considered the scheduling of phosphodiesterase type-5 (PDE5) inhibitors including a proposal to create a Schedule 4 class entry.

BACKGROUND

There are 6 subtypes of phosphodiesterase inhibitors (PDEs). Sildenafil, tadalafil and vardenafil are inhibitors of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type-5 (PDE5) in smooth muscle, where PDE5 is responsible for degradation of cGMP. Sildenafil, for example, increases cGMP within vascular smooth muscle cells resulting in relaxation and vasodilation. In patients with pulmonary hypertension, this leads to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilation in the systemic circulation. In patients with erectile dysfunction, sildenafil enhances the effect of nitric oxide (NO) by inhibiting PDE5 in the corpus

cavernosum. When sexual stimulation causes local release of NO, inhibition of PDE5 by sildenafil causes increased levels of cGMP resulting in smooth muscle relaxation and inflow of blood to the corpus cavernosum.

The first consideration of a PDE5 inhibitor by the NDPSC was at the meeting held in August 1998. The Committee agreed that a Schedule 4 classification was appropriate for sildenafil as the Committee considered that the contraindications, precautions and drug interactions were such that medical advice was required. An entry in Appendix D to restrict prescribing was not considered appropriate. The Committee agreed that to avoid any inadvertent legal supply prior to scheduling that sildenafil be included in a separate part to SUSDP 13 Amendment 1 with an effective date of 23 September 1998. The Committee agreed that early implementation was in the interests of public health and that the decision should not be subject to the usual post-meeting public consultation period. This action indicates that the NDPSC had concerns about such substances being accessed without proper medical supervision.

At the February 2003 NDPSC Meeting, the Committee considered the scheduling of tadalafil, another PDE5 inhibitor. The Committee agree to include tadalafil in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate diagnosis and the use of this medicine required patient management and monitoring by a medical professional. Vadenafil was considered at the June 2003 NDPSC Meeting and was included in Schedule 4 of the SUSDP. These are the only three PDE5 inhibitors that have been considered to date.

DISCUSSION - SUBMISSIONS

At the October 2008 NDPSC Meeting, XXXXX Member recommended that the Committee consider the scheduling of PDE5 inhibitors as a class. The member informed the meeting that medicines manufactured overseas purporting to be complementary medicines had later been found by authorities to contain sildenafil. In December, Medsafe took regulatory action associated with six products sold from an Auckland supermarket selling imported herbal goods. One of the products contained the undeclared therapeutic substances sildenafil and homosildenafil.

In addition, on 8 August 2008 the Director-General of Health, Stephen McKernan, issued a warning about the potential health dangers associated with three products promoted and sold in New Zealand for sexual enhancement or the treatment of erectile dysfunction which may contain an undeclared therapeutic substance. The warning was issued following investigations by the Ministry of Health's medicines safety arm, Medsafe into the products; Rize 2 the Occasion (also known as Rize 2), Rose 4 Her and Viapro. The USFDA had issued a warning that products on the US market with these names had been tested and recalled after they were found to contain the substance thiomethisosildenafil.

A search of USFDA News uncovered similar regulatory action by the USFDA. In July 2008 US Marshals, at the request of the FDA seized $74,000 worth of Xiadafil VIP

tablets distributed by SEI Pharmaceuticals, Inc of Miami, Florida. The USFDA's chemical analysis found that the products contained hydroyhomosildenafil.

In addition, a search of the Medicines and Healthcare products Regulatory Agency (MHRA) website revealed a similar warning about herbal products marketed for the treatment of erectile dysfunction. The MHRA had received several warnings from overseas authorities about seven products all of which have been found to contain prescription-only medicines such as glibenclamide or sildenafil and its analogue, nor-acetildenafil and tadalafil.

Other searches revealed a number of number of papers dedicated to the analysis and detection of undeclared PDE5 inhibitors in health supplements. In one paper by Xiaowei et al (*Structural elucidation of a PDE5 inhibitor detected as an adulterant in a health supplement* Journal of Pharmaceutical and Biomedical Analysis Vol 48,4, 1 Dec 2008) a PDE5 inhibitor was detected and isolated from a health supplement claimed to be a preparation of fresh oyster extracts. In another paper by Gratz et al (*Analysis of undeclared synthetic phosphodiesterase-5 inhibitors in dietary supplements and herbal matrices by LC-ESI-MS and LC-LV,* Journal of Pharmaceutical and Biomedical Analysis, Vol 36, Issue 3, 15 Nov 2004) a liquid chromatography-electrospray ionisation-mass spectrometry (LC-ESI-MS) method was developed to screen for the presence of synthetic PDE5 inhibitors. Approximately half of the 40 botanical products analysed were found to contain undeclared synthetic PDE5 inhibitors.

Other papers by Penz Zou et al (*Isolation and identification of thiohomosildenafil and thiosildenafil in health supplements,* Journal of Pharmaceutical and Biomedical Analysis Vol 47, 9 June 2008 and *Identification of benzamidenafil, an new class of PDE5 inhibitor, as an adulterant in a dietary supplement* Journal of Pharmaceutical and Biomedical Analysis Vol 47 9 June 2008) have identified at least 3 types of PDE5 inhibitors in dietary supplements.

An internet search by the Secretariat revealed two other PDE5 inhibitors not yet considered by the NDPSC. Vivus Pharmaceuticals, an American company, is developing avanafil, a fast-acting, highly selective PDE5 inhibitor which was to start the phase 3 program in the second-half of 2008. Dong-A Pharmaceutical, a Korean company, manufactures and markets in Korea the product udenafil a long acting oral PDE5 inhibitor for erectile dysfunction.

A pre-meeting comment was received from XXXXX which was in agreement with the class entry; however it pointed out that the disadvantage of using a class classification is that in court, evidence must be adduced to prove that a particular drug is included in the class. XXXXX concurred with the submission made by XXXXX had no objections to the class entry but requested that the individual entries remain.

XXXXX noted that the proposal would help facilitate the regulation of certain herbal products containing PDE5 inhibitors and had no objection.

XXXXX supported the inclusion of a class entry on the basis that use of any drug from within this class should be under medical supervision as they are associated with serious precautions (in particular cardiovascular), contraindications and adverse reactions. This makes it appropriate that any drug from this class be included under Schedule 4.

XXXXX also noted that the class entry would ensure adequate measures are available to inhibit the illicit supply of PDE5 inhibitors.

DISCUSSION – RELEVANT MATTERS UNDER 52E

XXXXX

Members agreed that the relevant matters under section 52E (1) included (a) toxicity and safety, (c) potential hazards and (g) potential for abuse.

The Members noted that many of the PDE5 inhibitors found in herbal medicines could have a number of unknown risks as they had not been tested. For example, there was a potential that these substances could act on PDE enzymes other than PDE5.

The point was made that there is a difference between adulterated goods (containing substances not disclosed) and counterfeit goods (not containing substances they claim too). It was agreed that a class entry for PDE5 inhibitors would capture any adulterated goods containing PDE5 inhibitors.

The Committee noted that while a class entry would capture PDE5 inhibitors that may adulterate herbal medicines, the class entry would not and should not preclude scheduling new PDE5 inhibitors as they are evaluated through TGA registration processes. By listing the new substances as they are registered the SUSDP would provide insight into whether a particular PDE5 inhibitor had been considered by the Committee.

RESOLUTION 2009/55 - 18

The Committee agreed to include a class entry for phosphodiesterase type 5 inhibitors in Schedule 4.

Schedule 4 – New Entry

PHOSPHODIESTERASE TYPE 5 INHIBITORS **except** when separately specified in these Schedules.

11.2 HYDROQUINONE

PURPOSE

The Committee considered the scheduling of hydroquinone, including a proposal to amend the current exemption for use in hair dyes from 1 per cent to 0.3 per cent, in line with the European Union (EU) cut-offs.

BACKGROUND

Hydroquinone is a reducing agent that oxidizes to form quinone in air. It is used as a photographic developer, antioxidant, stabilizer (in paints, fuels, oils and polymers), as a chemical intermediate and in pharmaceuticals. Hydroquinone is also used as a skin depigmenting agent and in hair preparations. Hydroquinone is also known as 1, 4-dihydroxybenzene.

Hydroquinone increases melanin excretion from melanocytes and may also prevent its production. Topical hydroquinone may cause transient erythema and a mild burning sensation. Occasionally hypersensitivity has occurred. Concentrations of 2 to 4 per cent are commonly used; higher concentrations may be irritants and increase the risk of ochronosis. In addition to the risk of ochronosis it has been suggested that, based on animal studies, long-term use of hydroquinone might be carcinogenic.

Human External Use

Hydroquinone was first included in Schedule 4 in 1969 due to concerns being raised about the promotion and free availability of skin lightening creams which were being targeted to the PNG and Indigenous Australian populations. The February 1971 Meeting agreed to amend the Schedule 4 entry for hydroquinone to allow an exemption from scheduling for preparations of hydroquinone containing ≤ 2 per cent.

At the May 1986 Meeting, a recommendation to delete the ≤ 2 per cent exemption was made i.e. all human use hydroquinone becoming Schedule 4. The Committee considered the overall ADR profile for hydroquinone warranted inclusion in Schedule 4; however, this recommendation was not implemented. At the May 1987 Meeting it was agreed to foreshadow creation of a new Schedule 2 entry for hydroquinone for human therapeutic or cosmetic use at ≤ 2 per cent (with an Appendix F warning statement). This was confirmed at the July 1987 Meeting.

Following a request from XXXXX that the Committee give consideration as to whether hydroquinone was appropriately scheduled, the June 2008 NDPSC Meeting the Committee noted concerns about possible carcinogenicity of hydroquinone with prolonged usage.

The October 2008 NDPSC Meeting foreshadowed consideration of the rescheduling of hydroquinone and possible up-scheduling hydroquinone in preparations for human external use (excluding hair dyes) to Schedule 3.

A review of hydroquinone safety is currently being undertaken by the USFDA. In 2006, based on data regarding potential carcinogenicity and reports of ochronosis, the USFDA proposed to reclassify these skin bleaching products (specifically containing hydroquinone) as drugs and make them available by prescription only.

In Europe the use of hydroquinone in cosmetic preparations for skin lightening has been banned, but it is still available for prescription as a medicine. The Scientific Committee On Cosmetic and Non-Food Products (SCCNFP) have listed hydroquinone in Annex III - Part 1 *List of Substances which cosmetic products must not contain except subject to restrictions and conditions laid down* to European Council (EC) Directive 76/768/EEC of 27 July 1976 of the Cosmetics Directory.

Hair Preparations

The July 1987 Meeting agreed to a general exemption from scheduling for ≤ 1 per cent hydroquinone in hair preparations. No reasons were recorded for this decision.

The October 2008 NDPSC Meeting noted that the European Union (EU) cut-offs for hydroquinone as unapproved cosmetic ingredient (≤ 0.3 per cent in hair dyes) were more restrictive than the current SUSDP controls (allowing ≤ 1 per cent). Members agreed that they should re-examine the hair preparations exemption by foreshadowing consideration of aligning with the EU cut-off at the February 2009 NDPSC Meeting.

Salts and Derivatives

The May 1987 NDPSC Meeting noted that monobenzone was actually more potent than hydroquinone and agreed to foreshadow that it should be in Schedule 4, together with other derivatives of hydroquinone for human therapeutic or cosmetic use, with no exceptions (whereas hydroquinone had a Schedule 2 entry, see above history). The Members also noted that the other ether derivatives of hydroquinone were more potent than hydroquinone and had a similar side effect level to monobenzone.

The July 1987 Meeting amended the foreshadowed monobenzone entry by specifying capture of 'other alkyl ethers of hydroquinone for human therapeutic use or cosmetic use' rather than all derivatives. No reason was recorded. This remains the wording in the current monobenzone entry.

Therefore, hydroquinone salts or derivatives which are not alkyl ethers of hydroquinone are likely to be captured under the current hydroquinone entries through Paragraph 1(2)(c) of the SUSDP which indicates that "every salt, active principle or derivative of the substance, including esters and ethers, and every salt of such an active principle or derivative" will be captured by a schedule entry unless the contrary intention appears.

Members recalled that a substance is not classed as a derivative on the basis of a single prescriptive set of criteria. As set out under "Principles of Scheduling – Reading the Schedules":

- 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, and toxicologically) to a Scheduled poison or is readily converted (either physically or chemically) to a Scheduled poison. However, a substance is only considered a derivative of a Scheduled poison if it is not individually listed elsewhere in the Schedules, or captured by a more restrictive group or class entry. Additionally, some entries specifically exclude derivatives. Once a substance is determined to be a derivative of a Scheduled poison, the same scheduling requirements as the Scheduled poison, including limits on access, supply and availability, will apply.

DISCUSSION - SUBMISSIONS

Human External Use

Members recalled that the October 2008 NDPSC Meeting agreed that the Secretariat would monitor the situation and update them regarding the USFDA's progress on hydroquinone in skin bleaching products.

The Committee was advised that the USFDA had not yet reached a decision for hydroquinone. However, the Unified Agenda of the Federal Regulatory and Deregulatory Actions Spring 2008, contained a listing for skin bleaching products referenced as; – HHS/FDA Over the Counter (OTC) Drug Review – Skin Bleaching Products 0910 – AF53.

The Current Unified Agenda and Regulatory Plan stated that the Final Action for the rulemaking on hydroquinone in skin bleaching products will be completed in May 2009.

Hair Preparations

Members recalled the following XXXXX pre-meeting comment from the October 2008 NDPSC Meeting:

- In the EU hydroquinone is an approved cosmetic ingredient for use in hair dyes (≤ 0.3 per cent). The decision on the current level of hydroquinone in hair dyes is based on the February 1999 opinion of the SCCNFP on hydroquinone.
- The SCCNFP concluded that the use of hydroquinone as a constituent in oxidative hair dye formulations was safe in rinse-off cosmetic products which moreover are applied normally once a month; only a small quantity comes into contact with the scalp and hydroquinone disappears rapidly during the reaction time of the dyeing procedure down to less than 5 per cent within 10 to 30 minutes.

- Given the opinion of the SCCNFP, XXXXX believed that there was a good scientific basis for retaining the current Australian exemption for hydroquinone used in hair dyes from scheduling. The Committee noted a consequent lack of clarity as to support or otherwise of the retention of the ≤ 1 per cent value for this exemption given the statements above.

The Members also noted the following from discussion at the October 2008 NDPSC Meeting:

- The Committee noted that the EU cut-offs for hydroquinone as an approved cosmetic ingredient (≤ 0.3 per cent in hair dyes, ≤ 0.02 per cent in professional-use artificial nail systems) were as per the 1999 recommendations of the SCCNFP. The point was raised that hair dyes imported from Europe would be likely to meet the EU cut-off of 0.3 per cent, rather than the Australian cut-off of 1 per cent.
- Given that the SCCNFP recommendation was based on available evidence of safety, the Committee agreed that it should re-examine the 1 per cent cut-off for hair preparations by foreshadowing consideration of aligning with the EU cut-off of 0.3 per cent.

Members noted the following from the February 1999 SCCNFP minutes:

- A draft opinion from a working party which had evaluated the safety of hydroquinone as a hair dye constituent ("*SCCNFP opinion on hydroquinone as a skin depigmenting agent*" SCCNFP/0078/98). In this opinion it was concluded that hydroquinone should not be used as depigmenting agent in cosmetic products due to observed clinical side effects (ochronosis and leukomelanoderma).
- Hydroquinone is used as a coupler agent in oxidative hair dyes. Coupler agents in hair dyes are substances which induce or enhance chemical processes which lead to the formation of final dyes. Mostly a coupling substance itself disappears during the reaction time of about 10-30 minutes, within the first 10 minutes by up to more than 70 per cent.
- The SCCNFP concluded that the use of hydroquinone as a constituent in oxidative hair dye formulations as a coupler was safe (at up to 0.3 per cent) in this kind of rinse-off cosmetic products which moreover were applied for hair dyeing normally once a month.

Salts, Derivatives and Arbutin

Members were advised that following the October 2008 NDPSC Meeting a follow-up comment had been received from XXXXX:

- Asserting that the Committee had not given consideration to its previous proposal regarding derivatives of hydroquinone (discussed below)
- Reiterating its October 2008 proposal that the schedule entries for hydroquinone be separated from its derivatives before consideration of up-scheduling of hydroquinone,

to align with the EU. Without this separation, cosmetic ingredients such as arbutin would not be available on the Australian market, creating mis-alignment with the EU Cosmetics Directive.

- XXXXX suggested the addition of the words "excluding its derivatives" to the hydroquinone schedule entries.

Members also recalled the following from XXXXX pre-meeting comment to the October 2008 NDPSC Meeting:

- Raised a concern that there was some potential for confusion surrounding the schedule entry for hydroquinone and its application to derivatives of hydroquinone, such as arbutin (a glycosylated hydroquinone), and proposed that separate schedule entries for hydroquinone and its derivatives be considered.
- In the EU, hydroquinone and arbutin are treated separately as cosmetic ingredients. Arbutin is an approved cosmetic ingredient in the EU, for use as an antioxidant and skin conditioner with no limitations imposed.
- It was XXXXX understanding that arbutin is a naturally occurring substance found in leaves of bearberry, blueberry, cranberry or mulberry shrubs. These plant extracts are currently used in a number of cosmetic products in Australia at a low concentration. Arbutin is also found in most types of pears.
- Recently (15 April 2008), the Scientific Committee on Consumer Products (SCCP) published their opinion on arbutin. The SCCP was evaluating the safety of arbutin in cosmetic products in a concentration of up to 7 per cent. The general toxicological assessment of arbutin suggested that the substance may be safe. However, the SCCP raised some concerns over the bioavailability of hydroquinone under the conditions of intended use. No decisions have yet been made by the Commission of European Communities based on the SCCP opinion.
- XXXXX suggested:
    - Separating the schedule entry for hydroquinone from its derivatives for any further scheduling decisions.
    - Separate schedule entry for arbutin could be considered when the Commission of European Communities announce their decision on β-arbutin based on the SCCP opinion of April 2008.

Members additionally noted the following from the April 2008 SCCP opinion on arbutin:

Conclusion

- Although the general toxicological assessment of arbutin suggests that the substance may be safe, the bioavailability of hydroquinone under conditions of intended use of the substance is of concern. Whereas hydroquinone was initially permitted at a concentration of 2 per cent, a 1998 opinion of the SCCNFP recommended that the substance should not be used any more as a depigmentation agent in cosmetic

products due to observed clinical side effects, among which was exogenous ochronosis.

- Consequently, the SCCP considers the currently requested use of arbutin in cosmetic products unsafe.
- In addition, it was the opinion of the SCCP that the same concern can be expressed for other products that result in the release and/or formation of hydroquinone before or upon application on the skin.

Background

- Hydroquinone is currently listed in Annex III (entry 14) of the Cosmetics Directive 76/768/EEC. Its permitted use is restricted to hair-dye products and artificial fingernails. Since the banning of hydroquinone as a skin whitener, other substances have been used for this purpose, including arbutin.
- The effect of arbutin seemed to be due to the fact that it hydrolyses to hydroquinone. A simple conversion to hydroquinone was thought likely to imply that arbutin would currently be captured by the hydroquinone schedule entries. Arbutin is being used as an ingredient alone and as a component in skin lightening products.
- The SCCP was asked in July 2005 to review β-Arbutin (chemical name 4-hydroxyphenyl- β-D-glucopyranoside, INCI name Arbutin) to address the following:
  - Does the SCCP consider the use of β-arbutin to be safe for consumers in cosmetic products in a concentration up to 7 per cent?
  - Does the SCCP recommend any restrictions with regard to the use of β-arbutin in cosmetic products*?*

- Toxicity summary from submitted studies:

Endpoint	**Study conclusion**
Acute oral toxicity LD_{50}	9804 mg/kg bw (mouse), 8715 mg/kg bw (rat).
Acute dermal toxicity LD_{50}	> 928 mg/kg bw (rats and mice), the maximum practically applicable dosage.
Skin irritation	10 per cent aqueous solution was non-irritating to rabbit skin. Low irritation potential by human patch test. 0 per cent, 7 per cent and 10 per cent in arbutin containing products display low irritation potential in human tests.
Eye irritation	10 per cent aqueous solution had little potential for rabbit eye irritation.
Skin sensitisation	Not a sensitiser by Magnusson Kligman Guinea Pig Maximisation Test.
Repeated dose	no changes attributed to arbutin up to a dosage of 1000 mg/kg bw/day – can be considered the NOEL.
Sub-chronic (90 days) dermal toxicity	No changes attributed to arbutin up to a dosage of 618 mg/kg bw/day (the maximum technically applicable dosage) – can be considered the NOEL.
Mutagenicity/Genotoxicity *in vitro*	Nonmutagenic in reverse mutation tests in bacteria. Did not induce chromosomal aberrations at concentrations up to 0.34 mg/ml in Chinese hamster lung fibroblasts, irrespective of metabolic activation.
Carcinogenicity	Observed (non-)tumour lesions in mouse study are ones frequently observed in aging mice. The NOEL value for was therefore estimated to be 400 mg/kg bw/day in male and female mice. It was concluded that arbutin was not carcinogenic under the 18 month study conditions.
Reproductive toxicity	400 mg/kg/day does not affect reproductive functions of the parent and F1 rats, but caused body weight decrease in female foetuses, decreased organ weights of the unilateral ovary of female F1 rats. Estimate the no observable effect dose to be 100 mg/kg/day.
Toxicokinetics	Under in use conditions in human volunteers, hydroquinone is released to a relative level (compared to the arbutin + hydroquinone content) as high as 11.8 per cent (w/w).
Phototoxicity and photosensitisation	Little phototoxicity potential. Did not possess photoallergic potential under test conditions.

Issues to be considered

- In acidic medium, arbutin is easily hydrolysed into hydroquinone. This can be of relevance in case arbutin is incorporated in aqueous lotions with a slightly acidic pH, facilitating hydrolysis into hydroquinone within the formulation.
- Hydrolysis has been described to significantly take place in the case of oral intake of arbutin (stomach acids), but also to a lesser extent after dermal exposure. In addition, enzymatic biotransformation may be expected in both cases.
- In light of the above, it also needs to be noted that the ratio hydroquinone/(arbutin + hydroquinone) in the skin amounted up to 11.77 per cent in the skin metabolism study in human volunteers which is considerably higher than the ratio of the two substances in the applied product.
- Although this finding was not considered alarming by the performing laboratory because the absolute levels of arbutin and hydroquinone in the skin were considered relatively small and their contribution to the total body burden was considered negligible, it needs to be considered that this study was of limited size (18 volunteers) with only one type of formulation and that dermal absorption will be influenced by the vehicle used.
- Moreover, the dermal absorption of hydroquinone is reported to be 57 per cent, which is much higher than the dermal absorption value observed for arbutin.
- These considerations raise questions as to the safety of the use of 7 per cent arbutin in cosmetic products for skin bleaching purposes. If hydroquinone is released in relevant amounts either in the product or during the use of arbutin, the product could not be considered safe, since hydroquinone has been assessed as being unsafe for use in skin lightening applications due to the danger of ochronosis and leukomelanoderma and consequently has been banned for this use in the EU. The hydroquinone levels at which ochronosis has been described is 1 per cent and higher.
- As no data was available on concentration levels below 1 per cent, a lower threshold for the occurrence of ochronosis is difficult to establish. Although the risk for ochronosis may be relatively low, the occurring cases can be severe and irreversible.
- In the case of release of hydroquinone, the aspect of skin sensitisation has to be considered, since hydroquinone has been identified to be a skin sensitiser. Also, the concerns about cancer risks then become an issue.
- The use of arbutin at 7 per cent in skin bleaching products induces a complex situation for which the local application level and the bioavailability of hydroquinone cannot be generalized.

Members noted in particular that the document “SCCNFP opinion on hydroquinone as a skin depigmenting agent” indicated that the clinical adverse effects of skin bleachers based on hydroquinone and its ethers were represented by two main aspects: exogenous ochronosis and confetti-like pattern, leukomelanoderma.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under 52E(1) included (a) the toxicity and safety, (b) the risks and benefits, (c) the potential hazards, (e) the dosage and formulation and (d) the extent and patterns of use of a substance.

Human External Use

A Member expressed concern that the USFDA decision might take years, however it was confirmed that the final decision would be handed down in May 2009. Members agreed that it was important to wait for the decision of the USFDA, in order to consider its findings before making their decision.

The Committee therefore supported deferring a decision on the scheduling of hydroquinone in skin bleaching products (for external therapeutic use) until the USFDA report is available in May 2009, and thus anticipated addressing the issue at the June 2009 NDPSC Meeting.

Hair Preparations

A Member reiterated that many cosmetic products, for the Australian market (including hair preparations) are internationally sourced and thus likely to also be formulated to allow sale in the EU (i.e. compliant with ≤ 0.3 per cent hydroquinone).

A Member asserted, and the Committee generally agreed, that the ≤ 0.3 per cent hydroquinone cut-off in the EU was based on an extensive European review of the risks and that this provided ample evidence for the Committee to move in matching this cut-off.

Salts, Derivatives and Arbutin

The SCCP indicated, in relation to arbutin, that the bioavailability of hydroquinone under conditions of intended use of the substance is of concern. However, the Member noted that at this stage, the SCCP opinion had yet to be adopted in the EU. That said, this still provided a strong basis for not supporting the requested exemption from scheduling for salts and derivates of hydroquinone, especially arbutin.

A Member asserted that the SCCP arbutin report indicated that the risk from arbutin was less than that posed by hydroquinone, and that capture as a derivative of hydroquinone was therefore no longer appropriate. While one Member suggested deferring any decision on arbutin until the final EU decision, the Committee generally agreed that there appeared to be sufficient information to hand for considering a separate schedule entry for arbutin. A Member also noted that a specific entry would override capture as a derivative under the hydroquinone entry. Members therefore agreed to foreshadow consideration of a separate schedule entry for arbutin (glycosylated hydroquinone) at the June 2009 NDPSC Meeting.

A Member asserted that there were a number of other 'natural' plant extracts that would possibly be considered derivatives of hydroquinone which industry may wish to incorporate into cosmetic products. Another Member noted, however, that a number of hydroquinone derivatives shared hydroquinone's risk profile and, indeed, that some actually may be more of a risk than hydroquinone. The Member cautioned against a blanket approach to hydroquinone salts/derivatives and asserted that the June 2009 foreshadowed consideration should remain focused on arbutin alone.

The Committee therefore generally agreed that it was not appropriate to limit the current hydroquinone entry by excluding salts or derivatives. Members noted that, as foreshadowed for arbutin, it remained open for specific hydroquinone salts/derivatives to be considered for separate schedule entries, should sufficient data be provided to the Committee.

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The Committee decided:

- To defer a decision on hydroquinone in skin bleaching products until the USFDA's Final Action is known.
- To amend the exemption for hair preparations containing hydroquinone from 1 per cent to 0.3 per cent or less.
- That the current scheduling of hydroquinone remains appropriate with respect to salts and derivatives.
- To foreshadow specific scheduling entries for arbutin at the June 2009 NDPSC Meeting.

Schedule 2 – Amendment

HYDROQUINONE – Amend entry to read:

HYDROQUINONE (excluding monobenzone and other alkyl ethers of hydroquinone included in Schedule 4) in preparations for human external therapeutic or cosmetic use containing 2 per cent or less of hydroquinone **except** hair preparations containing 0.3 per cent or less of hydroquinone.

Schedule 4 – Amendment

HYDROQUINONE – Amend entry to read:

HYDROQUINONE (other than its alkyl ethers separately specified in this Schedule) in preparations for human therapeutic or cosmetic use **except**:

(a) when included in Schedule 2; or

(b) in hair preparations containing 0.3 per cent or less of hydroquinone.

11.3 CODEINE IN COMBINATION WITH AMMONIUM CHLORIDE AND MENTHOL

PURPOSE

The Committee further considered the scheduling of a particular OTC cough and cold linctus containing codeine, namely XXXXX.

BACKGROUND

Codeine as an opioid analgesic obtained from opium or made by methylating morphine, is much less potent as an analgesic than morphine and has relatively mild sedative effects.

Australia is a signatory to the United Nations Single Convention on Narcotic Drugs, 1961 and as such Australia must adhere to the provisions of the International Narcotics Control Board's (INCB) list of narcotic drugs under international control. This list only exempts codeine from the strictest controls (Schedule II) when it is "compounded with one or more other ingredients and containing not more than 100 mg of the drug per dosage unit and with a concentration of not more than 2.5 per cent in undivided preparations".

Where this exemption does not apply, codeine preparations are subject to Schedule II of the Single Convention. Thus, as per the intention of the Single Convention (which bases its exemption less on the potential for harm to an individual and more on the potential for illicit diversion) all single (active) ingredient undivided preparations of codeine are not exempted from any provision of the Single Convention.

At the November 1984 Meeting, the Committee noted that some jurisdictions were experiencing problems with codeine linctus. At this Meeting codeine linctus was considered to be a compounded liquid and thus Schedule 2 by the scheduling limits at the time.

At the August 1991 Meeting, the Committee confirmed that codeine linctus preparations were Schedule 8 products. However, because of wider legal implications for the jurisdictions, the question of interpretation of the schedule classification, along with the existence of a definition for "compounded" (a decision of the August 1991 Meeting), was to be referred to the NCCTG. Despite the intention to refer to the NCCTG, it appears that no further action was taken on the matter.

At the May 1998 NDPSC Meeting, the Committee considered interpretation of "compounded" and "therapeutically active substance" as they related to the various codeine and dihydrocodeine schedule entries. The Members noted that "therapeutically active" was not defined. A Member suggested that one option would be to re-examine products in the marketplace with a view to removing the phrase "other therapeutically

active substances" from schedule entries and replacing it with a specific list of acceptable combinations. Members agreed that although this issue needed to be resolved, it was not urgent and a paper exploring the above option could be prepared for consideration at a future Meeting. It is apparent that this issue was not pursued any further.

A similar issue was considered at the February 2006 NDPSC Meeting, the Committee confirming the current scheduling of codeine and agreeing that the interpretation of the current entry required that any single active preparation of codeine, including liquid preparations, is a Schedule 8 medicine.

At the October 2008 NDPSC Meeting, the Committee noted that neither menthol nor ammonium chloride are cough suppressants, and therefore the appropriateness of their inclusion in a formulation intended to suppress coughs was questioned. Further, as per the Martindale monograph, a therapeutic dose of ammonium chloride is around one to two grams every four to six hours and this particular formulation contains only 100mg/10mL. Given that menthol is mostly used via inhalation, its presence in an oral formulation intended for systemic effect (c.f. lozenge or pastille) may be inappropriate.

Members recalled the following information from XXXXX;

- There was only one product on the ARTG with menthol and ammonium chloride as active ingredients.
- Two other products listed ammonium chloride, menthol, diphenhydramine and sodium citrate as active ingredients. The ARTG had over five hundred products which listed ammonium chloride as an active.
- All three products were grandfathered onto the ARTG in 1991 containing both ammonium chloride and menthol together and no formal evaluation of these products had taken place.
- Ammonium chloride is a common active ingredient in OTC medicines. Menthol is listed as an active to a similar scale.

DISCUSSION – SUBMISSIONS

After the October 2008 NDPSC Meeting, the Sponsor was asked to provide justification for the inclusion of ammonium chloride and menthol in this formulation. The Sponsor's interim response was that clinical evidence of efficacy of the ingredients would be provided in time. The letter went on to say that the lack of evidence of 'efficacy' did not mean lack of 'efficacy'. It was further stated that there was proof from clinical trials that up to "85 per cent of the reduction in cough is based on the placebo effect" and that the active pharmacological component only contributed to 15 per cent of the reduction in cough.

The Sponsor provided a final response which included 55 separate references. The relevance of all of these references to the question of the appropriateness of inclusion of

ammonium citrate and menthol in a cough suppressant was not blatantly clear but the following points were made in an effort to support the claim that the ammonium chloride and menthol were therapeutically active:

- The Cochrane reviews' "Over-the-counter medications for acute cough in children and adults in ambulatory settings", and "Antihistamines for the common cold" were cited, but results were not discussed.
- The applicant reiterated the previous claim, "that lack of evidence for efficacy does not mean that there is a lack of efficacy". This statement was followed by a sentence which appeared to state that the Cochrane review found little evidence of efficacy of menthol or ammonium salts.
- The comment went on to provide detailed information as to the physiological effects which could be induced by a placebo and the possible contribution of the ingredients to the physiological effects of the medicine by having a bitter taste or distinctive smell, and the mechanisms involved. Detailed information was then put forward on the effects of sweet tasting medicines on the physiology.
- The working of cough medicines was described in three ways, the pharmacological effect, the true placebo effect and the physiological effect: none of which go to the question of clinical efficacy of the ingredients.
- Other arguments used were that the availability of the mixture goes to support the current policy of reducing reliance on antibiotic treatment for common colds and minor infections, and that the product is 'effective and inexpensive'. No hard evidence as to the therapeutic activity and efficacy of ammonium chloride or menthol was discussed or put forward.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E (1) included (g) the potential for abuse of a substance; (c) the potential hazards associated with the use of a substance; (e) the dosage and formulation of a substance; and (h) the purposes for which the substance is to be used.

The Committee again questioned the appropriateness of the inclusion of menthol and ammonium chloride's inclusion in a formulation intended to suppress cough. The Committee questioned the therapeutic efficacy of the linctus when, as per its Martindale monograph, a therapeutic dose of ammonium chloride is around one to two grams every four to six hours and this particular formulation contains only 200mg/10mL. The concentration of menthol was also considered less than what is likely to be effective as well as being an inappropriate route of administration.

Members agreed the applicant had not provided convincing justification for the inclusion of ammonium chloride and menthol in this formulation.

The Committee noted further advice on other OTC products on the ARTG which included a cough suppressant containing codeine and ethylmorphine and an anti-diarrhoeal containing codeine, dried aluminium hydroxide, light kaolin and pectin.

RESOLUTION 2009/55 - 20

The Committee agreed to defer further consideration of the scheduling of this cough linctus until matters relating to the scheduling of codeine and the definition of 'compounded' had been resolved.

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

12.1 SUSDP, PART 4

12.1.1 FAMCICLOVIR FOR HERPES LABIALIS

PURPOSE

The Committee considered a proposal to reschedule oral famciclovir from Schedule 4 to Schedule 3 (and inclusion in Appendix H) when used for the treatment of *Herpes labialis* (cold sores) in immunocompetent patients.

BACKGROUND

Famciclovir is a synthetic guanine derivative designated chemically as 9-(4-acetoxy-3 acetoxymethylbut-1-yl)-2-aminopurine. Famciclovir is the oral form of penciclovir. Famciclovir is rapidly converted in vivo into penciclovir, which has demonstrable in vitro activity against Herpes simplex viruses (HSV types 1 and 2) and Varicella zoster virus (VZV). The antiviral effect of orally administered famciclovir has been demonstrated in several animal models: this effect is due to in vivo conversion to penciclovir.

Penciclovir targets virus-infected cells where it is rapidly converted into penciclovir-triphosphate (mediated via virus-induced thymidine kinase). The triphosphate inhibits viral DNA polymerase by competition with deoxyguanosine triphosphate and is incorporated into the extending DNA chain, preventing significant chain elongation. Consequently, viral DNA synthesis and, therefore, viral replication are inhibited. This triphosphate persists in infected cells in excess of 12 hours. The long intracellular half-life of penciclovir triphosphate ensures prolonged antiviral activity, as demonstrated in cell cultures with HSV-1 and HSV-2 and in animal studies.

The June 1994 ADEC Meeting recommended approval for the registration of famciclovir for the treatment of *Herpes zoster* infection. The May 1995NDPSC Meeting recommended a Schedule 4 entry.

On 11 January 2007 famciclovir was approved by the TGA for the treatment of recurrent *Herpes labialis* at a total dose of 1500 mg administered either as a single dose or as 750 mg twice daily at 12 hourly intervals for two doses only (to a total dose of 1500 mg per episode).

Famciclovir is also TGA-registered for the treatment of recurrent episodes of genital herpes in adults and adolescents 12 years of age and older, and for suppression of recurrent genital herpes. Famciclovir is also indicated in immunocompromised patients for: treatment of uncomplicated *Herpes zoster*; treatment of recurrent *Herpes simplex*; suppression of recurrent *Herpes simplex*.

Members recalled that at its November 2001 NDPSC Meeting it agreed to exempt preparations containing 5 per cent or less of aciclovir for the treatment of *Herpes labialis* in packs containing 10 g or less, on the grounds that *Herpes labialis* was a short term and self limiting condition, appropriate for self-diagnosis and management by consumers. In addition, the product was simple to use and increased access to such a product would be beneficial to public health.

DISCUSSION - SUBMISSIONS

Applicant's submission

XXXXX made a submission to reschedule famciclovir for the treatment of *Herpes labialis* in immunocompetent patients from Schedule 4 to Schedule 3 and inclusion in Appendix H of the SUSDP.

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

- *Herpes labialis* is a short term and self-limiting condition, appropriate for self-diagnosis and management by consumers.
- Treatment should be initiated as early as possible after the start of a cold sore infection, as viral replication is most active in the prodromal period or within the first 8 hours after lesion onset. The maximal frequency of virus-positive lesions occurs in the first 48 hours. The window of opportunity therefore for providing clinical benefit is during the early and brief period of time that viral replication dominates over the rapidly developing host immune response i.e. within the first 4 hours.
- The availability of oral antiviral medication for the patient to self medicate within the first few hours of prodromal symptoms onset would achieve maximum possible suppression of viral replication.
- A dose of 1500 mg famciclovir in a single day (either as a single dose of 1500 mg or 750 mg bid) taken shortly after the onset of prodromal symptoms healed *Herpes labialis* lesions 2 days faster than placebo (Spruance et al *Single-dose patient-initiated famciclovir: a randomised, double-blind, placebo-controlled trial for episodic treatment of Herpes labialis* J Am Acad Dermatol 55:47-43 (2006))

- An acceptable safety and toxicity profile has been demonstrated for both a 1500 mg single dose regimen and a 750 mg bid two dose regimen.
- XXXXX. Famciclovir has been well tolerated in clinical trials with the most frequently reported adverse events being headache, fatigue and nausea. These were generally mild or moderate and occurred at a similar incidence in patients receiving placebo treatment.
- The extensive use of nucleoside analogues for the antiviral treatment of herpes infections for over 20 years has not been associated with an increased emergence of drug-resistant virus in immunocompetent or immunocompromised patients (Bacon TH et al *Herpes Simplex virus resistance to acyclovir and penciclovir after Two Decades of Antiviral Therapy*, Clinical Microbiology Reviews 16 (1): 114-128 (2003)). Given that the submission for famciclovir proposed a single day therapy and not a chronic suppressive therapy, viral resistance was not considered to be an issue.

The applicant addressed the following matters under 52 E:

a) **Toxicity and safety:** the human toxicity profile of famciclovir is well characterised and famciclovir has been well tolerated in human clinical studies with headache, fatigue and nausea reported as the main side effects in clinical trials at a similar incidence in patients receiving placebo treatment. There are no known contraindications apart from hypersensitivity to famciclovir (or penciclovir) and no clinically significant interactions have been identified.

b) **Risks and benefits:** evidence from preclinical studies has shown no potential for induction of cytochrome P450 and there have been only limited reports of acute overdosage, all of which have been asymptomatic. Post-marketing experience over a wide range of doses (including chronic administration) make a 1500 mg dose of famciclovir a suitable candidate for an OTC medicine. The key benefit for consumers is the availability of a single day antiviral treatment of 3 x 500 mg tablets to effectively treat cold sores.

c) **Potential hazards of use associated with the use of a substance:** the applicant stated that only limited acute overdosage with famciclovir has been reported with the PI advising that symptomatic and supportive therapy to be given as appropriate. In patients with underlying renal disease, acute renal failure has been reported rarely; however, it was noted that the famciclovir dosage in these patients had not been appropriately reduced for the level of renal function. Famciclovir for cold sores will be contraindicated in patients with renal disease or in the elderly. The applicant stated that as the dosage, duration and cost of famciclovir for cold sores is different from that required for other indications, such as genital herpes, which would prevent use for these conditions. In addition there is negligible risk to patients who are not overtly immunocompromised from famciclovir for cold sores over the counter as most immunocompromised patients would be routinely seeing a physician who could diagnose and treat herpes simplex virus with the appropriately approved regimen of an antiviral.

d) **Extent and patterns of use of a substance:** the applicant stated that the domination of the topical cream products in pharmacy demonstrated that patients preferred to self-medicate for recurrent cold sores rather than visit the doctor for a prescription which can delay the start of treatment.

e) **Dosage and formulation of a substance:** famciclovir for cold sores would be the same formulation as the current product available on prescription with the Schedule 3 OTC presentation specifically branded and labelled for the treatment of cold sores with appropriate dosage and warning advice.

f) **Need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose:** the applicant argued there was a range of OTC products available for symptomatic treatment of cold sores in Australia which provide symptomatic relief for pain and discomfort and need to be used several times daily for several days. There was some evidence that topical antiviral agents, aciclovir and penciclovir, shorten the duration of symptoms.

g) **Potential for misuse/abuse of the substance:** the applicant stated there was negligible potential for diversion of famciclovir for illicit use in view of the small pack size and it was unlikely that patients with genital herpes or *Herpes zoster* infections will use famciclovir for cold sores due to differences in dosages, quantities and cost.

h) **The purposes for which a substance is to be used:** famciclovir for cold sores will be used to treat recurrent episodes of *Herpes labialis* or "cold sores".

Separately, the applicant also provided a detailed assessment with respect to the Schedule 3 criteria set down in the Interim Guidelines for the NDPSC. Whilst most of the information in this part of the application was a re-ordering of the information presented under the provisions of 52E, the applicant made the following additional points:

- there would be low potential for harm from inappropriate use due to the small pack size,
- there are no identified interactions with any drugs and it can be taken without regards to meals,
- famciclovir has a wide therapeutic index with the likelihood of toxicity or overdose with the 1.5 g pack minimal,
- famciclovir for cold sores is unlikely to mask or compromise other medical conditions.

With respect to viral resistance, the applicant stated that over 20 years use of nucleoside analogues there has been no emergence of drug-resistant virus in patients and that famciclovir in a single dose (not chronic suppressive therapy) viral resistance should not result in increased viral resistance. The applicant cited a number of papers that it claimed supported

the position that the availability of famciclovir for cold sores as Schedule 3 will not lead to viral resistance. The papers are as follows:

- Morphin F et al. *Herpes simplex virus resistance to antiviral drugs* Journal of Clinical Virology 26: 29-37 (2003)
- Levin MJ et al. *Resistance of Herpes Simplex Virus Infections to Nucleoside Analogues in HIV-Infected Patients*. Clinical Infectious Diseases 39:S248–57 (2004)
- Sarisky RT et al. *Profiling penciclovir susceptibility and prevalence of resistance of herpes simplex virus isolates across eleven clinical trials*. Arch Virol 148: 1757–1769 (2003)
- Sarisky RT et al, *Difference in incidence of spontaneous mutations between Herpes Simplex Virus Types 1 and 2,* Antimicrobial Agents And Chemotherapy, 44 (6): 1524–1529 (2000)
- Shin YK et al *Susceptibility of Herpes Simplex Virus Isolates to Nucleoside Analogues and the Proportion of Nucleoside-Resistant Variants after Repeated Topical Application of Penciclovir to Recurrent Herpes labialis.* The Journal of Infectious Diseases 187:1241–5 (2003).
- Kreise1 JD et al *Recurrent Antiviral Resistant Genital Herpes in an Immunocompetent Patient*. The Journal of Infectious Diseases 192:156–61 (2005).

XXXXX. Common post-marketing adverse reaction report terms in decreasing order of frequency are nausea, headache, rash, dizziness, confusional state, fatigue, pruritus, pain, pyrexia, malaise, urticaria, hallucinations and paraesthesia which are included in the PI.

The applicant also addressed the NCCTG Schedule 3 Advertising Guidelines, stating that advertising would not lead to inappropriate use for other viral conditions such as *Herpes zoster* or genital herpes due to the pack size, presentation and cost disincentives. Cold sores are not a prohibited representation under the current Therapeutic Goods Advertising Code and the condition is already advertised to the public for other antiviral agents. The applicant stated that all advertising will direct consumers to consult with a pharmacist which will provide the opportunity for counselling. As consumers already self-medicate cold sores the applicant claimed that little patient education would be necessary and that these consumers would want to know about other treatments that are available.

NDPSC evaluation report

The NDPSC evaluation report recommended that rescheduling to Schedule 3 be approved but that the application for inclusion in Appendix H be rejected. The following points were made in the evaluation:

- No evidence of any abuse potential.
- Low potential for harm from inappropriate use given the pack size and the considerable experience of famciclovir use in children aged between 12 and 17 years.

- Use by immunocompromised patients would be inappropriate but unlikely to lead to any safety issues. Pharmacist education material prepared by the sponsor would direct these patients to their doctor.
- Clinical trials experience indicated that the active treatment was as well tolerated as placebo with adverse events being headache, fatigue and nausea all of which were generally mild or moderate in severity and occurred at the same rate as placebo.
- No known clinically significant interactions with famciclovir.
- Experience with overdose of up to 3000 mg of famciclovir which did not result in adverse effects. Overall the therapeutic index appeared to be wide and the risk of overdose with this presentation did not apply.
- Risk of masking a serious disease was low with the major issue being the misuse of the product for immunocompromised patients for whom a longer dosing regimen is required.
- No contraindications to a single dose except previous hypersensitivity to famciclovir which could be dealt with by the pharmacist.
- Proposed indication was a minor ailment which can be identified by the consumer and did not require medical management or supervision with early treatment being more effective.
- Viral resistance was addressed with evidence provided that no increase in resistance has developed over the past twenty years despite the widespread use of antivirals for herpes infections of various kinds.
- The evaluator noted that there was the potential for reduced transmission of *Herpes simplex* if oral famciclovir was used compared with no treatment, although there was no evidence to support an argument that it was more effective than topical treatment.
- Whilst the 'cold sore' indication was acceptable for advertising it was inappropriate to use an unscheduled substance eg aciclovir as a precedent for a Schedule 3 in terms of acceptability for advertising.
- The evaluator was not convinced that the applicant had demonstrated an advantage of directly advertised famciclovir for cold sores over unadvertised Schedule 3 availability. Any indication that advertising would have a public health benefit remained speculative.

Pre-Meeting Submissions

A pre-meeting comment was received from XXXXX, and supported by XXXXX. The following points were made:

- Possibility of immunocompromised patients and those with genital herpes describing symptoms of *Herpes labialis* with the intention of obtaining famciclovir for treatment of the former purposes.

- Wider availability may promote resistance to famciclovir and related drugs.
- Efficacy was supported by the literature and, in terms of practicality, would relieve pressure on overworked general medical practitioners.
- Inclusion in Appendix H was wholly inappropriate as once a drug is included in Appendix H, it is essentially 'sold' by a television advertisement and nothing the pharmacist can say or do seems to deter the public from demanding it be supplied.
- Appendix H has the effect of undermining the requirements of Schedule 3, state poisons regulations and the pharmacists professional and ethical obligations. XXXXX considered that once a drug was placed in Appendix H it becomes a de-facto Schedule 2 poison and considered that this appendix should be abolished.

A pre-meeting comment was received by XXXXX that did not support the down-scheduling and inclusion in Appendix H, for the following reasons:

- Pharmacists would be put under undue pressure to supply the product on all occasions when topical application with aciclovir would suffice and expose the patient to fewer risks than a systemic antiviral product.
- Inclusion in Appendix H would exacerbate such demand and at an early stage lead to public awareness of the efficacy of famciclovir for the treatment of other *Herpes simplex* virus infections eg genital herpes.
- Based on the varied approved indications for oral famciclovir including *Herpes zoste*r and *Herpes simplex* causing cold sores/genital herpes in immunocompetent and immunocompromised patients, over the counter availability of any antiviral, at this point in time, should be limited to topical preparations only.
- Down-scheduling of oral famciclovir, and subsequent widespread use would increase the risk of developing famciclovir resistant viral strains.
- Complexities associated with determining whether a patient was actually immunocompetent.

XXXXX did not support the proposal for a Schedule 3 classification and opposed Appendix H listing. Whilst it was accepted that there was little evidence, concerned was raised about a possible increase in antiviral resistant *Herpes simplex* virus. Also it may be difficult to implement a scheduling of a substance based on a person's health status such as "immunocompetent patients". Appendix H listing was opposed, given that the product has not had experience in Australia as a non-prescription medicine.

A pre-meeting comment was received from XXXXX that, whilst in agreement with re-scheduling of famciclovir to Schedule 3 for most of the reasons put forward by the applicant, added that the Committee should consider the suitability of other antivirals in the same class that are TGA-approved for cold sores for rescheduling.

DISCUSSION – RELEVANT MATTERS UNDER 52E

XXXXX.

Members agreed that the relevant matters under section 52E (1) included (b) the risks and benefits associated with the use of a substance, (f) the need for access to a substance and (h) the purposes for which a substance is to be used.

Members expressed some concern that the benefit of increased access to famciclovir for the treatment of cold sores did not outweigh the risk. Members noted that in immunocompetent patients,the condition was self-resolving and the benefit of oral treatment over topical therapy was questioned. The real value of oral agents was in immunocompromised patients because the disease can be more severe and prolonged. The ability of pharmacists to recognize who is immunocompromised would be limited. There is also a need for dose adjustment in patients with renal impairment and it would be unrealistic for a pharmacist to dose-adjust in a non-hospital setting.

Members noted that although resistance is rarely reported this does not mean that it does not occur. The risk of generating resistance in the community and putting immunocompetent patients at risk did not reflect a good risk benefit ratio. Members noted that there are topical treatments that are available for the treatment of this condition.

In addition, the Committee noted that the indication was for recurrent *Herpes labialis* and there was a risk that patients may treat themselves inappropriately for genital herpes. Such off-label use would be inappropriate for a number of reasons including the lack of opportunity to screen for other sexually transmitted diseases. Whether or not this might occur in practice was questioned by a Member.

Overall the Committee was of the opinion that the risks associated with down-scheduling outweighed the benefits and given that the Committee agreed not to down-schedule this substance, Appendix H listing could not take place.

RESOLUTION 2009/55 - 21

The Committee decided that the current scheduling of famciclovir remains appropriate.

12.1.2 XXXXX

RESOLUTION 2009/55 – 22

XXXXX.

12.1.3 GUAIPHENESIN

PURPOSE

The Committee considered the scheduling of guaiphenesin including a proposal to exempt modified release formulations of guaiphenesin for use in adults and children over the age of 12 with a maximum daily dose of 2400 mg.

BACKGROUND

Guaiphenesin is an expectorant. It is indicated to help loosen phlegm and thin bronchial secretions. It has been a scheduled substance since 1967. Guaiphenesin is also known as glyceryl guaicolate, guaicol glycerol and guaifenesin.

At the February 1998 NDPSC Meeting the Committee agreed to exempt guaiphenesin in oral preparations from Schedule 2 when accompanied by a statement warning against use in children under two years of age.

As a result of harmonisation between Australian and New Zealand the May 2001 NDPSC Meeting deleted the Schedule 2 entry and amended the Schedule 4 entry to its present wording.

DISCUSSIONS – SUBMISSIONS

Sponsor's Submission

XXXXX made a submission requesting that modified release formulations of guaiphenesin with a maximum daily dose of 2400 mg and a labelling restriction limiting use to persons over the age of 12 years be unscheduled. If the Committee did not see this option as suitable, the applicant stated that a Schedule 2 listing would be an acceptable alternative. While the applicant addressed each of the criteria under 52 E the submission stated, in summary, that:

- Guaiphenesin is the only treatment indicated for a productive cough in Australia. Over 80 OTC cough and cold preparations containing guaiphenesin are registered on the ARTG with 20 products containing guaiphenesin as a single active ingredient. No modified release single active guaiphenesin product is currently available.
- According to the current SUSDP the proposed modified release guaiphenesin preparations of 600 mg and 1200 mg would fall into Schedule 4.
- The most appropriate schedule would be 'unscheduled' due to guaiphenesin's long OTC history of use and its well known safety profile. It has been unrestricted in Australia since 2001 and since 1990 in the UK. Its inclusion would fulfil unmet consumer need for longer lasting cough relief.

- The proposed claims of modified release guaiphenesin are:
  - loosen mucus;
  - increase the volume and reduce the viscosity of tenacious sputum;
  - thin bronchial secretions to rid the bronchial passage ways of bothersome mucus and drain bronchial tubes;
  - make coughs more productive; and
  - reduce cough reflex sensitivity in patiens with upper respiratory tract infections (URI).
- XXXXX.
- Bioequivalence has been established between immediate release preparations (200 mg and 400 mg) and the modified release formulation (600 mg and 1200 mg). XXXXX:
  - XXXXX
- Modified release guaiphenesin will not lead to an increase of ADRs as the maximum daily doses of 1200mg and 2400 mg are already in place with the existing unscheduled guaiphenesin products.
- The USA has sold modified release tablets over the counter since 2002 and six years of post-marketing data is now available. XXXXX.
- XXXXX.
- A search of the ADRAC database showed 167 cases reported for products containing guaiphenesin. Of these:
  - only two were listed which contained guaiphenesin as the only active ingredient. Urticaria was the adverse event reported for one on the reports while the other included face oedema, pruritus and peripheral oedema;
  - 81 were guaiphenesin combined with other active ingredients; and
  - 86 were co-administered with other multiple active drug products.
- The toxicity and safety in animals had previously been discussed by the NDPSC. However, a literature review was conducted to see if any newer reports that may be relevant. None were found. Substantial data is available on modified release guaiphenesin and human safety, including nearly 6 years spontaneous adverse event reports from the USA.
- There are few risks associated with the use of guaiphenesin. There is a potential clinical risk of developing kidney stones with high doses and effects on patients with porphyria. These risks, however, are with all existing guaiphenesin products therefore introducing a modified release preparation does not introduce any new risks that have not been previously considered by the NDPSC.

The applicant proposed two options for the scheduling of modified release guaiphenesin.

NDPSC Evaluation Report

The NDPSC evaluation report recommended that modified release guaiphenesin be placed in a newly created Schedule 2 entry, with subsequent changes to the current Schedule 4 entry. Reasons for this recommendation were:

- While the application submitted bioequivalence data, no data was available for individuals under 12 or between 12 and 18 years of age. Although the product is not suitable for children less than 12 years of age, they may gain access to the medication if unscheduled.
- In the evaluators mind it was not established beyond doubt whether the levels of guaiphenesin in the blood would remained sufficiently high to be effective throughout the entire 12 hour period. Should blood levels not be sufficiently high over the entire 12 hours, this could result in individuals dosing more frequently.
- A release of high doses of guaiphenesin ("dose-dumping") could occur due to mastication.
- It was noted that unscheduled modified release products are rarely available to consumers outside a pharmacy setting. A Schedule 2 status would provide consumers with the opportunity for advice regarding the nature of the preparation.
- There maybe the possibility of an increase in the frequency of adverse events associated with the modified release formulation compared to the immediate release formulation. Post-marketing data on the modified release formulation would confirm or dispel this hypothesis.
- There are no controlled clinical studies examining efficacy of the modified release form of guaiphenesin. Further to this, there was a lack of safety data relating to the 1200 mg form of the modified release preparation.
- Although there is little potential for abuse, chronic use has occurred in patients seeking to abuse the sympathomimetic component of combined guaiphenesin and sympathomimetic amine preparations.
- The proposed dose levels are unlikely to be associated with major adverse effects when used appropriately, however this product must be presented in a context that minimises the chance that it will be used inappropriately and a Schedule 2 listing appeared to be sufficient, in combination with the appropriate warning labels and child closures.

As the application was received at the 16 week cut-off, no comment on the evaluation report was made.

Pre-meeting Submissions

XXXXX submitted a pre-meeting comment. The submission also referred to a recent study presented to the Australian Self Medication Industry (ASMI) Conference 2008 by

Fabian Dwyer, General Manager of IMS Australia & New Zealand. The study showed that cough is one of the top ten minor ailments burdening the UK health system. Further, most patients surveyed who visit their doctor with coughs leave with no prescription and are left to seek advice from a pharmacy or self-medicate. The submission asserted that these findings can be transferred to Australia.

XXXXX provided a pre-meeting comment and did not oppose the exemption of modified release formulations of guaiphenesin, as the maximum daily dose is the same as that of the unscheduled guaiphenesin products currently available. XXXXX encouraged further investigation and the following points were raised:

- A potential health and safety issues could exist for those currently using guaiphenesin long term for 'off-label' purposes and may see a modified release alternative more attractive. Such purposes include chronic fatigue syndrome and fibromyalgia.
- After a scholarly literature search, it was revealed that excessive doses of guaiphenesin are associated with urolithiasis/nephrolithiasis (kidney stones). The evidence was conclusive. Further to this, extensive internet material was identified which encouraged long-term use of guaiphenesin for a range of refractory conditions.
- If evidence exists in Australia for an increase in kidney stones (or an increase of misuse), then the scheduling and labelling of all guaiphenesin products would need to be reviewed. Patients and healthcare professionals would also require educating on this issue.
- Possible points of interest for investigating this issue could include:
    - Product data sales, marketing data, post-marketing surveillance data and spontaneous reporting system (e.g. ADRAC) data
    - Hospital data for rates of diagnosis of drug-related kidney stones
    - Data on growth in internet sites promoting chronic off-label use and associated hits.

XXXXX provided a pre-meeting comment. XXXXX did not object to the proposal provided the sponsor of any such product could provide evidence of both efficacy and safety of a formulation.

XXXXX provided a pre-meeting comment. XXXXX had no major objections to this proposal; however, the sponsors of any commercial product containing modified release guaiphenesin should produce convincing clinical and scientific evidence that their formulation is efficacious and that the modified release formulation is justified. It was also asserted that although the USFDA had approved guaiphenesin as the only effective expectorant, doubts remain about its efficacy.

XXXXX provided a pre-meeting comment which concurred with the statements provided by XXXXX.

A submission was received from XXXXX. The comment provided focused on the expected pharmacological profile of the proposed modified release guaiphenesin products. It was asserted that the daily dose would be the same as when taking currently-available cough and cold preparations. Further, due to guaiphenesin's short half life (claimed in this submission to be approximately one hour) which requires multiple dosing to achieve sustained concentrations, a modified release dose makes sense in pharmacokinetic terms, as it would achieve similar concentrations with a twice daily dosing. This submission also made reference to a recent Cochrane review *(*Smith, SM, Schroeder, K, & Fahey, T 23 January 2008, 'Over-the-counter medications for acute cough in children and adults in ambulatory settings', *Cochrane Database Syst Rev)* which demonstrated the efficacy of guaiphenesin. Also included were recent American College of Chest Physicians guidelines (Bolser, DC 2006, 'Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines', *Chest,* 129(1 Suppl):238S-249S) which included recommendations on the use of guaiphenesin. This submission concluded by supporting either the possible exemption from scheduling or appropriate down-rescheduling of modified release guaiphenesin.

DISCUSSION – RELEVANT MATTERS UNDER 52E

While the Committee agreed that data presented in the application established bioequivalence between the standard formulation and the modified release formulation, there was a lack of evidence in relation to the efficacy of either formulation. While efficacy is the remit of the regulator through the registration process, it is relevant to 52E(1)(b) the risks and benefits of a substance.

The use of guaiphenesin in the treatment of fibromyalgia and chronic fatigue syndrome was also discussed (52E(1)(h) the purpose for which a substance is to be used). A Committee member spoke of several overseas based websites which promote the use of modified release guaiphenesin formulations in the treatment of fibromyalgia (with the claim that the uricosuric effect of guaiphenesin leads to increased phosphate excretion). The doses recommended for the treatment of fibromyalgia appear to align with the strength of the proposed modified release formulation but for a duration of months, potentially years. While this is not an approved indication, and indeed there appeared to be no published controlled trials supporting its use, the Committee was concerned that sufferers may choose to access modified release formulations for this purpose, in light of promotion via the internet. The Committee also noted that enquiries on this have been made to some jurisdictions' drug information centres.

One of the pre-meeting submissions referred to a Cochrane review, claiming that it showed guaiphenesin had clinical utility in the management of cough. A Member informed the Committee that of the two trials referenced in this review, one indicated significant benefit against placebo while the other did not. Further, both trials used a liquid formulation of guaiphenesin, not a modified release formulation.

The Committee also discussed the lack of post-marketing data available on this particular formulation. Without such data, the Committee was unconvinced that a modified release

formulation should be released on the Australian market exempt from scheduling (52E(1)(a) toxicity and safety). Therefore, it was felt more appropriate that modified release formulations be only available from pharmacies so that professional advice would be available if required. It was concluded that a Schedule 2 listing for modified release guaiphenesin would be the most appropriate.

RESOLUTION 2009/55 – 23

The Committee decided to include modified release formulations of guaiphenesin in Schedule 2 and amend the Schedule 4 entry of guaiphenesin.

Schedule 2 – New Entry

GUAIPHENESIN in a modified release dosage form of 1200 mg or less of guaiphenesin with a recommended daily dose of 2400 mg or less when labelled not for the treatment of children under 12 years of age.

Schedule 4 - Amendment

GUAIPHENESIN – Amend entry to read:

GUAIPHENESIN for human therapeutic use **except**:

(a) in oral liquid preparations containing 2 per cent or less of guaiphenesin;

(b) in divided preparations containing 200 mg or less of guaiphenesin per dosage unit; or

(c) when included in Schedule 2.

12.1.4 DICLOFENAC

PURPOSE

The Committee considered the scheduling of diclofenac including a proposal to increase the pack size limit for the Schedule 2 listing from 20 dosage units to 100 dosage units.

BACKGROUND

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

Diclofenac was included in Schedule 4 in March 1981. The NDPSC then agreed to reschedule diclofenac 25 mg or less in packs of 30 or less for oral use to Schedule 3 in August 1999, as recommended by the Trans-Tasman Harmonisation Working Party, and listed it in Appendix H of the SUSDP in August 2001.

The February 2005 NDPSC Meeting agreed to include in Schedule 2 diclofenac in preparations containing 12.5 mg or less per dose in packs containing not more than 20 tablets or capsules. The Committee was convinced that the available data supported an acceptable safety profile of diclofenac 12.5 mg at a daily dose of up to 75 mg consistent with the criteria for Schedule 2 medicines. This decision harmonised the scheduling of diclofenac 12.5 mg with New Zealand.

The October 2007 NDPSC Meeting considered a proposal to increase the Schedule 2 pack size restriction from 20 dosage units to 40 dosage units. The following points were raised:

- The Committee agreed that there was an assumption on the part of consumers that the availability of a 7 day pack size as an Schedule 2 medicine meant that it was safe to take the product continuously for a 7 day period.

- Members discussed concerns regarding data showing that CV risk was emerging with short-term use of NSAIDs (52E (1)(b) risks and benefits).

- There were also concerns that the applicant had presented no new safety data for the more prolonged use that the proposed pack size may encourage i.e., that there had been no data provided showing the safety of 7 day use compared to 3 day use. The potential hazards (52E (1)(c)) in regards to CV risk, as well as the extent and patterns of use (52E (1)(d)), given that longer term use has increased risk, were relevant to this concern.

- The Committee agreed that the safety profile for acute risk was still emerging and that it is not yet established as to whether there was lower risk with the 7 day treatment. The Committee decided that the current scheduling of diclofenac remained appropriate.

DISCUSSIONS – SUBMISSIONS

Applicant's Submission

XXXXX made a submission to amend the Schedule 2 listing of diclofenac to increase the pack size which is currently restricted to 20 dosage units. The submission proposed to increase the pack size to "not more than 100 dosage units". The applicant felt that this change would align the low-dose diclofenac scheduling with the current pack size and scheduling of ibuprofen 200 mg.

The applicant aimed to address areas of concern raised by the October 2007 NDPSC Meeting after the submission to increase the pack size from the current 20 dosage units to 40 dosage units was rejected. While the provisions under 52E were separately addressed, the submission asserted that:

- The submission was specific to areas of consumer safety and misuse and is not intended to promote in any way that low-dose diclofenac should be used for chronic conditions.
- No new or updated toxicity data was included as the NDPSC had already viewed the most recent Periodic Safety Update (PSUR) data up to, and including, 2006. Moreover, the efficacy of low-dose diclofenac had already been reviewed and evaluated by the TGA OTC Medicines Section in the original medicine registration application submitted in 2004.
- Clinical evidence from a review article (Moore, N 2007, 'Diclofenac Potassium 12.5 mg Tablets for Mild to Moderate Pain and Fever – A review of its pharmacology, clinical efficacy and safety, *Clinical Drug Investigation*, 27(3): 163 – 195] stated that diclofenac potassium 12.5 mg or 25 mg was as effective as ibuprofen 200 mg or 400 mg in 'traditional' OTC indication i.e. acute lower back pain, tension-type headache, symptoms of cold and influenza (headache, muscle/joint ache, pain and fever) and dysmenorrhoea. The review by Moore (2007) also stated that these doses of diclofenac have quicker onset of action and longer duration of both antipyretic and analgesic efficacy than paracetamol 1000 mg.
- Moore (2007) further suggested that there are no differences in the frequency of adverse events between diclofenac potassium 75 mg/day, ibuprofen 1200mg/ day or placebo for up to seven days.
- Moreover, a trial referred to by Moore (2007) stated no serious adverse events occurred with either low-dose or high-dose diclofenac in any single dose or short-term multiple dose trial of up to 14 days. In a long term trial, of 90 days duration, there were three reports of serious adverse events which all occurred after 30 days. The applicant concluded that a pack providing treatment for 16 days would not created any additional hazards for the consumer.
- Moore (2007) asserted that for the same indication and duration low-dose ibuprofen and low-dose diclofenac potassium are comparable in the incident and relative risk of gastrointestinal events generally or severe gastrointestinal events specifically.
- The NDPSC had previously addressed cardiovascular safety. Further to this, the TGA NSAID review concluded that prescription products have precautionary statements included in the prescribing information to use the lowest effective dose for the shortest duration of time. As of April 2008 OTC NSAIDs are required, under RAMSL, to include the following labelling statement "*Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful*."

- XXXXX.

- Further to this, the applicant concluded that consumers view larger pack sizes of analgesics as being convenient since they are "on-hand" to self medicate whenever they have pain and that consumers are not likely to incorrectly assume that a larger pack size of diclofenac potassium 12.5 mg is safe to take for periods longer than the approved dosage (three days).
- There is over 30 years of post marketing surveillance for diclofenac and diclofenac potassium has a proven safety profile comparable to low dose ibuprofen.
- The applicant proposed wording for a new Schedule 2 entry.

NDPSC Evaluation Report

It was the evaluator's view that the application be rejected. Reasons for this recommendation are as follows:

- The application sought to allow up to 100 dosage units (16.5 days at 75mg a day). This increased maximum limit would increase the need for clinical data to support the safety of use if a whole pack is taken at the maximum recommended dosage until completed. This data had not been provided.
- The published review article had methodological weaknesses and did not disclose whether there was any clinical information comparing use of diclofenac at 75 mg per day for three days and for four to seven days. Information in the article suggested that relevant clinical data *may* have been published. Without this information, a decision required a judgement as to whether consumers would continue to observe the dosage instructions, except where longer use is warranted i.e. when recommended by a medical practitioner.
- The review article gave no information on how the analysed reports were sourced i.e. search strategies, and it was not possible to exclude that relevant information had not been analysed. Further, the review *did not comprehensively tabulate the extensive reference list of the reports that had been analysed*. Moreover, the referencing provided did not allow the reader to identify which reports the data has been extrapolated from.
- XXXXX
- Moreover, the date on which the survey was conducted proves (September 2008) relevant as changes to RASML affecting diclofenac were gazetted in April 2008. New products approved by ARTG are required to have the following statements:
  - "If you get an allergic reaction stop taking and see your doctor immediately."
  - Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.

Existing products were required to have these statements included on their packaging by 23 April 2009. It could not be determined if these statements were included as the only images of packaging and labelling provided were pictures in the Consumer Survey PowerPoint presentation.

- A question posed on the maximum number of tablets a consumer might take in a 24 hour period gave participants an option of 5 to 7 tablets. It was unclear why this was chosen as the maxium recommended daily dose for both diclofenac 12.5 mg and ibuprofen 200 mg is six tablets and the range of 5 to 7 tablets blurs the boundaries between those taking the maximum recommended dose and those taking small excesses.
- Subject to those matters, the intention of the majority of those interviewed was to take diclofenac (or ibuprofen) for ≤ 3 days, with between 10 per cent and 18 per cent indicating that they would take diclofenac (or ibuprofen) for from 4 to ≥ 8 days.
- The consumer survey concluded that "consumers are likely to be compliant with dosage instructions irrespective of the size of the pack". The evaluator had reservations about this conclusion, given the above information, as some consumers would not be compliant, regardless of the pack size.

Pre-meeting Submissions

A pre-meeting comment was received from XXXXX. XXXXX did not support increasing the pack size of 12.5 mg diclofenac and recommended that the pack size limit remain at 20 dosage units. The following points were made:

- The current 12.5 mg diclofenac pack size of 20 is more than adequate for use in approved indications and for the maximum six tablets in 24 hours dose. The Schedule 2 product is for 'short-term use' (less than or equal to a few days) and the current pack size allows for more than three days of treatment at the maximum dose. After this time it would be more appropriate to seek additional health advice.

- The proposed pack size of 100 tablets would allow for over 16 days supply at the maximum dosage and with the chance of no counselling at the point of sale concerns were raised that this larger pack size would lead to prolonged use.

- NSAIDs carry high risk of adverse effects, some which are severe. They can:
  - precipitate asthma attacks in susceptible individuals;
  - cause acute renal failure when taken concurrently with ACE Inhibitors/ Angiotensin II receptor antagonists and diuretics, especially in the presence of dehydration which can by caused by the use of diuretics;
  - cause gastric irritation which can lead to gastric ulceration and potentially life threatening perforation; and

– cause increased blood pressure and heart failure, due to side effect of the fluid retention, in predisposed individuals.

XXXXX provided a pre-meeting comment. XXXXX believed a pack size of 100 dosage units is not warranted and not supported from a quality use of medicines perspective. Products containing diclofenac 12.5 mg are intended for short term use and consumers maybe inadvertently perceive that conditions can be safely managed for a longer period of more a few days if a 100 pack size is available. Moreover, consumers may continue to self medication for over two weeks without reviewing their health status if they administer all 100 dosage units. Further to this, it was stated that consumers must be provided guidance for the use of NSAIDs including the opportunity to seek medical advice after a few days treatment if their health status had not improved. Concerns were also raised over the potential of diclofenac to develop or exacerbate cardiovascular, gastrointestinal or renal problems.

XXXXX provided a pre-meeting comment opposing the proposal to increase the pack size limit to 100 dosage units as this would contradict the advisory statement '*Do not use for more than a few days at a time unless a doctor has told you to. Do not exceed the recommended dose. Excessive use can be harmful.*' The increased pack size would provide in excess of two weeks supply at the maximum recommended dose. Moreover, it was stated that the side effects and drug interactions of NSAIDs are poorly understood by the general community and the introduction of a greater pack size has the potential to cause great harm with little potential benefit. The current pack size gives patients the opportunity to return to their pharmacist for assessment should they find, that after consuming an entire packet, their symptoms have not resolved.

XXXXX provided a pre-meeting comment and opposed the change believing that this was an unjustifiable incremental change to the control of NSAIDs. Mention was made of the "triple whammy" effect and the proposal would expose the public to a greater risk without justifiable benefit. An increased pack size would defeat the purpose of short-term treatment, which if unsuccessful, should result in patients seeking medical advice for diagnosis and further treatment.

XXXXX provided a pre-meeting comment in which they concurred entirely with the submission made by XXXXX.

A pre-meeting comment has been received from XXXXX. XXXXX stated diclofenac has a role in the management of muscolo-skeletal pain and that current pack sizes are adequate to treat appropriate minor conditions. It was asserted that a larger pack sizes would encourage patients to use higher doses, in particular patients who have previously had diclofenac on prescription. Experiences had shown patients using NSAIDs inappropriately; at higher doses and longer durations than recommended and as first choice for non-inflammatory conditions when a paracetamol based analgesic would be more appropriate.

DISCUSSION – RELEVANT MATTERS UNDER 52E

XXXXX.

A Committee member noted that the application presented arguments regarding equity i.e. other NSAIDs are available at Schedule 2 in large packet sizes. A Member stated that the issue of convenience should not be underestimated and that consumers should be given more credit in relation to sensible medicine use.

Market research conducted was only with pack sizes of XXXXX, not 100 dosage units (as per the applicant's proposal). While it was agreed that such consumer research can only measure consumers' intention to treat, some Members questioned whether the survey provided could reasonably be extrapolated to allow the same conclusions to be drawn for consumers provided with a 100 dosage unit pack. Further, concerns were raised over market research data presented by the applicant where XXXXX of those surveyed indicated they had not followed packaging instructions.

The Committee noted weaknesses in the published review article provided with the application, as raised by the evaluator. Further, the Committee noted that the only safety study which directly compared diclofenac to ibuprofen involved chronic dosing (three months) in the treatment of osteoarthritis (neither an OTC indication, nor an OTC duration of treatment). The issue of safety was discussed at length (52E(1)(a) toxicity and safety of a substance) and it was suggested that a 100 unit dosage pack might not have the same safety profile as a 20 unit dosage pack, regardless of the conclusions drawn by the consumer survey. It is well established that NSAIDs are a significant cause of morbidity in Australia and the risk of such relates directly to both the dose and duration of use.

The Committee discussed the fact that in comparable overseas markets, OTC diclofenac 12.5 mg is supplied in maximum pack sizes of 30 to 40 dosage units. Given this fact, XXXXX, the Committee also considered increasing the pack size to 40 dosage units (in addition to considering a pack size increase to 100 dosage units). The Committee considered both options and concluded that increasing the Schedule 2 limit on pack size of diclofenac 12.5 mg was inappropriate.

RESOLUTION 2009/55 – 24

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

12.1.5 *PIPER METHYSTICUM* (KAVA)

PURPOSE

The Committee considered a proposal to exempt *Piper methysticum* from scheduling

BACKGROUND

The active ingredients of *Piper methysticum* (kava), kava lactones (or kava pyrones), are pharmacologically active compounds naturally present in the kava plant. Nineteen kava lactones have been isolated from the kava root, of which six are the major constituents of kava (kawain, dihydrokawain, methsticin, dihydromethsticin yangonin, and demethoxyangonin). The proportions and potency of kava lactones vary according to the plant variety and also the method of preparation. The kavalactone content varies from 3 per cent to 20 per cent dry weight, even within the same subspecies. The concentration of kava lactones is generally highest in the lateral roots (approximately 15 per cent) and decreases progressively toward the aerial part of the plant. The effects of kava may also depend on how it is consumed in terms of whether it is used concomitantly with other drugs, food, alcohol or physical activity.

The absorption of kava lactones in the gastrointestinal tract is poor and variable. Kava lactones appear to be hydroxylated by the cytochrome P450 system and are eliminated by the kidneys and in the faeces. Kava is known to have several actions; the primary action is as a mild sedative. Other actions include local anaesthesia of the mouth and tongue, analgesia, ocular effects, anticonvulsive effects and antimycotic properties. It has been reported as an effective anti-anxiety treatment.

The October 2003 NDPSC Meeting noted a safety evaluation report prepared by the Kava Evaluation Group/Office of Complementary Medicines on kava containing medicines and decided there was a need to restrict the use of alcohol/acetone extracts of kava, including those for bulk supply to health care practitioners, due to the potential risk of liver toxicities.

The June 2004 NDPSC Meeting, agreed to include kava in Schedule 4 of the SUSDP, as well as adopting the exemptions specified in the TGA Regulations 1990. The Committee confirmed the decision at the October 2004 NDPSC Meeting. This decision made all kava Schedule 4; except dried whole or peeled rhizome, its aqueous dispersions or extracts, tablets of
125 mg or less of kava lactones per tablet, teabags of up to 3 g kava, and not more than 25 mg of kava lactones per dose, compliant with RASML and in topical or dermal preparations when included on the ARTG.

At the February 2008 NDPSC Meeting, in the light of a policy decision by the former Australian Government, the Committee reconsidered scheduling restrictions for kava and concluded that the potential for abuse and the hazard to public health of the whole or peeled rhizome meant that this form of kava should no longer be exempt from scheduling. Thus the decision meant that only those products on the ARTG containing kava were not Schedule 4.

DISCUSSION - SUBMISSIONS

Members noted that *Piper methysticum* (kava) was not included in the Government Gazettal notice for the February 2009 NDPSC Meeting. The NDPSC received a single submission, from XXXXX, requesting kava be rescheduled to its previous status of exempt from scheduling, as it was prior to the recent scheduling change. The submission dealt with kava as the traditional drink and as dried fresh or frozen rootstock. The applicants' claims against the scheduling criteria, Section 52E Matters to be taken into account in exercising powers, (a) to (i), are summarised;

(a) Toxicity and Safety of the Substance

- LD_{50} of kava resin given by intra peritoneal injection to mice, rats and rabbits ranged from 300 to 4000 mg/kg. With oral administration the LD_{50} in mice was 920mg. Doses of 50mg dihydromethysticin, administered 3 times a week to rats produced no evidence of chronic toxicity, however attempts to duplicate the findings have had limited success.
- The applicant claimed that clinical trials of kava had not revealed any hepatoxicity, but also stated that "kava has a tendency to have a toxic effect on the liver".

(b) Risks and Benefits Associated with the Use of the Substance

- Kava is used traditionally to treat anxiety, sleep disorders and other complaints.
- The applicant claimed that kava lactones are shown to affect a range of neurotransmitter systems, and that they have "dose dependent effects on the central nervous system, including anti-epileptic properties".

(c) *Potential Hazards Associated with the Use of a Substance*

- The applicant claimed that the World Health Organisation (WHO) found only 2 reports of possible adverse reactions to kava use. The applicant claimed that this figure was out of over '12 billion discreet doses prepared in the traditional way over 20 years'. The source of the 12 billion figure was not cited, nor could one be found in the WHO article. The applicant also claimed that when kava was taken in doses from 100 to 210 mg of kava pyrones (or kava lactones) per day the users had few adverse reactions. Adverse reactions are described including kava dermopathy of the hair nails and skin, rare allergic reactions including hearing loss and anorexia and possible extrapyramidal side effects such as involuntary oral and lingual reflexes and twisting movements of the head and trunk.
- The applicant reported that liver function tests can be elevated after 3 to 8 weeks of use, and may be followed by hepatomegaly; that kava can exacerbate hepatitis, but that this spontaneously resolves on cessation.

(d) Extent and Patterns of Use of a Substance

- The traditional use of kava was described.
- The inappropriate use of kava by NT remote indigenous communities was mentioned.

(e) Dosage and Formulation of a Substance

- Aqueous extract/suspension consumed in 100ml measures.

(f) Need for Access to the Substance, Taking into Account its Toxicity Compared with Other Substances Available for a Similar Purpose

- The applicant claimed that the scheduling of kava denied Australians of Pacific Islander origin their traditional and cultural use of kava. The Committee noted that it was the ban imposed by the Australian Customs Service on all kava imports, except those under medical or scientific research licence, which denied free access to kava.
- The applicant claimed that kava's closest alternative is alcohol with its related anti-social behaviour and associated health risks and that no deaths have been attributed to kava consumption.
- Fewer than 350 people in the NT were identified as being at risk of abusing kava.
- The applicant reiterated the argument that because the number of abusers of this substance was "insignificant" that it is not right to restrict the use of the substance to others.

(g) Purpose for which the Substance is to be used

- The applicant reiterated the original use of the substance in the Pacific Islands.

(h) Additional Matters; Economic and Trade Considerations

- The applicant reported that kava was a primary cash crop for Vanuatu, Tonga and Samoa, accounting for up to 30 per cent of their GDP, and inferred that the ban imposed by Australia may influence other countries to "harmonise' their policy to kava in line with Australia's. They noted that Australia is a signatory to the *Agreement on Technical Barriers to Trade* (World Trade Organisation), and may be subject to legal challenges (from kava producing countries) to remove technical barriers to the kava trade.

The application contained an extensive bibliography including fifteen articles by Alan R Clough. The articles were selected to present a picture of kava use in the remote NT; however, they pointed to a growing problem. The fact that some of these references countered the applicant's own position suggested that the applicant had not fully considered these when including them as supporting materials. The following summaries are from the three Clough papers included in the application as attachments;

- 'Health effects of kava use in eastern Arnhem Land Aboriginal Community' (*Internal Medicine Journal*, 2003, 33:336-340), examined the links between various health effects including sudden cardiac arrest and heavy kava use, in a cross-sectional study within a kava using community in Arnhem Land. Health effects of kava use such as abnormal liver function, kava dermopathy and decreased lymphocytes were observed in the study. The author stated, "The general increase in IgE and IgG levels and CRP reflect the burden of infectious pathogens associated with the continuing socioeconomic disadvantage of those living in remote Aboriginal communities. Elevated CRP is increasingly recognized as a marker of risk for cardiovascular

disease, and the generally high levels of CRP and homocystine across all groups in this Aboriginal community are of great concern." Markers for cardiovascular disease were higher in the indigenous population, but not higher in kava users. In effect the conclusions drawn in this paper did not support a relaxation of the current restrictions.

- 'Case-control study of the association between kava use and pneumonia in eastern Arnhem Land Aboriginal communities Northern Territory, Australia' *(Epidemiol Infect*, 2003, 131, 627-635). Kava, consumed in Arnhem Land since 1982, may be a risk factor for infectious disease including pneumonia. A case–control study (n=115 cases; n=415 controls) was conducted in 7001 Aboriginal people (4217 over 15 years). Odds ratios were calculated by conditional logistic regression with substance use and social factors as confounders. Pneumonia was not associated with kava use. The author found statistically significant associations between pneumonia admission and alcohol use, cannabis use and with petrol sniffing suggested that the effects of other substances, or combinations, may compound kava's effects in ways not yet understood. He postulated that if Aboriginal people continued to drink kava it would be prudent for them to moderate consumption even though an association with pneumonia has not been shown. Again, this paper did not provide evidence to refute current scheduling arrangements.
- 'Emerging Patterns of Cannabis and other substance use in Aboriginal Communities in Arnhem Land, Northern Territory: A study of two Communities' (Clough, AR, Menzies School of Health Research and Charles Darwin University, Darwin, NT*)* This study examined the effects of a variety of substances including kava, cannabis, alcohol, tobacco and petrol sniffing. The research focussed on cannabis and made only brief mention of kava. The conclusion was that action was required to reduce cannabis use especially in relation to other drugs. The paper did not state a position on current access arrangements to kava.

In Appendix A of the Supporting Data, the applicant stated that a disproportionate "amount" of papers on kava had come from Dr Alan Clough during the past 20 years. It was claimed that because Dr Clough was responsible for this research 'the body of research has been skewed'. The applicant made this statement even though fifteen of Clough's papers are listed in the supporting evidence section of the application. The following summaries of other articles listed by the applicant in the bibliography, but not attached to the application;

- 'Case-control study of the association between kava use and ischaemic heart disease in Aboriginal communities in eastern Arnhem Land (Northern Territory) Australia' (Clough, AR et al, 2004, *J Epidemiol Community Health*, 58(2): 140-141). Provided statistical evidence of the potential damage to cardiovascular system caused by misuse/addiction of kava.
- Letters to the Editor (Clough AR et al, 2006, *eMJA*, 184 (2):91-92). Alan R Clough et al wrote to the Medical Journal of Australia (MJA) reporting their concern that the NT's introduced regulations for kava supply control were not working (under the *Kava Management Act 1998*) in that;

- Kava licence areas permitted retailers to sell more than double the safe weekly limit of kava per person
- The illegal trade added perhaps $2 million per annum.
- The social, economic and health effects were unknown in the long term and had lead to a decline in participation in traditional ceremonies.
- Kava was the psychoactive substance with the greatest impact on the financial resources of communities and individuals in Arnhem Land.
- Kava's health effects include seizures and extreme weight loss, resulting in immunosuppressive effects, possible cardiovascular disease and potential fatal hepatotoxicity.

The letter recommended that the kava supply and its outlets be reduced, the amount of kava per person be reduced by half, quantities imported be limited, kava prices be reviewed, illegal sale of kava be rigorously enforced and that the *Kava Management Act 1998* be reviewed to facilitate the proposed changes. Competing interests: Alan Clough declared that he had been a member of the Northern Territory Licensing Commission, the body responsible for licensing kava in the Northern Territory.

- 'Enough! or too much. What is excessive kava use in Arnhem Land?' (Clough AR 2003 *Drug Alcohol Rev*, 22:43-51). The study described parameters for use in monitoring health, social and economic effects of kava use in Arnhem Land Aboriginal communities in the Northern Territory. Interview data combined with health worker assessments were compiled. Kava, supplied illegally, was still being used in Arnhem Land in 2001-02. In 2000, cases of dermopathy, abnormally low body mass index, low blood lymphocytes and abnormally high y-glutamyl transferase, characteristic of heavy use, occurred more frequently with increased kava use. Acute effects emerged at average consumption levels of from 310-440 g/week of kava powder. When kava users in one community began to consume it at an average of 240-425 g/week from mid-1990, 19 per cent of available cash resources were spent on kava with 11 per cent of cash resources leaving the local community economy. The proportion of men drinking kava reached 70 per cent and women 62 per cent from mid-1990, with 20 per cent of the population spending unprecedented amounts of time (14 + hours/week) in activities where kava was consumed. Their association with increased kava use suggested that approaches to minimizing harm from its abuse began with controlling supply. The article supported the banning of kava from Australia because of the negative health, economic and social effects on indigenous communities.

- 'Kava in Arnhem Land: a review of consumption and its social correlates. Comprehensive Review' (Clough, AR 2000, *Drug and Alcohol Review*, 19, 319-328). The paper stated that the way Aboriginal people drink kava has been confounded by claims, based on anecdotes of imputed health effects. Anecdotes and comments had promoted the perception that dosage levels among Aboriginal people were much greater than in Pacific island societies. This paper reviewed published data about kava consumption, and evaluated it with respect to information collected from observation of one Aboriginal community in Arnhem Land where people tended to consume kava

at a steady tempo; 37 g of kava powder containing around 3800 mg of kava lactones in 670 ml of water in an hour. The highest levels of consumption in Arnhem Land had been reported to be up to 900g/week of kava powder with heavy consumers drinking at least 610 g/week, levels comparable to estimates for Pacific-island societies. Results of the research included the finding that heavy users of kava in Fiji may consume over 701 and 1800 g/week, far more than in Arnhem Land. This paper questioned the anecdotal information that Aboriginal people were high consumers of kava, and placed their consumption in perspective compared to South Pacific countries, recommending that assumptions about usage need to be revisited. It did not support the continuation of the practice of drinking kava in indigenous communities.

- 'Brain dysfunction associated with petrol sniffing and kava drinking in Arnhem Land Aboriginal Communities' (Cairney, S 2003, unpublished Doctor of Philosophy thesis, La Trobe University, Victoria). In this article, Cairney reported that despite collecting data from reportedly the heaviest users of kava in the world, no impairment in saccade or cognitive function in individuals who were currently heavy users and had been for up to 18 years, nor in users who been heavy users, but had abstained for longer than 6 months; had been found. Current and ex-users showed a higher rate of kava dermopathy, lower body mass index, lowered blood lymphocytes and, in addition kava users showed elevated liver enzymes. This paper supported the need for further research into the health effects of kava.
- 'Saccade and Cognitive Function in Chronic Kava Users' *(*Cairney, S 2003, *Neuropsychopharmacology* 28). The author's findings mirrored those of the previous paper: that current and ex users showed a higher rate of kava dermopathy, lower body mass index, lowered blood lymphocytes and, in addition kava users showed elevated liver enzymes. The author concluded that, despite health consequences such as an increased risk of serious infection, potentially fatal liver damage, and loss of body fat and dermopathy, these data suggested that chronic kava use caused no disruption to human saccade and cognitive processes. The paper supported the need for further research into the effects of kava on liver function.
- Kava extract versus placebo for treating anxiety (Pittler, MH and Ernst, E 2003, *Cochrane Database of Systematic Reviews* Issue 1). Compared with placebo, kava extract was an effective symptomatic treatment for anxiety although, the size of the effect seemed small. The effect lacked robustness and was based on a relatively small sample. The data available from the reviewed studies suggested that kava was relatively safe for short-term treatment (1 to 24 weeks), although more information was required. The author concluded that trials with large sample sizes and long term safety studies were needed to clarify the resultant effects of kavas consumption. The paper's findings did not provide evidence supporting a rescheduling application.
- 'Hepatitis associated with Kava, an herbal remedy for anxiety' (Escher, M & Desmeules J 2001, *BMJ* vol.322*).* This article presented a case reported to the Swiss Pharmacovigilance Centre in Berne It described the history of a patient, in previous good health, with no pattern of drug or alcohol use, through a rapid onset of liver

failure, to a liver transplant. The patient took 3 to 4 capsules of kava extract daily for 2 months, to treat slight anxiety. He presented with jaundice, and dark coloured urine, and a 'tanned' skin colour. The patient's condition deteriorated within 48 hours. He developed stage IV encephalopathy and had to be intubated. This paper provided evidence to support further clinical studies on effects of kava on the liver and potential risks of liver disease resulting from kava ingestion are needed.

- 'The risk-benefit profile of commonly used herbal therapies: ginkgo,St John's wort, ginsent, Echinacea, saw palmetto and kava' (Ernst, E 2002 *American College of Physicians – American Society of Internal Medicine, Annals of Internal Medicine*, 136: 42-53). The author provided a clinically oriented overview of the safety and efficacy of kava and other herbs. He reported that kava was an efficacious short term treatment for anxiety, but not without side effects. Serious adverse effects had been reported but seem to be rare. Two post marketing surveillance studies involving more than 6000 patients found adverse effects in 2.3 per cent and 1.5 per cent of patients taking 120 to 240 mg of standardized extract. The author reported that problems arose when kava was self administered and when taken with other medications that act on the central nervous system or with alcohol. It did not support the potential for kava to be safely used in indigenous communities.

The applicant disagreed with the findings of the paper 'Kava and After in the Nhulunbuy Hinterland' (Hughes, H 8 October 2007, *Issue Analysis*, No.88, Centre for Independent Studies No.88) previously presented to the Committee at the February 2008 NDPSC Meeting. Members noted that Emeritus Professor Helen Hughes is a senior fellow at the Centre for Independent Studies in Sydney and had authored papers on economic and social issues in the South Pacific and Australia. The applicant claimed that the paper by Hughes was 'misleading' in that it cited the WHO as recommending that kava be available on prescription only.' In particular the applicant felt that the Committee relied too heavily on this reference in its February 2008 deliberations.

The Hughes' paper said:

– "The study found mixed evidence of liver damage from the use of kava in medications, **but WHO recommended that kava products should only be available on prescription.**" (p3)

The WHO paper said:

– ***"It would seem advisable that all kava products, prepared as pharmaceuticals, be available on prescription only*** *in order to better monitor the use and* ***apply necessary controls."*** *(p5, Recommendations, under Conditions of use)*

- The quoted texts purveyed essentially the same meaning, which made the claim of Hughes' paper seeking to mislead the reader, spurious to the argument.
- The applicant argued that the paper by Hughes had not addressed 52E. This paper was written by the researcher on behalf of The Centre for Independent Studies (CIS). CIS is the leading independent public policy 'think tank' within Australasia. The

paper was not intended to be an application to the NDPSC. There was therefore no expectation that it address matters under 52E.

- The Issues Analysis by Helen Hughes was used as a reference by the OCS. Points made by Hughes were; that the available limit of kava for legal consumption had been twice the safe limit per week of between 240 g and 400 g per week; that the interaction of kava with the other drugs of addiction was a known health risk; that due to the negative social and health outcomes of kava abuse, that the Commonwealth Government had no choice but to ban its use allowing limited imports for medical and scientific research and 2 kg per person as accompanied baggage; that commercial interests in kava promotion were the protagonists of perpetuating the sale of kava in the NT and Australia wide.

The Committee recalled XXXXX submission considered at the October 2007 NDPSC Meeting. The submission stated that there was a potential for abuse of the substance and thus hazards to public health exist if the whole or peeled rhizome of this substance is exempted from Schedule 4. The following is an overview of the points discussed:

- Kava was found to have the potential for abuse and misuse, resulting in both adverse health and social hazards in these remote indigenous communities. The previous exemption from the requirements of scheduling opened a pathway for diversion of legitimate kava products for illicit purposes in some communities.
- It was stated that it was unlikely that the tablet, capsule or teabags currently listed on the ARTG would be abused and, thus, the scheduling for these should not be altered.

It was noted that XXXXX supported the proposed change to a Schedule 4 entry for kava.

From June 2006, the previous Australian Government had serious concerns about abuse of kava in the NT following abuse in remote indigenous communities. Kava was consumed by some indigenous communities at up to 100 times the usual rate. At least eight communities in Arnhem Land, comprising about 7,700 people, identified significant kava use as a problem. Heavy use of kava caused weight loss, malnutrition, liver damage, hypertension and skin disorders. These health issues represented a real concern to the then Government and to the jurisdictional health departments. The following points list the restrictions which came into force under the Australian Customs Service as a result of the previous Australian Government's decision to restrict access to kava:

- The importation of kava without a permit issued by the Office of Chemical Safety, Treaties and Compliance Section, is now an offence under the Customs Act of 1901 and subject to prosecution.
- Consistent with the existing regulations set out in the Customs (Prohibited Imports) Regulations 1956, the importation of kava is now only permitted for medical or scientific purposes.
- Importation of 2 kg of dried or root kava per adult is now permitted with accompanied baggage in recognition of cultural significance of kava use by people of South Pacific Islander descent.

- The *Customs Act 1901* and Statutory Rules 1956 as amended, contains the listing; Schedule 4, 112B Kava, Customs (Prohibited Imports) Regulations 1956.

The Committee noted information from Food Standards Australia and New Zealand (FSANZ). The current status of kava in terms of the FSANZ Food Standard for kava is;

- The Australia New Zealand Food Standards Code (the Code) included a specific standard for kava i.e. Standard 2.6.3
- FSANZ was aware of recent changes to the SUSDP and to the Customs (Prohibited Imports) Regulations 1956.

XXXXX

The New Zealand Food Safety Authority (NZFSA) had issued a 'Privileged Statement', under delegated authority from the Director General of Agriculture and Forestry pursuant to Section 37 of the *Food Act 1981*, on the 16 August 2002. The statement advised New Zealanders that they should consider carefully when using dietary supplements containing kava; following the TGA's recall of all complimentary medicines containing kava, after the death of a woman from liver failure. The statement pointed out those traditional forms of the substance was not associated with serious liver damage, as was the concentrated form. It was stated that international evidence of adverse reactions to kava in dietary supplements had resulted in the Minister of Health's Medicines Adverse Reaction Committee addressing the issue.

The Committee noted that as this item had not been gazetted, there was no public comment.

The applicant suggested possible wording, should the Committee have wished to amend current scheduling.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee agreed that this matter be gazetted before it is considered as per established process protocols. Thus, the Committee agreed to include this matter in the pre-meeting Gazette Notice for the June 2009 NDPSC Meeting and to therefore foreshadow consideration of the scheduling of kava at that Meeting.

RESOLUTION 2009/55 – 25

The Committee decided to foreshadow consideration of the scheduling of kava at the June 2009 NDPSC Meeting.

12.1.6 TETRAHYDROCANNABINOL (THC) AND CANNABIDIOL (CBD)

PURPOSE

The Committee considered the scheduling of tetrahydrocannabinol and cannabidiol for the purpose of clarification.

BACKGROUND

The Committee noted that for many years cannabis had been listed in Schedule 9 of the SUSDP. At the November 1986 Meeting the Schedule 9 entry for cannabis was amended to read 'cannabis, cannabis oil and cannabis resin and extracts or tinctures of cannabis'. This was again amended at the July 1987 Meeting to read 'cannabis and extracts or tinctures of cannabis'. At the February 1999, May 1999 and August 1999 NDPSC Meetings, the Committee considered a proposal to amend the Schedule 9 entry for cannabis to exempt from scheduling when grown commercially for fibre production and manufactured goods containing hemp fibre. The cannabis entry was amended to read: "cannabis except (a) when separately specified in these Schedules; or (b) processed hemp fibre containing 0.1 per cent or less of tetrahydrocannabinol and products manufactured from such fibre."

Tetrahydrocannabinol was recommended to be entered onto the Prohibited List (the precursor to Schedule 9 which only commenced in 1971) at the June 1970 Meeting. At the November 1977 Meeting the Committee, after consideration of a submission from XXXXX, recommended amending the entry under tetrahydrocannabinols on the Prohibited List to read: "Tetrahydrocannabinols and 3- and 4'- alkyl homologues including DMPH and parahexyl, within one of those structural designations."

At the November 1997 NDPSC Meeting, the Committee considered correspondence from XXXXX requesting an exemption to the Schedule 9 entry for tetrahydrocannabinols to permit the legal production and marketing of hemp seed oil product containing 50 mg/kg or less of tetrahydrocannabinols. This was again considered at the February 1998 and May 1998 NDPSC Meetings when the Committee considered a request to exempt from the Schedule 9 entry for tetrahydrocannabinols (as distinct from the cannabis Schedule 9 entry) hemp seed oil and products for external use. The Committee supported this proposal and recommended that the Schedule 9 entry for tetrahydrocannabinols be amended by adding the following clauses (c) in hemp seed oil, containing 50 mg/kg or less of tetrahydrocannabinols, when labelled "not for internal use' or Not to be taken; or (d) in products for purposes other than internal human use containing 50 mg/kg or less of tetrahydrocannabinols.

At the July 1984 Meeting, the Committee noted that nabilone was a synthetic cannabinoid used as an anti-emetic in the treatment of nausea and vomiting caused by chemotherapy primarily for patients who were not responsive to conventional anti-emetic treatments. The Committee recommended Schedule 8 would be appropriate. In view of

this, the entry for tetrahydrocannabinols was to be amended to read: "tetrahydrocannabinols and 3- and 4' alkyl homologues including DMPH and parahexly, within one of those structural designations, except nabilone." At the August 1986 Meeting, the Committee once again recommended an amendment to the entry to read "tetrahydrocannabinols and their alkyl homologues except when separately specified in this Schedule."

Nabilone was considered for rescheduling from Schedule 8 to Schedule 4 at the February 2003 NDPSC Meeting. The Committee agreed that inclusion of nabilone in Schedule 8 remained appropriate as there was no evidence provided on abuse potential nor was there a clear pattern of use proposed. The Committee also noted that retention of nabilone in Schedule 8, rather than Schedule 4, did not disadvantage patients in terms of access and had no impact with regards to the Special Access Scheme.

At the November 1994 NDPSC Meeting, the Committee considered a recommendation of the NCCTG that Schedule 8 of the SUSDP be amended to include delta-9-tetrahydrocannabinol (dronabinol) for therapeutic use. The Committee also recommended an entry in Appendix D (i.e. Additional Controls on Possession or Supply of Poisons included in Schedule 4 or Schedule 8) that states "Poisons available only from or on the prescription or order of a medical practitioner authorised by the Secretary of the Commonwealth Department of Health and Ageing under section 19 of the *Therapeutic Goods Act 1989*" (ie Special Access Scheme). Members were advised in correspondence from the NCCTG Secretary that XXXXX had proposed that dronabinol be made available in Australia under the following guidelines:

> *The patients (to cater for Category A classification) need to be patients with advanced HIV disease, probably CDC Group IV, with loss of >10 per cent body weight and the wasting not to be due to a remedial cause (eg infection, tumour, etc). Generally these will be patients where investigations have failed to reveal any cause other than HIV as responsible for their anorexia, poor appetite and consequent loss of weight; the assumption is that these are patients who, with improved appetite, might stabilise or reverse their weight loss.*

Advice was noted from XXXXX that dronabinol was listed in Schedule II of the Convention of Psychotropic Substances 1971. The Committee noted that Schedule I of the Convention included drugs claimed to create a serious risk to public health, whose therapeutic value is not currently acknowledged. It included synthetic hallucinogens such as LSD in addition to natural hallucinogens like DMT (Dimethyltryptamine). MDMA or Ecstasy also falls under this category as does cannabis. Schedule II includes stimulants of the amphetamine type, of 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, three benzodiazepines (temazepam, flunitrazepam, nimetazepam) and some analgesics like buprenorphine. Schedule IV includes hypnotic and anxiolytic benzodiazepines (except temazepam, flunitrazepam, and nimetazepam), and mild analgesics, which engender an

appreciable dependence, but are mainly used in therapy. The Schedule 9 tetrahydrocannabinol entry was also amended to provide an exception for Schedule 8 entries.

DISCUSSION - SUBMISSIONS

There were a number of enquires to jurisdictions regarding the availability of XXXXX (THC + CBD) for use in multiple sclerosis and thus it was considered prudent to properly clarify the scheduling of these two substances. This product is a buccal spray developed by XXXXX. It contains delta-9-tetrahydrocannabinol XXXXX mg/ml (XXXXX) and cannabidiol XXXXX mg/mL (XXXXX). It is currently available in Canada where it has been approved under the Notice of Compliance with Conditions (NOC/c) Policy. The Committee noted that an NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada. Products thus approved are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile base on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada provides access to such products on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed-upon time frame.

In Canada, THC+CBD is indicated as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults. It is also indicated as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

In New Zealand THC+CBD can currently be prescribed under section 29 (Unapproved Medicine) of the *Medicines Act 1981* and the Medsafe website sets out the details for obtaining Ministerial consent to use THC+CBD as an unapproved medicine. XXXXX advised that NZ had interpreted the provisions of the *Misuse of Drugs Act 1975* (MODA) to capture tetrahydrocannabinol and all of the other cannabinoids contained in cannabis, including cannabinol within the Class B1 schedule of the Act. The MODA entry for cannabis preparations, and cannabis sativa, and cannabis fruit are generic, and therefore capture all alkaloids through the general catch-all provisions of a substance and its salts, esters, isomers, derivatives etc and the specifics of the entry which captures all preparations containing any tetrahydrocannabinols produced by subjecting cannabis plant material to any kind of processing.

In the UK, THC+CBD remains an unlicensed medicine and, as a cannabis-based medicine, is currently a Schedule 1 Controlled Drug. Schedule 1 Controlled Drugs are controlled by the *Misuse of Drugs Act 1971* to which the restrictions of the Regulations apply and, in addition, the production, possession and supply of which is limited in the public interest to purposes of research or other special purposes. A Home Office licence

is required for such purposes and in the case of THC+CBD, the Home Office has issued an open general licence permitting any doctor wishing to prescribe THC+CBD to do so under the Act. This licence also permits pharmacists to dispense THC+CBD and permits patients to possess THC+CBD if dispensed in accordance with a *bona fide* prescription. Other examples of Schedule 1 Controlled Drugs are coca leaf, lysergamide and psilocin.

According to the Product Monograph approved by Health Canada, mammalian tissues contain at least two types of cannabinoid (CB) receptor, CB1 and CB2. CB1 receptors are present at nerve terminals in the CNS and also in some peripheral tissues including dorsal root ganglia, sympathetic ganglia, adrenal gland, heart, lung, reproductive tissues, urinary bladder, gastrointestinal tissues, and immune cells. Within the brain, the distribution of CB1 receptors is heterogeneous, with a pattern consistent with the demonstrated effects of cannabinoids on motor function, cognition and memory. Relevant for pain modulation, CB1 receptors are found on pain pathways in the brain and spinal cord, as well as on terminals of peripheral nervous system primary afferent neurons where they may mediate cannabinoid-induced analgesia. CB2 receptors are present primarily on peripheral and central immune cells, where they may modulate immune function through release of cytokines. Cannabidiol (CBD) is an agonist of TRPV-1 (vanilloid) receptor with an inhibitory action on adenosine uptake. [A vanilloid is a type of nerve receptor which is closely related to cannabinoid receptors.]

The principal pharmacological effects of THC include analgesic, muscle relaxant, antiemetic, appetite stimulant and psychoactive effects. THC is metabolised to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), a psycho-active metabolite.

CBD has analgesic, anticonvulsant, muscle relaxant, anxiolytic, neuroprotective, anti-oxidant and anti-psychotic activity. The main primary metabolite of CBD is 7-hydroxy-cannabidiol.

XXXXX.

A PubMed search of the literature relating to cannabinoids and multiple sclerosis undertaken by the Secretariat, uncovered the following papers.

- 'A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol' (Russo, E et al 2006, *Medical Hypotheses* Volume 66, Issue 2, p234-246) examined the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD). The paper is of relevance because:
  - CBD was demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right.
  - A rationale for combination of THC and CBD in pharmaceutical preparations is presented.

- Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms were explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition.
- Combination therapy has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain.
- Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined.
- The hypothesis that the combination of THC and CBD increases clinical efficacy while *reducing adverse events was supported.*

- '*Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain'* (Iskedjian, M et al, January 2007, *Current Medical Research and Opinion*. 23(1):17-24):
  - Stated that debilitating pain, occurring in 50-70 per cent of multiple sclerosis (MS) patients, was poorly understood and infrequently studied.
  - Summarized efficacy and safety data of cannabinoid-based drugs for neuropathic pain.
  - Focused on baseline-endpoint score differences where the cannabidiol/THC buccal spray decreased pain 1.7 +/- 0.7 points ($p = 0.018$), cannabidiol 1.5 +/- 0.7 ($p = 0.044$), dronabinol 1.5 +/- 0.6 ($p = 0.013$), and all cannabinoids pooled together 1.6 +/- 0.4 ($p < 0.001$).
  - Noted that placebo baseline-endpoint scores did not differ (0.8 +/- 0.4 points, $p = 0.023$).
  - Noted that at endpoint cannabinoids were superior to placebo by 0.8 +/- 0.3 points ($p = 0.029$).
  - Dizziness was the most commonly observed adverse event in the cannabidiol/THC buccal spray arms (39 +/- 16 per cent), across all cannabinoid treatments (32.5 +/- 16 per cent) as well as in the placebo arms (10 +/- 4 per cent).
  - The meta-analysis concluded that cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in MS, although the review was based on a small number of trials and patients.
  - Pain related to *MS was assumed to be similar to neuropathic pain.*

An earlier study found in the PubMed search (Rog, A et al 27 September 2005, 'Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis' *Neurology*, 65(6):812-9) conducted a single-center, 5-week (1-week run-in, 4-week treatment), randomized, double-blind, placebo-controlled, parallel-group trial in 66 patients with MS and central pain states (59 dysesthetic, seven painful spasms) of a

whole-plant cannabis-based medicine (CBM), containing delta-9-tetrahydrocannabinol:cannabidiol (THC:CBD) delivered via an oromucosal spray, as adjunctive analgesic treatment. Salient points from the trial were:

- CBM was superior to placebo in reducing the mean intensity of pain (CBM mean change -2.7, 95 per cent CI: -3.4 to -2.0, placebo -1.4 95 per cent CI: -2.0 to -0.8, comparison between groups, p = 0.005) and sleep disturbance (CBM mean change -2.5, 95 per cent CI: -3.4 to -1.7, placebo -0.8, 95 per cent CI: -1.5 to -0.1, comparison between groups, p = 0.003).
- CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness, dry mouth, and somnolence.
- Cognitive side effects were limited to long-term memory storage.
- The study concluded that cannabis-based medicine was effective in reducing pain and sleep disturbance in patients with multiple sclerosis related central neuropathic pain and was mostly well tolerated.

There was also an extension trial to this study ('Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial', September 2007, *Clinical Therapeutics*, 29(9):2068-79) the purpose of which was to establish long-term tolerability and effectiveness profiles for THC/CBD oromucosal spray in CNP associated with MS. The uncontrolled, open-label trial was an indefinite-duration extension of a previously reported 5-week randomized study in patients with MS and CNP. The study concluded that:

- THC+CBD was effective, with no evidence of tolerance, in these select patients with CNP and MS who completed approximately 2 years of treatment (n = 28).
- Ninety-two per cent of patients experienced an AE, the most common of which were dizziness and nausea. The majority of AEs were deemed to be of mild to moderate severity by the investigators.

In regards to the current classification of cannabidiol in relation to the Convention on Psychotropic Substances 1971 and the Single Convention on Narcotic Substances 1961, XXXXX has advised that cannabidiol, as such, is not under international control. However, XXXXX did point out that as the pharmaceutical product THC+CBD contains cannabis extracts and cannabis extracts are included in Schedule I of the Single Convention on Narcotic Drugs of 1961, then this convention would apply to THC+CBD. According to Article 2 of the Single Convention, drugs included in Schedule I are subject to all control measures applicable to drugs under the Single Convention, including the mandatory submission of annual estimates and statistical returns as well as the control of international trade. That is to say, the obligations upon signatories for substances included in Schedule I relate to mandatory reporting of movement of these substances and these do not necessarily translate to mandatory restrictions on access. It was also pointed out that the substance delta-9-tetrahydrocannabinol in its isolated (synthetically manufactured) form is contained in Schedule II of the Convention on Psychotropic Substances of 1971.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Some jurisdictional Members noted that XXXXX it has been difficult for jurisdictions to approve access to these products as cannabidiol was considered a Schedule 9 substance. It was noted that access would be facilitated if cannabidiol was a Schedule 8 substance.

The Members noted the policy advice provided by the NCCTG in relation to the scheduling of dronabinol at the November 1994 NDPSC Meeting. However, the Committee did not consider it necessary to seek policy direction from the NCCTG on this occasion.

It was noted by a Member that enquiries received by jurisdictions to date were mostly from individuals (i.e. patients) or from general practitioners under instruction from their patients. It was asserted that this was not a routinely accepted treatment for multiple sclerosis-related neuropathic pain.

One Member requested that the Secretariat ascertain whether this product contained any other cannabinols, even in trace amounts. As this product was derived from an extract, it may contain other cannabinols.

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The Committee confirmed that tetrahydrocannabinol was captured by the current Schedule 8 entry for ‘dronabinol’ (delta-9-tetrahydrocannabinol) and agreed to foreshadow consideration of the scheduling of cannabidiol in Schedule 8 when prepared and packed for therapeutic use at the June 2009 NDPSC Meeting.

12.1.7 MAGNESIUM SULFATE

PURPOSE

The Committee considered a proposal to include magnesium sulfate in preparations for oral use for constipation in Schedule 3.

BACKGROUND

Magnesium sulfate is a chemical compound containing magnesium and sulfate, with the formula $MgSO_4$. In its hydrated form the pH is 6.0 (5.5 to 7.0). It is often available as the heptahydrate, $MgSO_4.7H_2O$, commonly called Epsom salts. Anhydrous magnesium sulfate is used as a drying agent. Epsom salts has been traditionally used as a component of bath salts. Oral magnesium sulfate is can be used as a saline laxative at the following doses: Adults: 15 g in 250 mL water daily. Children > 6 years: up to 10 g in 120 mL water daily; 2-5 years: up to 5 g in 120 mL water. Epsom Salts has been available for many years as an unscheduled powder in pack sizes from 375 g to 500 g with directions for use as a laxative, relaxing bath additive, fertilizer and fabric softener. It is also present in the following OTC products: XXXXX.

A capsule presentation containing 950 mg of dried magnesium sulfate with the trade name of XXXXX and manufactured by XXXXX was listed on the ARTG XXXXX under the Electronic Listing Facility (ELF). The product originally included the following indications: *"For weekly bowel conditioning. For the relief of constipation. For bowel preparation prior to colonoscopy."*

Magnesium sulfate had not previously been considered by the NDPSC; however, the Committee has considered other laxatives such as sodium picosulphate, sodium phosphate and polyethylene glycol at a number of its meetings.

Sodium phosphate in preparations for oral use for laxative or bowel cleansing purposes was first listed in Schedule 4 of the SUSDP in November 1997. However, sodium phosphate for the same indications was rescheduled to Schedule 3 in May 1999, following an appeal made to XXXXX by XXXXX against the inclusion of its product, XXXXX in Schedule 4. The February 2001 NDPSC Meeting adopted a recommendation of the 6th Meeting of the TTHWP, and rescheduled sodium phosphate for laxative use to Schedule 4, on public health and safety grounds. Oral preparations containing sodium phosphate for bowel cleansing prior to diagnostic, medical or surgical procedures, were retained in Schedule 3. The TTHWP also advised the NDPSC that adoption of this amendment would have no regulatory impact on existing products in Australia or NZ, as the indication for oral laxative use had been withdrawn prior to registration.

Sodium picosulfate was considered at the February 2002 NDPSC Meeting. The Committee agreed to include sodium picosulfate in Schedule 3 for oral use for bowel cleansing prior to diagnostic, medical or surgical procedures. This decision was made on the basis that advice and counselling by a pharmacist was essential for safe use of these products. The Committee noted problems of severe electrolyte disturbances raised by the ADRAC with low volume bowel cleansing products containing sodium picosulfate.

Polyethylene glycol (macrogol 3350) was considered at the May 2000 NDPSC Meeting. The Committee considered a submission requesting that preparations containing polyethylene glycol when used for the same purposes as sodium phosphate be scheduled in the same way. The Committee accepted the data that indicated toxicity associated with the use of macrogol 3350 as a bowel cleansing agent. Members also recalled that the adverse effects associated with sodium phosphate appeared to be related to dehydration and electrolyte imbalances associated with its action as a saline laxative. The Committee noted no evidence had been provided to indicate that there were safety concerns associated with the use of macrogol 3350 in laxative preparations. The Committee considered a scheduling distinction could be made in regard to macrogol 3350 preparations and therefore supported inclusion of macrogol 3350 in Schedule 3 when in oral preparations for bowel cleansing purposes. The decision was based on consistency in scheduling this preparation with sodium phosphate for bowel cleansing and on the available data the toxicity profile of macrogol 3350 in bowel cleansing preparations is comparable to sodium phosphate.

The Committee recalled recent consideration of potassium chloride. The Committee, whilst concerned about the toxicity profile of slow release potassium chloride preparations with more than 100 mg of potassium chloride, also had to consider the inadvertent capture of a large number of complementary products such as oral re-hydration preparations, enteral feeding preparations and glucosamine sulfate products complexed with potassium chloride. At the June 2007 NDPSC Meeting, the Committee agreed to a Schedule 4 entry in oral preparations for human therapeutic use except for products with less than 550 mg of potassium chloride per dosage unit, or in preparations for oral rehydration therapy or bowel cleansing or enteral feeding preparations.

DISCUSSION - SUBMISSIONS

This matter was referred to the NDPSC by the ADRAC. At the April 2008 ADRAC Meeting the Delegate responsible for Listed medicines proposed to cancel the listing of XXXXX (magnesium sulfate–dried 950 mg capsules) on the grounds that this product did not appear to be safe for the purposes for which it was intended to be used. The ADRAC noted that from 4 July 2008 the listing conditions for this product were amended to read as follows:

- Non Standard Indications: For the relief of occasional constipation. Magnesium sulfate is a naturally occurring mineral that has been used for many centuries for bowel cleansing.
- Registration Conditions: The product claims must be restricted to the use of the product for the relief of occasional constipation (or words to that effect). The maximum dose of the product is to be 15 capsules, taken at intervals of at least 3-7 days. The directions for use must instruct the consumer to take 250 mL of appropriate fluid for every five capsules consumed. The product container must be supplied with a child resistant closure (CRC).

Despite the above changes, the ADRAC considered that there was still a considerable risk to consumers because of the following:

- Although the use of Epsom Salts as a laxative had fallen out of favour, the availability of this particular product may lead to a resurgence of use as a laxative and expose problems not currently seen e.g. potential resurgence of hypermagnesemia.
- In the absence of intervention by a healthcare professional, it was likely that the product 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 medicine/s as well as magnesium sulfate.
- Potential for gastric erosion was a concern; although this was now less concerning, given the reduction in recommended dose to 15 capsules.
- There was concern over swallowing safety, i.e. the risk of oesophageal obstruction.

- Nephrologists advised that there would seem to be little risk that a single dose of this medication taken by a person with chronic kidney disease (CKD) would develop troubling hypermagnesemia. However, the abuse of this medication would present a risk of hypermagnesemia for CKD patients. The greatest risk to CKD patients is the development of volume depletion and consequent worsening of renal failure. There is 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 ARBs (angitensin receptor blockers).

The Complementary Medicines Evaluation Committee (CMEC) also discussed this particular product XXXXX. The CMEC was advised that XXXXX was a new Listed medicine entered on the ARTG originally for the following indications: *"For weekly bowel conditioning. For the relief of constipation. For bowel preparation prior to colonoscopy"*. The CMEC members noted XXXXX the medicine did not appear to be safe for the purposes for which it was intended to be used. The decision was based on the following reasons:

- Concerns regarding the solubility of the medicine and potential for gut erosion.
- The capsule formulation had a potential for overdosing, particularly in children who would be deterred from swallowing Epsom Salts in powder form due to the unpleasant taste.
- A high recommended dose (30-65 capsules a day) with no emphasis on the importance of fluid intake.
- Risk to patients with impaired renal function that are susceptible to magnesium toxicity.

XXXXX

The CMEC members noted XXXXX. Whilst the CMEC had concerns about the product it did agreed it should remain eligible for Listing subject to further consideration by ADRAC.

The July 2008 ADRAC Meeting felt that consideration should be given to amending the Schedules to the SUSDP so that products such as XXXXX were available only on advice from a pharmacist i.e. Schedule 3. The ADRAC acknowledged that other products containing magnesium sulfate, but not used for constipation, may be affected by this recommendation, however, this was a matter for the NDPSC. The ADRAC suggested that the NDPSC may consider including in Schedule 3 magnesium sulfate when indicated for constipation or other bowel disorders.

A search of the ARTG revealed that several products may be inadvertently captured by a change in scheduling of magnesium sulfate including Kruschen Salts, Darby Mineral Salts and Epsom Salts.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) the extent and patterns of use of the substance, (e) the dosage and formulation of the substance and (h) the purposes for which a substance is to be used.

Members noted that despite minimal use of magnesium sulfate as a laxative there was still the potential for toxicity and even more so with a capsule formulation. The Committee noted that despite the label being changed to highlight the need to maintain adequate fluid intake and decrease the dose to 15 capsules over 45 minutes, there was still a safety concern.

One Member noted that if magnesium sulfate was scheduled, then manufacturers of the powdered product might simply remove dosage directions for constipation from the products and this might inadvertently result in a situation where there were no dosage instructions at all. Another Member noted that it was not magnesium sulfate as a powder that was of concern but the novel capsule presentation that had resulted in the increased risk. The Committee noted that if it concerned itself with only divided preparations for human therapeutic use in constipation, this would exclude other preparations containing magnesium sulfate from inappropriate inclusion in any scheduling change.

The Committee agreed that professional advice was necessary for this particular presentation and indication.

RESOLUTION 2009/55 - 27

The Committee agreed to foreshadow the inclusion of magnesium sulfate in Schedule 3 for human therapeutic use in divided oral preparations for constipation.

12.2 SUSDP, PART 5

12.2.1 IBUPROFEN

PURPOSE

The Committee considered the scheduling of ibuprofen and a proposal to include 400 mg ibuprofen in Appendix H.

BACKGROUND

Ibuprofen, a propionic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Ibuprofen is used in the management of mild to moderate pain and inflammation in conditions such as dysmenorrhoea, headache including migraine, post-operative pain, dental pain, musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, and rheumatoid arthritis including juvenile idiopathic arthritis,

peri-articular disorders such as bursitis and tenosynovitis, and soft-tissue disorders such as sprains and strains. It is also used to reduce fever.

Ibuprofen was first included in Schedule 4 of the SUSDP in February 1973. At the May 1989 Meeting, ibuprofen in packs of 24 or fewer tablets or capsules for the relief of dysmenorrhoea or of pain associated with inflammation was rescheduled to Schedule 3. The Schedule 3 entry was amended over several meetings since and in May 1995, ibuprofen when the only therapeutically active substance in divided preparations for oral use containing 200 mg or less of ibuprofen per dosage unit in a pack containing 50 or less dosage units and labelled with a recommended daily dose of not more than 1200 mg, was rescheduled from Schedule 3 to Schedule 2.

The June and October 2003 NDPSC Meetings agreed to exempt divided preparations containing 200 mg or less of ibuprofen per dosage unit in packs containing 25 or less dosage units when labelled with a recommended maximum daily dose of 1200 mg of ibuprofen and compliant with the mandatory label requirements from scheduling. The Committee agreed that exempting certain low dose ibuprofen oral preparations in small pack sizes from the requirements of scheduling was unlikely to lead to any public health concerns and that it would provide consumers with an additional choice of simple analgesic product available at general outlets.

At the February 2006 NDPSC Meeting, the Committee considered an application seeking reclassification from Schedule 4 to Schedule 2 of divided doses of ibuprofen 400 mg in oral preparations. The Committee agreed to include 400 mg ibuprofen per dose unit in packs of not more than 50 dose units and labelled not for the treatment of children aged less than 12 years in Schedule 3. Whilst the Committee remained reassured of the safety of OTC low-dose ibuprofen in small pack sizes when taken as directed, Members considered pharmacist involvement at point-of-sale was essential to minimise consumer confusion over the increased strength per dose unit of the proposed product and ensure appropriate use. The Committee also considered the inclusion of ibuprofen 400 mg in Appendix H. Members did not support the Appendix H listing for this product on the basis that direct-to-consumer advertising of high dose ibuprofen was unlikely to have any public health benefits.

DISCUSSION - SUBMISSIONS

XXXXX.

Applicant's Submission

A scheduling submission was received from XXXXX, seeking to include ibuprofen 400 mg in Appendix H.

- The applicant stated that the Committee's previous decision to retain the *status quo* scheduling for ibuprofen had been based on the belief that pharmacist involvement was important at point-of-sale to avoid consumer confusion over the increased 'per

dose unit' and 'ensure appropriate use'. The concern of the Committee was, however, that the 400 mg strength would be selected by consumers, when their condition may be adequately treated by the 200 mg dose, i.e. that consumers would assume that more is better when clinical trials prove that the 200 mg dose of ibuprofen was adequate to treat a majority of self-limiting conditions, including migraine. While the Committee understood that ibuprofen had limited negative health effects, the reason for rejecting the Appendix H listing was that in the interest of public health, consumption of higher than necessary amounts of a Schedule 3 drug would be encouraged by advertising.

- The applicant presented a regulatory table on the status of ibuprofen 400 mg in some overseas countries. Of the 24 countries, eight were prescription-only and the balance OTC/pharmacy only, with NZ mirroring Australia's scheduling.
- The applicant did not address each of the provisions of Section 52E, as required when using the re-scheduling template. Indeed, it was stated that sections (a), (b), (c), (d), (e) and (f) of Section 52E(1) were not relevant to the application, repeating the phrase, 'as ibuprofen was in use for many years in Australia without major safety issues' in each case. In addressing (g) – potential for abuse - the applicant stated that there was no evidence that ibuprofen was abused in any dosage. Under (h) – purpose for which a substance is to be used - the applicant listed the uses for ibuprofen as per the product information. The applicant did not refer to any additional matters.
- The applicant proffered that the 400 mg product would be differentiated from the 200 mg product by the addition of "DOUBLE STRENGTH" to the trade name, thus assisting consumer preference, but did not provide an example of this packaging.
- The applicant stressed that direct-to-consumer advertising would educate consumers about the availability of the 400 mg product and help those who took 2x200 mg tablets for severe pain, by requiring them to take only one 400 mg tablet. In the post-meeting comment the applicant said that the NDPSC Record of Reasons needs to clarify its definition of severe pain. The applicant stated in their post meeting response that their 200 mg dose had not been formulated for severe pain.
- The applicant stated that awareness of the 400 mg product would assist consumers to make 'an informed decision' by consulting their pharmacist. The Schedule 3 product was available only from the pharmacist, upon judgment by the pharmacist that the greater strength would be warranted. It was not made clear how advertising would assist the consumer; unless the intention was that the consumer would be aware of the 'double strength' product and be able to 'self select' the product from the retailer.
- The applicant said that the 400 mg would be cheaper and was not likely to cause any safety or inappropriate usage issues. While the cost may be a major factor in consumer preference for the product; this would be an advantage to the reseller, but its effect in terms of public health was not known.
- Under Part C – Supporting Data, the applicant supplied a supporting data summary. This was a summary by country. Australia had one adverse event for the substance (Case Id. 8 – 99144 – 091A), a bronchospasm, cough, dyspnoea, face oedema,

pruritus and rhinitis. However Canada, where ibuprofen is available OTC and in drug and non-drug outlets (except Quebec), had 67 events in the same period as Australia. The countries where ibuprofen is prescription only, had markedly fewer incidents (eg US 7, UK 14, France 4, and Ireland 1) than Canada, where it is available in non-pharmacy settings.

NDPSC Evaluation Report

The evaluation report stated that the applicant had addressed the Section 52E "matters to be taken into account", but did not directly address the matters set out in the NCCTG Schedule 3 Advertising Guidelines, although did 'touch on them' in the application. The following point summarise the evaluator's main points;

- The evaluator noted that the applicant's review of case records from their database did not provide a comparison with possible use of a 200 mg dose or the appropriateness of a 400 mg dose.
- The ADRAC printouts included with the application did not provide information specific to the safety experience of 400 mg doses in Australia. In the opinion of the evaluator, the applicant's analysis "lacks critical appraisal, especially in regard to the 400 mg dose forms".
- The evaluator commented that the data showed a "not insignificant proportion of overseas users of 400 mg ibuprofen" taking doses greater than the 400 mg. The evaluator stated that this information reinforced the need for pharmacist intervention with the 400 mg doses, but did not point to any need to review the current schedule entry.
- The evaluator further pointed out that pharmacist involvement at the point of sale was needed to encourage consumers to use the lowest effective dose of ibuprofen.
- The evaluator stated that a 'striking' aspect of the 67 Canadian reports was that 34 describe dysphagia, choking and related issues, implicating Advil Extra-Strength liquid filled capsules, which should be of concern to the TGA, if registration was sought in Australia. The applicant had not made a category by category analysis of the Canadian reports. The evaluator was concerned over the coding for overdose, and was able to identify a further ten reports (Nos 9 to 18) in which doses in excess of 400 mg were taken, but had not been coded as overdose.
- In relation to 52E, the evaluator noted that while the applicant had made a blanket statement for items (a) to (f), (that the criteria were not relevant because of the many years of use without an safety issue in Australia), the specific issue of the relevance of these criteria to the advertising of a Schedule 3 ibuprofen 400 mg product was left unanswered.
- Under (g) - potential for misuse/abuse, the evaluator noted that neither taking a 400 mg dose when 200 mg would suffice, nor taking more than one 400 mg dose, had been addressed.

- Under (h) - purposes for which the substance would be used - the product information list provided included only uses which would involve only mild to moderate pain, such as sore throat, cold, headache, muscle pain, had been listed. Schedule 3 availability of 400 mg ibuprofen was intended to enable the treatment of severe pain.
- Under 'Additional Matters', the applicant had not addressed separately the matters listed in the NCCTG Schedule 3 Advertising Guidelines. The evaluator did however; present a list, written as a response to the guidelines, giving examples of contraindications for the substance being given status in Schedule 3. This list included references to the Therapeutic Goods Advertising Code Council, on which the guidelines are modelled, the Therapeutic Goods Advertising Code, *Therapeutic Goods Act 1989* and the Therapeutic Goods Regulations 1990.
- The evaluator went on to refute each of the claims made by the applicant in the concluding statement.
- The evaluator recommended that the application for an Appendix H listing be rejected on the grounds that the information submitted did not support any meaningful public health benefits of direct-to-consumer advertising in Australia of high dose ibuprofen.

Pre-Meeting comment from the applicant

The applicant provided a response to the evaluator's comments, and made the following points:

- It was difficult to provide information expected by the evaluator in relation to product data because ibuprofen data were not cross-referenced. The applicant agreed that reports indicating ibuprofen 400 mg may have been recorded in the ibuprofen listing, which included ibuprofen 200 mg.
- On the point of the failure to request Public Case Detail Reports from the Adverse Drug Reactions Unit (ADRU) and manually locate relevant reports; the applicant said that there was a limitation on how an applicant could analyse adverse event reports obtained from ADRU or any source.
- In relation to the evaluator's comment that Section 52E needed to be addressed in more detail the, applicant stated 'This criteria is not relevant as ibuprofen was in use for many years in Australia without major safety issues'. The applicant asserted that the NDPSC would not have allowed ibuprofen as a general sale medicine if it (NDPSC) had any safety concerns. The applicant's dismissal of the NDPSC's requirement to address these provisions resulted in a less-than-ideal data package.
- As to (h) - purpose for which the substance is to be used - the applicant stated that uses for ibuprofen, would often involve only mild to moderate pain, and cited references to 'Records of Reasons – 46th and 47th meetings that the Schedule 3 availability of 400 mg ibuprofen was intended to enable the treatment of severe pain on the advice of a pharmacist. The applicant further stated that it was not intended to change the status of supply of ibuprofen 400 mg distributed by a pharmacist, but to

inform the consumers of the availability of a 400 mg product enabling the consumers to discuss their needs with their pharmacist.

- The applicant pointed out that the evaluator had conceded that some supporting material had been included, indirectly, in the concluding statement. It was stated that the applicant did not wish to repeat information well-known to the Committee.
- The applicant pointed to ADRAC as the source for information on ibuprofen use in Australia, in defence of a lack of data specific to the Australian market, referred to by the evaluator.
- The applicant said that direct-to-consumer advertising of ibuprofen 400 mg was 'not likely' to compromise the safety of Australian consumers, considering that the 200 mg product was available from supermarkets.

Pre-meeting submissions

The NDPSC received a submission from XXXXX, which stated support for inclusion in Appendix H, given the established safety profile at the dosage level.

XXXXX provided a submission which opposed the Appendix H listing of ibuprofen for the following reasons:

- It was felt that if a decision was made to place a substance in Schedule 3, then inclusion in Appendix H was wholly inappropriate.
- It was stated that once a drug was included in Appendix H, it was essentially 'sold' by a television advertisement and nothing the pharmacist could say or do seemed to deter the public from demanding it be supplied.
- XXXXX
- It was suggested that Appendix H had the effect of undermining the requirements of Schedule 3, State & Territory poisons regulations and the pharmacist's professional and ethical obligations. That was to say that once a drug is placed in Appendix H it becomes a de facto Schedule 2 medicine and considered that this appendix should be abolished.

XXXXX made a submission in which concurrence with XXXXX was expressed, opposing the Appendix H listing of ibuprofen.

XXXXX made a submission, 'categorically' opposing an Appendix H listing for ibuprofen for the following reasons:

- Consumers might seek a product for treatment of conditions other than those for which it was approved or in circumstances outside of its approval.
- In Western Australia, the Poisons Regulations 1965 require;

> Before a substance included in Schedule 3 is delivered as part of a retail sale, the *pharmaceutical chemist or graduate trainee shall take all reasonable steps to ensure that there is a therapeutic need for the substance.*

- Appendix H listings takes away the right of the pharmacists to refuse supply and compromises the ability of the pharmacist to comply with this aspect of the Poisons Regulations 1965.
- Experience with oral fluconazole showed that the "informed consumer" had decided on the basis of advertising which product was the best and most effective for the treatment of the condition that they thought they had, and that pharmacists struggle to convince such consumers otherwise.

XXXXX presented a submission supporting the entry of ibuprofen into Appendix H, if there was sufficient evidence to support the public health benefits of direct-to-consumer advertising of the high dose ibuprofen. The submission made the following points:

- The 400 mg strength tablet was available to adults and children over 12 years of age, with a divided daily dose of 1200 mg (3x400 mg) or less.
- Packs of 12 and 24 of the 200 mg were available in Schedule 2 with the above maximum daily dose.
- Schedule 3 diclofenac was included in Appendix H.
- The pharmacist would be available for client counselling about lowest effective dose, renal and gastro-intestinal effects and drug interactions.
- Any advertising should be clear that this product would be twice the strength of the unscheduled and Schedule 2 products.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under 52E(1) included (b) risks and benefits associated with the substance, (c) the potential hazards associated with the use of the substance, (d) extent and patterns of use of a substance, (e) dosage and formulation of a substance, (f) the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose and (g) the potential for abuse of a substance.

Members discussed the perception that an advertised product was one with high perceived safety margin and concluded that consumers may demand the higher dose product for conditions which would respond to lower dosages. Members noted that there was already substantial consumer awareness of the availability of ibuprofen as a treatment for short term acute pain, given its status as both a Schedule 2 medicine as well as an unscheduled product. Members further noted that use of 400 mg of ibuprofen would have greater risk than 200 mg, especially when 200 mg may be a sufficient dose for many patients. However, the submission did not address this issue sufficiently to allay the Members' concerns.

Among the comments submitted to the Committee was that an Appendix H listing had the potential to undermine the role of the pharmacist as consumers might demand products they had seen advertised irrespective of any advice provided by a pharmacist. Members disputed this assertion, noting given that all Schedule 3 products must be sold with the supervision of a pharmacist and that advice was provided on such products at the time of request.

Members noted that in making a decision on the suitability of an Appendix H listing, consideration of the potential public health benefit was paramount. Members agreed that the applicant had not put forward a satisfactory case to establish the public health benefits of advertising ibuprofen 400 mg. Further, Members noted that advertising the product at higher doses might stimulate demand for which may not be clinically justified.

A Member stated that while ibuprofen 400 mg had a role in the management of acute conditions, it also came with an increased risk to the consumer. Given this potential increased risk to consumers combined with the already increased consumer awareness of the availability of ibuprofen, albeit as a Schedule 2 medicine, the Committee concluded that the public health benefit of advertising the 400 mg strength of ibuprofen was not effectively demonstrated.

RESOLUTION 2009/55 - 28

The Committee decided that the current scheduling for ibuprofen 400 mg remained appropriate.

12.2.2 PANTOPRAZOLE

PURPOSE

The Committee considered the scheduling of pantoprazole including a proposal to include pantoprazole 20mg in Appendix H.

BACKGROUND

Pantoprazole is a proton pump inhibitor (PPI). It is indicated for the treatment of peptic ulcer disease and gastro-oesophageal reflux disease (GORD).

Pantoprazole was first considered for scheduling at the February 1995 NDPSC, where it was included in Schedule 4. The June 2005 NDPSC Meeting agreed to include pantoprazole, in oral preparations containing 20 mg or less of pantoprazole for the relief of heartburn and other symptoms of GORD in packs containing not more than 14 days supply, in Schedule 3. A delayed implementation date of 1 May 2006 was set down. This application also proposed an Appendix H listing however the Committee felt there was insufficient information at the time to allow direct-to-consumer advertising.

After discussions at the October 2005 NDPSC Meeting and the February 2006 NDPSC Meeting, it was agreed to delay the implementation date for Schedule 3 listing to 1 May 2008.

DISCUSSION - SUBMISSIONS

XXXXX made a submission requesting the inclusion of pantoprazole (in oral preparations containing 20 mg of less of pantoprazole for the relief of heartburn and other symptoms gastro-oesophageal reflux disease, in packs containing not more than 14 days supply) to be added to Appendix H. The applicant stressed that this change would not require any changes to other scheduling entries for pantoprazole currently in the SUSDP.

The application separately addressed the matters under Section 52E. In summary, the submission asserted that:

- Reflux symptoms had been safely managed by OTC medications for decades with consumers being able to self-diagnose these symptoms and safely treat them. NDPSC had already established that pantoprazole 20 mg was suitable for supply as a Schedule 3 medicine. Schedule 3 preparations of pantoprazole were launched to the general public in mid-October 2008 with considerable resources having been put into developing and disseminating a pharmacy training program.

- Advertising directly to current frequent heartburn suffers was expected to encourage them to at least talk to their pharmacist and would positively impact public health by promoting a better use of professional expertise resulting in a more appropriate medication choice.

- Toxicity and safety had previously been addressed by the NDPSC. Three years had passed, therefore a brief summary of updated safety data was provided demonstrating that pantoprazole was unlikely to present a direct danger when used correctly without medical supervision. XXXXX.

- Pantoprazole had been available in Sweden OTC since February 2000 and had been advertised. Post-marketing data from Sweden had revealed no increase in adverse events XXXXX.

- The USFDA approved OTC omeprazole (a PPI) in 2003. Following this, a three month observation study was conducted to determine whether consumers could: correctly self-select the product for frequent heartburn, comply with the product label (which calls for 14 consecutive days of once-daily dosing), use more than 14 doses only under the advice of a physician. Interviews were conducted at five shopping malls across the USA with 1999 heartburn suffers identified. Of these, 866 determined that the OTC omeprazole product was appropriate to use and were given a diary to document product usage and physician contact. 758 (88 per cent) returned diaries. It was concluded from the data that consumers accurately self-selected if an

OTC PPI was appropriate, complied with the 14 day course and appropriately sought medical advice for longer-term management of frequent heartburn.

- A report compiled on behalf of the Australian Gut Foundation found that the greatest economic cost from GORD was not the value of healthy life lost but rather loss of productivity.

- ADRAC reported 304 cases relating to the use of pantoprazole from 1 May 2000 to the date of the submission. Of these, none resulted in death and analysis revealed that only 16 were directly related to pantoprazole and only one was considered life-threatening. The case involved dyspnoea and the patient recovered after ceasing pantoprazole.

- The applicant also addressed the "Schedule 3 advertising guidelines". The major assertions made were as follows:

  – The applicant stated that advertising would disseminate information and increase consumers' awareness of new medicines directly. Moreover, it would help dispel the misconception that heartburn does not need medical intervention. Data presented by the applicant stated that in the gastrointestinal category, supermarket sales had increased, whilst pharmacy sales had decreased. Therefore, whilst people were self-medicating, they were doing so in an environment without access to professional advice. Advertising would also raise awareness that pharmacists were able to provide advice (aided by the educational materials provided) about heartburn management and more effective treatment options. It would at the very least encourage consumers to talk to their pharmacists, driving more sufferers into pharmacies which would positively impact public health by promoting better use of professional expertise.

  – An Appendix H listing would not change the level of involvement or recommendation behaviour required by pharmacists or the way consumers were informed about the product. XXXXX. The applicant also stated that if Appendix H listing is granted, it would be able to develop a comprehensive pharmacy assistant training program, taking the onus from pharmacists and enabling them to perform their duties to support the pharmacist better. It would not change the fact that a pharmacist must be involved in the sale.

  – Without advertising, consumers may continue to be unaware of the new, potentially more effective product to manage their condition.

- The applicant proposed wording for the Appendix H listing.

NDPSC Evaluation Report

The NDPSC evaluation report recommended that this application be rejected at this time. Reasons for this recommendation were:

- The majority of material presented by the applicant had been accepted by the Committee at the June 2005 NDPSC Meeting when pantoprazole was rescheduled to Schedule 3, i.e. the favourable risk/benefit ratio and its safety for short-term use (with the pharmacist advice). Although this material further supported the rescheduling decision, it did not contribute to whether or not there was a potential public health benefit to be gained by advertising the product. Pantoprazole 20 mg in packs not containing more that 14 days supply only became available to the general public in late 2008, although the Schedule 3 listing was approved in June 2005. Pharmacists have only had three months experience with the supply of pantoprazole as a Schedule 3 product and with the new educational materials.
- A previous application for inclusion in Appendix H had been rejected partly because the pattern of OTC use had not yet been established. Data from Sweden was provided in the current application, however there was no evidence that there were sufficient similarities in the pattern of use between Sweden and Australia. It therefore appeared that this application was premature and it would be more appropriate to wait for Australian data before making a decision regarding advertising. The applicant proposed to supplement this data by using consumer and pharmacist generated reports from October to mid-January 2009 and then providing this data for the Committee's consideration. With only three months worth of data, and from the initial launch when usage would not be expected to be high, it would be inadequate for the Committee to make an informed decision. Moreover, the late submission of data would mean it would not be available to the evaluator.
- Although it was possible to speculate the possible public health benefits, additional information was required to determine the likelihood and magnitude of such a benefit. It may yet become evident that patients with frequent heartburn would present themselves to a pharmacy for advice without the presence of advertising. It was suggested that an application be submitted at a time when at least 12 months worth of data was available for inclusion.

Pre-Meeting Response from Applicant

The applicant provided a pre-meeting comment in response to the NDPSC evaluation report. The following points were raised:

- The applicant addressed the evaluator's concerns that the data provided in the application did not contribute to the question of the potential public health benefit. The applicant felt it was appropriate to provide updated data for this application and that it also reinforced the highly favourable risk/benefit ratio of pantoprazole 20 mg. Moreover, the applicant stated that the data provided served to highlight facts which were absent from the previous application, namely; that pantoprazole 20 mg had been available OTC in Sweden for eight years and that in all markets in which PPIs had

been made OTC, they had been advertised from launch (with the exception of Australia).

- Further, the applicant asserted that whilst the information provided did not directly inform on Australian use patterns, it demonstrated that the use of OTC pantoprazole and other OTC PPIs had been entirely appropriate in a variety of markets.

- The applicant disagreed with the suggestion that the pharmacy training program had little relevance in regards to public health benefits of advertising pantoprazole 20 mg to the public. Advertising is expected to raise public awareness of the product and as such a pharmacist's ability to supply and provide advice on the product. Education and training underpin the professional advice patients receive as well as impacting on early identification of patients who require referral to a GP.

- The applicant agreed that an advertising campaign directed at the general public would not aid the pharmacy assistant training and was not the intent of the application. Rather, due to current *Therapeutic Goods Advertising Code* requirements, pharmacy assistants are not defined as healthcare professionals and hence are considered consumers. Without an Appendix H listing, there is a restriction on communicating with them and such a listing would be pivotal for adequate training.

- The evaluator agreed with the point made regarding that public health benefits had some merit but suggested that there was insufficient information to judge the likelihood and magnitude of such benefits. The applicant felt that declining an Appendix H listing would only delay the potential positive impact in regards to more appropriate treatment and healthcare professional intervention. Data presented, albeit from US experience with OTC omeprazole, showed quantifiably the benefits of actively making consumers aware of alternative treatments.

- Comments made by the evaluator, stating that the majority of eligible patients would present to a pharmacy without the need for advertising were questioned by the applicant. Data on market trends presented in the application contradicted this statement. The Australian based data showed that a large number of people with heartburn self-medicate using unscheduled products from supermarkets and that there had been an increase in supermarket sales and a decrease in pharmacy sales in the gastrointestinal category.

- In response to the evaluator's comments on advertising, not giving consumers a wider choice as they already have access to pantoprazole 20 mg, the applicant responded that without branded advertising to drive consumer awareness of alternative treatments, frequent sufferers of heartburn would continue to manage their condition as they have always done.

- The evaluator expressed concerns about lack of Australian data on the pattern of OTC use of pantoprazole 20 mg. The applicant reiterated pantoprazole's wide therapeutic

index and low risk of inappropriate use as well as the inclusion of eight years of Australian Schedule 4 data and eight years of OTC data from Sweden.

- The evaluator stated that at the time of the application, pharmacists would only have had three months' experience with pantoprazole 20 mg as an OTC product. The applicant asserted that, if this proposal was approved at this time, the effective date would be 1 September 2009, therefore pharmacists would have 11 months' experience before advertising commences.

Pre-Meeting Submissions

XXXXX provided a pre-meeting comment. No objection was raised to this proposal but the sponsor was encouraged to continue to work with relevant pharmacy stakeholders to deliver pharmacist education, information and training for non-pharmacist staff. Liaison with the sponsor had taken place to deliver education, training and resources nationally and further believed one of the reasons for an Appendix H listing was to enable the use of the brand name in educational events and resources for non-pharmacist training, i.e. pharmacy staff. Moreover, several Schedule 2 and unscheduled products were already advertised which were also used to treat uncomplicated gastro-oesophageal reflux disease.

XXXXX submitted pre-meeting comment. There was no objection to the inclusion of pantoprazole 20 mg in Appendix H and it was suggested that community pharmacy was ready to meet the increased demand that may result in a professional and appropriate manner. It was noted that pharmacists had comprehensive training materials available to them and that the PSA had an excellent two page summary protocol (with flow chart and detailed explanation) available at their website. Although extensive counselling would take place at the point of sale, it was suggested that any advertising should strongly feature the 14-day treatment. Further, the previous NDPSC decision was recalled from June 2005 in which an application for Appendix H listing was rejected as at the time 'the pattern of OTC use would need to be established with Schedule 3 availability'. Therefore, no objection was raised to the proposal, given that adequate data was now available in the current application.

A pre-meeting comment was made by XXXXX. The proposal to list pantoprazole 20 mg in Appendix H was opposed as such advertising would most likely impair, rather than enhance, a pharmacist's ability to fulfil the requirements in the relation to the supply of pantoprazole as a Schedule 3 medicine. Moreover, there are several different treatment options for the management of heartburn and GORD available without a doctor's prescription. The PSA guidelines for the supply of Schedule 3 pantoprazole state that pantoprazole should be used only by patients with more frequent symptoms and that those with less frequent symptoms use another form of medication.

XXXXX submitted pre-meeting comment opposing the Appendix H listing. Opposition to the original down-scheduling of pantoprazole 20 mg from Schedule 4 was recalled and it was stated that a listing in Appendix H encouraged self-diagnosis. It was further stated

that PPIs were not the same as H_2 receptor antagonists in that they were not for immediate relief of symptoms. Moreover, on many occasions it had been stated that once a drug was listed in Appendix H, it was essentially 'sold' by advertising and nothing a pharmacist said or did would deter the public from demanding its supply. Appendix H had the ability to undermine the requirements of Schedule 3, State & Territory regulations and a pharmacist's ethical and professional obligation. Further, complaints from the general public who had been refused the sale of a Schedule 3 product had been received by XXXXX.

XXXXX submitted pre-meeting comment which concurred with the statements put forward by XXXXX.

A pre-meeting comment was submitted by XXXXX supporting an Appendix H listing as heartburn and indigestion are conditions which have been managed by OTC products for many years. Further, as pantoprazole 20 mg is Schedule 3, it can only be purchased after consultation with a pharmacist who has the appropriate knowledge and tools to dispense this product.

A pre-meeting comment was submitted by XXXXX. XXXXX, the proposal for Appendix H listing was supported as there seemed to be little risk. The educational materials provided to pharmacists appeared to be helpful in identifying points of referral, i.e. sending patients with frequent heartburn to their medical practitioner for advice. Moreover, these pharmacist interactions may also help identify individuals who are at risk of oesophago-gastric cancer at an earlier age. It also provides patients with an opportunity to discuss life-style measures that might be important in long-term management.

XXXXX, submitted a pre-meeting comment. XXXXX which provided input on the education program and the co-management of heartburn and XXXXX for an educational article of GORD. The comment supported the Appendix H listing of pantoprazole 20 mg and noted its excellent safety profile, as it is no different to that of the other non-prescription acid suppressant ranitidine which is available in supermarkets. Moreover, allowing advertising would draw in patients who are untreated or under-treated and do not get professional assessment. In turn, these patients can be assessed by pharmacists, who have been provided with educational support, and referred to a GP is required.

A pre-meeting comment was submitted by XXXXX, supporting an Appendix H listing as it would have a public health benefit for a significant proportion of the Australian population. By allowing advertising, heartburn sufferers would be made aware of the availability of an alternate and more effective treatment option. It would not allow for inappropriate patterns of use due to its Schedule 3 classification, as pharmacist involvement was mandatory for every sale. Moreover, pharmacist involvement would ensure that a trained professional was correctly identifying suitable patients. It was noted that pharmacists are well placed to deal with both symptom based and direct product requests and have been provided with specific training materials (by the sponsor) which have been complemented by the PSA's InPHARMation program and pharmacy education

evenings. Further to this, it is stated that an Appendix H listing would not contravene the wider regulatory system including the *Therapeutic Goods Advertising Code* and the Therapeutic Goods Regulations.

DISCUSSION – RELEVANT MATTERS UNDER 52E

The Committee recalled that its initial decision to down-schedule pantoprazole from Schedule 4 to Schedule 3 in June 2005 also included the rejection of a proposal to include pantoprazole in Appendix H. At the time, the Committee agreed that it would not consider an Appendix H listing until patterns of use of pantoprazole as a Schedule 3 medicine had been established. The Committee also noted that the primary purpose of direct-to-consumer (DTC) advertising of Schedule 3 medicines, as articulated in the TGA report which guided the NCCTG's 1997 decision to allow such advertising, was the protection of public health and improvement in health outcomes. Thus, whether or not this application effectively demonstrated DTC advertising of pantoprazole would result in an improvement in public health outcomes was crucial to the Committee's consideration of the matter.

The Committee noted the report in the most recent *Australian Adverse Drug Reactions Bulletin* (Volume 28, Number 1, February 2009) which described three large retrospective studies suggesting an association between proton pump inhibitors (including omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole) and an increased incidence of fractures.

The claim by the applicant that an Appendix H listing would allow training for pharmacy assistants was not seen as relevant to the matters which the Committee must consider. Further, the Committee acknowledged the data presented on the economic costs of GORD, but agreed that this was not relevant to the matters it must consider.

The Committee noted the data provided on overseas OTC use of pantoprazole (and other proton pump inhibitors). It was agreed that such data did not take into account prescribing patterns in these countries and the Committee was aware that Australia has a relatively high prescribing rate for proton pump inhibitors, on a per capita basis.

In summary, the Committee agreed that the lack of Australian data on pantoprazole as an OTC medicine meant that no conclusions could be drawn on risks and benefits, potential hazards, extent and pattern of use and other relevant matters, in the context of advertising and public health benefit. Without such data, no conclusions on the likelihood of improvements in health outcomes could be drawn. Thus, the Committee felt that considering an Appendix H listing for pantoprazole at this stage was premature. The Committee agreed that this was in keeping with the recommendation of the June 2005 NDPSC Meeting that Australian-specific OTC data would be required to inform any decision on the appropriateness of an Appendix H listing.

RESOLUTION 2009/55 – 29

The Committee agreed that the current scheduling of pantoprazole remained appropriate.

13. MATTERS REFERRED BY THE REGISTRATION PROCESS FOR PRESCRIPTION MEDICINES

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY THE NDPSC)

13.1.1 GEMTUZUMAB OZOGAMICIN

PURPOSE

The Committee considered the scheduling of the new medicine gemtuzumab ozogamicin.

BACKGROUND

Gemtuzumab ozogamicin is a drug-antibody conjugate for the treatment of acute myeloid leukemia. It is an alternative to chemotherapy for patients who are 60 years of age or older who have suffered a relapse.

XXXXX.

DISCUSSION - SUBMISSIONS

XXXXX

The Committee noted XXXXX.

The Committee noted the Micromedex Drugdex evaluation on gemtuzumab ozogamicin, in particular the following black box warning that it is to be administered intravenously only by or under the immediate supervision of a physician knowledgeable in treating patients with acute leukemia and only in facilities equipped to monitor and support such patients:

- Black Box WARNING
  - Gemtuzumab ozogamicin should be administered under the supervision of physicians experienced in the treatment of acute leukemia and in facilities equipped to monitor and treat leukemia patients.
  - There are no controlled trials demonstrating efficacy and safety using gemtuzumab ozogamicin in combination with other chemotherapeutic agents. Therefore, gemtuzumab ozogamicin should only be used as single agent chemotherapy and not in combination chemotherapy regimens outside clinical trials.

- Severe myelosuppression occurs when gemtuzumab ozogamicin is used at recommended doses.
- Gemtuzumab ozogamicin administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events …
- Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of gemtuzumab ozogamicin as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem-cell transplant (HSCT).

The Committee also noted the international status of gemtuzumab ozogamicin:

- approved in the USA in May 2000 for the indication for the treatment of patients with CD33 positive acute myeloid leukemia in first relapse who are 60 years of age or older and who are not considered candidates for cytotoxic chemotherapy;
- approved in Argentina, Brazil, Chile, Colombia, Cyprus, India, Israel, Japan, Korea, Mexico, Singapore, South Africa, Thailand and Venezuela;
- the EU recommended refusal in September 2007 *for the treatment of acute myeloid leukaemia* due to its poor risk-benefit profile, with refusal confirmed in January 2008 on re-examination of the opinion;
- not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (d) extent and patterns of use, (e) dosage and formulation, (f) need for access and (h) purpose for which a substance is to be used.

The Committee considered the pharmacological action of gemtuzumab ozogamicin which consists of calicheamicin conjugated with humanised CD33 antibody. Given that both moieties have a pharmacological action (the antibody delivering the cytotoxic to the site of action), the Committee took the pragmatic approach of scheduling the molecule as a whole, rather than scheduling each moiety separately.

RESOLUTION 2009/55 - 30

The Committee decided to include the new chemical entity gemtuzumab ozogamicin in Schedule 4.

Schedule 4 - New entry

GEMTUZUMAB OZOGAMICIN.

13.1.2 CILOSTAZOL

PURPOSE

The Committee considered the scheduling of the new medicine cilostazol.

BACKGROUND

Cilostazol is a quinolone derivative which inhibits cellular phosphodiesterase (more specifically for phosphodiesterase III). It is used in the management of peripheral vascular disease.

XXXXX:

DISCUSSION-SUBMISSIONS

The Committee noted XXXXX:

- XXXXX

The Committee also noted the Micromedex Drugdex extract on cilostazol, the US approved product information and the following conclusion from the USFDA's approval notice:

> "Consideration of cilostazol raised complex benefit/risk considerations. Clearly effective for a debilitating condition whose current treatment is often inadequate, cilostazol is a member of a pharmacologic class that is dangerous to people with severe heart failure and unstudied in other people. Cilostazol has been studied in people without heart failure, without evidence of harm, but much more data would be needed to determine that there is no risk at all. Although cilostazol would not be approvable for a trivial condition, the Cardio-Renal Advisory Committee and FDA concluded that fully informed patients and physicians should be able to choose to use it to treat intermittent claudication. Patients and physician labelling will describe the basis for concern and the incomplete information available."

The Committee further noted that cilostazol was not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

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

RESOLUTION 2009/55 – 31

The Committee decided to include the new chemical entity cilostazol in Schedule 4.

Schedule 4 - New entry

CILOSTAZOL.

13.1.3 BAZEDOXIFENE

PURPOSE

The Committee considered the scheduling of the new medicine bazedoxifene.

BACKGROUND

Bazedoxifene is a selective oestrogen receptor modulator (SORM) developed for the prevention and treatment of postmenopausal osteoporosis.

XXXXX.

DISCUSSION-SUBMISSIONS

XXXXX.

The Committee noted XXXXX.

The Committee noted the Micromedex Drugdex evaluation on bazedoxifene, in particular that there was no record of teratogenicity or a pregnancy category although another selective oestrogen receptor modulator, raloxifene, was a pregnancy category X medicine. The Committee further noted that raloxifene was considered during a review of Appendix D/Category X medicines in October 2007, but that it did not warrant inclusion in Appendix D due to its specialist indication for postmenopausal osteoporosis.

The Committee noted that bazedoxifene was not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (d) extent and patterns of use, (e) dosage and formualtion and (h) purpose for which a substance is to be used.

As bazedoxifene and raloxifene are both selective oestrogen receptor modulators with the same indication, it was agreed that an Appendix D listing for bazedoxifene was not warranted either.

RESOLUTION 2009/55 - 32

The Committee decided to include the new chemical entity bazedoxifene in Schedule 4.

Schedule 4 - New entry

BAZEDOXIFENE.

13.1.4 AMBRISENTAN

PURPOSE

The Committee considered the scheduling of the new medicine 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 the right atrial pressure in patients with pulmonary arterial hypertension.

The October 2008 ADEC Meeting recommended approval of a submission from GlaxoSmithKline Australia Pty Ltd to register Volibris film-coated tablet containing the new chemical entity ambrisentan 5 and 10 mg for the indication:

> *The treatment of*
> - *idiopathic pulmonary arterial hypertension*
> - *pulmonary arterial hypertension associated with connective tissue disease in patients with WHO functional class II, III or IV symptoms*

XXXXX.

DISCUSSION-SUBMISSIONS

The Committee noted the minutes of the October 2008 ADEC Meeting, XXXXX.

The Committee noted that the approved product information for Volibris records that teratogenicity is a class effect of endothelin receptor antagonists and, as such, is contraindicated in women who are or could become pregnant and women of child-bearing potential who are not using reliable contraception. Women must not become pregnant for at least 3 months after stopping treatment with ambrisentan. The product information also included the boxed warning "TERATOGENICITY Volibris may cause birth defects and is contraindicated in pregnancy".

The Committee noted that other endothelin antagonists, bosentan and sitaxentan, are included in Appendix D, sub-paragraph 6. Given the class effect of endothelin receptor antagonists as teratogens, the Committee agreed that an Appendix D listing for ambrisentan was also appropriate.

The Committee noted the international status of ambrisentan:

- EU marketing authorisation was granted in April 2008 (Volibris) *for the treatment of patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity*
- USA approval granted in June 2007 (Letairis) *for the treatment of pulmonary arterial hypertension (WHO Group 1) in patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening*.
- not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (d) extent and patterns of use, (e) dosage and formulation, (f) need for access and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 33

The Committee decided to include the new chemical entity ambrisentan in Schedule 4. The Committee also decided to include ambrisentan in Appendix D, sub-paragraph 6.

Schedule 4 - New entry

AMBRISENTAN.

Appendix D, sub-paragraph 6 – New entry

AMBRISENTAN for human use.

13.1.5 METHYLNALTREXONE

PURPOSE

The Committee considered the scheduling of the new medicine methylnaltrexone.

BACKGROUND

Methylnaltrexone bromide is a peripherally-acting antagonist of the mu-opioid receptor which targets binding sites in tissues, such as the gastrointestinal tract, decreasing opioid-associated constipation without compromising the analgesic effects in the central nervous system.

The October 2008 ADEC Meeting recommended approval of a submission from Wyeth Australia Pty Limited to register Relistor solution for injection containing the new chemical entity methylnaltrexone bromide 12 mg/0.6mL for the indication:

The treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient.

XXXXX.

DISCUSSION - SUBMISSIONS

XXXXX

The Committee noted the minutes of the October 2008 ADEC Meeting, XXXXX.

The Committee noted the international status of methylnaltrexone:

- approved in the USA in April 2008 for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient;
- EU marketing authorisation granted July 2008 for the treatment of opioid-induced constipation in advanced illness patients who are receiving palliative care when response to usual laxative therapy has not been sufficient;
- notice of compliance issued in Canada in March 2008 for the treatment of opioid-induced constipation in patients with advanced illness, receiving palliative care. When response to laxatives has been insufficient, Relistor should be used as an adjunct therapy to induce a prompt bowel movement. Relistor is not indicated for use in children and adolescents;
- not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (d) potential hazards, (e) extent and patterns of use, (f) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 34

The Committee decided to include the new chemical entity methylnaltrexone in Schedule 4.

Schedule 4 - New entry

METHYLNALTREXONE.

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13.1.6 ETRAVIRINE

PURPOSE

The Committee considered the scheduling of the new medicine etravirine.

BACKGROUND

Etravirine is a non-nucleoside reverse transcriptase inhibitor with activity against HIV-1. It is given with other antiretrovirals for the treatment of HIV infection in treatment-experienced patients, who have evidence of viral replication and HIV-1 strains resistant to a NNRTI and other antiretrovirals.

The October 2008 ADEC Meeting recommended approval of a submission from Janssen-Cilag Pty Ltd to register Intelence tablet containing the new chemical entity etravirine 100 mg for the indication:

> *Treatment of HIV-1 infection, in combination with other antiretroviral agents, in antiretroviral treatment-experienced adults who have evidence of viral replication and resistance to Non-nucleoside Reverse Transcriptse Inhibitors and other antiretroviral agents.*
>
> *This indication is based on 24 week analyses from 2 randomised, double-blind, placebo controlled trials of etravirine. Both studies were conducted in clinically advanced, 3-class antiretroviral (NNRTI, N[T]RTI, PI) treatment-experienced adults (see Clinical Trials Section).*
>
> *Treatment history of patients and genotypic testing should be performed to guide the use of etravirine.*

XXXXX.

DISCUSSION-SUBMISSIONS

The Committee noted:

- the relevant extract of the minutes of the October 2008 ADEC Meeting;
- the Micromedex Drugdex evaluation on etravirine;
- the international status of etravirine: approved in 2008 in New Zealand, the USA, Europe and Canada for use in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus type 1 infection in antiretroviral treatment-experienced adult patients.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used

RESOLUTION 2009/55 - 35

The Committee decided to include the new chemical entity etravirine in Schedule 4.

Schedule 4 - New entry

ETRAVIRINE.

13.1.7 RIVAROXABAN

PURPOSE

The Committee considered the scheduling of the new medicine rivaroxaban.

BACKGROUND

Rivaroxaban is an oral direct inhibitor of activated factor Xa that is under investigation in thromboembolic disorders.

The October 2008 ADEC Meeting recommended approval of a submission from Bayer Australia Limited to register Xarelto film-coated tablet containing the new chemical entity rivaroxaban 10 mg for the indication:

> *Short term prevention of venous thrombosis in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement)*

XXXXX.

DISCUSSION – SUBMISSIONS

The Committee noted the relevant extract of the minutes of the October 2008 ADEC Meeting, XXXXX. The Committee further noted the approved PI for Xarelto.

The Committee noted that there was no evaluation for rivaroxaban on Micromedex Drugdex and only limited details on Martindale.

The Committee also noted the international status of rivaroxaban:

- Micromedex Drugdex 'investigational drugs' records that a new drug application for prevention of DVT/PE in patients undergoing hip or knee replacement surgery was lodged with the USFDA in July 2008;
- marketing authorisation was granted in the EU in September 2008 for the indication 'Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery';
- notice of compliance issued in Canada in September 2008 for the indication 'for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery';
- not yet classified in New Zealand.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 36

The Committee decided to include the new chemical entity rivaroxaban in Schedule 4.

Schedule 4 - New entry

RIVAROXABAN.

13.1.8 SUGAMADDEX

PURPOSE

The Committee considered the scheduling of the new medicine sugamaddex.

BACKGROUND

Sugammadex is a novel agent for reversal of neuromuscular blockade by recuronium in general anaesthesia. It is the first selective relaxant binding agent.

The October 2008 ADEC Meeting recommended approval of a submission from Organon (Australia) Pty Ltd to register Bridion injection solution containing the new chemical entity sugammadex 100 mg/mL for the indication:

> *Reversal of neuromuscular blockade induced by rocuronium or vecuronium.*

XXXXX.

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the October 2008 ADEC Meeting, XXXXX.

The Committee noted the Micromedex Drugdex evaluation on sugamaddex and also noted the following international status:

- USFDA website includes notice of consideration and minutes of the March 2008 Anesthetic and Life Support Drugs Advisory Committee Meeting concerning a new drug application for Bridion (sugammadex). No other information on the USFDA website as to its current status. Wikipedia records non-approval in August 2008;
- marketing authorisation granted in the EU in July 2008 for the indication *reversal of neuromuscular blockade induced by rocuronium or vecuronium* to be administered by or under the supervision of an anaesthetist. On the basis of quality, safety and efficacy data submitted, it was considered there was favourable benefit to risk balance;
- Classified as a prescription medicine in New Zealand in June 2008.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 37

The Committee decided to include the new chemical entity sugamaddex in Schedule 4.

Schedule 4 - New entry

SUGAMADDEX.

13.2 FOR INFORMATION(SUBSTANCES ALREADY SCHEDULED)

13.2.1 DABIGATRAN

PURPOSE

The Committee noted ADEC's consideration of the new chemical entity dabigatran.

BACKGROUND

Dabigatran etexilate is a low-molecular-weight direct thrombin inhibitor delivered by the oral route. Following oral administration, dabigatran etexilate is rapidly converted to its active form, dabigatran.

The October 2007 NDPSC Meeting included dabigatran in Schedule 4 to harmonise with New Zealand.

XXXXX.

The October 2008 ADEC Meeting XXXXX recommended approval of the submission from Boehringer Ingelheim Pty Ltd to register Pradaxa capsule containing the new chemical entity dabigatran etexilate 75 mg and 110 mg for the indication s*hort term prevention of venous thrombosis in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement).*

XXXXX.

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of XXXXX the October 2008 ADEC Meeting and further noted the approved PI for Pradaxa.

RESOLUTION 2009/55 - 38

The Committee noted ADEC's consideration of the new chemical entity dabigatran, which was scheduled through the harmonisation process at the October 2007 NDPSC Meeting.

13.2.2 DAPTOMYCIN

PURPOSE

The Committee noted ADEC's consideration of the new chemical entity daptomycin.

BACKGROUND

Daptomycin is an antibacterial agent of a new class of antibiotics, the cyclic lipopeptides. It is a natural substance that has clinical utility in the treatment of infections caused by Gram-positive bacteria; it retains potency against antibiotic-resistant Gram-positive bacteria, including isolates resistant to methicillin, vancomycin and linezolid; it binds to bacterial membranes and causes a rapid depolarization of membrane potential in both growing and stationary phase cells, where the loss of membrane potential causes inhibition of protein, DNA and RNA synthesis resulting in cell death with negligible cell lysis.

The June 2008 NDPSC Meeting included daptomycin in Schedule 4 to harmonise with New Zealand.

The October 2008 ADEC Meeting recommended approval of a submission from Novartis Pharmaceuticals Pty Ltd to register Cubicin powder for injection containing the new biological entity daptomycin 350 mg and 500 mg for the indication:

> *Treatment of adults with complicated skin and skin structure infections, who require initial parenteral therapy, and who have intolerance to alternative agents (especially penicillin allergy), and when caused by organisms known to be susceptible to daptomycin.*
>
> *Daptomycin is also indicated in adults for Staphylococcus aureus bloodstream infections (bacteremia), including right-sided native valve infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. The efficacy of daptomycin in patients with prosthetic heart valves or in left-sided endocarditis due to Staphylococcus aureus has not been demonstrated. In the setting of Staphylococcus aureus bacteraemia, left-sided endocarditis should be excluded before using daptomycin.*
>
> *Daptomycin is active against Gram positive bacteria only. In mixed infections where Gram negative and/or certain types of anaerobic bacteria are suspected, daptomycin should be co-administered with appropriate antibacterial agent(s).*
>
> *Consideration should be given to official guidance on the appropriate use of antibacterial agents.*
>
> *Daptomycin is not indicated for the treatment of pneumonia.*

XXXXX.

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the October 2008 ADEC Meeting.

RESOLUTION 2009/55 – 39

The Committee noted ADEC's consideration of the new chemical entity daptomycin, which was scheduled through the harmonisation process at the June 2008 NDPSC Meeting.

14. OTHER MATTERS FOR CONSIDERATION

Nil.

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

Nil.

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 MATTERS REFERRED BY THE MCC

16.1.1 ETRAVIRINE

Considered at Agenda Item No.13.1.6

16.1.2 ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN)

PURPOSE

The Committee considered the scheduling of the new medicine alpha$_1$-proteinase inhibitor (human).

BACKGROUND

Alpha$_1$-proteinase inhibitor (A1-PI) is a blood modifier agent prepared from pooled human plasma used as replacement therapy in patients with emphysema who have congenital alpha1-antitrypsin deficiency. Administration is by intravenous infusion or injection.

- Alpha$_1$-antitrypsin deficiency is a chronic, hereditary disorder that can cause severe tissue damage death and is characterised by chronic obstructive pulmonary disease and chronic liver disease associated with a lack of A1-PI.
- A1-PI is the primary antiproteinase in the lower respiratory tract where it inhibits neutrophil elastase, an enzyme that destroys pulmonary tissue.
- A1-PI is produced in the liver but exerts its main effects in the lungs as an inhibitor of neutrophil elastase, an enzyme released in response to inflammation. Congenital deficiency of the inhibitor leaves the lungs vulnerable to destruction by elastase, leading to the development of emphysema usually in the third or fourth decade of life.
- Hepatic manifestations of deficiency include hepatitis, cirrhosis and hepatoma. Panniculitis and vasculitis may also occur less frequently in some phenotypes.

A recombinant form of A1-PI is under investigation for nebulised delivery in congenital alpha1 antitrypsin deficiency and cystic fibrosis. A1-PI is also under investigation for the prevention of bronchopulmonary dysplasia in preterm neonates.

The June 2008 New Zealand Medicines Classification Committee (MCC) Meeting classified the new chemical entity alpha$_1$-proteinase inhibitor (human) (Zemaira) for chronic augmentation and maintenance therapy in individuals with alpha$_1$-proteinase inhibitor deficiency and clinical evidence of emphysema, as a prescription medicine.

DISCUSSION - SUBMISSIONS

The Committee noted the following:

- the relevant extract of the minutes of the June 2008 MCC Meeting;
- the Micromedex Drugdex evalution on A1-PI;
- the USFDA approval summary and PI for Aralastat (approved December 2002) and Zemaira (approved July 2003);
- EU Commission granted A1-PI orphan designation in June 2008.

The Committee noted that A1-PI did not fit the criteria for exemption under the Appendix A entry for human blood products and that it required a separate entry under Schedule 4.

On this point, the Committee noted that while this substance was obtained from blood, it was an enzyme inhibitor rather than a blood product per se. Further, given its indication, it would be used by respiratory physicians not haematologists.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 40

The Committee decided to include the new chemical entity alpha$_1$-proteinase inhibitor (human) in Schedule 4.

Schedule 4 - New entry

ALPHA$_1$-PROTEINASE INHIBITOR (HUMAN).

16.1.3 TOCILIZUMAB

PURPOSE

The Committee considered the scheduling of the new medicine tocilizumab.

BACKGROUND

Tocilizumab is a recombinant monoclonal antibody that targets the interleukin-6 receptor and is used for the treatment of Castleman's disease, a rare lymphoproliferative disorder. It is also under investigation for the treatment of rheumatoid arthritis and systemic-onset juvenile idiopathic arthritis.

The June 2008 New Zealand Medicines Classification Committee (MCC) Meeting classified the new chemical entity tocilizumab as a prescription medicine for the indication *for the treatment of moderate to severe active rheumatoid arthritis in adult patients* to be used alone or in combination with methotrexate and/or other disease-modifying anti-rheumatic drugs.

DISCUSSION - SUBMISSIONS

The Committee noted the following:

- the relevant extract of the minutes of the June 2008 MCC Meeting;
- in November 2008, the EU's EMEA Committee adopted a positive opinion recommending the granting of a marketing authorisation for the medical products RoActerma (tocilizumab), 20 mg/ml concentrate for solution for infusion for treatment of moderate to severe active rheumatoid arthritis in adult patients;
- in July 2008, the USFDA Arthritis Advisory Committee (AAC) recommended approval of the biologics license application for Acterma (tocilizumab) for the proposed treatment of adult patients with moderately to severely active rheumatoid arthritis. The AAC raised issues including lack of data in patients over 75 years of age and patients with chronic obstructive pulmonary disease; that regular monitoring of liver enzymes was necessary; and concern with the combination of tocilizumab and NSAIDs or corticosteroids.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 41

The Committee decided to include the new chemical entity tocilizumab in Schedule 4.

Schedule 4 - New entry

TOCILIZUMAB.

16.1.4 DAPOXETINE

PURPOSE

The Committee considered the scheduling of the new medicine dapoxetine.

BACKGROUND

Dapoxetine is a rapidly absorbed, short-acting SSRI (selective serotonin reuptake inhibitor).

The June 2008 New Zealand Medicines Classification Committee (MCC) Meeting classified the new chemical entity dapoxetine hydrochloride as a prescription medicine for the proposed indication *for the treatment of premature ejaculation in men 18 to 64 years of age who have all of the following:*

- *persistent or recurrent ejaculation with minimal sexual stimulation before, on or shortly after penetration and before the patient wishes; and*
- *marked personal distress or interpersonal difficulty as a consequence of PE; and*
- *poor control over ejaculation.*

DISCUSSION - SUBMISSIONS

The Committee noted the relevant extract of the minutes of the June 2008 ADEC Meeting. The Committee also noted advice from XXXXX.

The Committee also noted the following:

- limited information on Martindale and Micromedex:
  - dapoxetine hcl was being investigated specifically for on-demand treatment of premature ejaculation;
  - USFDA issued a 'Not Approvable" letter in October 2005, with a new drug application resubmitted in 2007;
- USFDA only records date of initial new drug application;
- no results from EMEA or Health Canada online search;
- abstract and review summaries obtained from the US National Library of Medicine NCBI PubMed website, which either concluded that dapoxetine was an effective and generally well tolerated treatment for men with moderate to severe PE or concluded that further studies were required to determine efficacy in PE;
- March 2008 Presseportal media article reporting that a marketing authorisation application for dapoxetine indicated for premature ejaculation was submitted to the EU in December 2007, that a file was also submitted in Australia and New Zealand and regulatory submissions in other regions of the world were expected to follow.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that the relevant matters under section 52E(1) included (a) toxicity and safety, (b) the risks and benefits, (c) potential hazards, (d) extent and patterns of use, (e) dosage and formulation and (h) purpose for which a substance is to be used.

RESOLUTION 2009/55 - 42

The Committee decided to include the new chemical entity dapoxetine in Schedule 4.

Schedule 4 - New entry

DAPOXETINE.

16.2 MEDICINES HARMONISED

16.2.1 MARAVIROC

BACKGROUND

The June 2008 NDPSDC Meeting included maraviroc in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified maraviroc as a prescription medicine through the New Zealand new medicines classification process.

RESOLUTION 2009/55 - 43

The Committee noted the harmonisation of maraviroc.

16.2.2 LENALIDOMIDE

BACKGROUND

The June 2008 NDPSDC Meeting included lenalidomide in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified lenalidomide as a prescription medicine through the New Zealand new medicines classification process.

RESOLUTION 2009/55 - 44

The Committee noted the harmonisation of lenalidomide.

16.2.3 SUGAMMADEX

BACKGROUND

The June 2008 MCC Meeting classified sugammadex as a prescription medicine through the New Zealand new medicines classification process.

DISCUSSION - SUBMISSIONS

The Committee noted that at Agenda Item 13.1.8, the NDPSC included sugammadex in Schedule 4 through the TGA prescription medicine registration process.

RESOLUTION 2009/55 - 45

The Committee noted the harmonisation of sugammadex.

16.2.4 IDURSULFASE

BACKGROUND

The June 2008 NDPSDC Meeting included idursulfase in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified idursulfase as a prescription medicine through the New Zealand new medicines classification process.

RESOLUTION 2009/55 - 46

The Committee noted the harmonisation of idursulfase.

16.2.5 CADMIUM COMPOUNDS AND CADMIUM SULPHIDE

BACKGROUND

The October 2007 and February 2008 NDPSDC Meetings included cadmium compounds in Schedule 4 to prevent human therapeutic use of these substances.

The June 2008 MCC Meeting classified cadmium as a prescription medicine to harmonise with Australia.

RESOLUTION 2009/55 - 47

The Committee noted the harmonisation of cadmium.

16.2.6 FRACTIONATED AND RECOMBINANT BLOOD PRODUCTS

BACKGROUND

The October 2007 NDPSDC Meeting included fractionated blood products and equivalent recombinant products in Appendix A to allow the exemption of such products from the requirements of scheduling.

The June 2008 MCC Meeting reclassified fractionated and recombinant blood products from prescription medicines to general sale medicines to harmonise with Australia.

RESOLUTION 2009/55 - 48

The Committee noted the harmonisation of fractionated and recombinant blood products.

16.2.7 PANITUMUMAB

BACKGROUND

The February 2008 NDPSDC Meeting included panitumumab in Schedule 4 through the TGA prescription medicine registration process.

Panitumumab was classified as a prescription medicine in New Zealand under the generic entry for monoclonal antibodies. However, the June 2008 MCC Meeting included panitumumab in a separate prescription medicine entry to harmonise with Australia.

RESOLUTION 2009/55 - 49

The Committee noted the harmonisation of panitumumab.

16.2.8 MIGLUSTAT

BACKGROUND

The October 2007 NDPSDC Meeting included miglustat in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified miglustat as a prescription medicine to harmonise with Australia.

RESOLUTION 2009/55 - 50

The Committee noted the harmonisation of miglustat.

16.2.9 AGOMELATINE

BACKGROUND

The October 2007 NDPSDC Meeting included agomelatine in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified agomelatine as a prescription medicine to harmonise with Australia.

RESOLUTION 2009/55 - 51

The Committee noted the harmonisation of agomelatine.

16.2.10 ZONISAMIDE

BACKGROUND

The October 2007 NDPSC Meeting included zonisamide in Schedule 4 through the TGA prescription medicine registration process.

The June 2008 MCC Meeting classified zonisamide as a prescription medicine to harmonise with Australia.

RESOLUTION 2009/55 – 52

The Committee noted the harmonisation of zonisamide.

16.3 MEDICINES UNHARMONISED

16.3.1 POTASSIUM CHLORIDE

PURPOSE

The Committee noted New Zealand's consideration of potassium chloride.

BACKGROUND

The May 2007 New Zealand Medicines Classification Committee (MCC) Meeting:

- considered NDPSC's recommendation to harmonise potassium chloride for internal use, except when in products containing less than 600 mg per dose unit, for oral rehydration, for oral bowel cleansing prior to diagnostic, medical and surgical procedures, for enteral feeding. These exemptions would be general sale or unscheduled medicines;

- decided not to harmonise with Australia, recommending that there should be no change to the current scheduling of potassium, basing its decision on the grounds that there was no public safety reason to move to a more restricted level of access;

- agreed that the quantity of elemental potassium present in glucosamine sulfate complexed products be investigated.

The December 2007 MCC Meeting, after considering the issue of potassium in glucosamine sulfate complexed products:

- recommended that potassium be classified as a pharmacy-only medicine when for internal use in slow release or enteric coated forms, in medicines containing more than 100 mg per recommended dose, in glucocasmine sulfate complexed products containing more than 100 mg of elemental potassium per recommended dose except when carrying a label warning against use with kidney problems and a statement of the potassium content per dose, except in medicines for oral rehydration therapy, parenteral nutrition replacement or dialysis;

- recommended that potassium should be a general sale medicine when for external use, for internal use in medicines containing 100 mg or less per recommended dose, in glucosamine sulfate complexed products containing more than 100 mg of elemental potassium per recommended dose when carrying a label warning against use with kidney problems and a statement of the potassium content per dose, in medicines for oral rhydration therapy, parenteral nutrition replacement or dialysis.

Medsafe agreed in principle with the recommendation to require specific labelling statements on glucosamine sulfate complexed products. However, there was no mechanism under the Dietary Supplement Regulations to require warning statements on dietary supplements and recommended that a decision be postponed until the next MCC meeting.

DISCUSSION - SUBMISSIONS

The February 2009 NDPSC Meeting noted the relevant extract of the minutes of the June 2008 MCC Meeting where the classification of potassium chloride was further considered. In particular, it was noted that:

- glucosamine products were not currently regulated as medicines in New Zeland;
- Medsafe had no means of identifying glucosamine sulfate complexed products, establishing their potassium content or enforcing label warnings;
- implementation of this recommendation could cause some complementary products to become scheduled medicines;
- no previous evidence of harm caused by their potassium content;

- Medsafe's suggested alternative level of classification to harmonise with the Australian cut-off point between pharmacy-only and general sale medicine of 600 mg of potassium chloride per recommended dose;
- the intention of Medsafe to preserve the current status of glucosamine sulfate complexed products;
- as there did not appear to be any problems in either Australia or New Zealand relating to the potassium content in glucosamine sulfate complexed products, the MCC agreed that Medsafe's advice should apply and that the proposed schedule entries for potassium be modified slightly to maintain the current classification of potassium while ensuring that glucosamine complexed products containing 600 mg or less of potassium chloride were not inadvertently captured as pharmacy-only medicines;
- the MCC recommended that:
  - potassium should be classified as a pharmacy-only medicine when for internal use:
    - in slow release or enteric coated forms
    - in medicines containing more than 100 mg per recommended dose
    - except in medicines for oral rehydration therapy, parenteral nutrition replacement, dialysis or in glucosamine sulfate complexed products containing 600 mg or less of potassium chloride per recommended dose.
  - potassium should be a general sale medicine when:
    - for external use
    - for internal use in medicines containing 100 mg or less per recommended dose except in glucosamine sulfate complexed products containing 600 mg or less of potassium chloride per recommended dose
    - in medicines for oral rehydration therapy, parenteral nutrition replacement, dialysis.

RESOLUTION 2009/55 - 53

The Committee noted New Zealand's consideration of potassium chloride and that Australia and New Zealand remain unharmonised.

16.4 OTHER MATTERS

16.4.1 COUGH AND COLD MEDICINES

DISCUSSION - SUBMISSIONS

The Committee noted the following from the relevant extract of the minutes of the June 2008 New Zealand Medicines Classification Committee (MCC) Meeting in which consideration was given to whether or not all cough and cold preparations should be contraindicated for use in children under 2 years of age, and which followed the recommendation to reclassify sedating antihistamines to prescription medicines when for children under 2 years of age and recent moves in the United States of America (USA).

- Two USFDA expert committees (the Non-Prescription Drugs Advisory Committee and the Pediatric Advisory Committee) had jointly considered a petition to the USFDA to contra-indicate cough and cold medicines, including sedating antihistamines, for use in children under 6 years of age, recommending that cough and cold medicines should not be used in children under 2 years of age. Further investigation was to be undertaken with regard to use of these medicines in children from 2 to 6 years of age.

- The New Zealand Medicines Adverse Reactions Committee (MARC) had already moved to contraindicate all cough and cold medicines in children under 2 years of age, including nasal drops, but excluding saline drops and vapour rubs which could still be used in infants under 2 years of age. MARC's recommendation was based on the very limited evidence of efficacy in this age group, an absence of evidence-based dosage advice and evidence of significant toxicity in overdose. Medsafe had already commenced the process of phasing-in changes to dose instructions on product labels.

- MCC agreed that:
  - in view of action already taken as a result of the MARC recommendation, there was no need for reclassification of these medicines, but suggested that an article be published in *Prescriber Update* to inform doctors about use of cough and cold medicines in children under 2 years of age
    [Prescriber Update Vol. 29 No.1 of June 2008
    http://www.medsafe.govt.nz/profs/PUArticles/PDF/PrescriberUpdate_Jun08.pdf];

  – no further recommendation was required.

The Meeting was informed that New Zealand was keeping a watching brief on moves in the USA and in Canada.

RESOLUTION 2009/55 - 54

The Committee noted the MCC's consideration of cough and cold medicines in children under 2 years of age.

16.4.2 CHLORAMPHENICOL

DISCUSSION - SUBMISSIONS

The Committee noted that chloramphenicol is a prescription medicine in Australia and New Zealand and currently harmonised.

The Committee noted that the June 2008 MCC Meeting continued its consideration of chloramphenicol, in particular whether chloramphenicol eye preparations should be reclassified from prescription medicines to restricted medicines with particular interest in matters relating to the possible development of antibiotic resistance and to proposals for pharmacist training in the sale of such products.

The Committee noted the minutes of the June 2008 MCC Meeting, including the following.

- With regard to resistance, there had been no response from the Institute of Environment and Research (ESR) to a query about resistance figures for chloramphenicol.

- Consultation documents relating to the reclassification of chloramphenicol eye ointment from the Medicines and Healthcare Products Regulatory Authority (MHRA) in the United Kingdom had stated that there were no resistance issues to prevent reclassification to an OTC status. However, there had been no supportive data in the consultation material. The Committee agreed that more information should be sought from the MHRA on resistance data to support the reclassification of chloramphenicol.

- The effects of chloramphenicol have been debated and a Cochrane review in 2006 noted that bacterial conjunctivitis is frequently self-limiting but that the use of antibiotics can speed recovery. Any advantages from reclassification would be small rather than outstanding.

- A major advantage of OTC sale would be the avoidance of a delay in treatment which would be likely to occur through the need to consult with a doctor. However, some 65 per cent of red-eye conditions were viral and differentiation between viral and bacterial infections was difficult with doctors recognising this and moving away from use of chloramphenicol for all eye infections.

- There appeared to be little evidence of resistance at this point. However, wider use could lead to the development of resistance and that increased use from OTC sale was undesirable.

- Pharmacist training would be important if chloramphenicol were to be reclassified. As there had been no response from a sponsor company there had been no proposal for pharmacist training in diagnosis and appropriate use of the medicine. The Pharmaceutical Society of New Zealand had suggested possibilities for educational material that might eventuate should this medicine be reclassified. It was reported that pharmacist training in use of the medicine was good in Great Britain and it was suggested that one or more of the New Zealand pharmacy professional bodies might provide guidance on the sale of these eye products. Standardisation of product doses and course instructions and of required warning statements would be necessary. It was noted that pharmacists were interested in treating eye conditions but that more training was necessary particularly in relation to the need for medical referral of contact lens wearers with eye problems.

- The MCC concluded that they did not yet have sufficient information available to make a recommendation and agreed upon the following actions.

- The MHRA should be approached with a request for data on safety issues, including resistance issues, which led to the reclassification of chloramphenicol.
- ESR should be approached for data about resistance to chloramphenicol.
- Views should be sought from ophthalmologists and optometrists.
- Sponsor companies should be invited to make submissions for reclassification including proposals for training pharmacists in diagnosis of eye conditions and appropriate sale of chloramphenicol.
- Input should be sought from the Pharmacy Council and the Pharmaceutical Society particularly with regard to pharmacist training.

- The MCC agreed that when sufficient information from the above sources had been collected, the matter should be returned to the Committee for further consideration.

The Meeting was informed that the matter was discussed further at the November 2008 MCC Meeting. Although no specific safety issues were identified with regard to the administration of chloramphenicol to the eye, feedback from professional bodies was that they were opposed to down-scheduling based on concerns over the diagnosis of the cause of an acute red eye in the pharmacy setting where equipment was lacking. It was also felt that more training provisions were necessary and MCC would continue consideration.

RESOLUTION 2009/55 - 55

The Committee noted MCC's consideration of the reclassification of chloramphenicol eye preparations.

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

Nil.

19. INFORMATION ITEMS (PHARMACEUTICALS)

19.1 XXXXX

19.2 PAYING FOR SELF-MEDICATION

The Committee noted the article *Paying for self medication in Australia*, published by the Centre for Independent Studies in the Summer 2008-09 issue of 'Policy'.

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES AND ERRATA

21.1.1 NICABAZIN/NICARBAZIN

PURPOSE

The Committee considered the spelling of the Appendix B entry for 'nicabazin'.

BACKGROUND

Nicarbazin is a feed additive used in broiler chicken feeds for the prevention of coccidiosis, one of the more common and costly diseases in poultry. Coccidiosis is caused by seven different species of coccidia (genus *Eimeria*) which are single celled parasites that live in the gut wall of their host.

The August 1995 NDPSC Meeting deleted Appendix B from the SUSDP, which included 'nicarbazine' at that time.

At the November 2001 and February 2002 NDPSC Meetings, 'nicabarzin' was listed for inclusion/exclusion during consideration of the reinstatement of Appendix B.

At the October 2002 and February 2003 NDPSC Meetings, 'nicabazin' was listed for inclusion/exclusion during consideration of the reinstatement of Appendix B.

DISCUSSION - SUBMISSIONS

The Committee noted that the changes in spelling during consideration of the Appendix B reinstatement appear to have been typographical errors. Results from online searches as follows:

Website searched	Search results for 'Nicabazin'	Search results for Nicarbazine	Search results for 'Nicarbazin'
APVMA Pubcris	Nil	Nil	Yes
PubChem	Nil	Yes (same compound ID and IUPAC as 'nicarbazin'	Yes
WHO	Nil	Nil	Yes
USFDA	Nil	US Federal Register Vol.66 No.95 May 2001 - 'nicarbazine' was replaced by 'nicarbazin' as a new animal drug for use in animal	Yes

		feeds (21 CFR Part 558)	
European Food Safety Authority	Nil	Nil in English Yes in French	Yes
INCHEM	Nil	Nil	Yes

The Committee agreed that 'nicarbazin' was the correct spelling.

RESOLUTION 2009/55 - 58

The Committee decided to amend the spelling of 'nicabazin' in Appendix B to read 'nicarbazin'.

Appendix B, Part 3 – Amendment

NICABAZIN - Amend entry to read:

SUBSTANCE	DATE OF ENTRY	REASON FOR LISTING	AREA OF USE
NICARBAZIN	Jun 1969	d	2.3

21.1.2 SOMATOTROPIN, EQUINE

PURPOSE

The Committee considered the anomaly of the inclusion of equine somatotropin in both Schedule 4 and Appendix B of the SUSDP

BACKGROUND

The February 1997 NDPSC Meeting did not consider that a schedule classification for equine somatotropin was justified on the basis of toxicity, consistency with other animal somatotropin and perceived lack of a public health problem.

The February 1998 NDPSC Meeting included equine somatotropin in Schedule 4 as it considered that if the administration of a product to an animal requires professional supervision and advice in order for proper management of the animal's condition, a Schedule 4 classification was appropriate as this would ensure veterinary intervention before administration.

The February 2002 NDPSC Meeting considered the reinstatement of Appendix B, originally deleted from the SUSDP in August 1995, which included an entry for equine somatotropin. The February 2002 NDPSC Meeting requested that the Secretariat check to see if the entries for porcine somatotrophin and equine somatotropin were appropriate. However, there is no indication in the Secretariat records that this issue was discussed any further. equine somatotropin continued to be included for Appendix B reinstatement

consideration at the subsequent June and October 2002 and February 2003 NDPSC Meetings.

The February 2003 NDPSC Meeting reinstated Appendix B, including the entry for equine somatotropin.

DISCUSSION - SUBMISSIONS

The Committee noted that the inclusion of equine somatotropin during reinstatement of Appendix B was an oversight and agreed that it should be deleted.

The Committee also noted the inclusion of bovine somatotrophin and porcine somatotrophin in Appendix B. The Committee requested that these entries, and somatotropins/somatrophins entries in Appendix B in general, be investigated for consideration at the June 2009 NDPSC Meeting. The Committee also requested that the spelling and formatting of the bovine, porcine and equine entries be investigated with regard to the consistency throughout these entries.

RESOLUTION 2009/55 - 59

The Committee decided to delete equine somatotropin from Appendix B.

Appendix B - Amendment

SOMATOTROPHIN, EQUINE – Delete entry.

21.1.3 POISONS INFORMATION CENTRE

PURPOSE

The Committee considered posting-meeting comment regarding the inclusion of Poisons Information Centre (PIC)telephone numbers in Appendix E, Part 1 Warning Statements.

BACKGROUND

The October 2008 NDPSC Meeting considered inconsistent wording used in the references to the PIC as part of the review of references in the SUSDP. The Meeting noted:

- only Appendix E, Part 1 standard statements A and SP1 contained both Australian and New Zealand PIC contact numbers; standard statement Z contained only the Australian PIC contact number; and standard statements E2, S2, S3, S4 and S5 contained only the reference to the Poisons Information Centre;
- numerous substances listed in Appendix E Part 2 included a combination of standard statements A, E2,S2, S3, S4, S5, SP1 and Z.

On this basis, the October 2008 NDSPC Meeting agreed that:

- all references to PIC were to be worded "a Poisons Information Centre (e.g. phone Australia 131 126; New Zealand 0800 764 766)", with the exception of Appendix E - Introduction, Appendix F – Introduction and Appendix F – Part 1, warning statement 99; and
- there should not be a mandate in all references to use the Australian and New Zealand national PIC telephone numbers, although these should be included in the reference as examples.

DISCUSSION - SUBMISSIONS

The Committee noted comment from XXXXX which sought clarification, as follows, on the number of times the PIC contact details were to be repeated on a label:

- most poisons require standard statement A as a minimum which already gives the PIC contact details;
- based on the wording of the Appendix E introduction, XXXXX have assumed that the PIC contact details do not have to be repeated for every statement on the label, i.e. once is sufficient.

The Committee noted that, although Appendix E Part 1 advises that standard statements are to be grouped together, the Appendix E Introduction advises that:

- the code [Appendix E] has been prepared as a guide for health authorities and manufacturers in drafting suitable first aid directions;
- standard statements specified in this appendix may be varied provided that the intent is not changed.

The Committee agreed that, in line with its decision of October 2008, Appendix E did not mandate repetition, but did allow flexibility in label wording, provided that the intent was not changed.

RESOLUTION 2009/55 – 60 (Confirm Resolution 2008/54-6)

The Committee confirmed the amendments under Resolution 2008/54-6 concerning the references to the Poisons Information Centre.

21.1.4 APPENDIX A, CHEMISTRY SETS

PURPOSE

The Committee noted an update of the Australian Standard referenced at Appendix A 'chemistry sets'.

BACKGROUND

The October 2008 NDPSC Meeting noted that the Australian Standard AS 1647-1995 Part 3 Section 6.15 referenced under the Appendix A 'chemistry sets' entry had been superseded and that the Secretariat was undertaking a review of this reference. The Committee agreed that, the Secretariat would make any necessary 'editorial' amendments to references with referral to the Committee only for its information.

Review of reference

- The requirements of AS 1647-1995 Part 3 Section 6.15, as currently referenced in the Appendix A 'chemistry sets' entry, are as follows:

AS 1647.3-1995 *Children's toys (safety requirements) – Part 3: Toxicological requirements*
6.15 Chemistry sets **6.15.1 Prohibition** Chemistry sets shall not include the following: (a) Asbestos (b) Ammonium nitrate (c) Lithium hydroxide (d) Other substance which need to be handled with extreme caution Note: asbestos, ammonium nitrate and lithium hydroxide are specifically prohibited from chemistry sets because these substances may cause asbestosis are liable to explode or are extremely caustic. **6.15.2 General** The substances in chemistry sets shall comply with all the relevant

statutory requirements for chemicals.

6.15.3 Labelling A chemistry set may include components (eg a chemical or a burner) that are hazardous to health, but which are essential to the function of the chemistry set, provided that the principal display panel of the chemistry set package is labelled as follows:

(a) with the word 'WARNING' or 'CAUTION' in letters that are not less than 5 mm in height and

(i) in red, where red contrasts with the colours of the toy or the principal display panel; or

(ii) in another primary colour that contrasts with the colours of the toy or principal display panel in every other case

(b) with a statement describing the hazard, in easy-to-read and readily understandable English, in letters not less than 1.5 mm in height.

(c) with a statement to indicate that:

(i) the toy is intended for use by a child aged 10 years or more; and

(ii) the toy is to be used only under adult supervision.

The labelling shall be positioned such that it is distinctively apart from other wording or non-contrasting designs on the principal display panel.

- AS 1647.3-1995 was withdrawn in May 2003;

- Standards Australian website records that AS 1647.3-1995 was superseded by AS 8124.3:2003 *Safety of toys – Part 3: Migration of certain elements*, which

  – covers the migration of the elements antimony, arsenic, barium, cadmium, chromium, lead, mercury and selenium from toy materials and from parts of toys, except materials not accessible. For example, coatings of paints, polymeric materials, paper and board, textiles, glass/ceramic/metallic & other materials, pencils and liquid ink in pens, pliable modelling materials, finger paints, etc;

  – does not cover chemistry sets as per the requirements of former Australian Standard AS 1647.3-1995.

- AS 8124.3:2003 is a part of Australian Standard AS 8124 *Safety of toys Set*, a Series of Standards, some based on the International Standards, identifying various safety requirements and test methods for the design and manufacture of children's toys;

- Australian Standard AS 8124.4:2003 *Safety of toys – Part 4: Experimental sets for chemistry and related activities* covers chemistry sets:

  – applies to chemistry and supplementary sets, toys for experiments within the fields of mineralogy, biology, physics, microscopics and environmental sciences whenever they contain one or more chemical substances and/or preparations;

- defines a chemistry set as being a toy consisting of one or more chemical substances and/or preparations with or without equipment intended for carrying out chemical experiments. This definition also covers toys for experiments within the fields of mineralogy, biology, physics, microscopics and environmental sciences whenever they contain one or more chemical substances and/or preparations;

- specifies requirements for the maximum amount of certain substances and preparations used in experimental sets for chemistry and related activities and also specifies requirements for marking, contents list, instructions for use and for equipment intended for carrying out the experiments.

DISCUSSION - SUBMISSIONS

The Committee noted that a review of the Australian Standards found that the requirements of the new Australian Standard AS 8124-2003 Part 4 were in line with the requirements of the now outdated Australian Standard AS 1647-1995 Part 3 Section 6.15.

RESOLUTION 2009/55 - 61

The Committee noted that the reference to the Australian Standard in the Appendix A 'chemistry sets' entry would be amended to reflect the current Australian Standard AS 8124.4-2003 *Safety of toys - Part 4: Experimental sets for chemistry and related activities.*

Appendix A - Amendment

CHEMISTRY SETS – Amend entry to read:

CHEMISTRY SETS:

(a) toy, when complying with the requirements of Australian Standard AS 8124.4-2003 *Safety of toys - Part 4: Experimental sets for chemistry and related activities*; or

(b) for educational 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.

21.1.5 AUSTRALIAN CODE FOR THE TRANSPORT OF DANGEROUS GOODS BY ROAD AND RAIL

PURPOSE

The Committee considered amending the reference to the Australian Code for the Transport of Dangerous Goods by Road and Rail under Part 1, Interpretation, to reflect the 7th Edition.

BACKGROUND

The October 2008 NDPSC Meeting noted that in a legal update dated 6 December 2007, the Deacons website recorded that

- the new *Australian Code for the Transport of Dangerous Goods by Road and Rail* (7th Edition) (ADG7) had been released, that it would replace the 6th Edition (ADG6) and was scheduled for implementation in 2008;
- although the ADG7 is scheduled for implementation in 2008, it will not be legally enforceable in a State or Territory until it had been incorporated into its respective legislation;
- although the ADG7 would replace the ADG6, the ADG6 would continue to apply as an alternative to the ADG7 for a specified transition period. Under the Model Legislation, there is a transition period of 12 months. Given the delay by the States and Territories to implement the Model Legislation or develop similar legislation implementing the ADG7, it is unclear at this stage whether the States and Territories would implement a transition period of 12 months or whether they would adopt a shorter transition period such as six months.

The October 2008 NDPSC Meeting further noted that the following new entry would be included under Part 1, Interpretation of the SUSDP:

> **"Australian Code for the Transport of Dangerous Goods by Road and Rail"** means the sixth edition of the document of that name.

DISCUSSION - SUBMISSIONS

The Meeting was informed that there were a number of variances across State/Territory legislation with regard to the implementation of ADG7, with either the adoption of ADG7 outright, or the adoption of both ADG6 and ADG7 with a transition period of up to 12 months or amendments to legislation currently being drafted.

The Industry Member informed the Meeting that the ADG7 required labelling with regard to GHS. Classification codes are based on GHS, not scheduling, and the Member would need to look into this issue in more detail.

The Meeting agreed that the issue be resolved out of session.

<u>OUT OF SESSION CONSIDERATION</u>

The Secretariat sought further advice from the States and Territories as to the current status of the ADG7 in their respective jurisdiction:

Jurisdiction	ADG7 only	ADG6 & 7 with transition	Legislation in progress	Outcome preference
NSW				Defer to Oct09 as an editorial
VIC		to 1 Jan 2010		
QLD				Defer to Oct09 as an editorial
WA	storage & handling	transport elements – to 1 Jan 2010		
SA		to 1 Jan 2010		Editorial amend with deferred implementation date of 1 Jan 2010 to provide advance warning of compliance
TAS				
NT				
ACT	?	?	?	

New South Wales – The ADG6 is currently referenced through the Road and Rail Transport (Dangerous Goods) (Rail) Regulation 1999. The Dangerous Goods (Road and Rail Transport) Bill 2008, which adopts the ADG7, was assented on 3 December 2008, but it is not known when it will be proclaimed or if any new regulations will allow a transition period from the ADG6 to the ADG7.

Victoria – the Dangerous Goods (Transport by Road and Rail) Regulations 2008 has been enacted allowing duty holders to use either ADG6 or ADG7 until the end of 2009 with the ADG6 to be phased out on 1 January 2010.

Queensland – the ADG7 is referenced in the Transport Infrastructure (Dangerous Goods by Rail) Regulation 2008, in force from 1 January 2009.

Western Australia – for *storage and handling*, the ADG7 was fully implemented on 1 March 2008 by adoption through the Dangerous Goods Safety (Road and Rail Transport of Non-explosives) Regulations 2007. For *transport* elements, which are the main thrust of the ADG, the transition period was intended to be complete with ADG7 fully implemented in Western Australia from 1 January 2009. However, as other jurisdictions had not yet fully implemented ADG7 and a national approach on dangerous goods transport was supported, a further transition period will conclude on 1 January 2010.

South Australia –the Dangerous Substances (Dangerous Goods Transport) Regulations 2008 references the ADG7 and came into operation 1 January 2009 with a 12 month transition period during which compliance with either ADG6 or ADG7 is acceptable.

Tasmania – the ADG6 is still referenced through the Dangerous Goods (Road and Rail Transport) Regulations 1998). New legislation is being developed with the timeline for adoption of ADG7 uncertain.

Northern Territory – currently seeking approval to adopt the ADG7, XXXXX it is not yet known XXXXX when the legislation will be implemented.

Australian Capital Territory – unknown.

Given that the SUSDP only refers to the ADG in the context of describing the terms 'oxidising substance' and 'flammable liquid' as well as reference to 'a Class label as specified in the ADG', such references are not in any way an endorsement of the ADG. As such, whether or not jurisdictions had adopted ADG6 or ADG7 was not relevant to the purpose for which the SUSDP refers to the Code. Importantly, these terms are consistently described across both ADG6 and ADG7.

Given the SUSDP's status as a Legislative Instrument, there is an obligation to refer only to the most recent iteration of the ADG, that being ADG7.

This matter was discussed with the Jurisdictional and Industry Representatives out of session who gave support to referencing the ADG7.

21.2 SUSDP AMENDMENT

RESOLUTION 2009/55 – 62

The Committee noted the drafted SUSDP No. 23 Amendment No. 3 and that there were editorial amendments or errata to the Amendment.

21.3 SUSDP 23 AMENDMENT 3 – EDITORIALS

PURPOSE

The Committee considered a number of proposed editorial changes to SUSDP 23 Amendment 3.

BACKGROUND

A review of a draft SUSDP 23 Amendment 3 (SUSDP 23/3), based on decisions from the October 2008 NDPSC Meeting, has put forward a number of editorial changes which may more accurately reflect the intent of these decisions.

DISCUSSION - SUBMISSIONS

Members noted a number of suggested changes to SUSDP 23/3 from XXXXX:

- Paragraph 16 (Paints) – suggested adding "; or" between sub-paragraphs (1) and (2) for consistency and clarification.
- Schedule 4 ethylhexanediol – suggested deleting "only", asserting that this was superfluous and not part of normal conventions.
- Schedule 6 formaldehyde and paraformaldehyde entries – suggested reinstating the current parent paragraph in both entries, and deleting sub-paragraph (g) as a consequence. The following was raised:
  - This provided more clarity in this "opening" position than buried at the end of the entry, and it was consistent with other entries.
  - It may well be that the original wording in the draft was arrived at for a reason XXXXX was not aware of, but, in the absence of any information in that regard, personally felt that it could revert back.
- Was not comfortable with the wording of sub-paragraphs (e) and (f) i.e. "all other cosmetic preparations", then "in other preparations", but could not see a logical way around it at this stage.
- Schedule 7 benomyl entry – suggested adding an "s" to "paint" for consistency with other entries. The Members also noted a separate suggestion that this entry was missing the usual "of" i.e. "containing 0.5 per cent or less <u>of</u> benomyl".
- Appendix I (Uniform Paint Standard) – suggested deleting "for" in sub-paragraph 1.(1) so that it read more logically and clearly i.e. "...for application to ... a roof or any surface to be used...".
- Appendix I – Noted that the formatting of the Third Schedule needs to be tidied up so that the percentage values line up directly below the "Proportion" column, not following on directly after "Lead or lead compounds" in the "Substance" column. Members noted that this was just a formatting correction for the draft SUSDP 23/3 document rather than a formal editorial change.

DISCUSSION – RELEVANT MATTERS UNDER 52E

Members agreed that these editorial suggestions added clarity to the intent of the October 2008 NDPSC decisions and should be incorporated into SUSDP 23/3 (with a note explaining that the relevant decisions also include editorial changes as identified at the February 2009 NDPSC Meeting under item 21.3).

Following a post-meeting review of the draft SUSDP 23/3, XXXXX, also recommended that Paragraph 16 (2) be amended, for consistency with the wording used for paints in 16.(1)(b)(iv), by replacing:

- element present as "calculated on the non-volatile content" or "in the dried film".

with

- element present "calculated on the non-volatile content" or "in the dried film" of the tinter.

RESOLUTION 2009/55 - 63

The Committee decided to clarify a number of entries in SUSDP 23/3 by editorially amending the relevant decisions from the October 2008 NDPSC Meeting as follows:

- Paragraph 16 (Paints) – adding "; or" between sub-paragraphs (1) and (2).
- Schedule 4 ethylhexanediol – deleting "only".
- Schedule 6 formaldehyde and paraformaldehyde entries – reinstating the current parent paragraph in both entries, and deleting sub-paragraph (g).
- Schedule 7 benomyl entry – adding an "s" to "paint" for consistency with other entries. Also add the usual "of".
- Appendix I – deleting superfluous "for" in sub-paragraph 1.(1).

The Committee also noted an additional post-meeting clarification to Paragraph 16 (Paints), sub-paragraph (2) – deleting the "as" before "calculated on the non-volatile…" and adding "of the tinter" following "in the dried film".

Part 2 – Labels and containers – Amendment

Paragraph 16 – Amend entry to read:

Paints

16. The requirements of paragraph 7 do not apply to:

(1) paint (other than a paint for therapeutic or cosmetic use) which:

(a) contains only Schedule 5 poisons; or

(b) is a First Schedule or Second Schedule paint that is labelled with:

(i) the word "WARNING", written in bold-face sanserif capital letters, the height of which is not less than 5 mm, on the first line of the main label with no other words written on that line; and

(ii) the expression "KEEP OUT OF REACH OF CHILDREN", written in bold-face sanserif capital

letters, the height of which is not less than 2.5 mm, on a separate line immediately below the word "WARNING"; and

(iii) the appropriate warnings specified for the paint in Appendix F, written immediately below the expression "KEEP OUT OF REACH OF CHILDREN"; and

(iv) the name and proportion of the First Schedule or Second Schedule poisons it contains, provided that where the substance is a metal or metal salt the proportion is expressed as the metallic element present "calculated on the non-volatile content" or "in the dried film" of the paint; or

(2) a tinter which contains:

(a) only Schedule 5 poisons; or

(b) a poison included in the First Schedule or Second Schedule to Appendix I, provided that it is labelled with the name and proportion of that poison, and where the poison is a metal or metal salt, the proportion is expressed as the metallic element present "calculated on the non-volatile content" or "in the dried film" of the tinter.

Schedule 4 – Amendment

ETHYLHEXANEDIOL – Amend entry to read:

† ETHYLHEXANEDIOL for animal use.

Schedule 6 – Amendments

FORMALDEHYDE – Amend entry to read:

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

(a) for human therapeutic use;

(b) in oral hygiene preparations;

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

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

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations; or

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

CONTAINS FORMALDEHYDE.

PARAFORMALDEHYDE – Amend entry to read:

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

(a) for human therapeutic use;

(b) in oral hygiene preparations;

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

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

PROTECT CUTICLES WITH GREASE OR OIL;

(e) in all other cosmetic preparations; or

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

CONTAINS FORMALDEHYDE.

Schedule 7 – New entry

BENOMYL **except** in paints containing 0.5 per cent or less of benomyl.

Appendix I – Amendment

Amend Appendix I to read:

This Appendix provides regulations for adoption by the States and Territories.

1. A person must not manufacture, sell, supply or use a First Schedule Paint for application to:

   (1) a roof or any surface to be used for the collection or storage of potable water; or

   (2) furniture; or

   (3) any fence, wall, post, gate or building (interior or exterior) other than a building which is used exclusively for industrial purposes or mining or any oil terminal; or

   (4) any premises used for the manufacture, processing, preparation, packing or serving of products intended for human or animal consumption.