Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

National Drugs and Poisons Schedule Committee

Record of Reasons

48th Meeting
10-12 October 2006

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GLOSSARY

ABBREVIATION	*NAME*
AAN	Australian Approved Name
AC	Active Constituent
ACC	Australian Crime commission
ADEC	Australian Drug Evaluation Committee (TGA)
ADI	Acceptable Daily Intake
ADR	Adverse drug reaction
ADRAC	Adverse Drug Reactions Advisory Committee (TGA)
AE	Adverse events
AGVET	Agricultural/veterinary
AHMAC	Australian Health Ministers' Advisory Council
ANZAN	Australian and New Zealand Association of Neurologists
ANZTPA	Australia New Zealand Therapeutic Products Agency
APMF	Australian Paint Manufacturers' Federation
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute Reference Dose
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods (TGA)
AUSTR	ARTG product Registration
AUSTL	ARTG product Listing
BAN	British Approved Name
CAS	Chemical Abstract Service
CEF	Community Engagement Forum
CHC	Complementary Healthcare Council of Australia
CIC	Commercial in confidence
CMEC	Complementary Medicine Evaluation Committee (TGA)
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-Resistant Closure
CRP	Child-Resistant Packaging
CRP	Chemicals Review Program
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
DAP	Drafting Advisory Panel (NDPSC)
DHA	Department of Health and Ageing
DPSSC	Drugs and Poisons Schedule Standing/Sub Committee (NHMRC committee and predecessor to the NDPSC)
DSEB	Drug Safety and Evaluation Branch (TGA)
EAGAR	Expert Advisory Group on Antimicrobial Resistance
ECRP	Existing Chemicals Review Program (APVMA)
EPA	Environment Protection Authority

ERMA	Environmental Risk Management Authority (New Zealand)
ESR	Institute of Environmental Science and Research
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (US)
FOI	Freedom of Information
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System for Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General Practitioner
GPS	Global Positioning System
HCN	Health Communication Network
HSE	Health Safety and Environment Working Group
HVE	High volatile esters
IDC	Interdepartmental Committee
INN	International Non-proprietary Name
ISO	International Standards Organization
JAEG	Joint Agency Establishment Group (TGA)
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
LC_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD_{50}	The concentration of a substance that produces death in 50% of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight
LOEL	Low Observable Effect Level
LRCC	Low regulatory concern chemicals
MCC	Medicines Classification Committee (New Zealand)
MCS	Multiple Chemical Sensitivity
MEC	Medicines Evaluation Committee (TGA)
MODA	NZ Misuse of Drugs Act
MOE	Margin of exposure
MOH	Ministry of Health (New Zealand)
MPA	Methacrylate Producers Association
NCCTG	National Coordinating Committee of Therapeutic Goods (TGA)
NDPSC	National Drugs and Poisons Schedule Committee (TGA)
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NIPAC	National Influenza Pandemic Action Committee
NNST	National Nanotechnology Strategy Taskforce
NOEL	No Observable Effect Level
NSAID	Non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
OGTR	Office of the Gene Technology Regulator
PMB	Non-Prescription Medicines Branch (TGA)

NZ	New Zealand
OCM	Office of Complementary Medicines (TGA)
OCS	Office of Chemical Safety (TGA)
ODBT	Office of Devices, Blood and Tissues (TGA)
OECD	Organisation for Economic Co-operation and Development
OOS	Out of Session
OTC	Over the Counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription Animal Remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PCWA	Pharmaceutical Council of Western Australia
PEC	Priority Existing Chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
RACGP	Royal Australian College of General Practitioners
RASML	Required Advisory Statements for Medicine Labels
RFI	Restricted Flow Insert
RSC	Review Steering Committee
SAS	Special Access Scheme (TGA)
SCCP	EU Scientific Committee on Consumer Products
SCCNFP	EU Scientific Committee on Cosmetic Products and Non-food Products
SMARTI	New Zealand register of medicines
SNRI	Serotonin & noradrenaline reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitors
STANZHA	States, Territories & 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
TGA	Therapeutic Goods Administration
TGAC	Therapeutic Goods Advertising Code
TGACC	Therapeutic Goods Advertising Code Council
TGC	Therapeutic Goods Committee (TGA)
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party (NDPSC)
TTMRA	Trans-Tasman Mutual Recognition Agreement
UK	United Kingdom
USA	United States of America
WHO	World Health Organization
WP	Working Party
WS	Warning statement

1.7 PROCEDURAL MATTERS

1.7.1 OPERATIONS/POLICIES OF THE COMMITTEE

1.7.1.1 DRAFT TEMPLATE FOR SCHEDULING/RESCHEDULING AND ELECTRONIC LODGEMENT OF SUBMISSIONS

PURPOSE

The Committee considered a draft electronic template for scheduling or rescheduling applications.

BACKGROUND

The February 2006 NDPSC Meeting considered the following relating to the process and content for scheduling/rescheduling applications:

- progress of the phased introduction of electronic (e) agenda papers for NDPSC meetings, including development of an application form/template for submissions.
- the nature of information released with the Record of Reasons, particularly regarding the issues of confidential information and transparency.
- **XXXXX**

While considering the above issues the Committee also recalled that there was general support at the October 2005 NDPSC Meeting for the concept of a form being developed for applicants in which they would have to identify, and justify, what information was to be treated as confidential. The Members concluded that the idea of a form could be extended to a template setting out the preferred format for submissions to the Committee. The Committee therefore agreed to develop a template to facilitate the scheduling/rescheduling process.

The June 2006 NDPSC Meeting agreed to foreshadow adoption of a template for scheduling/rescheduling applications and to post the draft template onto the NDPSC website for stakeholder comments prior to the October 2006 NDPSC Meeting.

DISCUSSION

The Committee recalled that in the February 2006 consideration of the e-agenda implementation the issue of electronic submissions was discussed. A Member suggested that a template could be developed where applicants had to fill in fields which correlated with the NDPSC scheduling criteria (while still being free to add additional data as the applicants wish). The Committee at that time generally felt that such a template would:

- Provide help and guidance to industry.
- Improve the efficiency with which the Committee could consider applications as all data would be clearly identified and associated with specific criteria.

The Committee also recalled that the June 2006 NDPSC Meeting generally agreed on the following plan for developing an NDPSC template:

- Member's recommended changes to be incorporated into the draft template.
- Draft template to be loaded onto the NDPSC website before the October 2006 NDPSC Meeting to allow stakeholder feedback.
- Draft template, and any stakeholder feedback, to be considered at the October 2006 NDPSC Meeting. The Draft template could then be finalised.
- Trial the use of the NDPSC template with some sponsors.

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

XXXXX believed that the format and content of the template would provide greater clarity and uniformity and should assist applicants in providing the required regulatory information, thus avoiding unnecessary delays resulting from incomplete submissions. **XXXXX** therefore supported the introduction of the template.

- However, **XXXXX** did not agree with the proposed confidentiality arrangements as outlined in the templates guidance notes under the heading "Confidentiality". **XXXXX** strongly believed that extending the disclosure of information in relation to applications beyond those currently being applied could not be justified. (The Members noted Secretariat advice that, as set out in item 1.7.1.2, there were currently no guidelines being applied. The Secretariat treated confidentiality in a subjective manner based on what appeared appropriate, given precedent and experience.)
- **XXXXX** noted that the generation of supporting regulatory data and the compilation of applications were resource intensive and costly. **XXXXX** asserted that in the absence of market exclusivity provisions, the non-disclosure of certain information, including applicant details, was the only mechanism that afforded innovators an opportunity to recoup some of the costs associated with rescheduling applications. **XXXXX** would be pursuing the introduction of market exclusivity provisions in relation to rescheduling applications under the ANZTPA. For the moment **XXXXX** strongly advocate that the status quo be maintained.
- **XXXXX** believed that the confidentiality arrangements outlined in the proposed template should be consistent with those cited in NCCTG's "starting point for consultation".
- **XXXXX** also discussed the early notification of decisions prior to release of the Record of Reasons by the **XXXXX**. **XXXXX** proposed incorporating a confidentiality clause into the template as a means of securing the continuation of this arrangement. This clause should clarify that "information provided before the gazettal of the Record of Reasons is intended for internal company use only" and highlight the obligation of applicants to maintain confidentiality in relation to information provided. (Member's noted that the second clause under "Declaration" in the draft template set out a similar provision).

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

- **XXXXX** believed that the template provided a positive step towards facilitating the preparation of submissions. The template was easy to follow, clear and concise. **XXXXX** noted that the template presented the information in a logical format and removed much of the repetitiveness that, in **XXXXX** opinion, existed in the current system. Additionally, it gave an adequate indication of what was needed under each section, whilst providing for additional matters to be included at the discretion of the applicant or upon the request of NDPSC.
- **XXXXX** was of the opinion that the use of the template would make future submissions more content focused. Benefits would include that it ensured that applicants present a clear and concise rationale for rescheduling along with the relevant data.
- However, **XXXXX** requested that the Committee consider the definitions of commercially sensitive and/or confidential information used in the template's guidelines. **XXXXX** asserted that the current statement would require written justification for any materials that the applicant felt should be regarded as commercially sensitive other than details about formulation, manufacture or sales. **XXXXX** believed that for such a system to be viable the Committee would need to issue specific guidelines as to what it will accept as valid reasons for keeping information confidential. (The Committee considered that inclusion of a section on confidentiality in the NDPSC Guidelines, discussed in item 1.7.1.2, would provide the guidance sought by **XXXXX** for medicines).
- **XXXXX** also asserted that the Committee consider whether requiring applicants to submit references in an electronic format might infringe copyright.

A pre-meeting comment was received from **XXXXX.** The Committee particularly noted the following:

- **XXXXX** supported the use of a template for scheduling/rescheduling applications, noting that it would provide useful guidance for applicants as to the preferred format for submissions, and thereby provide consistency for the Committee in reviewing applications.
- However, **XXXXX** asserted that the use of the information provided through the template needed to be clarified. **XXXXX** did not support applications being made publicly available or used for compilation of the gazette notices or the Records of Reasons. **XXXXX** requested that the Committee clearly state whether or not it intended to make applications publicly available. **XXXXX** asserted that any changes to the current process for the gazette notices or Records of Reasons would need to be foreshadowed in detail, and undergo further consultation.
- **XXXXX** also requested that the Committee note its comments on the issue of commercial-in-confidence (see item 1.7.1.2) when considering the template. In relation to the template **XXXXX** specifically noted:

- That the template did not fully reflect the NCCTG's starting point as to details that should routinely be considered confidential. The template only specified formulation, manufacture and sales. **XXXXX** asserted that sponsor (applicant) details and product name should be included. The Members agreed and amended the guidance notes on page 2 of the template to also include sponsor and product name as being CIC information.
- Compliance with specific scheduling criteria being sought – **XXXXX** asserted that it was important that a specific section be devoted to commenting on the characteristics of a medicine directly against the criteria for defining different Schedules. (Members noted that the guidance notes for Part B of the template indicated an expectation that "the following issues will be addressed as fully as available data allows (as appropriate to the Schedule proposed)". It was also explained that the Committee was required to consider these criteria as they are set out under Section 52 E of the Act. **XXXXX** when discussing the "criteria" for defining different Schedules appeared to mean the general NDPSC guidelines for each Schedule.)

- **XXXXX** also asserted that the template would be enhanced by including sections for pharmacology and labelling. (Members considered that inclusion of such sections would not be appropriate given the broad spectrum of applications received by the Committee).
- **XXXXX** also reiterated the above concern about providing references electronically, noting that it favoured this approach but that there might be copyright implications.

A pre-meeting comment was received from **XXXXX** noting that feedback from its constituents will be provided through **XXXXX**. **XXXXX** advised that the medicines industry applauded the Committee's progression of the template. It was asserted that industry were very optimistic that the template would facilitate industry's own processes in generating submissions. Industry was also highly supportive of the option to lodge submissions electronically.

Members were also advised **XXXXX** welcomed the discussion and supported the Committee's moves to trial the template, noting that there was going to be a template under ANZTPA and that the NDPSC template would allow a form to evolve that was acceptable to everyone.

Members discussed the copyright concerns raised by some pre-meeting comments above and agreed that it did not appear to be an issue. It was noted that references had always been a component of NDPSC applications (and indeed for the many applications made to regulators such as the TGA and APVMA) and did not see that moving from hard-copy to electronic would make any difference. The Committee confirmed that it did not intend to distribute these references.

A Member noted that a pre-meeting comment for an item at the Meeting had used the draft template posted on the NDPSC website. The Member also asserted that it should be

clear that the template was not for applications going to regulatory agencies such as the APVMA. The Committee confirmed that the template was intended for use by applicatants regarding scheduling or rescheduling of a substance made directly to the Committee i.e. not for those coming to the Committee via a regulatory agency. The Members also confirmed that the template was not intended to be used for general communications from stakeholders to the Committee such as pre- and post-meeting comments.

A Member recalled that the June 2006 NDPSC Meeting had noted a template used by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) for presenting toxicology data. The Committee agreed to include a reference to this document in the NDPSC template as it may be of assistance to some stakeholders, particularly those less familiar with presenting toxicological data (the NICNAS document *Schedule Attachment Part C1* was listed on the following NICNAS web page: http://www.nicnas.gov.au/Forms/New_Chemicals/STD_LTD_Electronic_Templates/Template.asp).

A Member asserted that specific guidance would become possible following the proposed splitting of the NDPSC into medicines and chemicals committees, as the focus and stakeholders, of these new committees would be different. The Committee noted, however, that the present template needed to remain generic because of the nature of the types of submissions currently considered by the NDPSC from different sectors.

Members also felt that it was important to trial the template with stakeholders and agreed to invite stakeholders making a submission to the June 2007 NDPSC Meeting to voluntarily use the template.

The Committee also noted that the current NDPSC guidelines continued to stipulate a requirement for applications to be lodged in hard-copy (25 copies). Members agreed that in moving to an e-agenda process it was appropriate that the guidelines be amended to allow electronic lodgement of submissions, preferably using the template.

OUTCOME

The Committee agreed:

- To amend the current NDPSC guidelines to allow electronic submission as an alternative to the mandatory submission of 25 hard copies of an application.
- To recommend to NCCTG that it endorse this change.
- That the proposed template, as amended at the Meeting, provided suitable guidance to industry and would improve the efficiency with which the Committee could consider applications.
- To post the template on the NDPSC website including a request that stakeholders making a submission to the June 2007 NDPSC Meeting consider a voluntary use of the template to trial the process.

- To advise NCCTG of the February 2007 consideration of the proposed template and invite NCCTG's comments, particularly with regard to the adoption of the Template for the June 2007 NDPSC Meeting.

NDPSC GUIDELINES – Amendments to Chapter 2.

***FORMAT OF THE APPLICATION* – Amendment to follow the section heading.**

Applicants are strongly encouraged to use the NDPSC electronic template available from the following website: http://www.tga.gov.au/ndpsc. Should a non-electronic application be submitted, the document will need to comply with the following format requirements.

***PRODUCTION OF THE DOCUMENT* – Amendment to follow the section heading.**

Applicants are strongly encouraged to use the NDPSC electronic template available from the following website: http://www.tga.gov.au/ndpsc. Should a non-electronic application be submitted, the document will need to comply with the following guidelines for document production.

***LODGEMENT OF APPLICATIONS TO NDPSC*– Amendment to follow the section heading.**

Applicants are strongly encouraged to lodge applications to the NDPSC electronically using the electronic template available from the following website: http://www.tga.gov.au/ndpsc. No hard copies are required to accompany application lodged electronically. Should a non-electronic application be submitted, the applicant will need to comply with the following guidelines for lodgement of applications.

***ADDRESS FOR APPLICATIONS* – Amendment to immediately follow the heading "Re-scheduling of Medicines, New and Rescheduling Applications for Domestic or Other Chemicals"**

Electronic lodgements

Applicants are strongly encouraged to lodge applications to the NDPSC electronically using the electronic template available from the following website: http://www.tga.gov.au/ndpsc. Preference is for electronic lodgements to be made utilising the following email address: ndpsc@health.gov.au. Alternatively, a CD containing the electronic application may be sent to the postal address below.

Hard copy lodgements

Applications….

1.7.1.2 CONFIDENTIAL INFORMATION AND RELEASE OF INFORMATION IN THE RECORD OF REASONS FOR MEDICINES

PURPOSE

The Committee considered changes to NDPSC operational requirements regarding commercial-in-confidence (CIC) and transparency of information for medicines scheduling.

BACKGROUND

The October 2002 NDPSC Meeting, after considering a comment on the inaccuracy of the NDPSC guidelines, agreed to edit these guidelines to remove outdated or incorrect material (including Chapter 5 – *Guidelines for use of Confidential Information*). The Committee flagged that the NDPSC Guidelines Working Party may need to be reconstituted following the Galbally report to re-write the guidelines. However, re-writing of the guidelines was not progressed due to work being undertaken with the implementation of Galbally Recommendation 7 (splitting of the NDPSC into two separate committees) as part of the establishment of the ANZTPA.

The October 2005 NDPSC Meeting considered two examples of stakeholder concern about the release of "confidential" information. Members agreed that no changes to the Secretariat's editing of the Record of Reasons were warranted at that time and confirmed the current practice of the Secretariat as appropriate. The Committee further agreed to reconsider this issue at the February 2006 NDPSC Meeting as an opportunity existed to progress some of the moves towards further transparency before the trans-Tasman arrangements come into force.

The February 2006 NDPSC Meeting noted that NCCTG had yet to formally consider the issue of confidentiality. The Committee agreed to refer this issue to NCCTG and to use NCCTG's considerations as a basis for further progression. The June 2006 NDPSC Meeting noted the May 2006 NCCTG Meeting's consideration of this issue and agreed:

- to foreshadow consideration of changes to the operational requirements for the NDPSC regarding CIC and transparency of information for medicines scheduling. Comments were particularly invited from stakeholders on the NCCTG's proposed starting point for consultation and on defining any additional types of information over which stakeholders sought confidentiality.
- to consider the stakeholder responses addressing release of information that were submitted in relation to the consultation on '*A proposed new model for the scheduling of medicines and poisons within the Joint Agency*' (the Draft Model).
- to develop a consistent process with JAEG for consulting with industry on this issue to avoid introducing inconsistencies with ongoing ANZTPA consultations.

DISCUSSION

Currently the Record of Reasons is produced from the Ratified Minutes through deletion of material considered by the Secretariat to be commercially sensitive (i.e., formulation detail, manufacturing method, sponsor name, product name, sales information), details from the evaluation reports for new agricultural/veterinary products and extracts from the ADEC minutes. This process was often subjective and the onus for identifying confidential information had fallen on the Secretariat. The Record of Reasons also usually excluded items such as Committee procedures, information items, policy items under development and Members reports.

The current Record of Reasons, with its increased details and information compared to historical standards, was introduced in part because of pressure from stakeholders for increased transparency about the reasons for a decision. The Secretariat, in including information in the Record of Reasons, advised that it was being pushed by two different agendas:

- a drive for transparency about the basis for NDPSC decisions. The opportunity to comment on a decision loses meaning if stakeholders cannot access the details of the reasons behind a decision.
- continuing strong pressure on the Secretariat by some stakeholders to have as little information about their product(s) as possible available to the public.

The Secretariat also advised that the above agenda arose with the issue of the pre-meeting gazette notice. While, in general, there was a desire for more transparency in the gazette notices, the individual applicants were often reluctant to have additional information in the gazette notice. The Secretariat had attempted to encourage applicants to include a proposed gazettal notice in their submission but this generally did not occur.

Members recalled that at the October 2005 NDPSC Meeting there was general agreement that if companies have a particular concern about confidential information in their submission they should be indicated as such. The issue of identifying and justifying confidential information was also discussed under item 1.7.1.1.

The Committee also recalled the following from the June 2006 NDPSC Meeting:

- The NCCTG:
  - affirmed that it was anticipated that the new Medicines Scheduling Committee would release more information publicly than the NDPSC currently released;
  - considered that the starting point for consultation with industry stakeholders should be that the only information that should be routinely withheld from public release was CIC information (i.e., formulation detail, manufacturing method, sponsor name, product name and sales information);

- particularly considered that the existence of an application or the identity of a substance that was the subject of a rescheduling application was not CIC information;
- suggested that the NDPSC should be prepared to work with industry groups on defining any additional types of information over which industry stakeholders sought confidentiality;
- noted that commercial and market advantage could be gained from the limited release of information from the NDPSC. Once guidelines were in place for wider release of information, applicants would be able to adjust the timing of the lodgement of their submissions to take account of the policies on public release of information.

- The NCCTG therefore:
  - supported a greater level of transparency in the release of information, consistent with the requirements of CIC material and public need;
  - recommended that the NDPSC consult with industry stakeholders to define the level of transparency that was appropriate;
  - recommended that stakeholder responses that were submitted in relation to the consultation on the Draft Model be considered in reviewing the NDPSC guidelines on release of information.
- A Member asserted that there was a need to consult with industry to come to an agreed position and to determine how maximum transparency/minimum CIC might work in the scheduling process. The Chair advised that **XXXXX** had not done this consultation, although it did co-ordinate the consultation process in 2005 for the Draft Model and that the industry feedback from this included concerns about confidentiality of information.
- The Committee discussed what would be an appropriate process for consulting – noting that the issue of CIC/release of information had already been flagged by **XXXXX** in the 2005 consultation document. The Committee wanted to ensure that it did not go outside the scope of this earlier consultation as this could result in inconsistency with the emerging ANZTPA framework. In considering a process a Member enquired about whether NCCTG had considered the industry feedback and if NCCTG could therefore provide guidance prior to initiating another consultation process. The Committee was advised that such detailed consideration had yet to occur.
- A Member insisted that sufficient advance notice must be included in any change to the current understanding of what was disclosed in the Record of Reasons and that the Committee would have to be clear about any timelines for change.
- Members also recalled that **XXXXX** did not support inclusion of information from agricultural/veterinary evaluations in the Record of Reasons. A Member therefore suggested that the Committee defer consideration of the confidential information

issue for the poisons side of scheduling, noting that APVMA had specific legislative requirements that may impede development of a consistent position. The Committee agreed that it was appropriate to separate consideration of confidentiality for medicines scheduling from poisons scheduling given that there will shortly be different operational requirements.

The Members noted the following from **XXXXX** pre-meeting comment:

- At this stage **XXXXX** did not propose any changes to existing confidentiality arrangements, i.e. extending beyond those currently in place and the categories mentioned above by NCCTG.
- **XXXXX** noted that the confidentiality arrangements proposed in the template for rescheduling applications (discussed under item 1.7.1.1) also required consideration here.

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

- **XXXXX** asserted that providing meaningful comment, particularly in response to the pre-meeting gazette notice, was often difficult due to the limited background information provided. Therefore, **XXXXX** considered review of processes surrounding transparency a positive move.
- Whilst **XXXXX** agreed with the proposed NCCTG's starting point, meaningful comment relating to additional types of information that should be considered CIC was greatly influenced by the framework under which scheduling would operate with ANZTPA. In the absence of this, **XXXXX** expected that any changes to the current process for compilation of the Record of Reasons proposed by the Committee would be foreshadowed in detail, and undergo further consultation.
- In addition, **XXXXX** was pleased to see consideration being given to a mechanism by which applicants have the opportunity to justify specific information being kept confidential. **XXXXX** would vigorously oppose the absence of such a mechanism.

Members were advised that the Secretariat had informed **XXXXX** of the impending consideration of confidential information for medicines scheduling and requested that **XXXXX**:

- **XXXXX**.

The Committee noted that advice had been provided by **XXXXX** which included the following:

- After the 2005 consultation on the Draft Model, 19 stakeholder submissions were received. It was noted that a key issue raised by stakeholders in consideration of the draft *Guidelines for Public Consultation* and *Use of Confidential Information* was the proposed arrangements for CIC material. Members particularly noted:
    - The draft guidelines regarded sales data, details of manufacturing processes and formulation details as confidential information.

- Applicants would be required to identify and justify any further claims of confidentiality based on relevant freedom of information legislation and intellectual property rights.

- It was also noted that several submissions called for the scope of material accepted as being CIC to either be expanded, or for a process to be built in whereby the applicant would have an opportunity to review the material to be published on the website, prior to release. The Committee noted that:
  - **XXXXX** considered that the accepted list of CIC information should be extended to cover other information such as labelling, in-house unpublished clinical data and market research data without the need for justification. (The Members were advised at the Meeting that **XXXXX** agreed that this issue was a process in evolution and that it was happy with the NCCTG's proposed starting point and the Committee's progress to date).
  - **XXXXX** was concerned about the protection of CIC information and that the policy not to release CIC may not be consistently applied and thereby disadvantage sponsors. **XXXXX** proposed a provision in the model to allow a sponsor to review the proposed website information prior to release.
  - **XXXXX** asserted that issues surrounding the handling of clinical data should be clarified.
- In considering these comments NCCTG agreed that while only minimal information should generally be accepted as CIC, provision should be made for further information to be treated as CIC on a case by case basis.
- **XXXXX**

Members were also advised that the Secretariat wrote to **XXXXX** and **XXXXX** requesting information about their procedures around the issue of CIC and transparency of information. **XXXXX** provided a summary of its procedures on these issues for the information of Members.

XXXXX advised that **XXXXX** appreciated the clarity of NCCTG's proposed starting point and the provision allowing justification of additional information as CIC on a case-by-case basis. It was asserted that **XXXXX** was comfortable with the Committee's proposed guidelines on medicines CIC information. Another Member noted that case-by-case consideration, while not an insignificant undertaking, had value as it would also allow an appropriate evolution of the guidelines.

XXXXX noted that in NZ the applicant was identified. A Member further noted that an issue in NZ with the disclosing of information was those cases where most of the justification for reclassification was driven by unpublished data (which was then claimed to be confidential).

A Member noted that the Committee would need to try and work in parallel with the development of this issue for ANZTPA. It was noted that while the Committee could not

get too far ahead of ANZTPA it still wanted to progress and improve the Secretariat's operations and efficiencies. The Committee agreed that it was therefore important that the Secretariat and **XXXXX** work closely together on these issues.

XXXXX felt that the proposed guidelines were a positive move for transparency. **XXXXX** noted that progress in this area could lead to the evolution of a workable model for the new Medicines Schedule Committee. **XXXXX** thought that the Committee had a great opportunity to develop practices, in partnership with industry, that were mutually agreeable and which contained no surprises.

OUTCOME

The Committee:

- Agreed to foreshadow consideration at the February 2007 NDPSC Meeting of the following proposed entry for Chapter 5 of the NDPSC guidelines.
- Agreed that the proposed entry would apply to medicines only.
- Agreed to refer the proposed guideline changes to NCCTG for consideration and approval.
- Agreed that no changes to the Secretariat's editing of the Record of Reasons were warranted at this time and confirmed the current practice of the Secretariat as appropriate.

NDPSC Guidelines – New entry for Chapter 5.

MEDICINES INFORMATION

Medicines Information released to the public in the Record of Reasons

The only information that will be routinely withheld from public release is commercial-in-confidence information (i.e., formulation detail, manufacturing method, sponsor name, product name and sales information).

The applicant must provide a written justification for any other material the applicant wishes to be treated as commercially sensitive. The nominated contact person will be notified if this justification has not been upheld prior to the release of the Record of Reasons.

Applicants should note that the existence of an application or the identity of a substance that is the subject of a rescheduling application is not commercial-in-confidence information.

In addition, items such as Committee procedures, information items, policy items being developed and Members reports will not usually be included in the Record of Reasons.

Medicines Information released to the public in the pre-meeting gazette notice.

The pre-meeting gazette notice may include details of the substance or issue under consideration, including the intent of any scheduling/rescheduling proposals. Applicant should include a proposed gazettal notice in their submission, including a justification if the applicant wishes information withheld from the pre-meeting gazette notice.

1.7.1.3 DERIVATIVE DEFINITION AND USAGE

PURPOSE

The Committee considered the usage of the term "derivative" in the SUSDP, including the possibility of creating a definition.

BACKGROUND

At the May 1995 NDPSC Meeting, during discussion of retinyl palmitate, it was noted that because of the inclusion of then sub-paragraph 76(7) in the SUSDP, it could be interpreted that esters and ethers were not included as derivatives of poisons other than those included in Schedule 8. The Drafting Advisory Panel was requested to redraft the section to clarify the meaning. The August 1995 NDPSC Meeting therefore agreed to "every salt, active principle or derivative of the poison, including esters and ethers, and every salt of such an active principle or derivative".

The May 1996 NDPSC Meeting considered correspondence which illustrated that there may be some ambiguity in how the term "derivative" may be interpreted for scheduling purposes. Discussion remained focused, however, on a number of specific substances and did not address the broader usage of derivative in the SUSDP.

The June 2006 NDPSC Meeting considered a scheduling submission regarding potassium azeloyl diglycinate (PAD). The Committee noted that there was no definition of derivative in the SUSDP but generally agreed that in this instance it was appropriate to consider PAD as a separate substance (rather than a derivative of azelaic acid) as it had different biological properties and a different use. However, Members remained concerned by the lack of clarity about what was meant by derivative in Part 1, Paragraph (2)(c) and agreed to foreshadow consideration at the October 2006 NDPSC Meeting of the usage of "derivative" in the SUSDP, including the possibility of creating a definition.

DISCUSSION

The Committee again noted the following from the June 2006 NDPSC Meeting:

- A number of possible solutions to the derivative issue were put forward, including:
    - A suggestion that "derivative refers to a compound which could be obtained from a substance and which retains the essential characteristics of this parent substance,

including its chemical structure. A derivative does not include structural analogues."

- It was noted that a strict chemical definition of derivative could potentially capture a vast number of compounds which may, in many cases, result in an inappropriate level of scheduling. A suggested solution was to specify a limit on the complexity of the chemistry required to get from the parent to the derivative for the substance to still be considered a derivative. Members generally agreed that it would be difficult to craft a workable complexity limit and that this may require broad stakeholder input.
- A suggestion that a definition of derivative could be based on or include a rider of "similar characteristics in use". Alternatively, the definition could be based around "mechanism of action". It was noted, however, that currently esters and ethers were specifically included and that these often had dissimilar characteristics in use or mechanisms of action to that of the parent compound.

- An alternative approach was a suggestion that reference to derivative be removed from Part 1, Paragraph (2)(c) to give "every salt or active principle of the substance, including esters and ethers, and every salt of such an active principle". Members noted that this left the issue of minor chemical tinkering of substances to avoid scheduling (e.g. alternative halogenation for some compounds) despite these substances having a strong risk of similar toxicological effects etc to that of the scheduled substance.
- Following on from the suggestion to remove reference to "derivative", a Member proposed that a pragmatic approach would be to consider all substances brought to the Committee as individual substances and as such, if scheduling were warranted, move to capture these through specific entries. No ready solution was proposed to deal with those substances which had previously not had specific entries because they were deemed to be captured as derivatives, or on how to apply group entries if derivatives were not to be captured.

Members also noted the current definitions of derivative under the Australian Customs Act:

- *Customs (Prohibited Imports) Regulations 1956* - derivative:
  - in relation to a chemical or compound – any substance chemically derived from the chemical or compound and from which the chemical or compound may be regenerated, and includes a salt of the chemical or compound; and
  - in relation to an isomer, or a mixture of isomers, of a chemical or compound – any substance chemically derived from the isomer or mixture of isomers and from which the isomer or mixture of isomers may be regenerated, and includes a salt of the isomer or mixture of isomers.
- *Customs (Prohibited Exports) Regulations 1958* - derivative:

- Means a substance chemically derived from a drug or from which a drug may be regenerated, including a salt.

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

- **XXXXX** recognized that this was a potentially difficult issue to resolve.
- **XXXXX** did not agree with the suggestion to consider all substances brought to the Committee as individual substances. **XXXXX** did not feel that this offered a pragmatic solution, particularly given that a number of substances were currently considered to be captured under Part 1 Paragraph (2)(c).
- **XXXXX** asserted that it would appear that removing the term "derivative" from Paragraph (2)(c) was a practical solution. **XXXXX** asserted that if the Committee agreed to do this it would be necessary that such a move be foreshadowed and that further consultation be undertaken to fully understand all the regulatory implications.
- Members noted that there was no suggestion as to how to deal with substances currently scheduled through being a derivative. It was noted that these substances would become unscheduled until identified (and then separately considered for scheduling) and there was a question as to who would be responsible for identifying which substances may need to be considered.
- Aside from consideration of the appropriate use of the term derivative, **XXXXX** opposed any other change limiting the remaining provisions of Part (2)(c), i.e. "every salt or active principle of the substance, including esters and ethers, and every salt of such an active principle".

A pre-meeting comment from **XXXXX** advised that, while it supported the introduction of measures that would provide clarity for applicants with regard to this issue, **XXXXX** would be concerned if the introduction of a definition or deletion of the term "derivative" resulted in an inadvertent increase in the level of regulation.

A pre-meeting comment from **XXXXX** noted that **XXXXX**.

The Committee also noted the following from **XXXXX**:

- **XXXXX** noted that there were likely to be cases where particular classes of chemical modification would share the properties of the originally scheduled chemical, but this would not apply for all scheduled chemicals or derivative classes.
- **XXXXX** asserted that the use of a common "mechanism of action" would partially resolve the above issue, but was likely to be very difficult to apply in practice, because data would often not be available. There may also be similar difficulty in defining a "common mechanism of action".
- **XXXXX** also noted that simplification of the definition to a simple group of close chemical relatives, e.g. salts, would not address the issues relating to minor modifications to avoid scheduling. **XXXXX** noted that while individual scheduling

addressed all of these issues there would be difficulties in determining each of the individual scheduling decisions, particularly with respect to time and data availability.

- **XXXXX** therefore proposed:
  - Use of a list of individual derivatives or classes of derivatives for a given entry rather than an approach of strictly defining the meaning of the term "derivative"
  - Creation of a simplified process for appending new substances or groups of substances to the existing entry with focus on ascertaining a common mechanism of action.

    Members noted that it was unclear how such a new process would comply with the legislated process for scheduling. Also, the question remained about substances currently scheduled through being a derivative, as discussed earlier.
  - That the Committee consider a limited definition of "derivative" (e.g. all salts of the named substance) in addition to a list of specified derivatives or groups of derivatives.
- **XXXXX** noted that this proposal avoided consideration of complete data sets for substances currently considered to be derivatives of Schedule entries, and allowed for the specific circumstances to be taken into consideration, which would not be the case under a strict definition of the term "derivative".

The Committee confirmed that it did not believe that there was currently a problem, and agreed that they had not mis-scheduled substances through the current application of derivative. This Meeting's consideration of derivative was instead driven by a desire to increase transparency and provide clarity.

A Member advocated leaving existing entries alone at this stage and that these entries only be revisited if an issue or concern arose or a sponsor asked for a ruling. The Member was very concerned about defining derivative and having retrospective, probably unintended, impact. The Members were advised that while the *NZ Misuse of Drugs Act* (MODA) used the term derivative, the Act did not have a definition. A Jurisdictional Member advised the Meeting that their MODA also used the term derivative and the jurisidiction would oppose its removal.

A Member noted that for a derivative to be appropriately captured under a parent compound schedule, the derivative should not be more toxic than the parent. Higher toxicity should require a separate scheduling consideration.

A Member noted that the usage of derivative was not a major concern for pharmaceuticals as each active went through the regulator who was able to refer such actives to the Committee if necessary. However, it was acknowledge that the derivatives issue could have a large impact on chemicals, particularly domestic chemicals.

A Member proposed that a practical solution for future entries, particularly chemicals, would be to clearly specify if the entry was not intended for derivatives i.e. chemical x

and its salts; or chemical x excluding its derivatives. The Member suggested that the Committee could ask evaluators that when they provide their assessment they could specify (as best the data allows) whether derivatives should be allowed or limited to either certain classes of derivate or to no derivatives.

The Committee considered the following proposed definition (as amended at the Meeting):

"Derivative" means:

(a) a substance which is not individually listed elsewhere in the schedules;

(b) a substance that is structurally, pharmacologically and toxicologically similar to a parent substance;

(c) a substance that might readily convert to the parent substance; or

(d) a substance that the Committee or appropriate Australian Regulator has determined retains the essential characteristics of a parent substance.

A Member noted, however, that flexibility should be maintained. The Member asserted that it was likely that the Committee would soon be dealing with a range of nucleic acid type products where the concept of simple salts etc would not be the issue. Without flexibility in the derivative usage, the Member asserted that the Committee would be hard pressed to appropriately schedule a rapidly evolving class of substances.

A Member suggested that the above definition, while possibly useful as a guide to the evaluators, particularly **XXXXX** or **XXXXX]**, was too prescriptive and inflexible for inclusion in the SUSDP. Further to the suggestion above, evaluators could address the proposed elements - (b) or (c) above, if there was data to do so – to give the Committee information for deciding if there should be a limitation or specification on the application of derivative for a substance. This would leave sufficient flexibility to deal with the diversity of substances that are scheduled.

The Committee agreed that it was not appropriate to define derivative in the SUSDP as this concept was too complex for a prescriptive, inflexible, approach. Members instead agreed to include a paragraph under the "Principles of Scheduling" section of the SUSDP setting out the Committee's intent with regard to applying derivative to Schedule entries. This paragraph would explain why the Committee was trying to capture certain substances as derivatives and what the Members want to convey or prevent. Members agreed that such a paragraph would be transparent and assist users of the SUSDP.

The Secretariat agreed to prepare a draft which would then be circulated to a working group (consisting of **XXXXX** as well as **XXXXX**).

OUTCOME

The Committee agreed to foreshadow consideration at the February 2007 NDPSC Meeting of a draft paragraph for inclusion under the "Principles of Scheduling" section of the SUSDP to clarify the intent of the Committee in using derivative in the context of a Schedule entry.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Principles of Scheduling, Reading the Schedules – Amend entry: a new paragraph to follow the existing "It is important to remember that a Schedule entry includes preparations containing the poison in any concentration and all salts and derivatives of the poison unless it specifically states otherwise. (See Interpretation PART 1 [paragraph 1(2)])."

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

1.8 NDPSC WORKING PARTIES

1.8.1 TRANS-TASMAN HARMONISATION WORKING PARTY (TTHWP)

1.8.1.1 UNHARMONISED MEDICINES IN THE AUSNZ SCHEDULING DATABASE

PURPOSE

The Committee considered TTHWP recommendations for harmonisation.

BACKGROUND

The June 2006 TTHWP Meeting noted the completion of the processing of all records in the AusNZ Scheduling Database for medicines listed in Schedule 2, Schedule 3, Schedule

4 and Schedule 8 and equivalent New Zealand classifications, where available. The TTHWP considered each remaining unharmonised substance and agreed that the TTHWP's recommendations be included on the agenda of the June 2006 NDPSC Meeting.

The June 2006 NDPSC Meeting endorsed the recommendations from the June 2006 TTHWP Meeting (Table 1) and foreshadowed consideration of the remaining unharmonised medicines at the October 2006 NDPSC Meeting to allow appropriate public consultation. Similarly, the Committee agreed that the recommendations to NZ (Table 2) to harmonise the scheduling of certain medicines should be referred to the MCC for consideration. The Committee further agreed that consideration of some substances would need to be deferred (Table 3) to a future meeting to allow a more thorough risk and regulatory impact assessment and that other substances in Table 4 would remain unharmonised at this time. Members noted the request from industry to consider harmonisation of the scheduling of aspirin, paracetamol and salicylamide with New Zealand at the February 2007 NDPSC Meeting.

DISCUSSION

The Chair of the TTHWP updated the Committee on the progress of the Working Party to date. It was advised that:

- The TTHWP had agreed to recommend to the NDPSC the approach of transferring medicines currently included in Schedule 5 and Schedule 6 to the medicine Schedules while maintaining the intent to supply these medicines to the public outside the pharmacy setting provided they complied with the appropriate signal heading and precautionary warning statement requirements. To achieve this, the TTHWP proposed that primary entries for medicines currently included in non-medicine Schedules be created in the appropriate medicine Schedule and exempt these medicines from the Schedules through 'reverse scheduling' provisions. Members were advised that to expedite consideration of this matter by the NDPSC, the TTHWP agreed to seek in-principle approval from the NCCTG for this policy approach to allow consideration at the February 2007 NDPSC Meeting.
- The TTHWP advised that it planned to hold its last meeting in February 2007. At this meeting, the TTHWP would review the status of all medicines included in Table 4 (Minutes of the June 2006 NDPSC Meeting) which listed medicines which were to remain unharmonised at this time and re-confirm or amend their status as appropriate. The outcome of this meeting would be tabled at the February 2007 NDPSC Meeting.

The Committee noted and agreed to the following changes to Table 1 which was considered at the June 2006 NDPSC Meeting:

- Diphemanil, dichlorophen, dimethothiazine, eplerenone, glycopyrronium, mequitazine, pregnenolone, thenyldiamine, thiourea and urethane Schedule entries that were omitted from the entries in Table 1 were added and the corresponding recommendations amended accordingly.

- The recommendations to separately list chloromesterone and 4-chlorotestosterone were amended to cross-referencing these compounds instead to dehydrochloromethyltestosterone and clostebol, respectively, as they are synonyms and as such were already appropriately scheduled and essentially harmonised with New Zealand (also listed in Appendix D).
- An alternative option was proposed for levocetirazine, i.e. cross-reference to cetirizine, instead of including a separate entry for levocetirazine in Schedule 4 as this was already covered by the Schedule 4 and Appendix K entry for cetirizine under the provisions set out in SUSDP Part 1, 1(2).

  The Committee supported this approach on the basis of simplicity and on the grounds that users were likely to refer to the index first when searching for entries in the SUSDP.
- Human protein C consideration of harmonisation was deferred pending the outcome of the review of blood products.
- Duloxetine (see item 13.1.2), nicotinic acid (see item 12.1.4), prochlorperazine (see item 12.1.6) were tabled at the October 2006 NDPSC Meeting as separate items due to other considerations.
- The recommendation in relation to rifamycin and rifampicin was amended to allow separate listings for these medicines as they are different compounds although listed as synonyms in the SUSDP and Table 1.
- The recommendation and proposed entry for thyrotropin was amended to remove "TSH" from the substance entry and cross-reference thyroid stimulating hormone to thyrotropin in the index of the SUSDP.
- Chlorquinaldol and halquinol were covered by the entry for "clioquinol and other halogenated derivatives of 8-hydroxyquinoline" in Appendix C for human internal use, except when being used solely for experimental purposes in humans, and Schedule 4 for topical preparations. To reflect this, the recommendation was amended to "cross-reference chlorquinaldol and halquinol to clioquinol in the index of the SUSDP". In addition, the Committee agreed to recommend that New Zealand delete the General Sale entry for external preparations to harmonise with the Schedule 4 status in Australia but retain the Prescription Medicine entry for chlorquinaldol and halquinol due to the lack of an equivalent mechanism to Appendix C in New Zealand. On this basis, the Committee agreed that chlorquinaldol and halquinol be also included in the list of medicines for which harmonisation could not be achieved at this time.

The Committee was advised that following the June 2006 NDPSC Meeting the following actions were taken:

- Comment was sought from **XXXXX** concerning the proposal to delete the exemption for protamine in insulin products but no comment was received at the time of the Meeting.

- Comment was sought from **XXXXX** to ensure that the proposed entry "Urethane for human therapeutic use" would not have any unintended impact on medical devices. **XXXXX** subsequently advised that the proposed change would impact on a large number of low risk dental products which were currently exempt from scheduling on the basis that they contained urethane derivatives which were excluded from the current Schedule entry for urethane. **XXXXX** advised that dental medical devices using urethane derivatives are low risk Class I or IIa medical devices according to the classification rules set out in Schedule 2 to the *Therapeutic Goods (Medical Devices) Regulation 2002* and that such devices are not covered by the Appendix A general exemption which applies only to Class III medical devices. Members were advised that in contrast to Australia, New Zealand medicine entries did not include derivatives or medical devices. On this basis, the Committee agreed to retain as is the current entry in Schedule 4 of the SUSDP for urethane which was already harmonised with New Zealand.
- General comments on the recommendations in Table 1 were sought from **XXXXX** and **XXXXX**. **XXXXX** indicated that it did not have any comments to put forward for consideration while no response was received from the **XXXXX** area.
- The draft Schedule entries which reflected the harmonisation recommendations in Table 1 were forwarded to the NDPSC Drafting Advisory Panel (DAP) for comment prior to the Meeting.

Members endorsed the DAP's proposed modifications to the draft entries arising from TTHWP recommendations foreshadowed at the June 2006 NDPSC Meeting to maintain consistency with other entries in the SUSDP. Furthermore, the Committee discussed the following issues in more detail:

- The proposed entry for Ephedra spp in Schedule 4 was not required as this class entry was already harmonised with New Zealand. Ephedra spp was mistakenly identified as unharmonised as the descriptor "spp" was inadvertently omitted in the substance entry in Table 1.
- The draft Schedule 5 and Schedule 6 methyl salicylate entries appeared to be problematic because the existing exemption for "admixtures" specified in Schedule 6 also covered preparations containing 25% or more of methyl salicylate which were included in Schedule 5. Furthermore, it was highlighted that the minutes of the August 1983 DPSSC Meeting noted that 5 ml methyl salicylate was likely to be a lethal dose and it was marketed as 'fragrant oil' at that time. Members also noted that some therapeutic products may contain more than 25% methyl salicylate. The Committee agreed to defer and foreshadow consideration of this matter at the February 2007 NDPSC Meeting to allow a review of toxicological data and scheduling history of methyl salicylate. Members noted that the current entries for methyl salicylate appeared to have inadvertently omitted the inclusion of preparations containing more than 50% methyl salicylate in Schedule 6 of the SUSDP. Furthermore, the Committee agreed that the term "see also Schedule 4" in the draft Schedule entries for methyl salicylate should be replaced with a more appropriate

wording for consistency with the style and format of scheduling conditions adopted in the SUSDP.

- Members noted that the proposed deletion of "acetate" from the pregnenolone acetate entry in Schedule 4 to retain only the parent compound and removal of the exemption for topical preparations was expected to have no regulatory impact on existing products as there were none listed on the Australian (ARTG) or New Zealand (SMARTI) database for medicines.

Members were also advised that the intent to consider the proposed inclusion in Schedule 4 of the animal-derived enzyme "hyaluronidase" to harmonise with New Zealand was inadvertently omitted from the pre-October 2006 NDPSC Meeting gazette notice. On this basis, the Committee agreed to consider this matter at the February 2007 NDSPC Meeting.

Members noted the following pre-meeting comments from the **XXXXX:**

- **XXXXX** expressed concern that harmonisation decisions given effect before the ANZTPA became operational could adversely impact on products which may require to be relabelled to reflect new product registration information, particularly OTC products which may be re-registered under the ANZTPA arrangement. This also meant that in addition to label changes, product documents such as Certified Product Details may need to be amended accordingly if registration details were altered. The Committee was of the view that scheduling decisions which came into effect before the ANZTPA became operational should not have any impact on labelling. It was noted that the approved nomenclature of medicines required on product labels were not based on SUSDP entries but on the approved ingredient names established by the TGA and eventually the ANZTPA. In regards to the concern on warning statements and safety directions for medicines listed in the SUSDP, members noted that these were enforced at registration through compliance with the *Required Advisory Statements for Medicine Labels* (RASML), not the SUSDP, and therefore scheduling decisions should not have such ramifications on labelling.
- **XXXXX** proposed the following amendments to the recommendations in Table 1:
  - Alendronic acid, alendronate sodium monohydrate and alendronate sodium trihydrate should be listed separately in the SUSDP.

    Members noted that listing alendronic acid in the SUSDP would capture all salts and derivatives including alendronate sodium monohydrate and alendronate sodium trihydrate.
  - Recommendations relating to ciclopirox, colaspase, ergocalciferol, goserelin, levocetirizine, lithium, metronidazole, nicotine, protamine sulphate and vitamin D were supported and **XXXXX** asked for the right to comment on subsequent decisions.
  - The proposed class entry for heparin to harmonise with New Zealand and the approach of separately listing low molecular weight heparins including enoxaparin and logiparin was supported.

- A separate Schedule 4 entry for hyaluronidase was supported. It was also pointed out that the information in Table 1 considered at the June 2006 NDPSC Meeting incorrectly stated that there were no products listed on the ARTG containing hyaluronidase.

  The Committee was advised that there was one injectable product and two medical devices containing hyaluronidase listed on the ARTG. The Committee agreed to foreshadow harmonisation with New Zealand and list the enzyme, hyaluronidase, in Schedule 4 of the SUSDP as this was currently unscheduled.

- The recommendations relating to Macrogol 3350, sodium valproate and triamcinolone were supported.

The Committee's attention was drawn by a member to the anomaly where an Appendix C substance, aminophenazone, which is also known as amidopyrine, was included in Schedule 4 to harmonise with the New Zealand Prescription Medicine status at the February 2006 NDPSC Meeting. The Committee agreed to delete the Schedule 4 entry for amidopyrine which was included in SUSDP 21 Amendment 1 and to include this substance in the list of medicines for which harmonisation could not be achieved at this time. New Zealand was to be advised of this outcome.

DECISION 2006/48 - 1

On the grounds of harmonisation, the Committee agreed to amend the SUSDP based on the recommendations in Table 1 which was endorsed at the June 2006 NDPSC Meeting with minor amendments to reflect the outcome of matters discussed and agreed to at this Meeting.

Schedule 2 – Amendments

CICLOPIROX – amend entry to read:

CICLOPIROX in preparations for dermal use containing 2 per cent or less of ciclopirox **except** in preparations for dermal use for the treatment of tinea pedis.

DICYCLOMINE – delete entry.

LITHIUM – amend entry to read:

LITHIUM in preparations for dermal use containing 1 per cent or less of lithium **except**:

(a) when present as an excipient at 0.25 per cent or less of lithium; or

(b) in preparations containing 0.01 per cent or less of lithium.

MERCURIC OXIDE – delete entry.

SILVER – amend entry to read:

SILVER for therapeutic use **except**:

(a) in solutions for human oral use containing 0.3 per cent or less of silver when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or

(b) in other preparations containing 1 per cent or less of silver.

TERBINAFINE – amend entry to read:

TERBINAFINE for dermal use **except** in preparations for the treatment of tinea pedis.

TRIAMCINOLONE – amend entry to read:

TRIAMCINOLONE in aqueous nasal sprays delivering 55 micrograms or less of triamcinolone per actuation when the maximum recommended daily dose is no greater than 220 micrograms, for prophylaxis or treatment of allergic rhinitis for up to 6 months in adults and children 12 years of age and over.

Schedule 3 – New Entry

CLEMASTINE in preparations for oral use.

Schedule 3 – Amendments

CICLOPIROX – amend entry to read:

CICLOPIROX in preparations for dermal use **except**:

(a) when included in Schedule 2; or

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

CIMETIDINE – amend entry to read:

CIMETIDINE in a primary pack containing not more than 14 days supply.

GLYCOPYRROLATE (glycopyrronium) – amend entry to read:

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

MACROGOL 3350 – amend entry to read:

MACROGOLS in preparations for oral use for bowel cleansing prior to diagnostic, medical or surgical procedures.

MALDISON (malathion) – amend entry to read:

MALATHION in preparations for human external use **except** in preparations containing 2 per cent or less of malathion.

TRIAMCINOLONE – amend entry to read:

TRIAMCINOLONE for buccal use in preparations containing 0.1 per cent or less of triamcinolone in a pack of 5 g or less.

Schedule 4 – New Entries

CEPHAELIS IPECACUANHA **except** in preparations containing 0.2 per cent or less of emetine.

COBALT for therapeutic use.

DIBOTERMIN.

DIHYDROTACHYSTEROL.

EPINASTINE.

ETHIONAMIDE.

ETHYLHEXANEDIOL.

FLUORESCEIN in preparations for injection.

GEMIFLOXACIN.

HEXOPRENALINE.

IBRITUMOMAB.

LEVOSIMENDAN.

LOGIPARIN for internal use.

MELAGATRAN.

MERCURIC OXIDE for human therapeutic use.

METHYL MERCURY for therapeutic use.

NIMORAZOLE.

PEGINTERFERON.

PERMETHRIN for human therapeutic use **except** in preparations containing 5 per cent or less of permethrin.

PHENISATIN.

PIRACETAM.

RIFAMYCIN.

RIFAPENTINE.

THYROTROPHIN-RELEASING FACTOR.

VIPRINIUM.

XIMELAGATRAN.

Schedule 4 – Amendments

ACTINOMYCIN D (Dactinomycin) – amend entry to read:

DACTINOMYCIN.

AGALSIDASE ALFA – amend entry to read:

AGALSIDASE.

AGALSIDASE BETA – delete entry.

ALCURONIUM SALTS – amend entry to read:

ALCURONIUM.

ALENDRONATE SODIUM – amend entry to read:

ALENDRONIC ACID.

AMIDOPYRINE – delete entry.

ASPIDOSPERMA QUEBRACHO – delete entry.

BENZILONIUM BROMIDE – amend entry to read:

BENZILONIUM.

CHYMOPAPAIN – amend entry to read:

CHYMOPAPAIN for human therapeutic use.

CLEMASTINE – amend entry to read:

CLEMASTINE **except** when included in Schedule 3.

COLASPASE (L-asaraginase) – amend entry to read:

COLASPASE.

CYCLOPROPANE – amend entry to read:

CYCLOPROPANE for therapeutic use.

DARBEPOETIN ALFA – amend entry to read:

DARBEPOETIN.

DECAMETHONIUM SALTS – amend entry to read:

DECAMETHONIUM.

DEMECARIUM BROMIDE – amend entry to read:

DEMECARIUM.

DICHLOROPHEN – amend entry to read:

DICHLOROPHEN for human therapeutic use.

DICYCLOMINE – amend entry to read:

DICYCLOMINE.

DIPHEMANIL METHYLSULPHATE – amend entry to read:

DIPHEMANIL **except** in preparations for dermal use.

DROTRECOGIN ALFA – amend entry to read:

DROTECOGIN.

EDROPHONIUM SALTS – amend entry to read:

EDROPHONIUM.

EFORMOTEROL (formoterol) – amend entry to read:

FORMOTEROL.

EMEPRONIUM SALTS – amend entry to read:

EMEPRONIUM.

ENFLURANE – amend entry to read:

ENFLURANE for therapeutic use.

EPOETIN ALFA – amend entry to read:

EPOETINS.

EPOETIN BETA – delete entry.

EPROSARTAN MESYLATE – amend entry to read:

EPROSARTAN.

ETILEFRIN HYDROCHLORIDE – amend entry to read:

ETILEFRIN.

FLUOCINOLONE ACETONIDE – amend entry to read:

FLUOCINOLONE.

FLUROXENE – amend entry to read:

FLUROXENE for human therapeutic use.

FORMEBOLONE (formyldienolone) – amend entry to read:

FORMEBOLONE.

FOSPHENYTOIN SODIUM – amend entry to read:

FOSPHENYTOIN.

GLYCOPYRROLATE (glycopyrronium) – amend entry to read:

GLYCOPYRRONIUM in preparations for injection.

GOSERELIN ACETATE – amend entry to read:

GOSERELIN.

HALOTHANE – amend entry to read:

HALOTHANE for therapeutic use.

HEPARIN – amend entry to read:

HEPARINS for internal use **except** when separately specified in this Schedule.

HEXAMETHONIUM BROMIDE – amend entry to read:

HEXAMETHONIUM.

HEXOCYCLIUM METHYLSULPHATE – amend entry to read:

HEXOCYCLIUM.

ISOFLURANE – amend entry to read:

ISOFLURANE for therapeutic use.

LANATOCIDE C – amend entry to read:

LANATOSIDES.

LAUDEXIUM METHYLSULPHATE – amend entry to read:

LAUDEXIUM.

LAURETH-9 – delete entry.

LAUROMACROGOLS – amend entry to read:

LAUROMACROGOLS in preparations for injection **except**:

(a) when present as an excipient; or

(b) when separately specified in these Schedules.

LEAD COMPOUNDS – amend entry to read:

LEAD for human therapeutic use.

LIOTHYRONINE SODIUM (Triiodothyronine) – amend entry to read:

LIOTHYRONINE.

LITHIUM – amend entry to read:

LITHIUM for therapeutic use **except**:

(a) when included in Schedule 2;

(b) when present as an excipient in preparations for dermal use containing 0.25 per cent or less of lithium; or

(c) in preparations containing 0.01 per cent or less of lithium.

METHACHOLINE SALTS – amend entry to read:

METHACHOLINE.

METHANDIENONE (metandienone) – amend entry to read:

METANDIENONE.

METHANTHELINIUM BROMIDE – amend entry to read:

METHANTHELINIUM.

METRONIDAZOLE BENZOATE (benzoyl metronidazole) – delete entry.

MITOZANTRONE (mitoxantrone) – amend entry to read:

MITOXANTRONE.

NITROUS OXIDE – amend entry to read:

NITROUS OXIDE for therapeutic use.

OCTATROPINE METHYLBROMIDE – amend entry to read:

OCTATROPINE.

OXITROPIUM SALTS – amend entry to read:

OXITROPIUM.

OXYPHENONIUM BROMIDE – amend entry to read:

OXYPHENONIUM.

PANCURONIUM BROMIDE – amend entry to read:

PANCURONIUM.

PENTAERYTHRITOL TETRANITRATE – amend entry to read:

PENTAERYTHRITYL TETRANITRATE.

PENTAMETHONIUM BROMIDE – amend entry to read:

PENTAMETHONIUM.

PENTOLINIUM SALTS – amend entry to read:

PENTOLINIUM.

PERHEXILENE – amend entry to read:

PERHEXILINE.

PHENETHICILLIN – amend entry to read:

PHENETICILLIN.

PHENTHIMENTONIUM BROMIDE – amend entry to read:

PHENTHIMENTONIUM.

PIPECURONIUM BROMIDE – amend entry to read:

PIPECURONIUM.

PIPENZOLATE BROMIDE – amend entry to read:

PIPENZOLATE.

PORACTANT ALFA – amend entry to read:

PORACTANT.

PRAMPINE SALTS – amend entry to read:

PRAMPINE.

PREGNENOLONE ACETATE – amend entry to read:

PREGNENOLONE.

PROTAMINE SULFATE – amend entry to read:

PROTAMINE.

QUININE – amend entry to read:

QUININE for human therapeutic use **except** when the maximum recommended daily dose is 50 mg or less of quinine.

RABIES VACCINES – amend entry to read:

RABIES VACCINE.

RAPACURONIUM BROMIDE – amend entry to read:

RAPACURONIUM.

RIFAMPICIN (rifamycin) – amend entry to read:

RIFAMPICIN.

RIMITEROL HYDROBROMIDE – amend entry to read:

RIMITEROL.

ROCURONIUM BROMIDE – amend entry to read:

ROCURONIUM.

SEMISODIUM VALPROATE – amend entry to read:

VALPROIC ACID.

SODIUM VALPROATE – delete entry.

STROPHANTHIN-K – amend entry to read:

STROPHANTHINS.

SUXAMETHONIUM SALTS – amend entry to read:

SUXAMETHONIUM.

SUXETHONIUM BROMIDE – amend entry to read:

SUXETHONIUM.

TERBINAFINE – amend entry to read:

TERBINAFINE **except**:

(a) when included in Schedule 2; or

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

TETRAETHYLAMMONIUM SALTS – amend entry to read:

TETRAETHYLAMMONIUM.

THIACETAZONE – amend entry to read:

THIOACETAZONE.

THIOUREA – amend entry to read:

THIOUREA for therapeutic use **except** in preparations containing 0.1 per cent or less of thiourea.

THIOTEPA (triethylene thiophosphoramide) – amend entry to read:

THIOTEPA.

THYROTROPHIN (T.S.H) – amend entry to read:

THYROTROPHIN.

TIEMONIUM IODIDE – amend entry to read:

TIEMONIUM.

TIROFIBAN HYDROCHLORIDE – amend entry to read:

TIROFIBAN.

TOLONIUM CHLORIDE – amend entry to read:

TOLONIUM.

TOLTERODINE TARTRATE – amend entry to read:

TOLTERODINE.

TRAZADONE – amend entry to read:

TRAZODONE.

TRICHLOROETHYLENE – amend entry to read:

TRICHLOROETHYLENE for therapeutic use.

TROMETAMOL – amend entry to read:

TROMETAMOL in preparations for injection **except** in preparations containing 3 per cent or less of trometamol.

UROFOLLITROPHIN – amend entry to read:

UROFOLLITROPIN.

VERCURONIUM BROMIDE – amend entry to read:

VERCURONIUM.

VINYL ETHER – amend entry to read:

VINYL ETHER for therapeutic use.

VITAMIN D – amend entry to read:

VITAMIN D for human therapeutic use **except** in preparations containing 25 micrograms or less of vitamin D per recommended daily dose.

The following entry for amidopyrine was published in SUSDP 21 Amendment 1 which should be deleted as the substance is already listed in Appendix C as aminophenazone.

Schedule 4 – ERRATUM

AMIDOPYRINE – delete entry.

Schedule 5 – Amendment

PERMETHRIN – amend entry to read:

PERMETHRIN (excluding preparations for human therapeutic use):

(a) in preparations containing 25 per cent or less of permethrin; or

(b) in preparations for external use, for the treatment of dogs, containing 50 per cent or less of permethrin when packed in single use containers having a capacity of 4 mL or less,

except in preparations containing 2 per cent or less of permethrin.

Schedule 6 – Amendment

PERMETHRIN – amend entry to read:

PERMETHRIN **except**:

(a) when included in Schedule 4 or 5;

(b) in preparations for human therapeutic use containing 5 per cent or less of permethrin; or

(c) in preparations containing 2 per cent or less of permethrin.

Schedule 7 – Amendment

CHOLECALCIFEROL – amend entry to read:

COLECALCIFEROL for use as a rodenticide.

Appendix D – Amendments

DARBEPOETIN ALFA – amend entry in paragraph 5 to read:

DARBEPOETIN.

EPOETIN ALFA – amend entry in paragraph 5 to read:

EPOETINS.

EPOETIN BETA – delete entry in paragraph 5.

UROFOLLITROPHIN – amend entry in paragraph 1 to read:

UROFOLLITROPIN (human follicle-stimulating hormone) for human use.

INDEX For SUSDP 22 Consolidation – Amendments

Cross-reference asaraginase to colaspase.

Cross-reference Aspidosperma quebracho to yohimbine.

Cross-reference calcium folinate to folinic acid.

Cross-reference chlorquinaldol to clioquinol.

Cross-reference colecalciferol and ergocalciferol to vitamin D.

Cross-reference chloromesterone to dehydrochloromethyltestosterone.

Cross-reference 4-chlorotestosterone to clostebol.

Cross-reference ipecacuanha to both Cephaelis acuminata and Cephaelis ipecacuanha.

Cross-reference halquinol to clioquinol.

Cross-reference laureth-9 to lauromacrogols.

Cross-reference levocetirizine to cetirizine.

Cross-reference thyroid stimulating hormone to thyrotrophin.

Cross-reference triethylene thiophosphoramide to thiotepa.

1.8.1.2 NEW MEDICINES IN NEW ZEALAND (MCC MEETING 34 & 35): ADRAFINIL, EXENATIBE, SITAGLIPTIN PHOSPHATE, SORAFENIB TOSYLATE, TELBIVUDINE, VARENICLINE TARTRATE

PURPOSE

The Committee considered harmonisation of scheduling of new medicines which were recently classified in New Zealand as Prescription Only medicines.

BACKGROUND

The New Zealand MCC Meetings 34 and 35, held in June 2006, agreed to classify adrafinil, exenatide, sitagliptin, sorafenib, telbivudine and varenicline as Prescription Only medicines in New Zealand. These medicines were not scheduled in Australia and on the grounds of harmonisation were included on the agenda of the NDPSC for consideration.

DISCUSSION

Members were advised that there were no products found on the ARTG containing adrafinil, exenatide, sitagliptin, sorafenib, telbivudine or varenicline.

Members noted the following information on the MCC minutes:

<u>34th MCC Meeting</u>

Adrafinil

- Adrafinil is a central stimulant and alpha(1)-adrenergic agonist chemically related to modafinil. It is usually used to treat mental function impairment in the elderly. Off-label use by individuals wishing to avoid fatigue has been reported.
- Adrafinil is a prodrug; it is primarily metabolized *in vivo* to modafinil, resulting in nearly identical pharmacologic effects. Unlike modafinil, however, it takes time for the metabolite to accumulate to active levels in the bloodstream.

- MCC agreed to include adrafinil as a Prescription Only medicine on the grounds of its abuse potential.

35th MCC Meeting

Exenatide

- Exenatide is an incretin mimetic agent that enhances glucose dependent insulin excretion and mimics several other antihyperglycemic actions of the incretin glucagon-like-peptide1 (GLP-1).
- Exenatide can improve glycaemic control in patients with type 2 diabetes by lowering fasting and postprandial glucose concentrations.
- The proposed indication is as adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea.

Varenicline

- Varenicline is a highly selective partial agonist of the $\alpha_4\beta_2$ acetylcholine nicotinic receptor that was specifically designed for use in smoking cessation. Mainly found in the brain, this receptor mediates the reinforcing properties of nicotine in animal models.
- Because of its agonist properties, varenicline is expected to reduce the severity of nicotine craving and nicotine withdrawal symptoms experienced upon cessation of smoking.
- Additionally, because of its antagonist properties, varenicline is expected to reduce the satisfaction associated with smoking, thereby decreasing the likelihood that a lapse during a quit attempt will lead to a return to regular smoking. These two properties are expected to provide increased rates of abstinence, both at the end of the treatment and in the long term.
- The proposed indication is for smoking cessation.

Sitagliptin

- Sitagliptin phosphate is an orally-active, potent, and highly selective inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes.
- The DPP-4 inhibitors are a class of agents that act as incretin enhancers. By inhibiting the DPP-4 enzyme, sitagliptin phosphate increases the levels of two known active incretin hormones, glucagons-like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP).
- Incretin hormones physiologically regulate blood glucose levels by increasing insulin response from pancreatic beta cells and suppressing glucagon secretion from pancreatic alpha cells when blood glucose levels are normal or elevated. These effects are not observed when blood glucose levels are low.

- Sitagliptin phosphate differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma PPARγ agonists, alpha-glucosidase inhibitors, and amylin analogues.
- Sitagliptin phosphate is indicated:

  - as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus.

  - in patients with type 2 diabetes mellitus to improve glycaemic control in combination with metformin or a PPARγ agonist when diet and exercise, plus the single agent, do not provide adequate glycaemic control.

Telbivudine

- Telbivudine is a specific and selective nucleoside with preferential inhibition of the synthesis of the 2nd strand HBV DNA synthesis.
- Telbivudine is a synthetic thymidine nucleoside analogue with activity against HBV DNA polymerase. It is efficiently phosphorylated by cellular kinases to the active triphosphate form, which has an intracellular half-life of 14 hours.
- Telbivudine-5'-phosphate inhibits HBV DNA polymerase by competing with the natural substrate, thymidine 5'-triphosphate. Incorporation of telbivudine-5'-triphosphate into viral DNA causes DNA chain termination, resulting in inhibition of HBV replication.
- The proposed indication is the treatment of chronic hepatitis B in patients with evidence of viral replication and active liver inflammation.

Sorafenib

- Sorafenib is a multikinase inhibitor targeting both tumour cells and the tumour vasculature. Sorafenib inhibits tumour growth of the murine renal cell carcinoma, RENCA, and a broad spectrum of human tumour xenografts in athymic mice accompanied by a reduction of tumour angiogenesis.
- The proposed indication is the treatment of patients with advanced renal cell carcinoma.
- Sorafenib is classified as Pregnancy Category D. Precautions include a pregnancy teratogenicity risk. Infant risk from breast feeding could not be ruled out.

Members noted that notification of the intent to consider the scheduling of the new medicines, on the grounds of harmonisation, were not included in the pre-October 2006 NDPSC Meeting gazette notice due to the timing of release of the MCC minutes.

OUTCOME

The Committee agreed to foreshadow the inclusion of adrafinil, exenatide, sitagliptin, sorafenib, telbivudine and varenicline in Schedule 4 of the SUSDP on the grounds of harmonisation and that appropriate use of these medicines would require diagnosis of medical condition and management of treatment by a medical practitioner.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 4 - New entries

ADRAFINIL.

EXENATIDE.

SITAGLIPTIN.

SORAFENIB.

TELBIVUDINE.

VARENICLINE.

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

2.1 SUSDP, PART 1

No items were considered.

2.2 SUSDP, PART 2

No items were considered.

2.3 SUSDP, PART 3

2.3.1 ITEM DELETED

2.3.2 STORAGE STATEMENTS FOR SCHEDULE 2 & SCHEDULE 3 MEDICINES

PURPOSE

The Committee considered a proposal to amend Part 3, Paragraph 43.

BACKGROUND

Currently the SUSDP recommends that States and Territories mandate the storage of poisons in Schedule 2, Schedule 3, Schedule 4 and Schedule 7 under Part 3, paragraphs 43 and 44:

43. A person who sells or supplies Schedule 2 poisons must keep those poisons in such a way that public access is restricted.

44. A person who sells or supplies Schedule 3, Schedule 4 or Schedule 7 poisons must keep those poisons in a part of the premises to which the public does not have access.

The June 2005 NDPSC Meeting discussed a request for the Committee to consider the storage requirements of poisons, in particular those in Schedule 3. The Committee noted that interpretation of paragraph 43 and 44 varied between jurisdictions and agreed that these paragraphs may not reflect the contemporary situation. Members therefore agreed to refer this matter to NCCTG for policy consideration.

DISCUSSION

NCCTG advised the Committee of its consideration of the issues raised at the June 2005 NDPSC Meeting. Members particularly noted:

- The May 2006 NCCTG Meeting agreed that the SUSDP should be amended to reflect the general requirements for the availability of Schedule 2 medicines, noting:
  - The current differing interpretations of paragraphs 43 and 44 did not support national uniformity.
  - A consistent approach was supported by the PSA's *Standards for the Provision of Pharmacist Only and Pharmacy Medicines in Community Pharmacy*.
  - Restrictions on access to Schedule 2 products in some States and Territories were imposed through "supply only from a pharmacy" i.e. there were no requirements for physical restrictions on access within the pharmacy.
  - Customers should not be able to self-select Schedule 3 products.
  - There may be increased pressure on a pharmacist to supply a certain Schedule 3 medicine if it was located in sight behind the counter.
  - It may be appropriate for some Schedule 3 medicines to be located in a more secure area (such as the dispensary) but this should be a matter of professional practice.
  - There should be a graduated set of storage controls in place for medicines available only from the pharmacy based on unrestricted access (open shelf), behind the counter access by pharmacy staff only and the dispensary.

Taking the above matters into account NCCTG agreed that:

- Paragraph 43 should be amended to read "A person who sells or supplies Schedule 2 poisons must keep those poisons in such a way that public access to advice from a pharmacist is available if required".
- The amendment would be a wording change only which would not impact on current pharmacy practice and that no consultation was required to be undertaken by the NDPSC. (Members noted Secretariat advice that the proposed amendment was included in the pre-October 2006 NDPSC Meeting gazette notice as it has been standard practice for the Committee to consult on changes to Parts 1-3 of the SUSDP even though consultation was only mandated for Schedule changes.)
- Consideration of any significant change in arrangements for the storage of Schedule 2 and Schedule 3 medicines should be delayed until the outcome of the Schedule 2/ Schedule 3 study (in response to Galbally Recommendation 5) was known.

The Committee also recalled the following from its June 2006 consideration of these issues:

- The Committee agreed that the crux of the current storage requirements issue was how jurisdictions interpret the intent contained in paragraphs 43 and 44.
- Members discussed the difference in jurisdictional interpretations of the "restricted access" requirement for Schedule 2 in paragraph 43:
    - Schedule 2 products in some jurisdictions were available for self-selection ("restricted" enforced at the purchase stage).
    - Some jurisdictions mandated that Schedule 2 products must be within a set distance from the dispensary while others mandated that Schedule 2 products be behind the service counter or in the dispensary ("restricted" in all these cases appeared to be interpreted to mean that the pharmacist exerted control which restricted public access, with the extent of this control varying by jurisdiction).
- Members also noted that there existed differences between the jurisdictions regarding storage restrictions for Schedule 3 products, including overlaps with the Schedule 2 requirements:
    - Some jurisdictions required Schedule 3 substances to be stored behind the counter or in the dispensary.
    - Other jurisdictions had a broader interpretation of "restricted access" and treated storage of Schedule 2 the same as Schedule 3, i.e. store so that the product was inaccessible to the public.
- In NSW, legislation for storage used the same phrasing for Schedules 3, Schedule 4 and Schedule 7, as NSW believed was implied by paragraph 44. NSW legislation stipulated "must keep the substance in a room or enclosure to which the public does not have access", interpreted to mean that dispensary storage was mandated.

- The Committee agreed that for the storage of Schedule 4 and Schedule 7 substances it was appropriate that these be in the dispensary or in a locked area to which there was no public access, as was current practice across the jurisdictions.
- It was suggested that jurisdictional divergences for storage of Schedule 2 and Schedule 3 products was a matter for NCCTG to consider resolving. A Member asserted that the intent of paragraph 43 was to have Schedule 2 products available in a pharmacy environment which enabled the consumers to readily communicate with the pharmacist if they needed additional advice. The Member also asserted that the intent of paragraph 44 was to have Schedule 3 products available with mandatory pharmacist intervention and counselling.
- Members agreed that paragraph 44, in dealing with Schedule 3, Schedule 4 and Schedule 7 together, did not reflect the contemporary situation in many jurisdictions. Particularly, some jurisdictions differentiate in how Schedule 3 products have to be stored compared to Schedule 4 products.
- The Committee noted that any change at the jurisdictional level of compliance could have large ramifications for the pharmacies who are complying with the existing interpretation of state legislation.

The Committee considered a **XXXXX** pre-meeting comment, and noted that:

- **XXXXX** asserted that the new wording for Paragraph 43 may be less restrictive than the existing wording because it could be interpreted that a pharmacy setting would always provide "public access to advice from a pharmacist… …if required" i.e. Schedule 2 products could be placed anywhere within the pharmacy premises.
- **XXXXX** asserted that unrestricted access to therapeutic products meant consumers may self-select without referral to advice from pharmacists or trained staff. **XXXXX** asserted that while self-selection was an important element of OTC medicines, pharmacists also regularly encountered consumers who were unaware of the potential for harm with Schedule 2 (and similar) products and when and why they should seek advice.
- **XXXXX** noted that storage requirements for medicines under ANZTPA are yet to be released.
- **XXXXX** therefore did not support the proposed amendment to paragraph 43 because:
    - The new wording could be interpreted as being less restrictive.
    - It could potentially allow unrestricted access to all Schedule 2 products within a pharmacy.
    - It would not necessarily enhance patient safety or promote quality use of medicines.
    - Through the different applications by States/Territories, the lack of consistency and uniformity across Australia will not be resolved.

- **XXXXX** suggested drafting of alternative wording would be useful.

The Committee considered the following from **XXXXX** pre-meeting comment:

- **XXXXX** did not support the proposed Paragraph 43 change and asserted that it would further weaken the regulatory framework for medicines in Australia. **XXXXX** also believed that the proposed amendment was open to interpretation.
- **XXXXX** asserted that Australia {*and New Zealand*} was in a unique position of having three non-prescription medicines' categories (Pharmacy, Pharmacist Only and Exempt from Scheduling) and that more medicines are available OTC than in similar countries (UK, Canada, France and USA). **XXXXX** asserted that with this wider availability of medicines without prescription safe-guard controls, it was important that the storage requirements over these OTC medicines were maintained.
- **XXXXX** noted that in most States and Territories Schedule 2 classification restricted public access to medicines in order to:
  - promote the opportunity for advice and information from a pharmacist;
  - manage the risk of abuse and misuse; and
  - manage the risk of misdiagnosis and inappropriate drug selection.
- **XXXXX** also reiterated the June 2006 NDPSC discussion about the current jurisdictional Schedule 2 storage requirements, particularly noting that in some States these storage requirements did not allow for self selection by consumers.
- **XXXXX** also understood that the proposed Paragraph 43 may allow greater public access within licensed person premises such as country stores which have no access to a pharmacist.
- **XXXXX** acknowledged that consumers have a shared responsibility for their health and should be able to self-select Schedule 2 medicines. **XXXXX** contended, however, that many consumers do not self-diagnose, do not select medicines appropriately and are unaware of the risks associated with a medicine they may have self-selected. A lack of storage restrictions would promote self-selection and the likelihood of the person checking with the pharmacist (or trained staff member) would decrease, increasing the likelihood of inappropriate medicine use.
- **XXXXX** asserted that the proposed amendment makes a mockery of the profession's significant attempts to implement professional standards to support the quality use of medicines (QUM). **XXXXX** believed it was important that there were storage restrictions for Schedule 2 medicines to support the pharmacist's oversight of requests and to allow intervention and/or counselling as required.

  Members noted a pharmacy practice article (September 2006, Pharmacy Review) which discussed storage policy for Schedule 2 and Schedule 3 medicines. The policy stated that Schedule 2 medicines were to be "stored in the Professional Services Area of the pharmacy, to be clearly distinguished from the general trading area". The

article also noted that, while not mandated, the Pharmacy Guild of Australia's best practice position was to have no direct access by consumers to Schedule 2 medicines.

- **XXXXX** asserted that if storage in any part of the pharmacy was allowed (including front-of-shop display bins, a practice often encouraged by sponsors keen to maximise customer through-put and sales), pharmacists responsible for the supervision of these products will find it difficult to supervise all transactions.
- **XXXXX** noted that the Galbally Review asserted that, in many cases, the risk to the individual purchasing a Pharmacy Medicine may be high or higher than the risk to a person purchasing a Pharmacist Only Medicine. **XXXXX** agreed that the safety profile of Pharmacy Medicines was such that they require pharmacist supervision.
- **XXXXX** noted that the Galbally Review also advocated a focus on the consumer rather than the product. It recommended that a risk-based code of practice could ensure that more effective counselling was provided when necessary, not because of the product's schedule "but because for that consumer the risk-based triggers were activated" and that "the triggers which should elicit pharmacist intervention should focus more on the particular consumer than on the substance". The implementation of this approach would be undermined if self-selection of medicines was promoted and the current storage restrictions were weakened.
- **XXXXX** asserted that it was imperative that the SUSDP impose some restriction to allow regulatory authorities to ensure that the supply of medicines was conducted professionally and responsibly and the public interest was protected. **XXXXX** recommended that the restrictions outlined in the current Paragraph 43 be retained or adapted to ensure consistency with current State and Territory legislative requirements with respect to storage of Schedule 2 poisons. (Members noted that QUM professional guidelines would still be in place, regardless of the amendment).

A pre-meeting comment from **XXXXX** supported the proposed amendment. **XXXXX** considered that this was a sensible and practical change that more accurately reflected the appropriate storage conditions of Schedule 2 Poisons.

A pre-meeting comment from **XXXXX** also supported the proposed amendment to Paragraph 43 as providing greater clarity while also creating what **XXXXX** asserted was the necessary and appropriate distinction between Schedule 2 and Schedule 3 poisons i.e. that Schedule 3 poisons should not be available for self-selection to ensure the mandatory intervention by a pharmacist while for Schedule 2 medicines advice was available when requested by consumers which did not preclude self-selection.

XXXXX advised that current professional practice was about restricting Schedule 2 access to promote consumers seeking pharmacist advice, and that the apparent relaxation of controls could send a message counter to that of the professional bodies' QUM. In response, a Member noted that while NCCTG's recommended paragraph may seem to be a relaxation of controls for some jurisdictions, there was nothing to stop individual pharmacies applying additional controls as may be dictated by professional practice.

A Member also asserted that the whole point of there being a Schedule 2 category was to control access by requiring these medicines to only be available in a pharmacy, not to control where in a pharmacy they had to be stored or sold. The Member noted that the original intent was to differentiate Schedule 2 from Schedule 3, in that Schedule 2 products could be self-selected and that if the consumer wished to seek advice then a pharmacist's advice would be available.

A Member noted that currently every State and Territory had laws restricting Schedule 2 products to pharmacies (with some licensed exemptions), and also requiring a pharmacist on the premises whenever the pharmacy was open. The Member therefore questioned what the proposed paragraph was supposed to add. Another Member agreed that harmonisation at this basic level was a necessary first step to any longer term moves towards national consistency.

A Member noted that the wording did not reflect the current practice of Schedule 2 licenses in which Schedule 2 products were supplied by non-pharmacies using State or Territory licensing – e.g. remote rural shops, optometrists, nurse practitioners, midwives, podiatrists, physiotherapists etc. The proposed wording mandated that "advice from a pharmacist is available if required", a requirement that was not appropriate for many of these non-pharmacy suppliers. The existing paragraph 43 did apply to these alternative suppliers as the mandatory requirement was "public access is restricted". A Member asserted that a similar difference between the new and existing paragraph appeared to also apply to supply by doctors and to wholesalers of Schedule 2 products.

The Committee agreed that the proposed new paragraph 43 should only be read in reference to supply and sale in a pharmacy setting. The non-pharmacist supply and/or sale would remain a matter for individual State or Territory licensing. The Committee also noted that this paragraph did not restrict States or Territories from applying more stringent controls on pharmacies (and indeed was advised by a number of Jurisdictional Members that they would not be relaxing their current more restrictive access controls).

Another Member suggested that the proposed paragraph should perhaps have started with "A pharmacist…" instead of "A person…". The Committee noted, however, that this probably would not cover a pharmacist's assistant or any other pharmacy employee who would normally be involved in the sale of Schedule 2 products. Indeed, if "A pharmacist…", a strict reading of the paragraph could imply that a pharmacist would need to directly make each and every sale of a Schedule 2 product. The Members agreed that "A person…" remained the appropriate start to the proposed paragraph.

DECISION 2006/48 - 2

The Committee noted the NCCTG recommendation and agreed to:

- amend Part 3, Paragraph 43 to stipulate that the supply restriction for Schedule 2 Medicines was "public access to advice from a pharmacist is available if required"; and

- defer any consideration of Paragraph 44 until the matter had been considered by NCCTG.

PART 3 – MISCELLANEOUS REGULATIONS – Amendment

Storage – Paragraph 43 – Amend entry to read:

43. A person who sells or supplies Schedule 2 poisons must keep those poisons in such a way that public access to advice from a pharmacist is available if required.

2.4 SUSDP, PART 5

No items were considered.

AGRICULTURAL/VETERINARY, INDUSTRIAL AND DOMESTIC CHEMICALS

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

3.1 SULFENTRAZONE

PURPOSE

The Committee considered post-meeting correspondence in respect to the scheduling of sulfentrazone.

BACKGROUND

At June 2006 NDPSC Meetomg noted that **XXXXX** had sought approval of a new active constituent, sulfentrazone. **XXXXX**

XXXXX

The Committee agreed to include sulfentrazone in Schedule 7 of the SUSDP having regard to its toxicity and, in particular, its developmental and reproductive toxicity. This recommendation would come into effect on 1 January 2007.

DISCUSSION

The Committee noted post-meeting correspondence which had been received from **XXXXX**. **XXXXX** noted that:

- **XXXXX**

Prior to receiving the post-meeting correspondence from **XXXXX**, the Secretariat had been approached with a request that the Committee's recommendation not be progressed. The Secretariat advised that the Committee's decision to place sulfentrazone in Schedule 7 could now not be undone without further information and reconsideration by the Committee.

The applicant was informed that the SUSDP listed all substances, not just currently marketed substances and inclusion in the SUSDP was in no way any indication of a product being available. Also, should they wish to write to the Committee explaining that they have withdrawn their application with the APVMA, this correspondence would be put to the Committee as a post (June 2006) meeting submission.

The Committee was requested to consider setting-aside its decision to include sulfentrazone in Schedule 7 of the SUSDP, noting that the applicant did not agree with the toxicological assessment and did not have the opportunity to comment on **XXXXX** report prior to the June 2006 NDPSC Meeting .

The Committee received, from **XXXXX**, a detailed account of the events which **XXXXX** contended had led to their inability to comment on the scheduling proposal put forward in **XXXXX** toxicological assessment report prior to consideration by the NDPSC. **XXXXX.**

The Committee was mindful of the fact that confusing circumstances had surrounded the timing of the referral of **XXXXX** toxicological assessment report to **XXXXX** which had in turn impacted upon the applicant's opportunity to comment on the report prior to consideration of scheduling by NDPSC. The Committee therefore agreed to set aside its previous decision and to reconsider the matter at its February 2007 NDPSC Meeting.

Whilst the Committee was sympathetic to **XXXXX** and the mitigating circumstances surrounding their submission, the Committee wished to make it clear that the decision in no way set a precedent for future sponsors. The Committee only set aside the decision of the June 2006 NDPSC Meeting (and will re-gazette for the February 2007 NDPSC Meeting) to ensure that due process is followed in this particular instance.

The Committee was advised **XXXXX** and APVMA that to avoid similar confusion to that which had arisen in this matter, the **XXXXX** and APVMA would in future amend correspondence to applicants to make it clear that scheduling and associated issues subsequent to the completion of the **XXXXX** assessment should be addressed directly with the NDPSC Secretariat and not the **XXXXX** or APVMA.

DECISION 2006/48 – 3 (Set aside decision 2006/47-11)

The Committee noted the post-meeting comments received from **XXXXX** and agreed to set aside its previous decision.

OUTCOME

The Committee also agreed to foreshadow consideration of the inclusion of sulfentrazone in Schedule 7 at the February 2007 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 7 - New Entry

SULFENTRAZONE.

3.2 INDOXACARB

PURPOSE

The Committee considered a post-meeting submission in response to the scheduling of indoxacarb.

BACKGROUND

The June 2006 NDPSC Meeting noted that **XXXXX** submitted a data package to **XXXXX** via the APVMA, seeking registration of a new product **XXXXX** containing **XXXXX .**

Indoxacarb is an oxadiazone insecticide for use in the control of insect pests and is currently included in Schedule 6 of the SUSDP.

The application before the June 2006 NDPSC Meeting sought a cut-off from Schedule 6 for indoxacarb based on **XXXXX.**

XXXXX.

The Committee agreed to amend the entry for indoxacarb to reflect that it is a mixture of the R and S enantiomers.

The Committee further agreed to include indoxacarb in Schedule 5 of the SUSDP when included in preparations containing 1 per cent or less of indoxacarb and when packed in child resistant packaging.

DISCUSSION

XXXXX provided a post-meeting submission seeking amendment to the Committee's decision on the scheduling of indoxacarb.

XXXXX specifically noted that:

- Imposing a CRC is not necessary and may inadvertently capture other indoxacarb-containing products for which a CRC is unnecessary.
- The acute toxicological studies provided for products containing low concentrations of indoxacarb support a cut-off to unscheduled status.
- **XXXXX**
- Packaging is not related to scheduling and should be considered as part of the risk assessment of the registration process.
- **XXXXX**
- The requirement for CRCs will diminish the impact of CRCs when there is a real need.

XXXXX requested that the scheduling of low concentration indoxacarb products be reconsidered at the October 2006 NDPSC Meeting.

The Committee did not agree with the view expressed by **XXXXX** that packaging was not related to scheduling. Part 2 of the SUSDP addressed "Labels and Containers". The Committee further reaffirmed its view that the product as proposed to be formulated and packaged presented a potential risk to children and therefore a CRC was appropriate. Should a new formulation for "commercialisation" be presented for APVMA approval, then the scheduling and the need for a CRC could be reviewed.

OUTCOME

The Committee agreed to confirm its decision (Decision 2006/47-10) to include indoxacarb in preparations containing one per cent or less of indoxacarb when packed in child resistant packaging in Schedule 5 of the SUSDP.

4. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

4.1 POTASSIUM AZELOYL DIGLYCINATE

PURPOSE

The Committee considered the scheduling of potassium azeloyl diglycinate (PAD).

BACKGROUND

PAD is the potassium salt of a condensation product of azelaic acid and glycine. Currently there is no entry for PAD in any of the Schedules.

The June 2005 NDPSC Meeting considered a submission from **XXXXX** requesting that PAD, asserted to be a derivative of azelaic acid, be exempt from the requirements of scheduling when used in cosmetic products at low concentrations. The Committee,

noting that the available toxicity data for PAD was deficient, agreed that the current scheduling of azelaic acid remained appropriate.

The June 2006 NDPSC Meeting noted a new submission from **XXXXX** that again requested that PAD be exempt when used in cosmetic products at low concentrations. The Committee, while it agreed that PAD was not a derivative of azelaic acid, decided to defer consideration of the scheduling of PAD to allow time for an additional evaluation of toxicological data and the testing methods used to derive this information. The Committee further agreed to foreshadow consideration of the usage of "derivative" in the SUSDP, including the possibility of including a definition (see item 1.7.1.3).

DISCUSSION

Members recalled that the June 2006 NDPSC Meeting noted that the data in **XXXXX** submission indicated a low toxicological profile for PAD and that PAD was most likely to be either unscheduled or Schedule 5 based on this information. However, concerns remained over the acceptability of the test methods employed to generate the toxicological data.

The Committee was advised that **XXXXX** had undertaken an additional evaluation of the **XXXXX** submission's toxicological data. Members particularly noted the following from this evaluation:

- Data in the following table was based on information **XXXXX** submitted for a product containing 28-32% PAD in aqueous solution **XXXXX:**

Endpoint	***Result***	***Comment***
Acute toxicity	Oral(rat)LD_{50}: >2000 mg/kg bw Dermal: No data Inhalation: No data	30% PAD tested. Therefore, LD_{50} for 100% PAD is ~ > 667 mg/kg bw.
Skin Irritation	Non-irritant in **XXXXX** test. Non-irritant at 7% in **XXXXX** human volunteers	Non-validated test; concentration not provided
Respiratory Irritation	No data	
Eye Irritation	Slight irritant at up to 100% in *in-vitro* **XXXXX** test Minimal irritant in **XXXXX** test	Non-validated test; concentration not provided
Skin Sensitisation	Non-sensitising at 7% in **XXXXX** human volunteers. Non-sensitising at 5% in **XXXXX** human volunteers.	Non-validated test; no induction phase Non-validated test; no induction phase Non-validated test; no use of

	Non-sensitising at 5% in a repeat insult induction/challenge test in **XXXXX** volunteers.	maximally tolerated doses for induction phase
Respiratory Sensitisation	No data	
Phototoxicity	Non-phototoxic up to 100μg/ml in *in-vitro* **XXXXX** test	
Repeat dose toxicity	No data	
Mutagenicity	No data	
Carcinogenicity	No data	
Reproductive toxicity	No data	

- **XXXXX** asserted that the oral toxicity data above was consistent with a Schedule 5 entry or no requirement for scheduling, noting that **[XXXXX** had proposed a LD_{50} of > 5000 mg/kg bw for 30% PAD but **XXXXX** deemed this to be inappropriate as no study at 5000 mg/kg bw of 30% PAD was conducted.
- **XXXXX** also asserted the eye irritation potential for PAD at low concentrations (≤ 1%) was likely to be consistent with no requirement for scheduling, but drew the following issues to the Committee's attention:
  - The **XXXXX** study provided by **XXXXX** concluded that 30% PAD was non-irritating. However, **XXXXX** noted that the highest irritation score (IS) obtained was, according to the study classification scheme, at the highest margin of the non-irritant category. According to a review of different **XXXXX** protocols a test substance with this IS was commonly scored as a 'weak or slight irritant'. **XXXXX** also noted that the second *in-vitro* eye irritation test (yet to be internationally validated) provided by **XXXXX** predicted 30% PAD to be an ocular minimal irritant.
  - **XXXXX** also asserted that there were difficulties in establishing the irritant potential from current *in-vitro* tests alone. An overview of the European framework for animal testing indicated that *in-vitro* alternatives to *in-vivo* tests have been accepted for regulatory purposes for materials identified as severely irritating. However, chemicals that provide a negative reaction in *in-vitro* tests still require *in-vivo* tests to confirm the absence of eye irritation potential.
  - **XXXXX** acknowledged these limitations but agreed that 30% PAD was likely to be a slight eye irritant in humans.
- **XXXXX** agreed that 30% PAD was unlikely to be phototoxic.
- **XXXXX** also asserted that the skin sensitisation potential was consistent with no requirement for scheduling.
- **XXXXX** noted that the likely total exposures to PAD at proposed concentrations (≤ 1%) would be regarded as very low and limited to dermal and infrequent ocular routes.

XXXXX also drew the Committee's attention to **XXXXX** toxicity statements for azelaic acid, particularly:

- Data claiming that azelaic acid was non-mutagenic in an Ames assay, a HGPRT test in Chinese hamster ovary cells, a human lymphocyte test and a dominant lethal test in mice. The azelaic acid data also noted embryotoxic effects with maternally toxic doses (2,500 mg/kg bw/day in rats).
- Due to the lack of controlled studies in pregnant women, azelaic acid should be used during pregnancy only if clearly needed. Also, as there was a possibility of milk partitioning, a need for caution when administering products containing 20% azelaic acid to nursing mothers. Also noted was the possibility of allergic reactions from azelaic acid products. No references were provided for these claims.
- **XXXXX** advised that the levels of PAD proposed to be used in products (≤ 1%) were significantly lower than those for azelaic acid (20%) for which these precautions were noted. However, the **XXXXX** submission stated that the modification of azelaic acid to form PAD increased water solubility and bioavailability. Therefore, the extent to which these precautions should be extrapolated to low concentrations of PAD was not known.

XXXXX recommended that the Committee consider exempting from scheduling PAD at low concentrations (≤ 1%). Members were advised that the evaluator had confirmed that **XXXXX** did not have sufficient data to make a recommendation regarding a parent entry for PAD > 1%.

Members recalled the following from its June 2006 considerations:

- The proposed cosmetic products were expected to use PAD at levels of between 0.25 and 1.0%. The Committee was advised that there were no products listed on ARTG using PAD. PAD was not listed on the Australian Inventory of Chemical Substances (AICS). **XXXXX**
- The June 2006 NDPSC Meeting noted the following from the **XXXXX** evaluation:
    - **XXXXX** disagreed with **XXXXX** assertion that PAD was a derivative of azelaic acid. Members agreed that, for clarity, PAD should be considered a separate substance for the purposes of scheduling (i.e. not a derivative of azelaic acid and therefore may require a specific PAD entry in the SUSDP).
    - **XXXXX** asserted that it would require the following data to undertake a proper assessment for PAD:
        - Physical and chemical specifications.
        - Acute dermal toxicity, skin and eye irritation and skin sensitisation data.
        - Dermal/percutaneous absorption.
        - Repeated dose toxicity.
        - Mutagenicity/genotoxicity.

- **XXXXX** noted that most of these tests involved the use of animals and that there were to date no validated *in-vitro* alternative methods. **[XXXXX** therefore asserted that all deviations from this required set of data, including omissions, must be explained and scientifically justified.
- **XXXXX** provided a comment on the June **XXXXX** evaluation advising that there was insufficient time for **XXXXX** to provide the toxicological and chemical data required in the **XXXXX** evaluation.

Members were advised that **XXXXX** pre-meeting comment noted the SUSDP azelaic acid entries and asserted that PAD was a soluble azelaic acid derivative.

Members generally agreed that the data indicates that PAD was likely to be a low toxicity compound, and it was probable that Schedule 5 would be appropriate. However, the Committee also agreed that questions remained around the quality of the toxicological data and the use of *in-vitro* tests used in place of the standard *in-vivo* tests.

Members particularly considered the evaluator's comments on **XXXXX** assertion that the oral LD_{50} fell into GHS category 5 (i.e. > 5000 mg/kg bw). Members noted that testing had actually only been up to 2000 mg/kg bw of a 30% PAD solution (i.e. the oral LD_{50} was greater than ~667 mg/kg bw). The data provided did not allow the Committee or the evaluator to determine how much greater than 667 mg/kg bw the oral LD_{50} value could be. Members agreed that such data would probably give a value consistent with Schedule 5, but could not discount that the lower possible oral LD_{50} values would warrant a Schedule 6 entry. The Committee did agree that it was reasonable to consider a cut-off of 1% or less of PAD for cosmetic use.

DECISION 2006/48 - 4

The Committee agreed:

- to include a Schedule 6 parent entry for potassium azeloyl diglycinate as, while likely to have low acute oral toxicity, the identified deficiencies in the toxicology data and the uncertainty in relying on an extrapolation of the acute oral toxicity results in setting a parent entry warranted a cautious approach pending further information; and
- to exempt less than 1% PAD for cosmetic use from the requirements of scheduling as there was no significant safety issues for this use pattern and concentration.

Schedule 6 – New Entry

POTASSIUM AZELOYL DIGLYCINATE **except** in preparations for cosmetic use containing 1 per cent or less of potassium azeloyl diglycinate.

4.2 N-OLEYL-1, 3-DIAMINOPROPANE AND N-COCO-1, 3-DIAMINOPROPANE

PURPOSE

The Committee considered the scheduling of N-oleyl-1,3-diaminopropane and N-coco-1,3-diaminopropane.

BACKGROUND

Following the publication of the outcome in relation to C-Treat 6, **XXXXX** raised the issue of an apparent inconsistency between a decision in respect to the inclusion of N-tallow alkyl-1,3-propanediamine acetate and tallow alkylamine acetates in Schedule 6 and the decision taken in 2003 not to refer for scheduling N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane which were similar products and proposed for similar use, ie in the treatment of large industrial seawater cooling systems to control deposits, corrosion and marine growths. The decision not to refer N-oleyl-1,3-diamineopropane and N-coco-1,3-diaminopropane for consideration of scheduling was on the basis of the policy excluding industrial biocides from scheduling.

The Committee requested that N-oleyl-1,3-diaminopropane and N-coco-1,3-diaminopropane be considered for scheduling at the June 2006 NDPSC Meeting where it was agreed, based upon their highly irritating and corrosive effects on skin, eyes and mucosa, to foreshadow inclusion of N-oleyl-1,3 diaminopropane and N-coco-1,3-diaminopropane in Schedule 6 for consideration at the October 2006 NDPSC Meeting.

DISCUSSION

The Committee noted that it had not received any public comment on the gazetted proposal to include N-oleyl-1,3 diaminopropane and N-coco-1,3- diaminopropane in Schedule 6 of the SUSDP.

DECISION 2006/48 - 5

The Committee agreed to confirm its foreshadowed decision to include N-oleyl-1,3 diaminopropane and N-coco-1,3- diaminopropane in Schedule 6 of the SUSDP.

Schedule 6 - New entries

N-OLEYL-1,3-DIAMINOPROPANE.

N-COCO-1,3-DIAMINOPROPANE.

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

5.1 SUSDP, PART 4

No items were considered.

5.2 SUSDP, PART 5

5.2.1 ITEM DELETED

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

6.1 IBAFLOXACIN

PURPOSE

The Committee considered the scheduling of ibafloxacin.

BACKGROUND

XXXXX submitted data to support the approval of a new active, ibafloxacin **XXXXX**. Ibafloxacin is a tricyclic tetrahydroquinoline derivative belonging to the group of fluorinated 4-quinolones. It is a broad spectrum antibiotic with bactericidal action against gram -positive and gram-negative bacteria. **XXXXX.**

DISCUSSION

XXXXX had undertaken an assessment of the toxicology data submitted in support of the application.

XXXXX

Based on the low acute toxicity of ibafloxacin, its intended use as a therapeutic agent that requires professional veterinary advice and management prior to use, **XXXXX** has suggested that the NDPSC consider it appropriate for ibafloxacin to be included in Schedule 4 with no cut-off to Schedule 5.

DECISION 2006/48 - 6

Based on its intended use as an animal therapeutic agent requiring veterinary advice and management in its use, the Committee agreed that ibafloxacin for veterinary use be included in Schedule 4 of the SUSDP.

Schedule 4 - New entry

IBAFLOXACIN for veterinary use.

6.2 PRADOFLOXACIN

PURPOSE

The Committee considered the scheduling of pradofloxacin.

BACKGROUND

XXXXX had submitted a data package seeking registration of **XXXXX**

However, this item was withdrawn by **XXXXX** following pre-meeting gazettal of items for consideration at the October 2006 NDPSC Meeting.

DISCUSSION

XXXXX.

As the item has been withdrawn, it was suggested that consideration of this item be deferred.

OUTCOME

The Committee noted that this item had been withdrawn by **XXXXX** after publication of the pre-October 2006 NDPSC Meeting gazette notice and therefore agreed to defer consideration until a future application is received.

6.3 CLOTHIANDIN

PURPOSE

The Committee considered the scheduling of clothianidin.

BACKGROUND

XXXXX submitted an application for the registration of a new product, **XXXXX** Clothianidin is currently included in Schedule 6 of the SUSDP. **XXXXX** has requested that the new product be considered for inclusion in Schedule 5.

DISCUSSION

XXXXX had undertaken an assessment of the toxicological data provided in support of the registration of **XXXXX. XXXXX** noted the following:

- Clothianidin belongs to the nitroguanidine subgroup of second generation neonicotinoid insecticides that act at the nicotinic acetylcholine receptor.
- **XXXXX**
- On the basis of its high acute oral toxicity in mice, clothianidin was (previously) included in Schedule 6. A cut-off was not established as the product considered at the time also had an acute toxicological profile consistent with inclusion in Schedule 6.
- **XXXXX**

- **XXXXX** suggested that the NDPSC may wish to consider it appropriate to include clothianidin in preparations containing 20 per cent or less of clothianidin in Schedule 5 of the SUSDP.

For the information of the NDPSC, **XXXXX** also provided a copy of the Advisory Committee on Pesticides and Health (ACPH) discussion of clothianidin (October 2002). This consideration by ACPH had been requested by the NDPSC during its earlier consideration of clothianidin.

OUTCOME

The Committee agreed to foreshadow that, based on the acute toxicity, clothianidin in preparations containing 20 per cent or less of clothianidin be included in Schedule 5 of the SUSDP.

FORESHADOWED DECISION (for consideration at February 2007 Meeting)

Schedule 5 – New entry

CLOTHIANIDIN in preparations containing less than 20 per cent of clothianidin.

Schedule 6 – Amendment

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

6.4 ACIBENZOLAR-S-METHYL

PURPOSE

The Committee reconsidered the scheduling of acibenzolar-S-methyl.

BACKGROUND

The Committee recalled that the February 2002 NDPSC Meeting noted that **XXXXX** had submitted data to support the approval of a new TGAC, acibenzolar-S-methyl **XXXXX.**

XXXXX

The Committee received **XXXXX** toxicology report on acibenzolar-s-methyl which noted that:

- **XXXXX**

The **XXXXX** evaluator recommended that, while acibenzolar-S-methyl was of low acute toxicity and was not genotoxic or produce developmental effects in the absence of maternal toxicity, it was associated with serious haematological toxicity and unexplained haemorrhagic discharge in pregnant rats and rabbits and may therefore be considered appropriate for inclusion in Schedule 6 or Schedule 7.

The February 2002 NDPSC Meeting was advised that no comment was received in response to the pre-meeting gazette notice and noted that the name acibenzolar-S-methyl was the ISO approved name.

A Member advised the Committee that the key to scheduling acibenzolar-S-methyl was the interpretation of the haematological toxicity and the consistent finding of haemorrhagic discharge across a number of species. The Member stated that the haematological findings were consistent with oxidative stress on the erythrocytes and drew the attention of Members to similarities to the haematological toxicity induced through oxidative stress by indoxacarb.

During discussion of the haemolytic toxicity, Members noted the following:

- The significance of this finding in relation to humans was unclear although similar findings with other substances had led to more restrictive scheduling eg indoxacarb.
- The importance of this finding in relation to at risk sub-populations was unknown.
- **XXXXX**
- Additional information should be sought from the applicant on the mechanism, interpretation and significance of these findings.

On consideration of the "haemorrhagic perineal discharge" **XXXXX**, Members noted that:

- **XXXXX**
- The use pattern on vegetables, method of application and relatively high dermal absorption provides a high probability of systemic exposure following occupational use in horticulture or market gardening.
- Inclusion of warning statement 67 (pregnancy warning) was not considered appropriate as **XXXXX**
- A NOEL had not been established for the discharge although it was clearly compound related.
- The possibility that acibenzolar-S-methyl may be selectively concentrated in the female sex organs (in particular the placenta) leading to toxicity.
- **XXXXX**
- There was concern expressed that the pathology reports **XXXXX** had failed to identify the source of the discharge. Members agreed that the source and genesis of the discharge required clarification.
- The applicant should be asked to provide comment on the possible mechanism, interpretation and public health significance of the perineal **XXXXX**

The relative merits of inclusion in Schedule 6, as opposed to Schedule 7, were canvassed among Members. While similarities with indoxacarb (Schedule 6) were noted along with the relative lack of acute toxicity, the Committee remained seriously concerned by the perineal discharge **XXXXX**. Members were advised that Schedule 7 would not prohibit experimental use of the substance. Members noted that Schedule 6 however, provided no impediment to general sale to the public.

The February 2002 NDPSC Meeting agreed that there were sufficient concerns regarding the findings of haemorrhagic perineal discharge and haemolytic anaemia observed in experimental studies to warrant inclusion of acibenzolar-S-methyl in Schedule 7 pending receipt of further information from the applicant.

The Committee requested that the applicant be asked to provide:

- Clarification as to the origin of the 'haemorrhagic perineal discharge" observed in both developmental studies, information as to the possible mechanism producing the discharge, and comment on the interpretation and public health significance of this finding.
- Comment on the possibility that the perineal discharge may be an indicator for breakthrough bleeding in the normal menstrual cycle and the likelihood that this may occur in humans following exposure.
- Any evidence that acibenzolar-S-methyl was selectively concentrated in the female sex organs.
- Comment as to the mechanism, interpretation and public health significance of the haemolytic anaemia observed in all the short and long term repeat dose studies.

DISCUSSION

XXXXX provided comment on the matters requested by the February 2002 NDPSC Meeting. These comments had been reviewed by **XXXXX** which noted the following:

(1) 'Clarification as to the origin of the haemorrhagic perineal discharge observed in both developmental studies, information as to the possible mechanism producing the discharge, and comment on the interpretation and public health significance of this finding'

XXXXX did not establish a NOEL for maternal toxicity in **XXXXX** developmental study because the haemorrhagic perineal discharge occurred at all dose levels tested.

XXXXX

It was noteworthy that in a rat single dose range-finding developmental study (Khalil, 1994), as few as two consecutive doses of 300 mg/kg bw/day) on gestation days 6-7, 8-9, 10-11, 12-13 or 14-15 could cause haemorrhagic perineal discharge and an increase in the number of early embryonic resorptions.

XXXXX

The available data about procoagulant and anticoagulant mechanisms in placenta is largely human data. It is however considered applicable to the rat on the basis that many aspects of placental development in the two species are analogous (Pijnenborg et al. 1981). Also, the physiological adaptations to haemostasis in pregnancy can be expected to be similar among mammals.

The special structure of the placenta requires efficient mechanisms for fast activation and localised regulation of coagulation (Lanir et al. 2003a). The presence of procoagulant and anticoagulant components on placental vascular endothelial cells and syncytiotrophoblast cells is essential for haemostasis. Sood et al. (2006) identified a panel of genes that determine the ability of foetal trophoblast cells to regulate haemostasis at the foetal-maternal interface. The expression and production of tissue factor, membrane phosphatidylserine and fibrin render the trophoblasts pro-coagulant and the risk of bleeding is minimised (Lanir et al. 2003b).

Placentation in the rat is characterised by an extensive invasion of trophoblast cells into the endometrial decidua and proliferating uterine arteries (Zybina & Zybina 2000). The infiltration of vessels causes significant alteration of the muscular wall with replacement of endothelium. De Rijk et al. (2002), in a histological study of the daily changes in pregnancy in rats from day 8 to 21, observed that the endothelial cells of larger vessels within the myometrium were covered by trophoblasts. This covering was initiated at day 14 and persisted until day 21 of pregnancy.

Vessel invasion in particular requires effective haemostatic control for preventing blood leakage from the developing placenta into the uterus. In the developmental toxicity study in rats discussed above, the rats were treated from gestation day 6-15 and showed the haemorrhagic discharge from day 13 through to day 21. It was apparent that the anticoagulant property of acibenzolar-S-methyl has reduced the pro-coagulant nature of placenta to the extent that leakage of blood into the uterine lumen occurred.

XXXXX

In a single dam, the most useful external guide to the effect of a haemorrhagic perineal discharge on embryonic survival will be the degree and persistence of uterine blood loss. An attempt to relate the simple appearance of the discharge to an embryonic effect is not valid except at the highest dose used in the study.

(2) 'Comment on the possibility that the perineal discharge may be an indicator for breakthrough bleeding in the normal menstrual cycle and the likelihood that this may occur in humans following exposure'

Anticoagulant therapy is frequently associated with heavier than normal menstrual bleeding. Since acibenzolar-S-methyl has anticoagulant properties it is anticipated to have similar effects.

(3) 'Any evidence that acibenzolar-S-methyl was selectively concentrated in the female sex organs'

In the study of Hassler (1995) referred to by **XXXXX** report indicated that at 24 hours following a single dose of 0.5 mg/kg bw, the tissue residues in the kidney were 3.2 and 3.6 ppm acibenzolar-S-methyl equivalents in males and females respectively with all other tissue levels below 1 ppm. At 7 days after this dose, residues were detected only in the liver and kidney. At 7 days after treatment with a single dose of 100 mg/kg bw detectable levels (0.32 to 1.09 ppm) were found only in plasma, muscle, kidneys, lungs and spleen. The potential for accumulation in female sex organs was not apparent in the results of this study.

(4) 'Comment as to the mechanism, interpretation and public health significance of the haemolytic anaemia observed in all short and long term repeat dose studies'

XXXXX did not set a NOEL for **XXXXX**. The LOEL was 5 mg/kg bw/day based on haematological effects and this was the lowest dose tested. **XXXXX** set the ADI for acibenzolar-S-methyl at 0.005 mg/kg bw/day on the basis of this LOEL using a safety factor of 1000.

XXXXX set a NOEL for the **XXXXX** of 1.14 mg/kg bw/day (for both males and females) based on decreased haematocrit and haemoglobin observed in females at 10.8 mg/kg bw/day.

The relative significance of the anticoagulative and erythrocyte oxidative effects in the aetiology of the anaemia observed cannot be readily established. **XXXXX**

Public Health

With respect to public health, **XXXXX** believes that if dietary exposure to acibenzolar-S-methyl does not exceed the ADI or ARfD then there are unlikely to be any concerns.

XXXXX Conclusion

XXXXX has concluded that dosing with acibenzolar-S-methyl causes delayed blood clotting and erythrocyte oxidative stress in a dose-dependent manner. However, since there was data to indicate that as few as two consecutive doses of 300 mg/kg bw/day on gestation days 6-7, 8-9, 10-11, 12-13 or 14-15 could cause haemorrhagic perineal discharge and an increase in the number of early embryonic resorptions in rats (Khalil, 1994) was not possible to identify a concentration in order to permit a cut-off to be established for acibenzolar-S-methyl.]

OUTCOME

The Committee agreed that **XXXXX** acibenzolar-S-methyl continue to be included in Schedule 7 of the SUSDP and also in Appendix J.

6.5 GHRH INJECTABLE PLASMID

PURPOSE

The Committee considered the scheduling of GHRH Injectable Plasmid.

BACKGROUND

XXXXX submitted a data package seeking **XXXXX** approval of **XXXXX**

DISCUSSION

The Committee received from **XXXXX**, an assessment of the toxicology data submitted in support of the application. The assessment noted that **XXXXX** is intended to increase the endogenous concentration of growth hormone-releasing hormone (GHRH) in food producing animals such as **XXXXX**. This increased synthesis of GHRH is intended to stimulate synthesis of growth hormone (GH), with positive effects on growth.

In mammals, GHRH is a 44-amino acid peptide hormone produced in the arcuate nucleus of the hypothalamus. GHRH is released from neurosecretory nerve terminals of arcuate neurons, and is carried by the hypothalamo-hypophysial portal circulation to the anterior pituitary gland where it stimulates GH secretion.

The actions of GHRH are opposed by another hypothalamic hormone, somatostatin, also known as growth hormone-inhibiting hormone (GHIH). Somatostatin is released from neurosecretory nerve terminals of periventricular somatostatin neurons, and is carried by the hypothalamo-hypophysial portal circulation to the anterior pituitary where it inhibits GH secretion by hyperpolarising the somatotropes (the cells in the anterior pituitary that secrete growth hormone). Somatostatin and GHRH are secreted in alternation, giving rise to the pulsatile secretion of GH. Growth hormone acts on tissues directly and also indirectly via the production in the liver in response to growth hormone of insulin-like growth factor I (IGF-I).

The somatostatin releasing neurons in the hypothalamus mediate negative feedback effects of growth hormone on its own release; the somatostatin neurons respond to high circulating concentrations of GH and IGF-I. Levels of the various hormones and factors are tightly controlled by each other in a natural “feedback loop”.

A hazard that must be considered in relation to the use of **XXXXX** Injectable Plasmid Encoding Porcine GHRH is the possible effects of self-injection of the plasmid leading to abnormal levels of hormones. Other potential hazards from self-injection include immunological responses to the plasmid DNA, as well as to the production of a peptide that is foreign to the human body (pig GHRH differs in three amino acids from the human hormone). Other hazards that need to be considered relate to public health concerns about the ingestion of artificially constructed DNA of the type used in this product. The DNA is being injected into the muscle of pigs and could conceivably enter

the human food chain. Another possibility is that higher than normal levels of GHRH, growth hormone or IGF-I may be found in the meat of pigs that have been treated with the product. Ingestion of the DNA or hormones is very unlikely to have any negative effects; however any risks should be assessed.

Other potential hazards include integration of the plasmid DNA into the host's chromosomes leading to mutagenesis and possible insertion carcinogenesis and the induction of anti-DNA antibodies with possible stimulation of the development of autoimmune diseases.

XXXXX noted that the use of this active will usually involve pigs being restrained under general anaesthesia for administration and electroporation. Induction of anaesthesia must be carried out by a registered veterinarian and it is proposed that the product be administered by a veterinarian or an appropriately trained technician under the direct supervision of a veterinarian.

However, apart from the anaesthesia, it does not appear that administration of the product itself will necessarily require veterinary skills and the hazards from self-injection of the product are limited. Most actives intended to affect hormone levels (e.g. somatostatin, equine somatotropin, gonadotrophin releasing hormone vaccine) are in Schedule 4 of the SUSDP. However the only likely hazard associated with the use of the present active is accidental self-injection without follow-up electroporation, which would be of limited concern.

Therefore, **XXXXX** suggested that NDPSC could consider that the **XXXXX** growth hormone-releasing hormone (GHRH), should be placed in Appendix B of the SUSDP. On the other hand, noting that veterinarians are experienced in giving injections to animals, the NDPSC may consider limiting the potential for self-injection by placing it in Schedule 4.]

XXXXX and **XXXXX** representative confirmed that **XXXXX** had been consulted and advised of this application during the course of the process assessment by both **XXXXX**. The advice from **XXXXX** could be made available to the February 2007 NDPSC Meeting.

OUTCOME

The Committee agreed to foreshadow that GHRH Injectable Plasmid be included in Schedule 4 of the SUSDP noting the need for veterinary supervision. The scheduling of GHRH would therefore again be considered at the February 2007 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 4 - New entry

GHRH INJECTABLE PLASMID.

6.6 CEFOVECIN

PURPOSE

The Committee considered the scheduling of cefovecin.

BACKGROUND

XXXXX has submitted a toxicology data package in support of their application seeking the approval of a new veterinary antibiotic namely, cefovecin sodium. **XXXXX**

Cefovecin sodium is a third generation antibiotic belonging to the cephalosporin group of antibiotics. It has a broad spectrum of activity against Gram-positive and Gram-negative bacteria. Cefovecin sodium differs from other cephalosporins in that it is highly protein bound and has a long duration of activity. The bactericidal action of cefovecin sodium is mediated via the inhibition of bacterial cell wall synthesis.

DISCUSSION

The Committee received an assessment of the toxicology of cefovecin from **XXXXX**. **XXXXX** toxicological assessment report noted the following:

- **XXXXX**
- Except for slight eye irritancy and the likelihood that it is a skin sensitiser, the overall acute toxicity profile of cefovecin sodium is low. The compound is probably not mutagenic.

Based on its intended use as a therapeutic agent requiring professional veterinary advice and management, the OCS suggested that the NDPSC may consider that Schedule 4 of the SUSDP is appropriate for cefovecin sodium.

DECISION 2006/48 - 7

The Committee agreed that cefovecin be included in Schedule 4 of the SUSDP based on its intended use as a therapeutic agent requiring professional veterinary advice and management.

Schedule 4 - New entry

CEFOVECIN for veterinary use.

6.7 PARAQUAT

PURPOSE

The Committee considered the scheduling of paraquat.

BACKGROUND

XXXXX had applied for the registration of **XXXXX**

At the June 2005 NDPSC Meeting, the Committee noted that **XXXXX** had applied for the registration of **XXXXX.** Subsequent NDPSC meetings gave further consideration to this application and the proposal by **XXXXX** that paraquat in this new formulation be included in Schedule 6 of the SUSDP.

DISCUSSION

The Committee noted that **XXXXX** had considered the information provided in support of this new application ie **XXXXX.** The Committee recalled previous **XXXXX** considerations given to the scheduling of paraquat, viz:

- When first considered by the DPSSC in 1964 paraquat was included in Schedule 6 on that the median lethal dose (LD50) of the paraquat manufacturing concentrate (ie. approx. 34% w/w paraquat cation) ranged from 100 to 249 mg/kg bw in rats. Paraquat is currently in Schedule 7 because other species such as guinea pig, rabbit, and cynomolgus monkey are extremely sensitive to the effects of paraquat, ie. LD50 = 22, 40-50 and 50 mg/kg bw, respectively. Humans are also extremely sensitive to paraquat with an acute oral lethal dose estimated to be in the range of 50-80 mg/kg bw (Pond, 1990).
- In 2000 the NDPSC initiated a Working Party to review the first-aid instructions for pesticide products with the view to ensuring that they reflected best clinical practice. The Working Party reviewed the clinical evidence in support of an emetic as a frontline first-aid treatment for accidental poisoning. The recommendations of the Working Party, which were accepted by the NDPSC, were that *inter-alia*:

  > "The induction of vomiting is no longer recommended as a standard first aid measure. Vomiting generally has not been proven to influence the clinical course following ingestion of poisons and may have adverse effects relating to further damage to the oesophagus or due to aspiration of the poison and other stomach contents."

- As a consequence of this recommendation the first-aid instruction to induce vomiting in the event of accidental poisoning is no longer considered appropriate for any pesticide product. This first-aid instruction has since been removed from all pesticide products listed in the FAISD handbook. **XXXXX**
- Given that the intrinsic toxicity of paraquat in **XXXXX** and there is doubt surrounding the clinical benefit of inducing emesis following accidental poisoning, there would appear to be no justification for a cut-off to a lower Schedule.
- Additional issues which argue against a cut-off for paraquat are the lack of an effective antidote or treatment for paraquat poisoning and the potential of paraquat products to enter the home garden market.

- The 2004 paraquat review evaluated a range of data on the treatment of paraquat poisoning. Collectively these studies have failed to identify an effective antidote or treatment regimen for paraquat poisoning and therefore the current approach used in the treatment for paraquat poisoning is supportive. In the absence of an effective antidote or treatment, the observation that paraquat is bioavailable at low doses in **XXXXX** is of concern.
- Another issue of concern is the potential for paraquat products to enter the home garden market if paraquat were to be included in Schedule 6 of the SUSDP. While it is noted that **XXXXX** is intended for professional use and that the smallest pack size is not amenable to home garden use **XXXXX** the inclusion of paraquat in Schedule 6 would remove the current Schedule 7 restrictions on access and availability. **XXXXX** does not consider that the submitted toxicity data provide sufficient grounds to allow any paraquat products on to the home garden market. The applicant has indicated that **XXXXX** is intended for professional use as an agricultural and horticultural herbicide and the issue of public access if paraquat were to be placed in Schedule 6 could be controlled by means of registration conditions.

In regard to the current application and supporting toxicological data, **XXXXX** noted in particular that:

- **XXXXX**
- Based on the apparent increased safety of this product the applicant has requested a reconsideration of the poisons Schedule for paraquat. Paraquat is currently listed in Schedule 7 of the SUSDP. The NDPSC recently (February, 2006) reviewed the safety of **XXXXX** formulation in relation to a similar product, **XXXXX** resulting in no change to poison scheduling of paraquat (Schedule 7).

XXXXX suggested that the NDPSC may consider that a cut-off of paraquat to a lower Schedule is not appropriate because the intrinsic toxicity remained unchanged and the clinical benefit of **XXXXX** In addition, there remained no effective antidote or treatment regimen for paraquat poisoning. Paraquat was also considered too hazardous for home-garden use.

In conclusion, **XXXXX** stated their support for the registration of **XXXXX** but could find no grounds to recommend a cut-off into Schedule 6 for paraquat. This position was based on the following considerations:

(1) the intrinsic toxicity of paraquat **XXXXX** remained unchanged and the clinical benefit of **XXXXX**;

(2) there was no effective antidote or treatment for paraquat poisoning; and

(3) paraquat products are considered too hazardous for home garden use and therefore it would be inappropriate for paraquat to be included in Schedule 6 of the SUSDP.

Pre Meeting Submission – XXXXX

A pre-meeting submission received from **XXXXX** noted the following points each of which were considered by the Committee:

- As noted, the NDPSC has acknowledged that "**XXXXX** formulations appear to be safer than existing paraquat formulations" and offer important advantages to users through reduced skin and eye irritancy. Despite acknowledging the apparent safety benefits of **XXXXX**, the Committee has consistently reached the conclusion that the safety benefits offered by **XXXXX** do not outweigh the potential risks associated with rescheduling the product under Schedule 6. That is, the safety benefits that **XXXXX** offers farmers are not sufficient to outweigh the risks that through rescheduling **XXXXX** as an Schedule 6 paraquat product, it may become more accessible (despite **XXXXX** product stewardship commitments), leading to an increase in the incidence of ingestion, and as a consequence of the inherent hazard posed by paraquat, an increased number of fatalities.
- While the lower concentration of active ingredient means that **XXXXX** is in relative terms a safer product than **XXXXX** recognises that the NDPSC, consistent with its previous rulings, may conclude that the risks associated with establishing a Schedule 6 listing continue to outweigh the safety benefits, and on this basis may recommend **XXXXX** also be included as an Schedule 7 product.
- As outlined in previous submissions, the increased cost of manufacturing **XXXXX** formulations, combined with commercial realities of the Australian paraquat market, mean that unless **XXXXX** products have a clear point of difference, such as an Schedule 6 classification, in the marketplace, it will not be **XXXXX**
- Given this situation, and mindful of the potential for the NDPSC to recommend that **XXXXX** be classified as a Schedule 7 product, **XXXXX** has been considering other options to a create an environment which will allow the safety benefits of **XXXXX** to be introduced into Australia, whilst addressing the NDPSC identified concerns.
- **XXXXX** believes this outcome may be best achieved through governments establishing **XXXXX** as a new standard for paraquat products in Australia.
- It would be possible to establish **XXXXX** as a standard through NDPSC amending the current Schedule 7 entry for paraquat products in the SUSDP to require the inclusion of **XXXXX.** In adopting this approach, the NDPSC would be reinforcing its previous acknowledgement of **XXXXX** safety advantages, and would create an environment allowing this safer product to be introduced into the Australian market, while averting the perceived risks associated with **XXXXX** introduction under an Schedule 6 listing.
- Establishing **XXXXX** as a requirement under the Schedule 7 entry for paraquat products would constitute a responsible and reasonable approach from the NDPSC, clearly consistent with Section 52E which requires the Committee to take into account (among other things) "the need for access to a substance, taking into account its toxicity compared with other substances available for a similar purpose", as well as "any other matters that the Committee considers necessary to protect public health,

including the risks (whether imminent or long-term) of death, illness or injury resulting from its use".

- On this basis, **XXXXX** requests that the NDPSC give formal consideration to amending the current Schedule 7 entry for paraquat products in the SUSDP to require the inclusion of **XXXXX.**
- **XXXXX** consider establishing **XXXXX** as a standard through **XXXXX**

XXXXX

In relation to the **XXXXX** study, [**XXXXX** pre-meeting submission had further noted that:

- In addition to the strong experimental evidence demonstrating the role of **XXXXX** technology in substantially reducing the oral toxicity, combined with reduced dermal and eye sensitivity of **XXXXX** paraquat products, **XXXXX** has now been provided with [**XXXXX**
- **XXXXX**]
- The results from **XXXXX** and the increasing number of medical case studies, demonstrate that **XXXXX** is performing in line with **XXXXX** expectations and is substantially improving the safety of paraquat products. These results have reinforced **XXXXX** confidence that **XXXXX** will:
  - eliminate fatalities resulting from the accidental ingestion of paraquat **XXXXX** formulations;
  - reduce the number of fatalities resulting from the deliberate ingestion of paraquat **XXXXX** formulations; and
  - reduce the irritancy of paraquat **XXXXX** formulations to the skin and eyes and in doing so minimise the impact of skin and eye exposure incidents.

Pre-Meeting Submission – XXXXX

The Committee also noted a pre-meeting submission from **XXXXX**

XXXXX noted the current Schedule 6 entry for paraquat **XXXXX** and as an interested party would appreciate being advised of the Committee's considerations, with the opportunity for further submission, if appropriate.

The Committee noted that the **XXXXX** study had not yet been submitted to **XXXXX** for evaluation. To date, only an abstract had been received and **XXXXX** was still waiting for the study *per-se*. It was observed however, that there were still fatalities following ingestion with the time to death being a little longer.

XXXXX

The Committee also commented that it appeared that **XXXXX** may have been under the impression that paraquat in combination with **XXXXX** (a Schedule 6 substance) would be more favourably considered for inclusion in Schedule 6. However, the higher Schedule took precedence. The Committee requested that **XXXXX** be advised of this.

XXXXX indicated that **XXXXX** supported a Schedule 7 classification and that a decision on whether the **XXXXX** formulation would be made the formulation of choice would be made following **XXXXX** consideration. **XXXXX** highlighted the implications for other companies should **XXXXX** make a decision to favour the **XXXXX** formulation.

OUTCOME

The Committee concluded that there was still insufficient evidence to support including paraquat in Schedule 6 of the SUSDP, noting that the company had committed to making the technology available. The Committee reiterated its view that **XXXXX** but that the Committee would consider an evaluation by OCS of the results of the study once the full details had been submitted by **XXXXX**.

The Committee agreed that the current scheduling of paraquat remained appropriate.

6.8 DICHLORPROP-P

PURPOSE

The Committee considered the scheduling of dichlorprop-P.

BACKGROUND

XXXXX has sought APVMA approval of the synthetic phenoxy herbicide dichlorprop-P and registration of the product **XXXXX**

DISCUSSION

The Committee received **XXXXX** assessment of the toxicology provided in support of the application which noted the following:

- **XXXXX**

XXXXX noted that the NDPSC had previously included dichlorprop racemate in Schedule 6 of the SUSDP based on the worst acute oral toxicity observed in **XXXXX** and severe eye irritation **XXXXX**. The R-isomer form of dichlorprop was found to share a similar toxicological profile to that of dichlorprop racemate when acute, short-term and subchronic studies were compared. **XXXXX** Given the similarity in toxicology profile including its potential to cause severe eye irritancy, the NDPSC may consider it appropriate to include dichlorprop-P in Schedule 6 of the SUSDP.

XXXXX also suggested that the entry in the SUSDP be: "Dichlorprop-P (the R-enantiomer)".

Pre-Meeting Submission, XXXXX.

XXXXX provided pre-meeting comment, noting that:

- **XXXXX**

- Dichlorprop is the ISO approved name for racemic (*RS*)-2-(2,4-dichlorophenoxy) propionic acid. Dichlorprop-P refers to the optically active isomer (*R*)-2-(2,4-dichlorophenoxy) propionic acid.

s52E (a) toxicity and safety of the substance

- Although significantly different with respect to phytotoxicity to target plant species, the mammalian toxicity of the racemic and the optical isomer has been found to be very similar. **XXXXX** recommends Schedule 5 be adopted for dichlorprop-P.

s52E (d) the extent and patterns of use of the substance

- Dichlorprop-P formulations are used at half the rate per applied hectare than the corresponding racemic form, thus reducing the potential for operator exposure and the overall environmental burden.

- **XXXXX XXXXX**

- **XXXXX** is an interested party and stakeholder with regard to the substance nominated in this submission and would appreciate being advised of the Committee's considerations, with the opportunity for further submission, if appropriate.]

DECISION 2006/48 - 8

The Committee agreed that, given the potential for severe eye irritancy, 2,4 Dichlorprop (including the R and S enantiomers) be included in Schedule 6 of the SUSDP.

Schedule 6 - Amendment

2,4 DICHLORPROP – amend entry to read:

2,4 DICHLORPROP (includes the R and S enantiomers).

6.9 PROFOXYDIM

PURPOSE

The Committee considered the scheduling of profoxydim.

BACKGROUND

XXXXX submitted data in support of approval by **XXXXX** of the active constituent profoxydim and for the registration of **XXXXX.** Profoxydim is cyclohexone oxime herbicide and is a mixture of two isomers, E and Z, of which the E isomer accounts for ~95% and the Z isomer for ~5%. **XXXXX**. Profoxydim inhibits production of the enzyme acetyl coenzyme A carboxylase.]

DISCUSSION

The Committee received from **XXXXX** an assessment of the toxicology provided in support of the application. Based on the findings of the toxicological studies, **XXXXX** assessment concluded that profoxydim was of low acute oral, dermal and inhalation toxicity in **XXXXX.** Profoxydim was not a skin irritant in **XXXXX** but was a slight eye irritant in **XXXXX .** It was a skin sensitiser in **XXXXX**

- **XXXXX**

Based on a consideration of its toxicological profile (slight eye irritant and a skin sensitiser), **XXXXX** suggested that the NDPSC may consider profoxydim appropriate for inclusion in Schedule 5 of the SUSDP, with a cutoff to unscheduled at 20%.

DECISION 2006/48 - 9

The Committee agreed that, based on the acute toxicological findings of slight eye irritancy and slight skin sensitisation, profoxydim should be included in Schedule 5 of the SUSDP except when in preparations containing 20 per cent or less of profoxydim.

Schedule 5 - New entry

PROFOXYDIM **except** in preparations containing 20 per cent or less of profoxydim.

6.10 2,4-DICHLOROPHENOXYACETIC ACID (2,4-D)

PURPOSE

The Committee considered the scheduling of 2,4-D following review under the Chemicals Review Program.

BACKGROUND

2,4-D [(2,4-dichlorophenoxy) acetic acid] is one of some 80 agricultural and veterinary chemicals identified for priority review under Australia's Chemicals Review Program (CRP) based on concerns over its potential to cause adverse effects in humans (including birth defects and carcinogenicity) and an incomplete data package. Following the data call-in process, a number of submissions on the toxicology of 2,4-D was received from industry and the public, and these data together with published data have been assessed in detail.

2,4-D is a selective herbicide first synthesised in 1941 and introduced into agricultural use in 1946. By the mid 1960s, 2,4-D and related chlorophenoxy chemicals were the most widely used herbicides. In Australia, 2,4-D had entered use by 1962 and 2,4-D and its analogues (2,4-D acid, salts and esters) are currently used for post-emergence control of broad-leaved weeds in aquatic areas, cereals, citrus orchards, grain crops, pastures, sugar cane, forestry, turf and non-crop land including industrial/commercial areas. 2,4-D also has growth regulatory uses in citrus.

DISCUSSION

The Committee noted that 2,4-D is currently in Schedule 5 of the SUSDP. It was placed in this Schedule in 1972 and confirmed in 1988, when the DPSSC considered the issue of potential carcinogenicity (astrocytomas in the rat) and concluded the finding to be of "debateable significance". In 1991 and 1993, the DPSSC considered whether there were any scheduling implications arising from the presence of small amounts of impurities in the active, ie. 2,4-dichlorophenol, dioxins and furans. The DPSSC concluded that 'no change' to the poisons scheduling of 2,4-D was warranted.

The current poisons Schedule for 2,4-D was established prior to the submission of numerous acute oral toxicity studies in rats and mice, with most of them demonstrating 2,4-D acid equivalent LD50 values of 563 mg/kg bw or less, ranging down to 242 mg/kg bw in mice and LD50 values of 764 mg/kg bw or less, ranging down to 285 mg/kg bw in rats.

XXXXX reported the following as part of its review of 2,4-D under the Chemical Review Program:

Acute Toxicity

XXXXX

Pre Meeting Submissions

A pre-meeting submission was received from **XXXXX** has noted that:

- 2,4-D is currently under review by the Australian Pesticides and Veterinary Medicines Authority (APVMA). **XXXXX** has responded to that review by supplying toxicology data as a member of the 2,4-D Taskforce.

- The APVMA review of the extensive toxicological database supplied by the 2,4-D Taskforce has not been published, and no concerns regarding the adequacy of the data have been made known to us as suppliers of the toxicological studies.

- **s52E (1) (a) toxicity and safety of the substance**

    - The continuation of the current Schedule 5 for 2,4-D, including its salts and esters, is supported by the data supplied to the APVMA Review of 2,4-D.

- **s52E (1) Labelling, Packaging and Presentation of the Substance**

    - The Committee may take into account the labelling, packaging and presentation of the substance (S52E (1) following (i)). As previously noted, the APVMA is currently reviewing 2,4-D. It is anticipated that the Review may require registrants of 2,4-D products to alter labels.

- **XXXXX** recommends to the Committee that any decision of the Committee to reschedule 2,4-D becomes operative co-incidentally with the final APVMA Report, allowing an orderly transition to any new requirement, including changes to signal headings, safety directions and first aid instructions.

The Committee agreed that changes to the scheduling of 2,4-D may have some regulatory implications as PubCRIS listed 168 registered products. The Chemical Review outcomes had not yet been concluded by the APVMA and it was understood that the focus of their attention at this time had been on the environmental concerns that were also identified as part of the review. It was suggested that if the NDPSC were to foreshadow changes to the scheduling of 2,4-D as suggested by **XXXXX** then the final outcome of the review could also reflect the scheduling outcomes including the expected industry comment.]

OUTCOME

The Committee agreed to foreshadow that, based on its acute toxicity, 2,4-D be included in Schedule 6 of the SUSDP with a cut-off to Schedule 5 for 2,4-D in preparations containing 20 per cent or less of 2,4-D.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 6 - New entry

2,4-D **except** when in Schedule 5.

Schedule 5 - Amendment

2,4-D in preparations containing 20 per cent or less of 2,4-D.

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

7.1 METHYL METHACRYLATE AND ETHYL METHACRYLATE

PURPOSE

The Committee considered scheduling of methyl methacrylate (MMA) and ethyl methacrylate (EMA) for cosmetic use.

BACKGROUND

The June 2006 NDPSC Meeting noted advice from **XXXXX** that MMA and EMA were being considered by **XXXXX** and that a submission to the Committee was expected in the near future. Members therefore agreed to include consideration of the scheduling of MMA and EMA in the pre-October 2006 NDPSC Meeting gazette notice.

MMA

Methyl methacrylate is a clear liquid with a distinctive, sharp, fruity odour. MMA is widely used because single molecules of MMA monomer link together to form a very strong, hard polymer that bonds tightly to a variety of other substances. The principal application of MMA is the production of polymethyl methacrylate acrylic plastics. MMA is also used for the production of the co-polymer methyl methacrylate-butadiene-styrene, used as modifiers for PVC. MMA polymers and co-polymers are also used for waterborne coatings, such as latex house paint.

MMA has also been used in cosmetic nail products, but following concerns about sensitivity and fingernail damage arising from the strength of the MMA nail coating, several countries have imposed restrictions and/or bans to the use of MMA in nail products.

EMA

EMA, a clear liquid, is a base material for coatings and adhesives. It is used in resins, solvent, oil additives, dental products, textile emulsions, leather and paper finishing. Additionally, as a result of international limits to the use of MMA in cosmetic nail preparations, EMA has been used as a substitute for MMA and is promoted as a safer alternative. These EMA nail products are sold as two part formulations with EMA being cross linked with methacrylates to form the finished nail.

The May 1974 DPSSC Meeting exempted several dozen compounds, including EMA, from scheduling without any clear rationale being recorded. Appendix B was deleted

from the SUSDP at the August 1995 NDPSC Meeting. The February 2003 NDPSC Meeting agreed to reinstate Appendix B, including the EMA listing.

DISCUSSION

Members noted the following from a **XXXXX** submission regarding cosmetic use of MMA and EMA:

- Recent concerns regarding the use of MMA in the cosmetic nail industry have been raised with **XXXXX** through public enquiries and the media.
- The FDA restricted the use of 100% monomer MMA in cosmetic nail products due to risk of sensitisation and fingernail damage by court action in 1970. In 2005, the FDA confirmed that MMA in cosmetic fingernail preparations was a "poisonous and deleterious substance" and approximately 30 US states have banned or recommended against the use of MMA in nail preparations. Health Canada imposed a ban in 2003 on all cosmetic nail products containing MMA on human health grounds. ERMA New Zealand has banned the use of MMA in cosmetic nail products through its *Group Standard for Cosmetics*, expected to come into force at the end of 2006.
- There were no bans or restrictions on the use of EMA overseas.
- Reports indicated that, in addition to the direct toxicological concerns arising from use of MMA, concerns arose from the harder nature of the bonding layer when MMA rather than EMA was used. These include difficulty in removal, requiring mechanical grinding or, alternately, 2 hour soaking in acetone, and mechanical damage to the nail plate when impact occurs on the finished nail in use, due to lack of "give".
- **XXXXX** sought information from industry on use of MMA and EMA in fingernail cosmetics:

  MMA

  - Two respondents indicated that they import MMA; one in nail polish at 20% and the other as part of an acrylic gel. However there was evidence, particularly from State OHS inspectors, that MMA was in use in nail salons, possibly imported from internet sources by small operators, or diverted from the greater than 20 tonnes/year imported for industrial use.

  EMA

  - 10 users imported EMA for fingernail use – quantity in the range of 8.3-9.9 tonnes/year.
  - In addition, **XXXXX** reported the availability of home fingernail enhancement kits containing liquid acrylic monomer, and it was not certain that in all cases the monomer was EMA rather than MMA. A search of the internet found artificial nail products containing "acrylic glue" for sale at Australian on-line pharmacies.

<u>Toxicity profile</u>

- Members also noted the following toxicity profiles provided by **XXXXX** (noting that there was strong evidence of cross-reactivity between MMA and EMA for sensitisation and additive effects for respiratory irritation):

  MMA

  - Low acute oral toxicity (LD_{50}: dog - 4700 mg/kg bw, rat - 7552-9440 mg/kg bw).
  - Low acute dermal (LD_{50}: rat > 5000 mg/kg bw) and inhalation toxicity (LC_{50}: rat and mouse - 3750-7268 ppm, 4 hour).
  - Severe dermal irritant. In humans, 5% MMA produced skin reactions in 18/20 volunteers.
  - Mild eye irritant.
  - Moderate respiratory irritant. Human data for occupational exposure indicated respiratory irritation by MMA occurred at concentrations lower than 112 ppm.
  - Evidence of moderate sensitising potential.
  - Low repeated dose toxicity.
  - Not determined to be mutagenic or carcinogenic.
  - Data indicated that MMA was not embryotoxic, foetotoxic or teratogenic.
  - In addition to health hazards MMA can also cause damage to the nail bed from chemical and/or mechanical issues.

  EMA

  - Low acute oral toxicity (LD_{50}: rabbit - 3600 mg/kg bw, rat - 14500 mg/kg bw).
  - Low acute dermal and inhalation (LC_{50}: rabbit - 8300 ppm) toxicity.
  - Slight skin irritant and slight to moderate eye irritant.
  - Moderate respiratory irritant.
  - Slight skin sensitising potential. No evidence was available to indicate respiratory sensitisation by EMA.
  - Low repeated dose toxicity.
  - Not determined to be mutagenic or carcinogenic.
  - Data indicated that EMA was not foetotoxic or teratogenic.

<u>Exposure and Risk</u>

- The most probable exposures related to inhalation of vapour and short term small volume skin contact in the immediate vicinity of the fingernail.
- Both exposure types were much more probable from home use than in salon use by trained personnel.

- The saturated vapour pressures of both chemicals are much higher than the concentrations at which respiratory irritation have been observed, and accordingly there was significant risk of respiratory irritation following use without efficient ventilation systems. The irritant response was likely to result in low risk of higher vapour exposures at concentrations giving rise to systemic effects.
- Short term small volume dermal exposure to either chemical on a repeated basis was likely to result in a primary risk of skin sensitisation rather than dermal irritation.
- Accordingly the risks of respiratory irritation and skin sensitisation were likely to be high under certain circumstances. For both endpoints, MMA was likely to result in a higher risk than EMA. The threshold for respiratory irritation was lower for MMA than for EMA, and the higher vapour pressure of MMA meant that the threshold concentration will be more rapidly attained in the absence of efficient ventilation. The results of animal testing indicate that MMA is a more potent skin sensitiser, at least in the induction phase, than EMA.
- The use profile indicated that use of EMA should be considered to be alternative to use of MMA, rather than cumulative. Only a single methacrylate monomer was likely to be used in an individual product, and customers were likely to generally frequent a single salon, resulting in exposure to the product in use in the salon of choice only. There may be some cross-exposure, particularly in cases where home products and salons are both in use by the customer, and treatment at a salon which used MMA may result in greater sensitisation to a home product containing EMA.

The Members noted a number of **XXXXX** recommendations:

MMA (recommendations are for MMA in monomer form only, and do not apply to polymers which include MMA in chemically combined form).

- The NDPSC may consider it appropriate to include:
  - MMA (excluding its derivatives), for use in cosmetic preparations for fingernail use in Appendix C of the SUSDP.
    - Members noted that non-fingernail cosmetics would pose a similar danger and agreed that Appendix C should apply to all cosmetic uses.
    - Members agreed that the inclusion of MMA in Appendix C was in no way intended to impact on legitimate industrial uses.
  - MMA (excluding its derivatives) in Schedule 6 for other uses. No minimum concentration should apply, as MMA is thought to be capable of inducing sensitisation at even low concentrations.
    - Members agreed that this was appropriate, but due to the pre-October 2006 NDPSC Meeting gazette notice stipulating consideration of MMA for cosmetic use, a general Schedule 6 (and Appendix F) entry would need to be foreshadowed for consideration at the February 2007 NDPSC Meeting. This would also help to identify any possible unintended consequences on legitimate industrial use.

EMA (monomer form only, as for MMA).

- The NDPSC may consider it appropriate to include:
  - EMA (excluding its derivatives), in Schedule 5 of the SUSDP.
  - No minimum concentration should apply, as EMA is a skin sensitiser.
  - Mandatory safety instructions based on the consumer risks which would arise from uninformed use of these chemicals.
  - Inclusion of EMA in Appendix F of the SUSDP:

Warning statement 28	Repeated exposure may cause sensitisation.
Safety Direction 4	Avoid contact with skin.
Safety Direction 9	Use only in well ventilated area.
Safety Direction 23	Keep away from heat, sparks and naked flames.

  - Members agreed the above recommendations were justified with a minor amendment such that the Schedule 5 entry would apply "for cosmetic use" only. The Committee agreed that there was no need to restrict other uses of EMA through scheduling.

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

EMA

- **XXXXX** noted the current Appendix B entry for EMA on the basis of low toxicity.

MMA

- **XXXXX** that MMA is used in the industrial manufacture of methacrylate resins and plastics with numerous applications.
- **XXXXX** also noted online industry advice regarding MMA for cosmetic nail use:
  - American Beauty Association, Nail Manufacturers Council:
    - "The Nail Manufacturers Council wants you to be informed about the potential dangers related to the use of MMA. We agree with the FDA that the use of liquid nail enhancement products containing MMA is unsafe and unwise."
  - The Methacrylate Producers Association (MPA):
    - "MPA members have for many years recommended that methacrylic acid and its esters in their unreacted monomeric liquid form not be used in cosmetics."
- **XXXXX** recommended that the Committee clearly distinguish the legitimate industrial uses of MMA, and that trace amounts of MMA that may be present in copolymers do not fall within the scope of any regulatory proposals for this substance. With regard to the latter, **XXXXX** suggested that the provisions of Article 4.2 of the EU Cosmetics Directive should apply – to the effect of:

- "The presence of traces of the substances listed in Annex II shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 2 (Article 2 states that cosmetics should not be harmful to humans in the normal and reasonably foreseeable conditions of use etc)."

  (Members noted that the general exemption under SUSDP Part 1, 1.(2)(i) would allow traces of unreacted monomer up to a concentration of 10 mg/kg(L)).

OUTCOME

The Committee agreed:

- That the severe dermal irritancy, moderate respiratory irritancy and evidence of moderate sensitising potential of methyl methacrylate constituted a moderate potential for causing harm (when for non-cosmetic uses), the extent of which could be reduced through the use of appropriate packaging and labelling.
- That the risk from methyl methacrylate relates to the monomer form only and not to polymers which include methyl methacrylate in chemically combined form.
- To foreshadow Schedule 6 (excluding derivatives) and Appendix F entries for methyl methacrylate.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 6 – New entry

† METHYL METHACRYLATE (excluding its derivatives).

Appendix F – New entry

Poison	**Warning Statement**	**Safety Directions**
Methyl methacrylate	28	4,9,23

DECISION 2006/48 - 10

The Committee agreed that:

- continued Appendix B listing of ethyl methacrylate was not justified given the irritancy and skin sensitisation risks;
- the low irritancy and skin sensitisation risks of ethyl methacrylate can be appropriately reduced through the use of appropriate packaging and labelling;
- the risk from ethyl methacrylate relates to the monomer form only and not to polymers which include ethyl methacrylate in chemically combined form;

- a Schedule 5 entry for ethyl methacrylate, excluding derivatives, be created and to create an Appendix F entry providing appropriate warning statements and safety directions;
- no concentration exemption should apply, as ethyl methacrylate was a skin sensitiser even at low concentrations.

The Committee further agreed that the cosmetic use of methyl methacrylate posed sufficient danger as to warrant prohibition of sale, supply and use through inclusion in Appendix C.

Schedule 5 – New entry

ETHYL METHACRYLATE (excluding its derivatives) for cosmetic use.

Appendix B – Amendment

ETHYL METHACRYLATE – Delete entry.

Appendix C – New entry

METHYL METHACRYLATE for cosmetic use.

Appendix F – New entry

Poison	**Warning Statement**	**Safety Directions**
Ethyl methacrylate	28	4,9,23

7.2 BASIC ORANGE 31

PURPOSE

The Committee considered scheduling of a new chemical, Basic Orange 31.

BACKGROUND

Basic Orange 31, a phenylenediamine azo linked to an imidazole, is used predominantly as a hair dye. Basic Orange 31 is not covered by the current phenylenediamines entries in the SUSDP.

Basic Orange 31 is the International Nomenclature of Cosmetic Ingredients (INCI) name for the chemical 2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride (CAS number 97404-02-9).

DISCUSSION

The Members were advised that NICNAS recently undertook an assessment of Basic Orange 31 and had recommended that the Committee consider Basic Orange 31 for scheduling. The NICNAS assessment was available from the following webpage http://www.nicnas.gov.au/PUBLICATIONS/CAR/NEW/LTD/LTDSUMMR/LTD1000SR/LTD1204.asp. Members particularly noted the following from this assessment:

- Basic Orange 31 was intended for both oxidative and non-oxidative hair dye products for domestic or salon use. The concentration of Basic Orange 31 will be ≤ 0.5%.
- Basic Orange 31 was a potential sensitiser and was considered to be severely irritating to the eye.
- The following toxicological data was presented:

Endpoint	*Assessment Conclusion*
Rat, acute oral	harmful, LD_{50} = 1000 - 2000 mg/kg bw
Rat, acute dermal	low toxicity, LD_{50} > 2000 mg/kg bw
Rabbit, skin irritation (acute)	slightly irritating
Rabbit, skin irritation (repeat dose)	slightly irritating
Rabbit, eye irritation	severely irritating (100%) slightly irritating (1%)
Guinea pig, skin sensitisation (adjuvant test)	no evidence of sensitisation
Skin sensitisation – LLNA	evidence of sensitisation
Phototoxicity	does not exhibit a phototoxic potential
Photoallergenicity	does not exhibit a photoallergenic and allergenic potential
Rat, repeat dose oral toxicity (14 days)	NOEL 15.5 mg/kg bw/day
Rat, repeat dose oral toxicity (90 days)	NOAEL 63 mg/kg bw/day, NOEL 18 mg/kg bw/day
Genotoxicity (bacterial reverse mutation)	non mutagenic
Genotoxicity (*in-vitro* chromosome aberration test chinese hamster cells)	clastogenic
Genotoxicity (*in-vitro* chromosome aberration test human lymphocytes)	non clastogenic
Genotoxicity (*in-vitro* cell gene mutation test)	non mutagenic
Genotoxicity (*in-vivo* mouse micronucleus test)	non genotoxic
Genotoxicity (*in-vivo* UDS test)	non genotoxic
Toxicokinetic studies	absorption 0.018+0.005 μg/cm2
Developmental and reproductive effects	maternal and foetal NOAEL 60 mg/kg bw/day

Hazard

- Based on the available data, NICNAS classified Basic Orange 31 as a hazardous substance. The classification and labelling details are:
  - R22 Harmful if swallowed

- R41 Risk of serious damage to eyes
- R43 May cause sensitisation by skin contact
- The GHS classification of Basic Orange 31 is:

Hazard	*Hazard Category*	*Hazard Statement*
Acute toxicity	4	Harmful if swallowed
Serious eye damage/irritation	1	Causes serious eye damage
Skin sensitiser	1	May cause allergic skin reaction
Chronic hazards to the aquatic environment	2	Toxic to aquatic life with long lasting effects

Risk

- Irritation and Sensitisation
  - The public would be exposed to the chemical at a maximum concentration of 0.2%. At this concentration Basic Orange 31 was unlikely to be a skin irritant, was expected to only be a slight eye irritant and was below the EC3 value for sensitisation. Therefore the risk of local adverse effects was considered to be low, however, the risk of sensitisation could not be ruled out.
  - The highest amount of Basic Orange 31/unit area on the skin was calculated as 26 μg/cm2 for the home-use product. Based on a worst-case EC-3 value of 0.9% a skin potency value for the notified chemical was calculated at 225 $\mu g/cm^2$. This gives a margin of safety of 8.6 for the estimated maximum dermal exposure of 26 $\mu g/cm^2$. Although this is lower than the desired margin of safety of 100, Basic Orange 31 was considered to be a less potent sensitiser than p-phenylenediamine.
  - The product labelling (for the two currently proposed hair dyes) advised that the product may cause an allergic reaction or cause skin irritation. A preliminary skin test was also advised which should identify individuals susceptible to sensitisation.
- Systemic effects
  - The highest public exposure to the notified chemical was estimated as 0.036 mg/kg bw/day (although due to expected low percutaneous absorption this is expected to be an overestimate). Based on the lowest NOEL of 15.5 mg/kg bw/day, derived from the 14-day rat oral study the lowest margin of exposure (MOE) was calculated as 435. MOE greater than or equal to 100 was considered acceptable to account for intra- and inter-species differences. Therefore the risk of systemic effects from use of hair dyes containing the notified chemical was considered to be low.
- Conclusion
  - There was no significant concern to public health when used in the proposed manner and provided the hair dye formulations were adequately labelled to

indicate sensitisation potential. NICNAS recommended that the following safety directions be mandated on the label:

- WARNING: This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
- If in eyes wash out immediately with water.
- Keep out of reach of children.

(Members noted that the above labels, except the wash out of eyes direction, were analogous to the exemption requirements from the Schedule 6 entry for hair dyes containing phenylenediamines.)

The Committee also noted an MSDS for a Basic Orange 31 hair dye product.

Members considered the following conclusions from the EU's Scientific Committee on Cosmetic Products and Non-food Products report (SCCNFP/0736/03 – report at http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out236_en.pdf.) on Basic Orange 31:

- Acute oral toxicity: no signs of toxicity or adverse effects. An LD_{50} > l000 mg/kg but < 2000 mg/kg was indicated. The acute dermal LD_{50} was > 2000 mg/kg bw. A repeated dose oral toxicity suggested a NOAEL of 53 mg/kg bw/day. The sub-chronic oral toxicity yielded a NOEL of 18 mg/kg bw/day and an NOAEL of 60 mg/kg bw/day.
- Basic Orange 31 did not reveal any teratogenic effects. The NOAEL was set at 60 mg/kg bw/day for maternal and foetal effects.
- The test material was considered to be slightly irritating to the skin. A 1% solution was slightly irritating to the eye.
- It was considered not to be a sensitiser. It induced delayed contact hypersensitivity in the murine Local Lymph Node Assay.
- Basic Orange 31 exhibited neither phototoxic nor photoallergic potential.
- A total of 0.009 % of the applied dose was reported to have penetrated, corresponding to a percutaneous absorption of 0.018 μg/cm². However, the substance was not tested in the presence of an oxidising agent. The applied dose of 101 mg/cm² is higher than the amount recommended by the SCCNFP (20 mg/cm²).
- Basic Orange 31 was tested in prokaryotic and mammalian cells for gene mutation, and in mammalian cells for chromosomal aberration *in-vitro*.
    - The *in-vitro* test for gene mutation in prokaryotes was negative in all the other tester strains and also in the presence of a reducing metabolic activation system.

- The *in-vitro* test for gene mutation in mammalian cells showed that the test agent was non mutagenic in the absence of an activation system and under normal or reduced activation systems.
- The *in-vitro* test for clastogenicity in human lymphocytes was negative in the presence of a normal metabolic system. The *in-vivo* micronucleus test in mice gave negative results.
- The *in-vivo*/*in-vitro* UDS on rat hepatocytes is negative for the treatment of 3 and 16 hours.
- Basic Orange 31 was therefore considered non mutagenic/genotoxic.

- The SCCNFP was of the opinion that Basic Orange 31 might be regarded as safe in general. However, the data was insufficient for a final evaluation.

Members also noted a request from the SCCNFP to the EU's Scientific Committee on Consumer Products (SCCP). The deadline for the SCCP was set at December 2006, by which time it was expected that a report would be provided on:

- Does the SCCP consider Basic Orange 31 to be safe for use in non-oxidative and oxidative hair dye formulations taken into account the scientific data provided?
- Does the SCCP recommend any restrictions with regard to the use of Basic Orange 31 in non-oxidative and oxidative hair dye formulations?

Members were advised that **XXXXX** pre-meeting comment noted the above SCCNFP report and the request to the SCCP. **XXXXX** asserted that the SCCP report may assist to inform the Committee's considerations and that the Members may therefore wish to defer consideration of this item until the SCCP report becomes available. Members agreed that it may be some time before the SCCP report was publicly released and that the Committee had sufficient data before it to allow consideration at this time. The Committee did agree to request that the SCCP report be tabled for the information of Members when it became available.

A Member also raised the issue of whether the sensitisation and irritancy risks from Basic Orange 31 were such that it should be banned for certain use patterns. Members raised particular concerns about use on the skin, for applications such as tattoo inks, and use in eyelash or eyebrow tints.

OUTCOME

The Committee agreed to foreshadow inclusion of Basic Orange 31 in Appendix C for skin colouration and dyeing of eyelashes or eyebrows because of potential sensitisation and the irritation risk to eyes.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Appendix C – New Entry

BASIC ORANGE 31 (2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride) in preparations for skin colouration and dyeing of eyelashes or eyebrows.

DECISION 2006/48 - 11

The Committee agreed:

- to include a new entry in Schedule 6 for Basic Orange 31 as it is a severe irritant to the eye and a potential sensitiser;
- that ≤ 1% Basic Orange 31 was not a skin irritant and only a slight eye irritant and that the risk of local adverse effects was low; and
- that the risk of sensitisation for ≤ 1% Basic Orange 31 when in hair dyes, while low, cannot be ruled out, but can be adequately addressed by appropriate labelling; and
- to therefore allow an exemption for hair dyes containing ≤ 1% Basic Orange 31, when appropriately labelled.

Schedule 6 – New Entry

BASIC ORANGE 31 (2-[(4-aminophenyl)azo]-1,3-dimethyl-1H-Imidazolium chloride) **except** in hair dye preparations containing 1 per cent or less of Basic Orange 31 when the immediate container and primary pack are labelled with the following statements:

> KEEP OUT OF REACH OF CHILDREN;
>
> If in eyes wash out immediately with water; and
>
> WARNING - This product contains ingredients which may cause skin irritation to certain individuals. A preliminary test according to the accompanying directions should be made before use. This product must not be used for dyeing eyelashes or eyebrows; to do so may be injurious to the eye.
>
> written in letters not less than 1.5 mm in height.

8. OTHER MATTERS FOR CONSIDERATION

No items were considered.

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

No items were considered.

PHARMACEUTICALS

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

10.1 MOMETASONE

PURPOSE

The Committee considered post-meeting comments regarding the June 2006 mometasone decision.

BACKGROUND

Mometasone furoate is a corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders. It is usually employed as a cream, ointment, or lotion containing 0.1% mometasone. When applied topically (particularly to large areas, when the skin is broken, or under occlusive dressings), or when given intranasally, corticosteroids may be absorbed in sufficient amounts to cause systemic effects. Mometasone undergoes extensive first-pass hepatic metabolism.

The August 1992 ADEC Meeting recommended approval of mometasone furoate for treatment of inflammatory and pruritic manifestations of corticosteroid responsive dermatoses, including psoriasis and atopic dermatitis. Approval was also recommended for treatment of psoriasis of the scalp and seborrhoeic dermatitis. The February 1993 DPSSC Meeting subsequently agreed to include a Schedule 4 entry for mometasone furoate. The August 1999 NDPSC Meeting amended this entry to the parent compound mometasone following a TTHWP recommendation.

The November 1999 NDPSC Meeting agreed to reschedule mometasone to Schedule 3 for use in aqueous nasal sprays for the treatment of seasonal allergic rhinitis (with certain dose and age conditions). The May 2000 NDPSC Meeting subsequently agreed to include mometasone in Appendix H. The October 2002 NDPSC Meeting agreed to extend the indications for mometasone in Schedule 3 to include "for the short term prophylaxis or treatment of perennial allergic rhinitis". The June 2003 NDPSC Meeting agreed to reschedule mometasone for the short term prophylaxis or treatment of allergic rhinitis, with dose and age restrictions, to Schedule 2 (and as there was no longer a Schedule 3 entry, mometasone was deleted from Appendix H). Mometasone in aqueous nasal spray for use outside the Schedule 2 restrictions (as well as all other mometasone preparations) remained Schedule 4. Minor editorial amendments to this entry were subsequently agreed to at the February 2004 and October 2005 NDPSC Meetings.

The June 2006 NDPSC Meeting agreed to reschedule 0.1% dermal mometasone preparations from Schedule 4 to Schedule 3 on the basis that the evidence provided by the sponsor adequately met the criteria for Schedule 3 inclusion, and that the concern in relation to inappropriate use of this potent corticosteroid would be waylaid through appropriate pharmacist eduction prior to product launch. The Appendix H inclusion was

not supported by the Committee at this stage due to a lack of OTC experience for this potent corticosteroid. The new Schedule 3 mometasone entry agreed to was:

MOMETASONE as the only therapeutically active substance in preparations for dermal use containing 0.1 per cent or less of mometasone in packs containing 30 g or less of the preparation.

DISCUSSION

The Committee was advised of two post-meeting comments **XXXXX** regarding the June 2006 mometasone rescheduling decision. Members particularly noted the following from these comments:

XXXXX

- The importance of appropriate pharmacist education prior to the launch of dermal preparations containing mometasone had been highlighted in the Record of Reasons of the June 2006 NDPSC Meeting. **XXXXX** asserted that although mometasone had a high efficacy and low or equivalent potential for adverse effects to other corticosteroids it was deemed prudent that pharmacist education and protocols were in place before the implementation date and certainly before any product launch took place.
- **XXXXX** advised that in preliminary discussions with the pharmacy profession, some concern was expressed that < 6 months was an inadequate period of time for familiarisation and training on the first of the medium-high potency dermal corticosteroids to be available as Schedule 3. While the training materials developed to date were seen to be useful for pharmacy intervention, **XXXXX** asserted that further treatment protocols needed to be developed.
- **XXXXX** advised that discussions have been ongoing with **XXXXX** and it seemed apparent that **XXXXX** would also welcome an opportunity to defer the implementation date to ensure the training programmes and materials are sufficient for **XXXXX** needs.
- **XXXXX** therefore requested that the Committee consider deferring the implementation date by 6 months to 1 June 2007. **XXXXX** advised that this timeline was seen as adequate by **XXXXX**.

XXXXX

- Disagreed with the rescheduling of mometasone for dermal use to Schedule 3 and raised a number of issues from the Record of Reasons of the June 2006 NDPSC Meeting
- Background: It was stated "While mometasone has been down-scheduled to Schedule 2 in aqueous nasal sprays for prophylaxis or treatment of allergic rhinitis, it has remained Schedule 4 for topical use (i.e. on the skin)". **XXXXX** asserted that this

statement was not accurate as the Schedule 2 entry for mometasone nasal sprays was restricted by a number of conditions.

- Discussion: **XXXXX** disagreed with a number of points from the June 2006 **XXXXX** submission:
  - The statement "Similar corticosteroid preparations have been reclassified to non-prescription status in Australia and elsewhere". **XXXXX** noted that mometasone furoate 0.1% was a Class 3 (Potent) corticosteroid whilst the other corticosteroids referred to were Class 2 (Moderate e.g. clobetasone and alclometasone) or Class 1 (Mild e.g. hydrocortisone).
  - The statement "While mometasone is prescription-only in other countries, many of these countries do not have a classification similar to Schedule 3". **XXXXX** noted that Canada, UK and New Zealand did have a classification similar to Schedule 3 (the Pharmacy Medicines classification in the UK was more similar to Schedule 3 than Schedule 2).
  - The safety and efficacy information provided by the applicant was disputed.
  - **XXXXX**
  - A copy of the EC Guidelines on "Clinical Investigation of Corticosteroids Intended for Use on the Skin" was provided. Section 2.1 of these guidelines asserted that absorption of topical corticosteroids, as well as most of the adverse reactions, were demonstrated to depend both on the substance and on factors including the physico-chemical properties of the base (as the presence of other components or excipients could modify the penetration through the stratum corneum). **XXXXX** therefore requested that the Committee take into consideration the appropriateness of utilising the efficacy and safety data generated by **XXXXX** formulations in assessing the safety of Schedule 3 **XXXXX** formulations that contained different excipients.
  - The statement "There is no potential for abuse and little potential for harm from inappropriate use with labelling, pharmacist counselling and pack size restrictions (30 g)" was disputed:
    - The Committee was referred to the March 2005 session of the FDA's Dermatologic & Ophthalmic Drugs Advisory Committee Meeting (DODAC) which reviewed the safety of dermatological topical corticosteroids. An assessment of spontaneous adverse event data indicated hypothalamic-pituitary-adrenal (HPA) axis compromise in 94 cases (65 adult, 29 paediatric). The gamut of manifestations had been adrenal insufficiency, Cushing's syndrome and growth retardation. The most common factors for adverse events occurred in the following setting:
    - Prolonged use of topical corticosteroid despite limitation on the labelling.
    - Use of a superpotent topical corticosteroid.
    - Use of multiple corticosteroid products.

- Concomitant use with other corticosteroid formulation.
- Use of excessive amount or possible inappropriate use.

- **XXXXX** therefore did not agree that there was "no potential for abuse and little potential for harm from inappropriate use". Irrespective of Pharmacist counselling, there was a risk that a minority of patients could use large amounts, and/or medicate for durations in excess of the label recommendations (particularly as the conditions being treated, such as psoriasis, are often chronic, or are characterised by recurrence).
- The statement "Available safety data shows that despite mometasone's moderate potency, there is a marked disassociation of potency from increased risk of side effects including dermal atrophy" was disputed:
  - The Committee was referred to the *Dermatological Therapeutic Guidelines*. In reference to the local adverse effects of topical corticosteroids at the site of application these guidelines claim that this "…consists of loss of dermal collagen (leading to skin atrophy, striae, fragility and easy bruising), telangiectasia and perioral dermatitis. Their intensity is proportional to the therapeutic effect and thus increases with the potency of the preparation".
  - Additionally, the EC Guidelines, Section 2.3.1, stated that the stronger the preparations the greater the chance of adverse effects such as skin atrophy, rosacea-like, perioral dermatitis, rebound, effect on the eye and depigmentation.
  - **XXXXX** asserted that the interaction between the development of side effects and body surface area, amount of drug used and potency of the medication was complex, and should therefore not be oversimplified. **XXXXX** did not believe that there was adequate data to support the contention that for mometasone there was a marked disassociation of potency from increased risk of side effects.

- **XXXXX** therefore felt that rescheduling mometasone to Schedule 3 without indication (exclude psoriasis and other chronic conditions) and age restrictions (12 years and above) could compromise the safe use of the product. **XXXXX** asserted that applying this age restriction for the scheduling of the dermal product would ensure consistency with the current scheduling for the OTC intranasal preparation.
- **XXXXX** also wished to point out that the current sales data for **XXXXX** indicate that the 15 g pack size consists of **XXXXX** of sales while the 45 g pack size consists of **XXXXX** of sales (i.e. the safety profile of mometasone derived from the ADRAC data was predominately based on the 15 g pack size). **XXXXX** therefore believe that should downscheduling occur, it would be appropriate to limit the pack size to 15 g.

Members also noted a letter from **XXXXX.** Members particularly noted:

- **XXXXX** views the June 2006 rescheduling of mometasone with grave concern.

- **XXXXX** noted that mometasone's use topically may, if used inappropriately, cause significant problems in the skin. Because it was widely prescribed and often not applied according to doctor's instructions, **XXXXX** asserted that it was currently the commonest cause of corticosteroid induced rosacea on the face and was a significant cause of atrophy of the skin, particularly in flexural areas. Anecdotally, dermatologists would each see at least several significant cutaneous adverse reactions associated with mometasone per week.
- **XXXXX** asserted that mometasone should only be used under strict medical supervision because of the potential for cutaneous side effects, such as corticosteroid-induced rosacea, permanent skin atrophy and striae, and a significant exacerbation of skin infections. **XXXXX** also asserted that these adverse events were common and of significant harm potential.
- **XXXXX** therefore requests that the Members reconsider the June 2006 mometasone decision.
- **XXXXX** also disagreed with a number of points from the June 2006 **XXXXX** submission:
- The statement "Similar corticosteroid preparations have been reclassified to non-prescription status in Australia and elsewhere…". **XXXXX** disagreed, noting that hydrocortisone was a weak topical corticosteroid with quite significantly reduced potency compared to mometasone. Also, if mometasone were down-scheduled, then there would be a convincing argument that all other topical corticosteroid preparations (with the exception of Diprosone OV) should also be reclassified.
- The statement "It has a better safety profile than betamethasone and an equivalent side-effect profile to hydrocortisone 1% and clobetasone 0.05%". **XXXXX** asserted that this was not the case in clinical practice, although it had been shown in some older short term studies. The side effect profile of mometasone, from the point of view of skin atrophy and the development of corticosteroid-induced rosacea, was equivalent to betamethasone valerate 0.05% and was certainly much more significant than the negligible side effect profile of hydrocortisone 1%.
- The statement "There is no potential for abuse and little potential for harm from inappropriate use with labelling, pharmacist counselling and pack size restrictions". **XXXXX** asserted that this was not the case. Despite regular advice from the doctor to avoid using mometasone on the face, this was commonly done and side effects such as corticosteroid-induced rosacea could occur within only a few weeks of regular use of this product. **XXXXX** asserted that there was great potential for abuse and significant potential for harm from inappropriate use of mometasone, despite labelling, pharmacist counselling and pack size reductions.
- The statement "Most side effects are transient and mild. More serious side effects were usually only seen in chronic use over large body areas". **XXXXX** noted that corticosteroid-induced rosacea can persist for months or even years. This side effect, as well as the side effect of atrophy and striae in flexural areas, could occur with as little as 15g used over a period of several weeks.

- The statement "Available safety data shows that despite mometasone's moderate potency, there is a marked disassociation of potency from increased risk of side effects including dermal atrophy". **XXXXX** asserted that whilst this may be the case in the early short term studies which were provided to the TGA for approval of mometasone, this was not the situation in clinical practice. Potency of the topical corticosteroids is directly proportional to the potential for inducing skin atrophy and other dermatological side effects. Mometasone was asserted to be Australia's most common cause of corticosteroid-induced skin atrophy and rosacea.
- The statement "Labelling will caution patients from using on skin infections (e.g. cold sores, shingles, chicken pox, thrush, tinea, ringworm and acne), in or around the eyes or groin or under occlusive dressing unless advised by a doctor to do so". **XXXXX** noted that patients often have difficulty distinguishing skin infections from moderate or moderately severe eczema. It was asserted that it was quite common in clinical practice to see patients with severe herpes infection on areas of skin eczema and impetigo which have been treated with mometasone. This was a dangerous situation with spread of the viral or bacterial infection, and will most likely occur more frequently should the scheduling change occur.
- The statement {paraphrased} "ADRAC indicates only 162 reports where mometasone was suspected as the cause of adverse reactions. The most prevalent skin disorders were dermatitis, rosacea, acne, rash and urticaria". **XXXXX** asserted that these figures demonstrated a marked underreporting. As mentioned above, **XXXXX** asserted that mometasone was the commonest cause of adverse skin reactions that dermatologists see due to topical corticosteroids. **XXXXX** suggested that dermatologists probably consider these far too common to report on a regular basis, noting that it was well known that non-life threatening side effects are significantly underreported.
- **XXXXX** also disagreed with the evaluation report statement "The evaluator considered that the request for down-scheduling for the stated indication was appropriate; it is for common conditions which would be easily identified by the consumer, with appropriate counselling from the pharmacist. Abuse potential is nil and harm risk is low for short term (up to four weeks) use". **XXXXX** asserted that the general public have significant difficulty in diagnosing their own skin condition. **XXXXX** further asserted that mometasone should only be used under strict medical supervision because of the high potential for cutaneous side effects (and strenuously asserts that there is not a "nil" risk). **XXXXX** also stated that the harm risk was quite significant in the sense that corticosteroid-induced rosacea takes a minimum of six weeks to significantly improve, and skin atrophy or striae may never improve. Blindness from eczema herpeticum of the cornea was likely to be permanent.

Members also noted the following from a **XXXXX** follow-up letter to that above:

- **XXXXX** was unable to enclose any specific publications which indicated or supported the well-recognised cutaneous side effects of mometasone furoate.

- As mentioned in **XXXXX** previous letter it was clear that there has been a significant underreporting of the cutaneous side effects of mometasone furoate within Australia and overseas. This was most likely related to the fact that this was seen so commonly in dermatological practice that it has been considered almost expected, rather than an uncommon side effect worthy of a publication or a specific reporting.
- **XXXXX** again asserted the need to overturn the down-scheduling of mometasone furoate.

The Members recalled that the application submitted to the June 2006 NDPSC Meeting included the following:

- Mometasone topical preparations have been available for many years on prescription with intranasal preparations being available without a prescription since 1999.
- Similar corticosteroid preparations have been reclassified to non-prescription status in Australia and elsewhere. Hydrocortisone is Schedule 2 (and equivalent in New Zealand) and both clobetasone and alclometasone are Schedule 3. Some hydrocortisone preparations are GSL in the UK, with restrictions.
- While mometasone was prescription-only in other countries, many of these countries did not have a classification similar to Schedule 3.
- Mometasone furoate 0.1% compares favourably to betamethasone dipropionate, is more effective than hydrocortisone salts, betamethasone valerate and clobetasone. It has a better safety profile than betamethasone and an equivalent side-effect profile to hydrocortisone 1% and clobetasone 0.05%.
- There was no potential for abuse and little potential for harm from inappropriate use with labelling, pharmacist counselling and pack size restrictions.
- Most side effects were transient and mild. More serious side effects were usually only seen in chronic use over large body areas.
- Administration of nasal, oral or topical mometasone had not produced any clinically significant decrease in serum cortisol levels and no symptoms of HPA axis suppression were observed in any patients treated topically up to 21 days. Available safety data showed that despite mometasone's moderate potency, there was a marked disassociation of potency from increased risk of side effects including dermal atrophy.
- While there have been reports of cutaneous atrophy after more than 3 weeks continuous therapy with several of the topical corticosteroids, studies with mometasone furoate 0.1% showed that up to 3 weeks therapy led to minimal side-effects occurring.
- Labelling would caution patients from using on skin infections (e.g. cold sores, shingles, chicken pox, thrush, tinea, ringworm and acne), in or around the eyes or groin or under occlusive dressing unless advised by a doctor to do so.

The Committee recalled the following from the June 2006 NDPSC Meeting:

Evaluation report

- The proposed labelling was for once-daily application for up to four weeks in adults and children over the age of two years for relief from inflamed and itchy skin conditions due to psoriasis, dermatitis and eczema. Included are warning statements required for topical corticosteroid preparations (see report for full list). CMI & approved PI would be consistent with current Schedule 4 product PI.
- Mometasone furoate has been available in Europe and the USA since 1987 and Australia since 1993. However, the evaluator pointed out that the corticosteroids which the sponsor listed as currently available without prescription in Australia (hydrocortisone, hydrocortisone acetate, clobetasone and alclometasone) are class 1 to class 2 (i.e. mild to moderate) corticosteroids whereas mometasone was a class 3 (potent) corticosteroid.
- The sponsor provided clinical trial data demonstrating efficacy of topical formulations for psoriasis, dermatitis and other paediatric and adult dermatoses when using for three to eight weeks.

With over fifteen years of clinical use, adverse effects (AEs) included expected events of stinging, burning, pruritus, folliculitis, dryness, tenderness and skin atrophy. These AEs were clearly stated in the draft PI and listed under warnings in the draft CMI. Clinical trials in healthy male volunteers did not produce any clinical decrease in serum cortisols or symptoms of HPA axis suppression for up to 21 days topically or 36 days intranasally.

Mometasone demonstrated only a low potential for overt skin atrophy even though it demonstrated clinical and statistical superiority over hydrocortisone in the treatment of psoriasis.

ADRAC reports back to 1990 showed 162 reports where mometasone was suspected possible, probable or certain association. The majority of AEs were skin and subcutaneous tissue disorders. The most prevalent skin disorders were dermatitis (9 reports), rosacea (11 reports), acne (5 reports), rash and urticaria (11 reports) and skin depigmentation (8 reports), consistent with the expected adverse event profile for this product as identified in the PI/CMI.

- The evaluator considered that the request for down-scheduling for the stated indication was appropriate; it was for common conditions which would be easily identified by the consumer, with appropriate counselling from the pharmacist. Abuse potential was nil and harm risk was low for short term (up to four weeks) use. There was also a low risk of masking a serious disease. Appropriate warnings appear in the proposed CMI.
- Mometasone was Category B3; no studies had identified corticosteroids as teratogenic. There were statements in the proposed PI that topical corticosteroids should not be used by pregnant women in large amounts for prolonged periods. Caution in lactation was also listed in the proposed PI/ CMI.

- As mometasone would be the most potent topical corticosteroid available OTC, the evaluator did not recommend Appendix H inclusion as close monitoring of safety would be prudent before promoting it more broadly through advertising.
- Sponsor's comment on the evaluation report.
- The sponsor stated that while they felt the evaluator was being overly cautious in not recommending Appendix H inclusion, they would be prepared to re-apply for Appendix H listing after the first year of OTC use.

Pre-meeting submissions

- **XXXXX**: did not support Schedule 3 listing for mometasone. **XXXXX** maintained that, while pharmacists would be able to properly advise on and prescribe potent corticosteroids such as mometasone, it was more appropriate that pharmacists had access to moderate corticosteroids first. It was also stated that professional protocols and educational packages should be made available to pharmacists prior to down-scheduling.
- **XXXXX** opposed Schedule 3 listing or Appendix H inclusion for mometasone. **XXXXX** expressed concern that mometasone would be the first OTC potent corticosteroid and thus the safety of OTC use of potent corticosteroids was as yet unestablished.
- **XXXXX** did not support either Schedule 3 listing or the Appendix H inclusion of mometasone. **XXXXX** believed that while acute inflammatory eruptions, including allergic dermatitis and eczema, were generally responsive to mild (e.g. hydrocortisone) or moderate (e.g. clobetasone) corticosteroids, chronic, thickened or hyperkeratotic dermatoses would require potent or very potent corticosteroids. The latter conditions required ongoing medical supervision and so were not appropriate for self-medication. Both mild (hydrocortisone and hydrocortisone acetate) and moderate (alclometasone and clobetasone) were already available without prescription in Australia. **XXXXX** discussed the risk factors for topical corticosteroids and suggested that, despite labelling restrictions, there was still potential for a potent corticosteroid such as mometasone to be inappropriately used and, in some cases, abused. **XXXXX** recommended that opinion on this matter be sought from **XXXXX.** The Committee felt that, on further discussion, such action would be unnecessary.

XXXXX

- **XXXXX** sought advice from **XXXXX** regarding data requirements for a proposed topical corticosteroid ointment containing mometasone furoate. The minutes from the **XXXXX** stated that although topical preparations containing mometasone were currently classified as Schedule 4, **XXXXX** had successfully justified the OTC route for the proposed product. The minutes further stated that **XXXXX** intend to use an FDA assay as part of their data package, rather than that which was set down in the relevant EMEA guidelines (guidelines routinely required to be met for marketing

applications for prescription medicines). **XXXXX** agreed that the sponsor's application should be reviewed by both **XXXXX** and **XXXXX**.

NDPSC considerations

- A Member pointed out that, although the moderately potent corticosteroids alclometasone and clobetasone were Schedule 3, neither of these substances was available as marketed OTC preparations (these substances were both rescheduled as a result of trans-Tasman harmonisation). Thus, the Member reiterated the importance of appropriate pharmacist education prior to a Schedule 3 launch of dermal OTC preparations containing mometasone.
- Another Member raised the issue of the correlation between potency and the side-effect profile: the data presented clearly indicated that the side-effect profile of mometasone warranted a Schedule 3 listing. The theoretical concerns regarding the use of a potent corticosteroid were not realised in clinical practise as it was clear that mometasone did not cause adrenal suppression in short term dermal use.
- Members agreed that mometasone had been safely marketed in the US and Europe for almost 20 years, and in Australia for approximately 15 years. Members accepted the evidence provided by the sponsor and the opinion by the evaluator that, compared to other corticosteroids, mometasone furoate topical formulations showed high efficacy and low or equivalent potential adverse effects.
- Members also considered other Schedule 3 criteria for the 0.1% dermal preparations of mometasone, i.e. the indications easily identified by consumers, with appropriate counselling from the pharmacist, minimal abuse potential, low harm risks for short term use (up to 4 weeks) and a low risk of masking a serious disease. The Committee hence considered down scheduling of 0.1% dermal preparations of mometasone appropriate.
- The Committee felt that Appendix H inclusion was not appropriate at this stage and that market experience for mometasone as an OTC product would need to be garnered before promoting this potent topical corticosteroid more broadly through direct-to-consumer advertising.

A Member sought clarification as to the position of **XXXXX** on the original decision. Members recalled that in the pre-meeting submissions to the June 2006 NDPSC Meeting, all of these parties were opposed to the Schedule 3 listing, but that **XXXXX** now support the Schedule 3 listing with appropriate pharmacist education.

A Member pointed out that **XXXXX** had a strong disagreement with the rescheduling of mometasone fuorate as **XXXXX** have seen cutaneous atrophy and rosacea with the product when applied to the face. **XXXXX** gave anecdotal reports of this from **XXXXX** but did not provide scientific evidence. It was pointed out that in the NHMRC's schedule of levels of evidence, anecdotal evidence is the lowest on the scale. The Member further recalled that the data provided previously to the Committee in June 2006 showed no

heightened risk of this with topical mometasone. Another Member noted that, as these reports were anecdotal, changing the Committees decision was difficult on the basis of that alone. At the very least, **XXXXX** should supply peer-reviews case studies over the anecdotal evidence they have provided. Another Member noted that the strong opposition of **XXXXX** to the rescheduling should be taken into account **XXXXX**

A Member noted that this is the first moderate to potent corticosteroid product contained in Schedule 3, but at the June 2006 NDPSC Meeting the Committee assessed it, on the basis of the evidence presented, as having the same safety profile as 1% hydrocortisone and that the post meeting submission from **XXXXX** did not provide any evidence, other than anecdotal, of this not being the case. Another Member agreed that in the original application, the data indicated that this was indeed a moderate potency corticosteroid and recalled that the Committee felt that the safety data presented showed no practical difference in AEs compared to other corticosteroids and that therefore, based on this evidence, the decision made by the Committee was sound. A Member noted that pharmacist training was not required when hydrocortisone 1% was down-scheduled, so if stakeholders felt that pharmacist training was required for down-scheduling of mometasone then the June 2006 decision might need to be revisited.

A Member noted that **XXXXX** were stating that the similar safety profiles of mometasone and less potent corticosteroids was not their experience in their routine dealing with the substance. Another Member noted that, even though there was no hard evidence presented to the Committee to support this statement, that the concern of **XXXXX** should be considered. A Member raised concern about setting aside the decision on the basis of anecdotal data and that any reconsideration of the scheduling of the product be re-gazetted to allow the sponsor to address the arguments raised in the post meeting comments as well as giving the Committee time to review the data provided and an opportunity consider other scheduling restrictions such as pack size and age limits. Another Member noted that if this product does behave like a potent corticosteroid then the data should be out there in the literature and that the Committee should consider it.

Members discussed whether reducing the pack size and limiting use of the product to over 12 years of age (as per **XXXXX** suggestion) would be an option to help allay concerns about the inappropriate use of the product on the face. One Member stated that the fact that consumers will find mometasone effective might lead them to use it inappropriately (e.g. on the face) and limiting pack size may not prevent this from occurring.

Members agreed that further advice about the safety and AE profile of topical mometasone be sought from **XXXXX** and that the sponsor be advised that the Committee would consider a further application and that, until such information was provided and reviewed, that the decision from the June 2006 NDPSC Meeting should be set aside.

DECISION 2006/48 - 12 (Set aside Decision 2006/47-22)

The Committee agreed to set aside the June 2006 NDPSC decision (2006/47-22) to reschedule mometasone fuorate in order to allow further consideration of concerns regarding the number and severity of potential adverse events experienced with the drug.

OUTCOME

The Committee agreed to foreshadow a consideration of the scheduling of mometasone for the February 2007 NDPSC Meeting and to contact **XXXXX** to provide data on adverse events related to the use of topical mometasone fuorate.

FORESHADOWED DESCISION (for consideration at February 2007 Meeting)

Schedule 3 – New Entry

MOMETASONE as the only therapeutically active substance in preparations for dermal use containing 0.1 per cent or less of mometasone in packs containing 30 g or less of the preparation.

Schedule 4 - Amendment

MOMETASONE – amend entry to read:

MOMETASONE **except** when included in Schedule 2 or 3.

11. OTHER OUTSTANDING MATTERS FROM PREVIOUS MEETINGS

11.1 FLUORIDES

PURPOSE

The Committee considered the scheduling of fluorides.

BACKGROUND

Prior to the June 2004 NDPSC decision the fluorides Schedule 2 entry was:

FLUORIDES for human therapeutic use (**except** in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or

(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion **except**:

(i) Dentrifices included in Schedule 3;

(ii) Dentrifices containing 1000 mg/kg or less of fluoride ion; or

(iii) other dental hygiene products containing 100 mg/kg or 100 mg/L or less of fluoride ion.

The 1000 mg/kg Schedule 2 exemption for dentrifices, and the general Schedule 2 exemption for preparations containing ≤ 15 mg/kg were introduced at the February 1986 DPSSC Meeting. Dentrifices with > 1000 mg/kg fluoride ion were included in Schedule 3 at the July 1987 DPSSC Meeting. The 2.5 % cut-off in the first line of part (b) in the Schedule 2 entry resulted from a February 2001 NDPSC decision to harmonise with New Zealand.

The February 2004 NDPSC Meeting agreed to exempt dental hygiene products which were not dentrifices, such as mouth rinse preparations, containing ≤ 220 mg/kg fluoride ion. This exemption was conditional upon compliance with a 120 mg pack size, child-resistant closure (CRC) and label warnings against swallowing the product and using in children under six years of age. Preparations that did not meet these conditions were included in Schedule 2. The June 2004 NDPSC Meeting varied the decision of the February 2004 NDPSC Meeting by replacing "for human therapeutic use" in the fluoride entries with "for human use". No Committee discussion was minuted regarding those non-therapeutic products for human use such as fluoride containing dental whiteners which were now captured.

Subsequent to the June 2004 NDPSC Meeting the Committee considered some minor changes to the Schedule 2 and Schedule 4 entries at the February, June and October 2005 NDPSC Meetings as a consequence of the introduction of the *Required Advisory Statements for Medicines Labels*.

The June 2006 NDPSC Meeting was advised by a Member that it appeared that the June 2004 amendment to the Schedule 2 fluorides entry had a wider regulatory impact than intended which needed to be considered by the Committee. The Committee agreed to gazette consideration of this issue at the October 2006 NDPSC Meeting.

DISCUSSION

The Committee noted Secretariat advice that currently all topical dental whiteners or bleaches which do not also make an oral hygiene claim with 15 mg/kg(L) > fluoride < 2.5% would be Schedule 2. Where a topical dental whitener or bleach also has an oral hygiene use the product would either qualify for an exemption under (b)(i),(ii),(iii) or (iv) or would be Schedule 2. Those with 15 mg/kg(L) > fluoride < 220 mg/kg(L) and not excluded by (b)(i) or (ii) would be captured under part (b)(iii) or (iv) - depending on whether or not they were therapeutic goods - by virtue of not being fitted with a CRC or labelled with the appropriate labelling. Where the CRC and labelling requirements were fulfilled such products would not be scheduled.

Members recalled the following from the February 2004 NDPSC Meeting consideration of dental hygiene products which were not dentrifices, such as mouth washes, containing 15 mg/kg < fluoride ≤ 220 mg/kg:

- Members noted that mouth rinses containing 0.02-0.05% sodium fluoride did not appear to pose any significant adverse effects in adults. The FDA fluoride limit was 0.05% w/w sodium fluoride for oral rinses and that this level had been extensively used safely in the US, UK, New Zealand and Australia. However, the *Review of Water Fluoridation and Fluoride Intake from Discretionary Fluoride Supplements, 1999* (NHMRC) raised concerns at the possibility of adverse effects (i.e. dental fluorosis) from excessive chronic fluoride ingestion by children.
- The Committee discussed the possible use of fluoride mouth washes by children and expressed concern that this could potentially lead to an increase in fluoride ingestion and the development of fluorosis. However, as the level of 220 mg/kg fluoride ion was still significantly lower than that in toothpaste the Committee considered that it was unlikely to pose any increased safety issues.
- Members agreed to increase the exemption cut-off for "other dental hygiene products" from 100 to 220 mg/kg (with labelling, pack size and CRC conditions). Members also agreed to amend the fluorides entries to remove the term "dentrifice" and replace it with "pastes, powders or gels for the cleaning of teeth" (although the Schedule 3 entry was just changed to "pastes, powders or gels for use on teeth").

The Committee noted Secretariat's advice that the Schedule 3 entry "for use on teeth", combined with the Schedule 2 exemption (b)(i) "for the cleaning of teeth", meant that products not for cleaning of teeth containing 1000 mg/kg < fluoride ≤ 2.5% were inadvertently captured by both Schedule 2 and Schedule 3.

Members also noted the following from the June 2004 NDPSC Meeting:

- Advice was noted that many dental hygiene products were Excluded Goods under the *Therapeutic Goods Act 1989* (the Act) and were therefore not subject to regulation by the TGA when for human therapeutic use. It was therefore suggested that "therapeutic" be removed from the lead-in words in the SUSDP fluoride entries.
- The Committee noted that the acute toxicity level given for accidental ingestion of sodium fluoride in children was 5 mg/kg fluoride. For a 10 kg child, this equated to ingestion of ~227 mL of mouthwash containing 220 mg/L fluoride. Members remained concerned at the risk of toxicity from ingestion of more concentrated fluoride products and agreed that CRC on these products should alert consumers to the potential toxicity as well as reinforce the message that such products were not appropriate for use in young children.

Members recalled that a Member's advice to the June 2006 NDPSC Meeting included:

- An assertion that the June 2004 amendment i.e. removal of "therapeutic" from the lead-in words in various fluoride entries, inadvertently made null and void application

of the *Excluded Goods Order*. The Member asserted that the section of the *Excluded Goods Order* relevant to oral hygiene products stated that the following products would be excluded:

- Oral hygiene preparations or devices (including dentifrices, mouth washes, breath fresheners, brushes and flosses) other than those:

  (a) included in a Schedule to the Poisons Standard; or
  (b) required to be included in the Australian Register of Therapeutic Goods

  provided the benefits claimed to result from the use of the goods are restricted to those consequential on improvements to oral hygiene or the use of fluoride for the prevention of tooth decay.

  (The October 2006 NDPSC Meeting was advised that fluoride use in some whiteners was to deal with the temporary tooth sensitivity by remineralizing teeth. As such, these products did not appear to contain fluoride for the purpose of oral hygiene or preventing tooth decay and did not qualify for the oral hygiene *Excluded Goods Order* exemption. However, "dental bleaches or dental whiteners" were separately declared in the *Excluded Goods Order* (No.1 of 2005) not to be therapeutic goods, and this declaration did not limit itself to preparations not included in the SUSDP.)

- The Member asserted that by removing "therapeutic" the Committee had made all of the previously unscheduled products, including whiteners and other fluoride products that met the criteria, Schedule 2 and therefore therapeutic goods.

Members noted a pre-meeting comment from **XXXXX** which supported the following pre-meeting comment from **XXXXX .**

Members considered the following from **XXXXX** pre-meeting comment:

- **XXXXX** asserted that removal of "therapeutic" had inadvertently captured non dental hygiene products into Schedule 2. **XXXXX** particularly noted that this appeared to include some dental bleachers and whiteners.
- **XXXXX** advised that dental whitener product development and innovation in recent years had seen the addition of fluoride into some formulations at a level consistent with that used in cosmetic toothpastes (1000 ppm). **XXXXX** asserted that the safety of fluoride in toothpastes at 1000 ppm had been confirmed and noted that the SUSDP exempted toothpastes with this level of fluoride from scheduling.
- **XXXXX** sought to ensure that product innovation of dental whiteners to include fluoride was not inhibited by products being regulated as Schedule 2 by virtue of the presence of fluoride, even though dental bleaches and whiteners were specifically excluded in the *Excluded Goods Order*. **XXXXX** asserted that dental bleachers and whiteners had never been regulated as therapeutic goods since the inception of the Act.

- **XXXXX** submitted that dental whiteners were appropriately controlled by the SUSDP entries for the whitening agents (hydrogen peroxide or carbamide peroxide) and there was no public safety benefit for these products being regulated as Schedule 2 if they additionally contained fluoride at a level that was consistent with exempted fluoride toothpastes. **XXXXX** proposed three options for amending the fluoride entries:

Option A – new exemption

- Add a product class exemption to the Schedule 2 Fluoride entry (b)(v) "dental whiteners and bleachers containing 1000mg/kg or less of fluoride ion".
    - Members noted that this option would apply to all whitening types (≤ 1000 mg/kg fluoride), including mouthwash or other formulations otherwise captured under (b)(iii) or (iv), which was inappropriate as the bioavailability of fluoride from products such as mouthwashes was likely to be greater than from pastes, powders or gels, a particular concern at > 220 mg/kg fluoride.

Option B – Amending Schedule 2(b)(ii)

- **XXXXX** proposed changing (b)(ii) to read "pastes, powders or gels for application to the teeth containing 1000mg/kg or less of fluoride ion".
- **XXXXX** noted that this revised wording expanded the existing exemption to include dental whiteners containing fluoride, yet confined the exemption to products that were applied directly to the teeth, and retained the fluoride threshold at that which had been considered appropriate for unscheduled products applied to the teeth such as toothpastes.
    - Members noted that this option did not address the scheduling of whitener formulations that were not pastes, powders or gels.

Option C – Reinstating the word "therapeutic".

- **XXXXX** asserted that this would automatically default this category of products out of the Schedule 2 entry, and that the safety of the product was rightfully controlled by the scheduling criteria of the primary active ingredient - the whitening agent. **XXXXX** noted, however, that this may require slight rewording of the existing exemptions in Part (b).
    - Members noted that this option would also exempt mouthwashes or any other non-therapeutic products currently captured under (b) (unless exempted by (b)(iii) or (iv) – in which case there were CRC and labelling requirements).

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

- **XXXXX** believed the products affected included those beyond "pastes, powders and gels for the cleaning of teeth" e.g. dental whiteners and bleaches that are for the application to teeth and still contain 1000mg/kg or less of fluoride ion.

- **XXXXX** supported revision of the wording to ensure these products were more correctly available as unscheduled products. **XXXXX** asserted that this would also avoid any complication of the original intention of the *Excluded Goods Order*.

Members also note that the Secretariat was advised by **[XXXXX** that it did not feel any need to comment on this issue.

A Member asserted that the risk of the fluoride content in teeth bleachers and whiteners would be similar to existing, non-whitening dental hygiene products i.e. toothpaste. The Committee agreed, noting that any separate concerns arising from the whitening active would be covered by the SUSDP entries for that active i.e. hydrogen peroxide. The Committee therefore agreed to align all fluoride containing bleaching and whitening formulations to the existing dental hygiene controls, not just pastes, powders or gels.

DECISION 2006/48 - 13

The Committee:

- Agreed that pastes, powders or gels containing 15 mg/kg < fluoride ion ≤ 1000 mg/kg for all applications to teeth (including dental hygiene, whitening and bleaching) did not warrant scheduling as there was little risk of these formulations being ingested in sufficient quantity to cause harm.
    - Members therefore agreed to amend Schedule 2(b)(ii), Schedule 4(b), Schedule 5(b) and Schedule 6(b) by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion".
- Confirmed that it was appropriate that all pastes, powders or gels for use on teeth containing > 1000 mg/kg fluoride be controlled by the Schedule 3 entry as the risks from this concentration of fluoride ion required pharmacist advice.
    - Members therefore agreed to amend Schedule 3 by replacing the current wording with "dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion"
- Agreed that other formulation types (i.e. not pastes, powders or gels) for topical oral use containing 220 mg/kg < fluoride ion ≤ 2.5 % (including dental hygiene and whitening) were to be Schedule 2 due to the increased risk of such formulations being ingested in a quantity which may cause harm.
- Agreed that the public health risks of topical dental hygiene, whitening or bleaching products containing 15 mg/kg < fluoride ion ≤ 220 mg/kg (except as specified by (b)(ii) in the Schedule 2 fluorides entry) would be acceptably minimised through labelling, pack size limitations and a CRC requirement. Where these conditions were not met capture by Schedule 2 was appropriate.
    - Members therefore agreed to amend Schedule 2(b)(iii) and (iv), Schedule 4(c) and (d), Schedule 5 (c) and (d) and Schedule 6 (c) and (d) to allow dental whiteners

and bleachers to qualify for these exemptions by adding ", whitening or bleaching" after the existing "other dental hygiene".

Schedule 2 – Amendment

FLUORIDES for human use (**except** in preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion):

(a) as sodium fluoride, in preparations for ingestion containing 2.2 mg or less of sodium fluoride per dosage unit; or

(b) in preparations for topical use containing 2.5 per cent or less of fluoride ion **except**:

(i) when included in Schedule 3;

(ii) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;

(iii) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*; or

(iv) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(A) Do not swallow; and

(B) Do not use [this product/name of product] in children six years of age or less.

Schedule 3 - Amendment

FLUORIDES in dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing more than 1000 mg/kg of fluoride ion.

Schedule 4 – Amendment

FLUORIDES in preparations for human use **except**:

(a) when included in Schedule 2 or 3;

(b) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

d) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

(ii) Do not use [this product/name of product] in children six years of age or less; or

(e) other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

Schedule 5 – Amendment

FLUORIDES in preparations containing 3 per cent or less of fluoride ion **except**:

(a) when included in Schedule 2, 3 or 4;

(b) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(d) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

(ii) Do not use [this product/name of product] in children 6 years of age or less; or

(e) other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

Schedule 6 – Amendment

FLUORIDES **except**:

(a) when included in Schedule 2, 3, 4 or 5;

(b) dental hygiene, whitening or bleaching products that are pastes, powders or gels for use on teeth, containing 1000 mg/kg or less of fluoride ion;

(c) other dental hygiene, whitening or bleaching products that are therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure, when compliant with the requirements of the *Required Advisory Statements for Medicine Labels*;

(d) other dental hygiene, whitening or bleaching products that are not therapeutic goods, containing 220 mg/kg or 220 mg/L or less of fluoride ion, in packs containing not more than 120 mg total fluoride, fitted with a child-resistant closure and labelled with warnings to the following effect:

(i) Do not swallow; and

(ii) Do not use [this product/name of product] in children six years of age or less; or

(e) other preparations containing 15 mg/kg or 15 mg/L or less of fluoride ion.

11.2 POTASSIUM CHLORIDE

PURPOSE

The Committee further considered the scheduling of potassium chloride, potentially with a view to amending the Schedule 4 entry to that which was foreshadowed at the February 2006 NDPSC Meeting.

BACKGROUND

Potassium chloride slow-release tablets have been supplied in Australia since 1967. The May 1982 DPSSC Meeting concluded that electrolyte balance control in patients at risk required proper supervision but made no recommendations for scheduling. The February 1985 DPSSC Meeting agreed (and confirmed in February 1986) that warning on the use of potassium supplementation being given to patients on potassium sparing diuretics was the responsibility of the doctor or pharmacist and that no scheduling action was required.

At the October 2005 NDPSC Meeting the Committee discussed a NSW State Coroner's Report into the death of **XXXXX** from an overdose of slow release potassium chloride. The Coroner recommended that slow release potassium chloride products be included in Schedule 4. At the February 2006 NDPSC Meeting, the Committee considered placing high dose oral potassium chloride in a Schedule other than Schedule 4. However, given that **XXXXX** referred to in the Coroner's report would have been at the same risk if the slow release preparation ingested had been Schedule 2 (given that it was purchased from a pharmacy) the Committee agreed to a Schedule 4 entry for potassium chloride. The Committee considered limiting the Schedule 4 entry to slow-release potassium chloride but instead agreed to a broader "oral preparations for therapeutic use".

The decision of the Committee at the February 2006 NDPSC Meeting (Decision 2006/46-27) was to include oral potassium chloride (>100 mg per dosage unit) for therapeutic use in Schedule 4 on the grounds that its toxicity profile required professional oversight, to exempt oral potassium chloride preparations containing than >100 mg per dosage unit for oral rehydration therapy and for enteral feeding and to recommend to the **XXXXX** that, in order to minimise any potential harm to children, child-resistant closures be mandatory for the scheduled potassium chloride products.

At the June 2006 NDPSC Meeting, it was brought to the Committee's attention that the February decision would inadvertently capture a large number of complementary products which contained glucosamine sulfate complexed with potassium chloride. A **XXXXX** was received from **XXXXX** detailing the ramifications of this and providing justification as to why such complementary products should not be scheduled. However, the Committee's concerns regarding the potential for any therapeutic product containing substantial amounts of potassium per unit dose to result in an inadvertent overdose similar to that which was investigated by the NSW Coroner firmly remained. The Committee concluded that toxicological data must be presented to them before they would consider exempting glucosamine sulfate complexed products from scheduling.

Such data would need to clearly demonstrate that products which contain substantial amounts of potassium per unit dose cannot result in high serum potassium levels. In order to allow all stakeholders time to provide such data, the Committee agreed to vary its February decision so that only slow release preparations would be captured by the new Schedule 4 entry. The Committee also agreed to foreshadow an amendment to the Schedule 4 entry, as outlined in the February 2006 decision.

DISCUSSION

The Committee noted that, at its Meeting held on 31 July, the Therapeutic Goods Committee subcommittee on child-resistant packaging considered stakeholder comment on the draft Australian & New Zealand Therapeutic Products Authority (ANZTPA) Managing Director's Order on Child-Resistant Packaging (CRP). As expected, the implications of the proposed entry for potassium salts featured in the stakeholder comments. The subcommittee considered that the entry in the First Schedule for this Order should remain as drafted, namely:

XXXXX

The Committee noted correspondence received from **XXXXX.** In this correspondence, the deliberations of the NDPSC were acknowledged but concerns were raised by **XXXXX** regarding the currently (seemingly) inadequate labelling of glucosamine sulfate – potassium chloride complexed products. It was stated by **XXXXX** that very few pharmacists or GPs are aware of the potential presence of potassium in glucosamine products and thus cannot warn consumers of the potential dangers nor make a meaningful ADRAC report. **XXXXX** asked that the Committee consider mandatory labelling that states the potassium chloride content, the potential for interaction with other drugs and a requirement for a "seek advice from a pharmacist or doctor if in doubt" label. **XXXXX** also asked that the Committee consider only allowing glucosamine sulfate complexed products be available in pharmacies (i.e. Schedule 2).

Pre-Meeting submissions

A pre-meeting submission was received from **XXXXX** and the following points were made:

- In summary **XXXXX** recommended that more consideration needs to be given as to which products should be targeted in the scheduling entry and that consideration should be given to scheduling elemental potassium, rather than just the chloride salt. **XXXXX** particularly noted a number of products with significant potassium content, namely **XXXXX** (potassium citrate) containing 10mmol K+/ tablet, Uricosal (potassium citrate) containing 18.4mmol K+/ 10mL, **XXXXX** (potassium bicarbonate) containing 2mmol K+/ 10mL and gastric lavage preparations such as **XXXXX** (potassium chloride) containing 10mmol K+ per sachet.

- **XXXXX** recommended against up-scheduling gastric lavage/ bowel preparations as the current Schedule 3 is felt to be appropriate.
- The term "dosage unit" in the paragraph "(a) when containing 100mg or less of potassium chloride per dosage unit" should be clarified in order to distinguish between divided and non-divided doses.
- On the matter of glucosamine sulfate complexed products **XXXXX** commented that such products have been available in Australia without restriction for several years with only one ADRAC report of hyperkalaemia with a "probable" link to a glucosamine sulfate complexed product. **XXXXX** stated that some manufacturers complex glucosamine with potassium chloride because it is relatively inexpensive and while companies can reformulate their products, a six to twelve month lag time for development, production assessment and approval of a new product may have a significant effect on both commercial viability of and consumer access to such products. Instead, **XXXXX** recommended exempting these products when labelled with:

  (a) a warning not to take in combination with other potassium containing products; and

  (b) a warning to obtain either a pharmacist's or doctor's advice if taking heart medication, antihypertensives or diuretics.

- On the subject of CRPs, **XXXXX** suggested allowing CRP glucosamine sulfate complexed product to remain unscheduled and those without CRPs to be scheduled either Schedule 2 or Schedule 3.
- **XXXXX** made the following suggestion for a scheduling entry for elemental potassium:

POTASSIUM SALTS in oral preparations for human therapeutic use, except:

(a) when containing 1.34mmol or less of elemental potassium (74.6mg KCl = 1mmol K+) per solid dosage unit;

(b) in non-divided dose formulations (liquid or powder) containing 1.34mmol or less of elemental potassium per maximum recommended dose and in which the immediate container is child-resistant;

(c) when complexed with glucosamine sulphate to improve compound stability

(d) in preparations for oral rehydration therapy;

(e) when included in combination with stimulant laxatives in preparations for oral use for bowel cleansing prior to diagnostic medical or surgical procedures; or

(f) in preparations for enteral feeding.

The Committee noted that if it were to schedule elemental potassium, rather than potassium chloride, this would effectively broaden the scheduling entry and thus require foreshadowing in order to be gazetted before consideration.

XXXXX stated in their submission that they supported the Committee's request to receive toxicological data before considering exempting products containing glucosamine complexed with potassium chloride from a foreshadowed Schedule 4 entry.

Advice was sought from **XXXXX** who in turn sought advice from **XXXXX**. **XXXXX**] raised the point that any decision to manage the risk associated with potassium chloride should be based on a thorough assessment of risk. That is to say that while medicinal products are required to be safe, safety does not mean zero risk. They state that a safe product is one that has reasonable risks, given the magnitude of the benefit expected and the alternatives available. **XXXXX** discussed the matter at length and recommended that, along with scheduling, consideration be given to the following options:

- Determination of a level of potassium chloride considered safe for different consumer groups;
- Need for specific experimental studies to assess the risk associated with oral glucosamine sulfate – potassium chloride products;
- Use of label and/ or warning statements stating potassium content and/ or targeting groups at risk;
- Education of health-care professionals regarding the risk of potassium ingestion from such complementary medicines;
- Use of appropriate packaging to minimise risk of accidental ingestion;
- Scheduling only slow-release preparations. **XXXXX** had canvassed the complementary medicines industry and ascertained that SR formulations of glucosamine sulfate – potassium chloride are not anticipated.

XXXXX noted that recently released nutrient reference values for Australia & New Zealand identified an adequate daily dietary intake of potassium from food sources of 4.7g for healthy adults.

XXXXX

A pre-meeting submission was received from **XXXXX** which focussed on two key areas, namely:

1) The process leading up to the scheduling of slow-release potassium chloride and the decision to foreshadow the scheduling of non slow-release formulations.

2) Toxicological data on potassium chloride.

1. The decision to schedule slow-release potassium chloride

- **XXXXX** quoted from the NSW Deputy Coroner's report and postulated that the recommendation from the Deputy Coroner **XXXXX .** Furthermore, **XXXXX** stated that the Deputy Coroner had no knowledge of what matters the Committee must take into account when considering the scheduling of a substance (as prescribed in s52E of the *Therapeutic Goods Act 1989*, "the Act"), even though **XXXXX** attempted unsuccessfully to garner such information.
- **XXXXX** addressed particular provisions of s52E of the Act and suggest that the Committee had over-stated the case for Schedule 4 listing under these provisions. Namely:

  (a) potential hazards associated with use of substance. **XXXXX** stated that only one recorded death has not been considered against the long-standing record of no harm.

  (b) extent and pattern of use of substance. **XXXXX** considered the situation resulting in **XXXXX** death was a one-off and does not properly reflect the real extent and pattern of use of this product.

  (c) potential for abuse of substance. The **XXXXX** death was a direct result of the "irresponsible practises" of **XXXXX**] and they may have acted in the same way had the product been a Schedule 4 medicine.

  (d) purpose for which substance is used. **XXXXX** noted that use as a "salt tablet" was not an intended indication, nor indeed was use in children.

- **XXXXX** considered that the statement in the Record of Reasons of the February 2006 NDPSC Meeting "it was noted that... there are high dose potassium chloride mixtures that were just as toxic" is not based on fact. **XXXXX** put forward that, because a slow-release formulation is in the body for longer, its toxicity profile would be different to immediate release formulations. **XXXXX** went on to state that for the Committee to call for empirical toxicological data to disprove their assumption that all other products containing potassium chloride are "just as toxic" goes against the requirements of the Act which applies a risk management approach to regulation. They extended the premise that, should the possibility of a child ingesting large amounts be a measure for restricting the supply of a substance, many foods, household chemicals, complementary and traditional medicines would become Schedule 4.

2. Toxicological data for potassium chloride

- **XXXXX** stated that the concentrations of potassium chloride in products complexed with glucosamine sulfate vary significantly. While the ARTG lists variations between 490mg and 1800mg KCl, the vast majority lie within 246mg to 390mg KCl which represents 128.9mg to 204.4mg of potassium. This correlates then to a total daily dose (two tablets) of between 257.8mg and 408.8mg of potassium. By contrast, a normal daily dose of **XXXXX** (between two tablets as an adjunct to potassium depleting diuretics to six tablets for hypokalaemia) is between **XXXXX** of potassium. The conclusion then drawn is that a dose of two **XXXXX** tablets is equivalent to 1.5 times the daily dose of standard complexed glucosamine sulfate.
- Looking at the pharmacokinetics of KCl, urinary excretion of K+ is used as the surrogate measure of bioavailability because homoeostatic physiological mechanisms make it impractical to assess bioavailability from serum K+ concentrations. Total body potassium is approx 135gm in a 70kg adult male, 98% of which is located intracellularly.
- Data quoted by **XXXXX** states that an 84mmol dose of K+ (equivalent to **XXXXX** tablets) in liquid formulations results in peak plasma levels of K+ of 1.72mmol/L over placebo c.f. slow-release formulations resulting in peak plasma concentration of K+ of 1.03mmol/L. **XXXXX** also noted that placebo arms of the studies demonstrated that plasma concentrations of K+ can vary greatly (4.0 to 4.6mmol/L quoted) as a result of dietary intake, physical activity and circadian K+ fluxes. **XXXXX** stated that a serum potassium concentration above 5.5mmol/L is uncommon until over 90% of renal function is lost and the glomerular filtration rate is less than 20mL/min.
- **XXXXX** quoted toxicological literature in determining hyperkalaemia and lethality dose ranges. The International Program on Chemical Safety Database (IPCS) establishes a risk range for hyperkalaemia of 2.0-2.5mmol/kg KCl, equating to (in a 70kg adult) 73.36 mmol K+ **XXXXX** (or approx fourteen standard range glucosamine sulfate complexed tablets). IPCS (sourced through TOXNET) establishes a probable lethal dose in a 70kg adult as between 18.34 and 183.4gm K+ (or approx 89 standard range glucosamine sulfate tablets **XXXXX**. Two case studies are quoted of **XXXXX** poisoning, one involving a 39yo woman who took eighty **XXXXX** tablets and another of a 24yo male who took 100 tablets, along with 30 **XXXXX** tablets and 15 **XXXXX** tablets after drinking heavily. Both individuals survived.
- **XXXXX** also quoted nutrient reference values for acceptable intake recently set down by the NH&MRC, as well as comparable values set down in the UK. **XXXXX** stated that the UK Expert Group on Vitamin and Minerals recently conducted a formal risk assessment on potassium which sets down that the estimated maximum daily intake of potassium is 4900mg (125.35mmol K+).
- **XXXXX** therefore proposed a cut-off of 600mg or less per daily dose of KCl, **XXXXX**. **XXXXX** further proposed, in order to address concerns about KCl intake in the elderly, that CMEC consider appropriate warning labels for unscheduled products containing less than 600mg KCl per daily dose.

XXXXX

- **XXXXX** also provided a pre-meeting submission. **XXXXX** addressed the provisions of s52E as well as providing a Health Risk Assessment of glucosamine sulfate – potassium chloride complexed product put together by a consultant on behalf of **XXXXX**. **XXXXX** concur that, while the accidental death of **XXXXX** which was the subject of the NSW Deputy Coroner's Report was a very serious matter, careful consideration must be given to the mitigating circumstances.
- **XXXXX** summarised the deliberations of the Committee at the February 2006 and June 2006 NDPSC Meetings and noted that focus did shift from slow-release potassium chloride preparations (as recommended by the Deputy State Coroner) to all "oral preparations for therapeutic use". **XXXXX** maintained that, contrary to the statement made at the February 2006 NDPSC Meeting, "it seemed unlikely that restricting supply of potassium chloride tablets to Prescription Only would have a significant public health impact"; to restrict potassium chloride as foreshadowed in the pre-October 2006 NDPSC Meeting gazette notice would have a significant impact on a large number of complementary medicine patients.
- **XXXXX** addressed each of the provisions on s52E in turn, as they related to potassium chloride in glucosamine sulfate complexed products.

  (a) Toxicity and safety of substance. **XXXXX** quoted an oral lethal dose of KCl in humans between 500-5000mg/kg with anacute oral LD50 in rats of 3020mg/kg. **XXXXX** calculated that the highest recommended daily dose of 2000mg/ day of glucosamine sulfate equates to a daily dose of 500mg KCl **XXXXX** 8mg/kg for a 60kg adult). **XXXXX** pointed out that it would be extremely rare for hyperkalaemia to occur in people not at risk when taking recommended doses of glucosamine sulfate – KCl complexed products.

  (b) Risks and benefits associated with use. **XXXXX** quoted recommended dietary intake for potassium at 2800mg for women and 3800mg for men. **XXXXX** stated that when used as a stabilising excipient with glucosamine sulfate, available evidence shows that the dose of KCl is not a risk factor.

  (c) Potential hazards associated with use. **XXXXX** quoted the one case report on the ADRU database where causality with glucosamine is listed as "probable". **XXXXX** took issue with the statement in the Record of Reasons of the June 2006 NDPSC Meeting that "the Committee felt that, rather than provide any assurance of safety, the ADRU data…. only served to highlight the potential problem that existed with these complementary medicines". **XXXXX** maintained that the complementary healthcare industry is fully aware of the legislative requirements to report ADRs.

  (d) Extent and pattern of use. **XXXXX** quoted 234 million dosage units per year.

(e) Dosage and formulation. **XXXXX** explained that KCl is added to glucosamine sulfate (derived from chitin) to improve the compound's stability in air. This is generally done at 250mg of K+ per 1000mg of glucosamine sulfate complex. **XXXXX** also touched on the NCCTG agreed principle of trans-Tasman harmonisation relating to the least restrictive schedule for both countries. **XXXXX** noted that the New Zealand General Sale listing for potassium is for 100mg (equivalent to 190mg potassium chloride).

(f) Need for access to a substance taking into account its toxicity and other substances available. **XXXXX** stated that symptomatic treatment is all that is available for osteoarthritis. They put forward that NSAIDs and COX-II inhibitors do not come without their own risks. **XXXXX** suggested that study results available demonstrate "methodological concerns" but then refer to an NH&MRC sponsored Randomised Clinical Trial evaluating glucosamine and chondroitin in patients with symptomatic arthritis. The results of this study are expected within three years.

(g) Potential for abuse. **XXXXX** stated that as there are no psychotropic effects from either moiety of the complex, potential for abuse is not an issue.

(h) Purposes for which a substance is to be used. **XXXXX** quoted figures from the Australian Institute of Health and Welfare (AIHW) stating that osteoarthritis ranked as the tenth leading cause of total disease burden in 1997-1998.

(i) Any other matters the Committee considers necessary etc. **XXXXX** believed that under s52E(1)(i), the Committee could take into account labelling and packaging (contrary to the statement made in the Record of Reasons of the June 2006 NDPSC Meeting that it is a registration matter) and further stated that CRCs on glucosamine complexed products would not be appropriate. **XXXXX** referred to a paper written by the AIHW on accidental poisoning of children and also made the point that child-resistant is not the same as child-proof and hence onus does lie with supervising adults to ensure safe storage.

- In summary, **XXXXX** stated that their preferred option is to limit scheduling to slow-release formulations and to monitor AEs for glucosamine complexed products through ADRAC. Otherwise, **XXXXX** recommended limiting scheduling to 600mg KCl per dosage unit with all products containing potassium chloride labelled "Keep Out of Reach of Children" and to recommend to CMEC to develop a warning statement for those at risk of hyperkalaemia.

XXXXX Health Risk Assessment

XXXXX prepared a Health Risk Assessment (HRA) on the potential risks to the community of use of glucosamine sulfate potassium chloride complex (GSPCC). The key risks (all assessed as very low to medium by the consultant) associated with use of GSPCC are:

- Inappropriate use due to lack of awareness leading to minor AEs (very low risk).
- Contamination with by-products such as shellfish protein leading to AEs/ loss of consumer confidence (low risk).
- Poisoning due to hyperkalaemia in children (low risk).
- Excessive therapeutic use leading to AEs (low risk).
- Under-use of GSPCC due to lack of awareness leading to additional burden on health care resources (medium risk).
- Excessive cost of GSPCC leading to decreased use and increased burden on other resources (medium risk).

The HRA concluded that, at normal doses, GSPCC represents little risk to the consumer and contributes to managing musculoskeletal injuries. The only potential AE is hyperkalaemia but this represents a low risk because it would not happen at normal doses. The potential for overdose by children is low, given normal care arrangements (as well as likelihood of successful intervention). The risk of hyperkalaemia in the elderly is unlikely considering the medical supervision that would take place in such groups. Another conclusion drawn is that from a risk based analysis approach, CRPs or scheduling would be inappropriate/ counter-productive. It is pointed out that CRPs have been bypassed in a number of childhood poisonings and that they present difficulties for one of the main user groups of GSPCC (the elderly). The consultants state that scheduling may introduce increased use of NSAIDs (with associated AEs) which may increase burden on healthcare providers.

The HRA made the following key recommendations:

- Review of labelling to confirm appropriate usage.
- Ongoing education/ awareness campaign regarding correct use/ benefits of GSPCC.
- Continuation of research into benefits of GSPCC.

XXXXX provided written advice via email to the Secretariat detailing the number of products on the ARTG containing GSPCC which would be potentially impacted by a decision to schedule only those products which contain 600mg or more of KCl. The correspondence referred to an attachment to a minute dated 7 June 2006 from **XXXXX** and concluded, with a number of caveats, that there would appear to be no currently listed glucosamine sulfate product listed on the ARTG containing more than 600mg KCl.

The Committee agreed that it was clear from many of the submissions that there is a general lack of awareness of the potassium content in certain glucosamine products by

both consumers and by medical practitioners. Indeed, one Jurisdictional Member spoke to a number of directors of pharmacy departments within large metropolitan hospitals and they were not aware that such products contained significant amounts of potassium chloride. Thus it seemed evident that it was on no-one's "radar" that these products may potentially cause hyperkalaemia in certain patient groups (i.e. elderly, those with renal impairment and those on potassium-sparing diuretics). The Committee was reassured by the commitment provided by **XXXXX** in regards to the use of label and/ or warning statements stating potassium content and/ or targeting at-risk groups.

The point was made that, in terms of risk, slow release formulations were of no greater or lesser concern than standard release or liquid formulations. The submission from **XXXXX** quoted pharmacokinetic data which showed higher peak plasma concentrations for the liquid formulation when compared with those from a slow release preparation.

Members agreed, given that bowel cleansing preparations are intended as single use only and also given that they are only purchased under the explicit instruction of a medical specialist, it would be unnecessary to re-schedule such preparations.

The Committee discussed the wording of the New Zealand classification for potassium. The New Zealand Member pointed out that in making the cut-off for Pharmacy Only 100mg of elemental potassium, they were unaware of the potassium content of glucosamine sulfate complexed products. Indeed the 100mg cut-off was set so as to capture products intended as potassium supplements rather than those containing potassium as an excipient. Thus the Committee agreed to refer this matter back to New Zealand for consideration.

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The Committee agreed that a 100mg cut-off was not one that was based on objective or quantitative data and was inappropriate. The Committee also agreed that the complementary medicine products containing potassium chloride complexed with glucosamine sulfate presented only a low level of risk and as such did not need to be restricted to Schedule 4. Given that the amount of two **XXXXX** tablets is equivalent to 1.5 times the amount of standard complexed glucosamine sulfate and that the risk of hyperkalaemia with glucosamine complexed products is low, it would be reasonable to set a cut-off which excludes such products from scheduling. The Committee therefore decided that a 600mg cut-off would be appropriate as this would ensure that no glucosamine sulfate complexed product currently on the ARTG would be captured. However, the Committee remained concerned that glucosamine sulfate complexed products could present a risk to certain vulnerable patient groups and therefore wished to refer this matter back to **XXXXX** requesting that they consider mandating for appropriate warning statements regarding potassium content.

Schedule 4 – Amend entry

POTASSIUM CHLORIDE in oral preparations for human therapeutic use **except**:

(a) when containing less than 600mg of potassium chloride per dosage unit;

(b) in preparations for oral rehydration therapy;

(c) in preparations for oral use for bowel cleansing prior to diagnostic medical and surgical procedures; or

(c) in preparations for enteral feeding.

11.3 SUMATRIPTAN

PURPOSE

The Committee further considered a proposal to include oral preparations containing 50 mg or less of sumatriptan in packs containing 2 dosage units or less for the treatment of migraine attacks in Schedule 3 and Appendix H of the SUSDP.

BACKGROUND

Sumatriptan is a selective serotonin agonist that acts at 5-hydroxytryptamine1B/1D receptor subtype (5-HT1B/1D) receptors. Activation of 5-HT1B receptors produces vasoconstriction of cranial arteries while activation of 5-HT1D receptors on nociceptive trigeminal nerve afferents reduces the release of vasoactive neuropeptides and inhibits transmission via second-order neurons of the trigeminocervical complex. These actions correlate with relief of migraine headache.

Sumatriptan was first considered by the Committee at the August 1992 DPSSC Meeting. The DPSSC included sumatriptan in Schedule 4 of the SUSDP.

At the June 2005 NDPSC Meeting, the Committee considered a proposal to include 2 tablets x 50mg or less of sumatriptan in Schedule 3. The Committee felt that there was no evidence of a suitable, validated diagnostic tool for pharmacists to accurately diagnose migraine. The Committee also had concerns about the safety profile of sumatriptan, particularly its cardiovascular and cerebrovascular side effects, and the high prevalence of diagnosed and undiagnosed cardiovascular disease in the community. On this basis, the Committee agreed that sumatriptan should remain a Schedule 4 substance. It was also noted that all other 5-HT1 agonists such as naratriptan and zolmitriptan are also classified as Schedule 4.

At the June 2006 NDPSC Meeting, the Committee considered a proposal to include oral preparations of sumatriptan 50mg in packs of 2 tablets for the treatment of migraine attacks in Schedule 3 and Appendix H. The Committee was informed that **XXXXX** had provided an updated dossier for reconsideration of the revised scheduling of sumatriptan which has taken into account the Record of Reasons of the June 2005 NDPSC Meeting. Concerns were raised over the possibility of patients overusing sumatriptan if they find

that the drug effectively treats their migraine. Further to this and of much greater concern to the Committee was the discussion over emerging evidence that sumatriptan is not entirely 'migraine specific'. It was therefore decided to seek advice from the **XXXXX** and, should they conclude that increased access to consumers with pharmacists' supervision is appropriate, they could provide valuable input into the development of the Migraine Questionnaire. The Committee agreed to defer a decision on the rescheduling of sumatriptan until such advice has been sought from **XXXXX**

DISCUSSION

Post-meeting response from Sponsor

An email was received from **XXXXX** relating to the Committee's deliberations at the June 2006 NDPSC Meeting. The email confirmed that local (ie Australian) consultations of the switch program and questionnaire have included both neurologists and general practitioners with specific interests in migraine or medical education. The email also stated that the original UK version of the questionnaire was developed in consultation with a number of UK neurologists and headache experts.

Further to the email, **XXXXX** provided a four page post-meeting comment addressing the arguments raised in the Record of Reasons of the June 2006 NDPSC Meeting. Members noted the following:

- In response to the evaluator's comment that the Australian Migraine Questionnaire study "inferred a potential 20% increase in over-diagnosis of migraine in true non migraine sufferers", **XXXXX** argued that by using the questionnaire, pharmacists identified subjects with history of heart disease and cardiovascular risk factors, and assessed all of these as being unsuitable for OTC sumatriptan. Thus, the results of the study showed that this tool provided more conservative results than did standard GP practice.
- **XXXXX** contested the evaluator's comment that the questionnaire has "significant deficiencies" and the Committee's concern that the questionnaire "didn't elaborate in strong enough terms the role of non-pharmacological therapy as first-line treatment of migraine such as lying down in a quite room". The sponsor clarified that **XXXXX** did not dispute the fact that OTC sumatriptan should not be considered as first line treatment for migraine. **XXXXX** also mentioned that non-pharmacological therapies have uncertain outcomes and are not prescriptive, and more importantly, delaying treatment with an effective medication (whether it is an analgesic or triptan) will only increase suffering for patients. The questionnaire was intended to be used in conjunction with proposed pharmacy protocols and training materials, which clearly state that the questionnaire should only be provided to a customer after the pharmacist has already assessed that OTC analgesics are not providing adequate relief.
- In regard to the statement in the Record of Reasons "the questionnaire quotes more than 4 per month", **XXXXX** pointed out that the explanatory text to the pharmacist states "Refer to a doctor if a customer has 4 or more attacks a month". This meant

that if a customer has more than 3 migraine attacks per month, the pharmacist would refer them to their doctor and prophylaxis may be appropriate, consistent with the National Prescribing Service guidelines.

- In response to the Committee's comment "suffering even one or two attacks per month on a regular basis may be enough to warrant regular prophylactic treatment", **XXXXX** pointed out that on the assumption that these attacks are severe and prolonged and the sufferer does not respond to acute treatment, the questionnaire would find them unsuitable for OTC sumatriptan.
- The sponsor felt that even though as stated by the Committee "patients are often advised by their doctor to always keep a spare dose of sumatriptan at home… thus there is no question of lack of access for these patients", this reasoning did not account for a large proportion of migraine sufferers. In particular, sufferers who do not currently consult a doctor, or those who in the past would have been denied access to a triptan because they did not satisfy the conditions of the PBS listing and may not have been offered a private prescription by the doctor who may have considered that it was too expensive at the time.
- Regarding the Committee's concern over emerging evidence that sumatriptan is not entirely migraine specific, **XXXXX** pointed out that in cases where patients with severe headache are misdiagnosed and given sumatriptan which provided some symptomatic relief, analgesics may also provide the same symptomatic relief. **XXXXX** also stated that it would be unlikely that sumatriptan would be found suitable for a patient with such a severe headache based on responses to the questionnaire.

Pre-meeting submissions

XXXXX provided a pre-meeting submission which included a cover letter with a table, minutes from an expert panel meeting and updated materials of the Migraine Questionnaire and management protocol. The main points of the cover letter were:

- In response to the Committee's concerns raised at the June 2006 NDPSC Meeting, **XXXXX** organised its own expert panel meeting in order to seek advice and input on the migraine questionnaire, to review the evidence to support efficacy of triptans, and to discuss the current place of triptans in the management of migraine.
- **XXXXX** agreed that the proposed Migraine Questionnaire and associated training material are a work in progress. **XXXXX** reiterated that further changes to the questionnaire can be made parallel to the rescheduling.
- **XXXXX** suggested that the NDPSC's concerns in relation to the emerging safety issues of both triptans and ergots potentially masking the symptoms of either meningitis or subarachnoid haemorrhage likely stem from 4 recent case reports in relation to 800 million attacks treated with sumatriptan. **XXXXX** pointed out that the materials seen to date by NDPSC did not include the training materials that would be available to pharmacists and GPs prior to the launch of OTC sumatriptan, which

would ensure that red flags indicative of serious secondary headaches can be recognised.

- **XXXXX** reiterated that they do not intend for OTC sumatriptan to be promoted as a first line therapy of migraine. The protocols and training materials made it very clear that OTC sumatriptan would only be considered for patients who have tried a simple analgesic or analgesic/antiemetic combination but did not achieved adequate relief.
- As mentioned earlier, the submission also included a table summarising the different types of migraines and management types encountered by different disciplines of healthcare professionals. This table supported **XXXXX** opinion that OTC sumatriptan would provide an alternative option for pharmacists, who encounter suitable customers with uncomplicated migraine who have not achieved benefit with simple analgesics.

The **XXXXX** submission included the minutes of a meeting convened by **XXXXX** involving clinicians in Neurology, General Practice as well as Pharmacy Practice. Included with the minutes were two attachments. The first was a flow chart and the second was an updated version of the Migraine Questionnaire. Changes were made to the Migraine Questionnaire **XXXXX**. Points made by the panel were:

- The panel agreed that the Migraine Questionnaire is useful for screening for contraindications and safety concerns as confirmed by the validation studies. **XXXXX** had included a flow chart plotting the results of the Australian validation study. The panel felt that pharmacists are more cautious than GPs in their approach to dealing with customer requests and therefore the Questionnaire serves as an appropriate prompt to increase referrals to the GP.
- The panel discussed the values of questions 3ii, 3iii and 8 and felt that the Migraine card could include a space for the GP to concur with the pharmacist assessment. The panel agreed that the proposed Migraine Questionnaire and associated training materials are a work in progress.
- The panel agreed that there is potential for medication over-use with regard to the wider availability of sumatriptan and ways to circumvent this must be covered in the training materials. Frequency of purchase considered in line with frequency of use noted on the Migraine Card can be used to refer patients who had bought more than 3 packs in a month to their GP for review of their migraines.
- Most of the panel members felt that concerns regarding masking of a more serious condition were largely misplaced as pharmacists would generally refer patients with uncharacteristically severe headache to their doctor if they were concerned there was a “sinister” cause. Furthermore, such patients could possibly get some relief from the use of simple analgesics without consultation with a pharmacist, which may also delay appropriate diagnosis. The panel also believed that the Migraine Questionnaire would recognise patients with a sudden severe headache as potentially describing subarachnoid haemorrhage. It was also agreed that information regarding differential diagnoses should be covered in the training materials.

- The pharmacists on the panel pointed out as a profession, they are already asking customers what they have used and whether it worked and will recommend what they think is most appropriate for a particular patient.

XXXXX provided a pre-meeting submission in which they support sumatriptan being down-scheduled to Schedule 3 without Appendix H inclusion. Their points were:

- **XXXXX** recommended an implementation date of July 2007, should the Committee decided to down-schedule, as this should provide sufficient lead-in time for the training of pharmacists. **XXXXX** felt that December, January and February are not good months for introducing newly available pharmacist-only medicines. At this busiest time of the year, community pharmacists would have difficulty in attending training programs.
- **XXXXX** had further consulted **XXXXX** regarding the appropriate training for pharmacists, and also provided copies of the training programme developed for the UK between **XXXXX** and **XXXXX. XXXXX** believed that this is a comprehensive training manual, however also felt that pharmacists need to have a level of awareness through comprehensive training before the product is launched as a Schedule 3 medication within Australia.
- **XXXXX** had some reservations about the proposed Migraine Questionnaire, namely the assumption of migraine too soon within the questionnaire. **XXXXX** had some discussion with **XXXXX** and **XXXXX** on this matter, however collaboration on the proposed questionnaire had so far been superficial and limited.
- **XXXXX** recommended against the inclusion of Appendix H, as this would lead to direct product requests from consumers undermining the pharmacists' assessment protocol for diagnosis and supply.

XXXXX provided a pre-meeting submission in which they oppose the down-scheduling and also the inclusion of sumatriptan in Appendix H. Their main points were:

- Sumatriptan did not possess a safety profile suitable for OTC medicine. As stated in the Record of Reasons of the June 2005 NDPSC Meeting the cardiovascular events reported in the PI include coronary vasospasm, myocardial ischaemia, myocardial infarction, angina and cardiac arrhythmias. The cerebrovascular events reported include cerebral haemorrhage, subarachnoid haemorrhage, cerebellar infarction and stroke. The June 2005 s further stated that the cardiovascular and neurological events reported were "serious and potentially fatal". Sumatriptan can cause an elevation in blood pressure and peripheral vascular resistance in patients, which would exacerbate any existing cardiovascular disease. It is therefore imperative that intervention by a GP occurs prior to administration of sumatriptan, and advertising of sumatriptan to potentially unaware consumer is therefore inappropriate. The PI for sumatriptan states that this medicine "should only be used where there is a clear diagnosis of migraine". **XXXXX** believed that there is insufficient means for pharmacists to accurately diagnose migraine, and questioned whether the questionnaire would be able to assist this.

- **XXXXX** pointed out that while sumatriptan is rescheduled in the UK and Germany, many products are available as OTC medicines in those countries and are not available OTC in Australia (such as some statins). All other 5-HT1 agonists (naratriptan and zolmitriptan) are Schedule 4 medicines.
- Regarding the potential for sumatriptan to mask the diagnosis of subarachnoid haemorrhage and meningitis, **XXXXX** believed that due to this issue, it is important that the administration of sumatriptan should have the intervention and clinical diagnosis by a GP. **XXXXX** further pointed out the possibility of serotonin syndrome with sumatriptan which was highlighted in the ADRAC bulletin in February 2004.
- **XXXXX** believed that there is no issue with access to sumatriptan, as established at the June 2006 NDPSC Meeting, patients with diagnosis of severe migraine are directed to have spare prescriptions or doses with them at all times. Further to this, pharmacists are able to supply Schedule 4 Medicines in cases considered to be an emergency, as listed under Part 3 paragraph 39 of the SUSDP. Three days of medicine only is supplied and the pharmacist determines whether there is an acute clinical need. If immediate administration is not possible, whilst not ideal, a delay will not alter the efficacy of sumatriptan, as listed in the PI.

XXXXX provided comments in a pre-meeting submission to the June 2006 NDPSC Meeting. Members recalled the following points:

- After initial diagnosis, migraine is a self-recognisable condition, with early initiation of therapy ensuring better treatment outcomes. Thus, pharmacists are well placed to provide professional advice and optimal treatment.
- **XXXXX** aired concern over the PBS authority listing and the fact it is not first line therapy. Thus, additional considerations may be required of the Committee in this near unique down-scheduling situation.
- **XXXXX** also make the point that sponsors must invest resources and work with the profession to provide appropriate materials for pharmacists. A longer lead time prior to implementation is suggested and Appendix H inclusion is opposed.

Members also recalled **XXXXX** comments at the June 2006 NDPSC Meeting in favour of including sumatriptan in Schedule 3. Mention was made of known precautions/ contraindications including SSRIs and nitrates and so **XXXXX** recommend change only after a set of guidelines, agreed to by professional pharmacy associations, are in place. **XXXXX** did not endorse Appendix H inclusion.

Advice from XXXXX

Advice was sought from the **XXXXX** on the rescheduling of sumatriptan following the June 2006 NDPSC Meeting. **XXXXX** has provided advice from two senior members, both well recognised in the field of headache and pharmacology (fol 56 – 60). **XXXXX** did not unanimously endorse the rescheduling of sumatriptan, however it was indicated that **XXXXX** preferred to lean on the side of caution at this point in time. Members noted the following specific points made by the two members of the **XXXXX:**

Member 1

- The member stated that there seems to be fewer side effects with naratriptan and zolmitriptan and that regardless of the outcome, the decision regarding rescheduling of sumatriptan should be a class decision and be applied to all triptans.
- The member had misgivings about the PBS phrase that ergots need to be tried first, and asked if ergotamine is also going to be rescheduled to OTC.
- The member was not too concerned regarding the possibility of sumatriptans masking the symptoms of subarachnoid haemorrhage and meningitis, and stated that this is a current risk with all other analgesics and any severe and atypical headache should be referred to the patient's doctor. However, the member was concerned about the risk of medication overuse headache, as he believed that the message to limit the frequency of analgesics (especially codeine) was yet to be thoroughly communicated to doctors and pharmacists.
- The member agreed that cardiovascular effects of triptans probably would not have been common, however that this was probably due to the fact that triptans are not usually prescribed to older patients or patients with existing heart conditions. The member believed that making triptans OTC would remove this protection, also the serious cases have been those where the heart disease was not known or detected. It was suggested that the ADRAC be asked for their list of reported ADRs in association with these drugs.

Member 2

- The member stated that one of the most pervasive difficulties in the treatment of migraine is the inadequate and delayed treatment of acute migraine attacks by many sufferers relying on OTC drugs which are of variable efficacy. The efficacy of triptans is well established, therefore there are considerable advantages to the ready availability of triptans.
- The member stated that the incidence of significant cardiovascular side affects is very small, and much lower than was originally considered to be the case when triptans were first introduced. The member also held the view that triptans are likely to replace the current OTC migraine treatment of combinations of codeine with simple analgesics or anti-inflammatory. The member further added that the side-effects of these preparations are well recognised, and the incidence of significant gastric toxicity from anti-inflammatory agents such as ibuprofen is considerably greater than the risk of cardiovascular effects from triptans.
- The member believed that the circumstances for the diagnosis of subarachnoid haemorrhage being masked by response to the associated headache to sumatriptan are fairly limited. The member argued that the risk of patients subsequently developing a subarachnoid haemorrhage after experiencing migraine, or patients with history of using triptans to treat migraine who might use triptans for the pain which is a result of subarachnoid haemorrhage assuming it simply to be a severe migraine, would be of equal consideration whether triptan had been prescribed from a doctor, or purchased

from a pharmacist. The member believed that the migraine questionnaire would be able to exclude patients presenting with a severe headache without a prior history of migraine, in other words their first or worst headache. Therefore, it was suggested that a question be added to the questionnaire "Are you currently suffering from a migraine headache? If so, is this the first or worst headache of this type that you have suffered from?". The member did not believe this issue was a strong reason to prevent the down scheduling of sumatriptan.

- The member stated that it is well established that triptans, ergotamines and codeine containing analgesics are all potent causes of medication overuse headache and therefore there should be considerable caution about using these preparations more than one or two days per week. Therefore, the member felt that the supporting document for pharmacists should include an instruction that patients reporting headache on eight or more days per month should not be provided with sumatriptan by the pharmacists and should be referred to a doctor.
- In conclusion, the member believed that the benefits of triptans as Schedule 3 medications outweigh the disadvantages. It was the member's opinion that the evidence which shows that triptans may at least partially suppress the headache associated with subarachnoid haemorrhage and presumably meningitis is important information, but would not necessarily impact on the changing of triptans to Schedule 3 medicines.

MCC Considerations

The Committee noted that at the MCC Meeting in June 2006, New Zealand reclassified sumatriptan when sold in packs containing no more than two 50 mg tablets to restricted medicine (Schedule 3). This decision was conditioned on the sponsor agreeing to a number of requests from MCC, including listing the precautions and contra-indications on the outside of the packaging. The MCC felt that misuse of medicine would be limited by the pack size as well as by the cost of the product. The results of the Migraine Questionnaire would also ensure that the consumer could be referred to a doctor when appropriate. The MCC also agreed that the consumer would need to complete a separate Questionnaire at different pharmacies and the wording of the indication should be "for the acute relief of migraine attacks with or without aura, in patients who have a stable, well-established pattern of symptoms".

XXXXX

One Committee Member pointed out that the population of patients that neurologists see with migraine is very different to the population of patients that would be seen by GPs, or pharmacists. The Member went on to state that if sumatriptan is clearly indicated for patients with stable, well-established pattern of symptoms, this group of patients are likely to be easier to be diagnosed and their conditions easier to be managed. Given this fact, pharmacists should be able to manage and prescribe efficiently for this particular group of patients.

Of concern to the Committee was the discussion over emerging evidence of a possible interaction between sumatriptan and serotonergic antidepressants causing serotonin syndrome. A Member noted that because of the high number of patients prescribed with serotonergic antidepressants in the community, there was significant potential risk of this drug interaction occurring, should sumatriptan be made available OTC. Members noted that the proposed PI for **XXXXX** stated that sumatriptan has the potential to interact with selective serotonin reuptake inhibitors (SSRIs) and symptoms of serotonin syndrome were also listed. The Committee felt that this was a plausible interaction pharmacologically, as both sumatriptan and serotonergic antidepressants act on the same neurological system and receptors. The Committee agreed that this emerging safety concern needed to be further looked into. It was therefore agreed that further information should be sought from the Adverse Drug Reactions Advisory Committee (ADRAC) regarding this interaction.

OUTCOME

Due to concerns relating to the potential for concomitant use of triptans and serotonergic antidepressants to precipitate serotonin syndrome, the Committee agreed to defer a decision on the rescheduling and Appendix H listing of sumatriptan pending review of emerging safety data.

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

12.1 SUSDP, PART 4

12.1.1 DILTIAZEM

PURPOSE

The Committee noted that the sponsor **XXXXX** had withdrawn their application to reschedule topical diltiazem from Schedule 4 to Schedule 3.

BACKGROUND

On 19 May 2006, **XXXXX** submitted an application for the Committee to consider the rescheduling of topical diltiazem. This application was evaluated and the evaluation report was provided to the sponsor for pre-meeting comment on 15 September 2006. The Secretariat was informed via email on 26 September 2006 that the sponsor wished to withdraw their rescheduling application.

DISCUSSION

As the Committee's consideration of diltiazem was included in the pre-October 2006 NDPSC Meeting gazette notice, pre-meeting submissions were received from **XXXXX** and **XXXXX**

As the item has been withdrawn, it was suggested that consideration of this diltiazem be deferred.

OUTCOME

The Committee noted that this item had been withdrawn by the applicant after publication of the pre-October 2006 NDPSC Meeting gazette notice and therefore agreed to defer consideration until a future application was received.

12.1.2 BUTOCONAZOLE

PURPOSE

The Committee considered a proposal to reschedule butoconazole 2% vaginal cream from Schedule 4 to Schedule 3 of the SUSDP.

BACKGROUND

Butoconazole is an imidazole derivative that has fungicidal activity *in-vitro* against Candida spp. and has been demonstrated to be clinically effective against vaginal infections due to *Candida albicans*. Imidazoles generally inhibit the conversion of lanosterol to ergosterol, resulting in a change in fungal cell membrane lipid composition. This structural change alters cell permeability and, ultimately, results in the osmotic disruption of growth inhibition of the fungal cell. *Candida albicans* has been identified as the predominant species responsible for vulvovaginal candidiasis.

Butoconazole was first considered by the Committee at the February 2005 NDPSC Meeting as part of the harmonisation process for drugs and poisons scheduling. The Committee noted that the 13th meeting of the TTHWP had proposed that where there were Schedule 2/Schedule 3 entries, but no products included on the ARTG/ SMARTI, the scheduling entry be deleted and the parent entry either retained or added to Schedule 4. The committee foreshadowed this recommendation for consideration at the June 2005 NDPSC Meeting by way of gazettal.

At the June 2005 NDPSC Meeting the Committee considered the proposal to reschedule to Schedule 4 any Schedule 2/ Schedule 3 SUSDP entries where no products were included on the ARTG/ SMARTI, including butoconazole. At the Meeting the Committee noted that concerns about the departure from the harmonisation policy framework but recalled that NCCTG had been advised of this and had agreed that it was appropriate in this instance. The committee then agreed to amend the scheduling of this substance to Schedule 4 in the interests of trans-Tasman harmonisation.

Butoconazole has been evaluated by the TGA. ADEC recommended approval at its 246th Meeting in June 2006, for the indication of local treatment of vulvovaginal candidiasis.

DISCUSSION

XXXXX submission

XXXXX submitted an application to down-schedule butoconazole and the data submitted supports the following arguments:

- Butoconazole is **XXXXX** use as an intravaginal single dose application. It is not intended for local application to the external vulva. Butoconazole was developed primarily as a gynaecological agent, unlike other imidazole agents.
- Butoconazole demonstrated *in-vitro* activity against Candida spp. and pre-clinical *in-vivo* activity against *C. albicans* **XXXXX** with an activity equivalent to miconazole and clotrimazole. However, only two studies were conducted with a formulation comparable to the proposed **XXXXX** product. These showed equivalence in efficacy and vaginal absorption to standard butoconazole cream.
- No pre-clinical intravaginal toxicity studies were conducted for the proposed product formulation, however studies conducted using **XXXXX** formulation showed drug irritation of the vaginal mucosa at doses up to double the proposed human dose (mg/kg). Systemic response to intravaginal application involved only slight increases in hepatic serum enzymes for studies shorter than 3 months duration.
- The **XXXXX** product NDA was initially submitted to the FDA in 1988 and was formally approved in 1997. The original submission was **XXXXX**
- **XXXXX**
- Studies showed that the **XXXXX** formulation was generally well tolerated in patients; however some patients did experience severe local irritation and discontinued from the trials. A skin tolerance study undertaken **XXXXX** showed no evidence of primary irritation or hypersensitivity.
- All other preparations for the treatment of vaginal candidiasis, including creams, pessaries and capsules (including clotrimazole single dose, miconazole and fluconazole) are available as over-the-counter preparations in Australia, thus butoconazole in preparations for vaginal use should also be designated as a Schedule 3 substance.
- Butoconazole has been approved for sale over-the-counter in the US since December 1995 and has been shown to have an acceptable safety profile with exposure to a large number of patients.
- There is no potential for abuse and little potential for harm from inappropriate use of the product.

NDPSC evaluation report

The Committee noted that the NDPSC evaluation report recommended that butoconazole be re-scheduled to Schedule 3. The following points were highlighted in the report:

- The evaluator noted that a woman's first vulvovaginal candidiasis infection requires diagnosis by a medical practitioner, but that subsequent treatment could be made available OTC, after consultation with a pharmacist. However, as recurrent candidiasis may be indicative of a more significant systemic illness, this possibility should be reflected in the PI/CMI as medical advice would need to be sought from a medical practitioner.
- Butoconazole has been available in the US since 1985 and available OTC since 1995. **XXXXX** was approved in the US in July 1997 as a single dose treatment, with the product coming to market in March 2000. The evaluator noted that this product is currently marketed as a prescription only drug in the US due to "pricing and the commercial strategy of the marketing application holder"
- The PSUR **XXXXX** showed only 60 AEs reported in over 4,280,000 exposures of the drug. Of these 60 AE's only 2 were reported as being serious. There was no history of hospitalisations, deaths or permanent impairment as a result of **XXXXX** use.
- The most commonly reported AEs for butoconozole were rash, itching, redness and swelling of the vaginal area and are of a comparable incidence to other, currently available anti-fungal preparations.
- The evaluator noted that the AE findings support the criteria for down-scheduling to Schedule 3, ie "safe in use, but requires professional advice or counselling by a pharmacist, for ailments or symptoms which can be identified by the consumer and verified by a pharmacist and do not require medical diagnosis or require initial medical diagnosis and does not require close medical management."
- The evaluator noted that clinical efficacy against a number of Candida species has been established by 3 separate clinical trials and that comparable clinical efficacy with **XXXXX** has been demonstrated in a single, post-marketing trial.

Pre-meeting response from Sponsor

XXXXX stated in writing that they did not wish to provide a pre-meeting response to the evaluators report.

Pre-meeting submissions

XXXXX provided a pre-meeting submission in which they recommend that butoconazole remain as a Schedule 4 substance. Their points were:

- **XXXXX** believed that, as the product is new to the market, it should initially be classified as Schedule 4 in order to allow doctors and pharmacists adequate time to familiarise themselves with the product and its appropriate place within the treatment spectrum
- **XXXXX** foresaw that, given the long history of use of the product in overseas markets and the similar safety and efficacy profile to other imidazoles, butoconazole would not need to remain as a Schedule 4 substance for a prolonged period of time.

- **XXXXX** requested that, if the Committee did decide that a Schedule 3 category was appropriate, the substance not be included in Appendix H at this stage as pharmacists would require time to familiarise themselves with the product and its place within the treatment spectrum before they were able to assist patients with product specific requests.

XXXXX provided a pre-meeting submission in which they requested further information regarding the proposed rescheduling of butoconazole. Their points were:

- **XXXXX** noted this proposal was in line with the current scheduling of other imidazole vaginal creams.
- **XXXXX** also noted that while there was one product containing butoconazole currently listed on the ARTG, it was not currently marketed in Australia.
- **XXXXX** was unable to make a decision on the appropriateness of the proposal given the lack of experience with and information about the product. Therefore **XXXXX** requested further information regarding the reasons for the proposed rescheduling of the substance.

A Member noted that the reason for the current Schedule 4 scheduling of butoconazole was the policy, under trans-Tasman harmonisation, to include any product which has been considered by the Committee but has no product on the market in Schedule 4 of the SUSDP. The Member further noted that all other imidazoles for vaginal use are included in Schedule 3. The Member also noted that the sponsor had not requested Appendix H listing but the Member would have no objection to this given all the other imidazoles for vaginal use are included. Another Member agreed that this was appropriate given the scheduling for other imidazoles. Members discussed automatic consideration of Appendix H listing when applying for Schedule 3 listing and were advised of the wording of the pre-meeting gazette notice for Schedule 3 products which states that such applications may be considered as a consequential consideration of the committee following the decision to include the substance in Schedule 3. The Committee considered whether Appendix H listing for this product would result in the product being advertised in such a way that would induce a large increase in use of the product when the Australian market has little experience with it. A Member pointed out that the product has been used overseas for a period of 10 years and that the clinical and safety data shows no difference from other imidazole antifungal agents.

A Member noted the concerns of **XXXXX** regarding the lack of experience of the market with the product. Members discussed this and felt that overseas market exposure to the product is of large enough size and experience to allay the concerns of **XXXXX**

DECISION 2006/48 - 15

The Committee agreed to include in Schedule 3 of the SUSDP butoconazole in preparations for vaginal use on the basis that the safety and efficacy of the agent is comparable to other imidazole anti-fungal agents which are currently included in

Schedule 3 of the SUSDP. The Committee also agreed to include butoconazole in Appendix H as this is in line with the scheduling for all other Schedule 3 imidazoles.

Schedule 3 – New Entry

BUTOCONAZOLE in preparations for vaginal use.

Schedule 4 – Amendment

BUTOCONAZOLE – amend entry to read:

BUTOCONAZOLE **except** when included in Schedule 3.

Appendix H – New Entry

Butoconazole

12.1.3 ALCLOMETASONE

PURPOSE

The Committee considered a proposal to include alclometasone in Appendix H of the SUSDP, allowing direct-to-consumer advertising of this substance.

BACKGROUND

Alclometasone dipropionate is a semi-synthetic chlorinated corticosteroid used topically for its glucocorticoid activity in the treatment of various skin disorders. Glucocorticoids have multiple mechanisms of action including potent anti-inflammatory activity, immunosuppressive properties, and antiproliferative actions. Anti-inflammatory effects result from decreased formation, release and activity of the mediators of inflammation which reduce the initial manifestations of the inflammatory process. The immunosuppressive properties decrease the response to delayed and immediate hypersensitivity reactions. The antiproliferative effects reduce hyperplastic tissue characteristic of psoriasis.

Alclometasone was first considered at the May 1988 DPSSC Meeting and was included in Schedule 4 following advice from the ADEC that it had recommended marketing approval for **XXXXX** cream and ointment.

The February 2000 NDPSC Meeting agreed on the rescheduling of alclometasone in preparations for dermal use containing 0.05 per cent or less of alclometasone in packs containing 30 g or less of such preparations from Schedule 4 to Schedule 3. The decision was made on grounds of comparable potency, efficacy and safety of alclometasone 0.05% with 1% hydrocortisone, a Schedule 3 drug. The NDPSC subsequently forwarded a recommendation to the New Zealand MCC to consider adopting a similar outcome.

However, MCC rejected this proposal on the advice of the **XXXXX** that the Schedule 4 classification remained appropriate. The May 2001 NDPSC Meeting reconsidered its decision at the request of the New Zealand MCC, and agreed to seek expert advice.

At the November 2001 NDPSC Meeting, the Committee received advice from **XXXXX** which raised concern over the absence of reliable safety data on the long-term use of topical alclometasone. The NDPSC noted submissions which recommended the retention of the Schedule 3 classification from **XXXXX** highlighting the importance of labelling and pharmacist counselling. The NDPSC also noted from the ADRAC that there had been 4 adverse reports associated with topical alclometasone **XXXXX** between 1988-1996, all of which were minor and application site reactions occurring after short periods of use (less than a week).

The NDPSC agreed not to harmonise with the New Zealand scheduling of alclometasone at the February 2002 NDPSC meeting on the basis that there was sufficient evidence to demonstrate that the safety profile and pattern of use of such preparations justified their continued availability as a Schedule 3 medicine.

At the February 2005 NDPSC Meeting, the Committee agreed to recommend to the New Zealand MCC that alclometasone be rescheduled to restricted medicine (Schedule 3), on the basis of established safety in use and to achieve harmonisation.

Other Schedule 3 dermal corticosteroids, 1% hydrocortisone and 0.05% clobetasone are included in Appendix H.

DISCUSSION

XXXXX submission

XXXXX submitted an application seeking approval to include alclometasone 0.05% **XXXXX** in Appendix H to allow branded advertising to consumers. The Committee noted the following major points from the submission:

- **XXXXX** supported the retention of its product in Schedule 3, containing 0.05% alclometasone, on the basis that the safety profile was consistent with a Schedule 3 classification.
- Hydrocortisone 1% and clobetasone 0.05% are included in the Appendix H of the SUSDP. As stated in the Ratified Minutes of the February 2000 NDPSC Meeting, and reconfirmed in the Record of Reasons of the February 2003 NDPSC Meeting under 13.1, “the relative potencies of clobetasone and alclometasone are comparable and the safety profile and efficacy of 0.05% alclometasone is similar to 1% hydrocortisone”. Alclometasone 0.05% also has the same TGA approved OTC indications and has the same advisory statements as clobetasone 0.05% and hydrocortisone 1%.
- Schedule 3 branded advertising of alclometasone would have a potential benefit of increasing consumer awareness thus interactions with pharmacists as the advertising

will emphasise seeking advice from the pharmacists prior to use. The additional benefits from advertising are increased consumer knowledge of both their condition, and the pharmacological options that are available.

- The potential benefit of increased public knowledge on early detection and treatment of skin conditions would result in fewer visits to General Practitioners and reduce the burden on the public health system.
- Hydrocortisones are well established in the marketplace as both Schedule 3 and Schedule 2 products. Advertising of alclometasone is unlikely to discourage pharmacists from recommending these products for consumers suffering milder skin conditions suitable for treatment with OTC dermal corticosteroids.
- The quality use of alclometasone can be achieved through responsible advertising and counselling by a pharmacist.

NDPSC Evaluation report

The Committee noted that the NDPSC evaluation report recommended the inclusion of alclometasone in Appendix H. This recommendation was based on the fact that this substance had a comparable efficacy and safety profile to other OTC topical substances for the same indication (i.e. hydrocortisone and clobetasone) which are in Appendix H. The following points were made by the evaluator:

- The evaluator agreed with the sponsor that the benefit of heightened awareness regarding early detection and treatment of skin conditions may result in fewer visits to general practitioners, which reduces the burden on the public health system.
- The evaluator had conducted a PubMed search and noted studies conducted in patients with eczema suggesting absence cutaneous atrophy with alclometasone dipropionate 0.05% vs hydrocortisone 1.0%, no disturbance in plasma cortisol levels and no suppression of the hypothalamic-pituitary-adrenal axis of normal volunteers.

Pre-meeting submission

XXXXX provided a pre-meeting submission in which they oppose the inclusion of alclometasone dipropionate 0.05% in Appendix H. **XXXXX** quoted the Record of Reasons of the June 2006 NDPSC Meeting regarding the Committee's decision to reject inclusion of mometasone furoate 1.0% in Appendix H due to a lack of OTC market experience. There is currently no post-market experience with alclometasone dipropionate 0.05% for topical use in either Australian or New Zealand market. **XXXXX** agreed that while there is a difference in potency between mometasome and alclometasone, on the basis of lack of post-market experience in Australia, alclometasone dipropionate 0.05% should not be included in Appendix H at this time. Market experience must be garnered before this change can be considered.

Pre-meeting response from Sponsor

Members noted a pre-meeting response from **XXXXX** supporting the evaluator's recommendation to include alclometasone in Appendix H, in view of the comparable efficacy and safety profile of alclometasone with hydrocortisone and clobetasone. **XXXXX** further stated that direct brand advertising of alclometasome would encourage consumers to self manage their skin condition, which would in turn reduce the number of visits to GPs, ultimately reducing the burden on the public health system.

Members agreed that there is currently no post-market experience with alclometasone dipropionate 0.05% for topical use in either the Australian or New Zealand market. Members recalled that the Committee had previously decided to reject the inclusion of mometasone furoate 1.0% in Appendix H due to a lack of OTC market experience.

It was also recalled that at the June 2006 NDPSC Meeting, the Committee agreed to down-schedule mometasone, a potent corticosteroid, from Schedule 4 to Schedule 3. However, after post meeting submissions were received, as well as correspondence from the **XXXXX** all highlighting the incidence of AEs with mometasone, the Committee had agreed to set aside the decision to reschedule mometasone (2006/47-22) pending further advice from **XXXXX.** While there was no comparison in potency between alclometasone and mometasone in the application, **XXXXX** submission to reschedule mometasone made a point that mometasone possessed "…the equivalent side-effect profile to hydrocortisone 1% and clobetasone 0.05%". As the side-effect profile of mometasone and alclometasone were both compared to hydrocortisone 1% and clobetasone 0.05%, Members agreed that the safety and AE profile of moderately potent topical corticosteroids (alclometasone and clobetasone) should also be reviewed as a whole and further data be sought from **XXXXX**.

A Member pointed out that the Committee's decision regarding mometasone concerns the substance's scheduling status and should remain independent of the decision to include alclometasone in Appendix H. The Member also pointed out that inclusion in Appendix H for alclometasone would not increase consumer access to the drug, merely allow consumers access to information via advertising. However, Members felt that deferring this decision is a consistent approach to this class of drug, and therefore important in the process of making the correct decision with regards to public health and safety.

OUTCOME

The Committee agreed to defer scheduling and inclusion in Appendix H decisions for moderately potent topical corticosteroids pending the foreshadowed consideration of all moderately potent corticosteroids at the February 2007 NDPSC Meeting when further data is received from **XXXXX** given the concerns regarding potential adverse events experienced with moderately potent corticosteroids.

12.1.4 NICOTINIC ACID

PURPOSE

The Committee considered a proposal to reschedule prolonged release formulations of nicotinic acid from Schedule 3 to Schedule 4 of the SUSDP.

BACKGROUND

Nicotinic acid and nicotinamide, the form that occurs naturally in the body, are water-soluble vitamin B substances that are converted to nicotinamide adenine dinucleotide (Nadide) and nicotinamide adenine dinucleotide phosphate (NADP). These coenzymes are involved in electron transfer reactions in the respiratory chain. Nicotinic acid and nicotinamide are readily absorbed from the gastrointestinal tract after oral doses and widely distributed in the body tissues. Nicotinic acid appears in breast milk. The main route of metabolism is their conversion to N-methylnicotinamide and the 2-pyridone and 4-pyridone derivatives; nicotinuric acid is also formed. Small amounts of nicotinic acid and nicotinamide are excreted unchanged in urine after therapeutic doses; however the amount excreted unchanged is increased with larger doses.

At the July 1963 scheduling meeting, the committee noted that nicotinic acid may be captured under the scheduling for "Vasodilator substances" included in Schedule 4. At the August 1977 DPSSC Meeting, after considering the advice from the 72nd and 73rd ADEC Meetings, the Committee agreed to include nicotinic acid in Schedule 4.

At the November 1986 DPSSC Meeting, the Committee considered a request from SA Health to clarify the wording of the Schedule 4 entry for nicotinic acid. After discussion the Committee agreed to amend the wording of the entry to only capture preparations containing greater than 250mg per recommended daily dose of nicotinic acid.

At the May 1987 DPSSC Meeting the Committee considered concerns regarding the side effect profile of the substance at high doses; however Members felt that, as these doses were captured by the scheduling, doctors would be able to counsel their patients. The Committee also considered potential therapeutic uses for nicotinic acid and noted that the only clear indication for use was hypercholesterolaemia and hypertriglyceridaemia. Given this information, the Committee foreshadowed a decision to amend the Schedule 4 limit from 250mg to 50mg.

The Committee re-considered the proposal to reduce the Schedule 4 limit of nicotinic acid from 250mg to 50mg at the July 1987 Meeting. The Committee noted industry submissions requesting the exemption of nicotinamide from scheduling requirements and after consideration recommended to amend the Schedule 4 limit to 50mg and to exclude nicotinamide from scheduling and to include nicotinamide in a new Appendix B entry. The Committee confirmed the amended Schedule 4 entry at the November 1987 DPSSC Meeting with the exception of the Appendix B entry.

At the August 1988 DPSSC Meeting the Committee considered a request from a Member to clarify the wording of the Schedule 4 entry for nicotinic acid to capture preparations with no labelled maximum daily dose. After consideration the Committee decided the current wording was adequate and no change was recommended.

Nicotinic acid scheduling was raised during harmonisation consideration at the October 1998 TTHWP and May 1999 NDPSC Meetings. The Committee noted a recommendation made at the October 1998 TTHWP Meeting that the Schedule 4 entry for nicotinic acid should be deleted and replaced with a Schedule 3 entry. The Committee endorsed this recommendation as being in line with the principles of harmonisation and advised that the Schedule 4 entry be deleted and replaced with a Schedule 3 entry for nicotinic acid for human therapeutic use except where containing 100mg or less per dosage unit.

At the August 1999 NDPSC Meeting, the Committee noted a submission regarding the appropriateness of deletion of the Schedule 4 entry for nicotinic acid. After consideration the Committee was satisfied that this decision remained appropriate. The matter was again considered at the November 1999 NDPSC Meeting and the Committee reiterated its decision that the scheduling entry for nicotinic acid remained appropriate.

DISCUSSION

XXXXX has been evaluated by the TGA. ADEC recommended approval at its 243rd Meeting in December 2005 for the indication of "the treatment of mixed dyslipidaemia, and primary hypercholesterolaemia, as adjunctive therapy to diet".

XXXXX submission

XXXXX has submitted an application to reschedule **XXXXX** nicotinic acid formulations **XXXXX** from Schedule 3 to Schedule 4 and the data submitted supports the following arguments:

- **XXXXX** is a **XXXXX** formulation of nicotinic acid (NA), which has an important role in elevating HDL-C and lowering TG. Both these lipid fractions are known to have an independent role in effecting CV risk and associated morbidity and mortality. Use of **XXXXX** may aid in the control of these risk factors. The proposed maximum daily dose of **XXXXX** is 2000mg/ day.
- NA was shown to decrease the release of free fatty acids into the plasma, partly by the inhibition of lipolysis in adipose tissue and increasing hepatic lipoprotein lipase activity. Studies also have shown inhibition of HMG-CoA reductase and a reversible increase in fatty liver - possibly due to the decreased release of lipids from this organ. Lipid accumulation in the liver was exacerbated in the presence of ethanol.
- Animal studies have shown no effects on blood pressure, heart rate, ECG or respiration. Further animal studies of flushing showed that cutaneous vasodilation induced by NA was prostaglandin mediated.
- **XXXXX**
- There is an apparent increase in hepatotoxicity (as per the Product Information **XXXXX** with the **XXXXX** formulation compared to the **XXXXX** This may be due to the PR formulation allowing a longer period of NA exposure above a critical

threshold for hepatotoxicity. Thus adequate monitoring of liver function should be conducted during treatment with the **XXXXX** formulation.

- **XXXXX**
- **XXXXX** would be targeted to patients with a high absolute risk of future cardiovascular events who are already taking specific low-density lipoprotein cholesterol (LDL-C) lowering medicines, but not obtaining satisfactory control of HDL-C. Standard LDL-C lowering medicines (eg statins) are prescribed and managed by medical practitioners. It would be incongruous to have statin therapy managed by a medical practitioner but have **XXXXX** therapy managed at pharmacy level. The measurement of lipid fractions is also required and uses complex methodologies that are unable to be conducted at a pharmacy level.
- The dosage of **XXXXX** must be carefully titrated in order to minimise AEs and it is also contraindicated in pregnancy and breastfeeding due to the potential for AEs for infants of mothers taking lipid-altering doses.
- Long term treatment with **XXXXX** requires the routine monitoring of liver function, muscle enzymes, coagulation and diabetes control so that any potential AEs can be avoided. This monitoring requires medical supervision. **XXXXX** lists a range of other cardiometabolic events that may be precipitated or exacerbated rarely during **XXXXX** therapy. The majority of these events require medical intervention by a physician.
- **XXXXX** is registered in over 40 countries world-wide. It is available by prescription only in all these countries, with the exception of Australia.

<u>NDPSC evaluation report</u>

The NDPSC evaluation report recommended that nicotinic acid prolonged release formulation be re-scheduled to Schedule 4. The following points were highlighted in the report:

- The evaluator noted that nicotinic acid (NA) has the properties of elevating HDL-C and decreasing triglycerides as well as increasing apolipoprotein-a (ApoA) and decreasing apolipoprotein b-100 (ApoB) levels.
- The evaluator also commented that although NA is an effective agent in hyperlipidaemia, it demonstrates a common adverse event of peripheral flushing which is potentially mediated by a prostaglandin effect. However, compared to **XXXXX** shows a reduced duration and intensity of this reaction.
- Due to its contraindication in pregnancy and AEs involving liver function, glucose tolerance, muscle enzymes and coagulation levels, long term use of **XXXXX** requires the routine monitoring of these parameters and this can only be conducted by a medical professional.
- **XXXXX** is registered in over 40 countries world-wide and is a prescription only item in all of these.

Pre-meeting response from Sponsor

XXXXX submitted a response supporting the recommendation made by the evaluator.

Pre-meeting submissions

No pre-meeting submissions were received.

The Committee noted that the wording of the Schedule 4 entry proposed by the Sponsor would not affect any products currently on the Australian Register of Therapeutic Goods (ARTG). A COGNOS report was run to confirm the number of single active NA products currently on the ARTG.

The Committee discussed the proposed wording for the entry as being too complex and whether the indication for treatment was required to be included in the wording of the entry. The Committee felt that indications are not what compounds are usually scheduled for; rather they are scheduled for safety and toxicity concerns. The Committee also noted that the inclusion of the indication would inadvertently capture lower dose than 375 mg products which are currently indicated for treatment of dislipidaemia and are not slow release formulations. The committee discussed that the slow release formulation of the product was most likely for ease of dosing and compliance and should have no bearing on the scheduling of the compound.

The Committee discussed the fact that the toxicity of the medication is what a medication should be scheduled for and what the appropriate toxicity cut-off limit for nicotinic acid was. A Member noted that a 250 mg tablet formulation has been available in the Australian market for a large number of years and no toxicity concerns have emerged at that dose. Members also noted that there is limited experience in the Australian market with preparations of NA higher than 250 mg. The Committee discussed this limit and agreed that medications containing more than 250mg nicotinic acid should be included in Schedule 4 given the safety profile and monitoring required for and absence of experience with higher doses of the drug.

The Committee also discussed that for simplicity of use and consistency of the SUSDP, Schedule 4 should be the base entry for the SUSDP and that NA then be exempted from this by inclusion in other Schedules.

DECISION 2006/48 - 16

The Committee agreed, on the basis of the toxicology of nicotinic acid and the experience of the Australian market with the product, to include nicotinic acid in Schedule 4 of the SUSDP except where contained in other Schedules and to amend the Schedule 3 entry to include products between 100 mg and 250 mg of nicotinic acid.

Schedule 4 - New entry

NICOTINIC ACID for human therapeutic use **except** when contained in other Schedules.

Schedule 3 – Amendment

NICOTINIC ACID – amend entry to read:

NICOTINIC ACID for human therapeutic use in dosage preparations containing 250 mg or less of nicotinic acid **except**:

(e) in preparations containing 100 mg or less of nicotinic acid per dosage unit; or

(f) nicotinamide.

12.1.5 FIXED DOSE COMBINATION OPIATE ANALGESICS

PURPOSE

The Committee considered the re-scheduling of fixed dose analgesics containing paracetamol in combination with either morphine 3mg, oxycodone 2mg or hydromorphone 0.5mg to Schedule 3 and also considered the re-scheduling of fixed dose analgesics containing paracetamol in combination with either morphine 7.5mg/ 10mg/ 20mg, oxycodone 5mg/ 7.5mg/ 10mg or hydromorphone 1mg/ 2mg/ 4mg to Schedule 4.

BACKGROUND

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

Hydromorphone, morphine and oxycodone are all opiate analgesics of varying potency. In terms of dose equivalents, according to Goodman & Gilman, an oral dose of 60mg of morphine is equivalent to an oral dose of 7.5mg of hydromorphone which is equivalent to a 5-10mg oral dose of oxycodone. These doses are all approximately equivalent to 200mg of oral codeine. The references provided in **XXXXX** of the submission state more or less the same equivalences.

Hydromorphone has not previously been considered by the Committee for any Schedule other than Schedule 8. In regards to oxycodone, the Committee received a submission in March 1981 relating to the use of oxycodone in compounded analgesics such as Percodan in long term treatment of pain. The Committee agreed to contact **XXXXX** regarding the addictive nature of the product. No further action was taken. For morphine, the

November 1971 DPSSC Meeting agreed to delete all entries other than the Schedule 8 entry. This decision was reconfirmed in July 1972.

DISCUSSION

Sponsor's submission

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

(i) Paracetamol compounded with low dose opioid equianalgesic to 15mg of codeine phosphate packed in blister or strip packaging or in a child-resistant closure containing 12 dosage units to Schedule 3; and

(ii) Paracetamol compounded with varying strengths of opioid in packages containing 24 or more dosage units to Schedule 4.

The applicants put forward the argument that the clinical use of paracetamol and opioid analgesia is well established and that the application involves neither new therapeutic agents nor novel indications. In summary, the submission contained the following sections:

- Justification for rescheduling in relation to the object of the *Therapeutic Goods Act 1989* – "the Act" (i.e. "to promote the development of a national system of controls relating to the quality, safety, efficacy & timely availability of therapeutic goods..."). The applicants argue that for poor metabolisers of codeine, other opiate analgesics are not as readily available without a doctor's prescription and thus time to access becomes a factor.
- A cost (risk) versus benefit analysis is explored. The benefits put forward were parity for slow metabolisers, more consistent analgesia for ultra rapid metabolisers, less reliance on codeine (which, it is stated, some clinicians find to be an inefficient analgesic) as well as providing alternative analgesics to NSAIDs. The costs include accidental poisoning, deliberate poisoning and medicinal misadventure and each of these are discussed in some detail in the submission.
- The decision by the Committee to down-schedule limited pack sizes of codeine phosphate 15mg combined with paracetamol was discussed and extracts from the Record of Reasons of the June 2003 NDPSC Meeting (when combination codeine phosphate 15mg/ paracetamol 500mg was included in Schedule 3) were included.
- The submission made mention of some OTC products containing morphine in the UK (eg Kaolin & Morphine mixture) resulting in very few adverse reports involving abuse. A number of specific Australian OTC products are listed and their total quantity of codeine calculated.
- Australia's obligations as a signatory to the *Single Convention on Narcotic Drugs 1961* were discussed. The applicant stated that the proposed analgesics are completely consistent with Australia's obligations under the Single Convention. The Committee

noted that hydromorphone, morphine and oxycodone are allowed no reporting exemptions (i.e. fall in Schedule 1) and so all movement of such products would require reporting under the obligations of the Treaty. The applicant pointed out that such reporting requirements do not implicitly require a Schedule 8 listing (although a Schedule 8 listing makes compliance with such reporting requirements far more straight forward).

- The EU Directive for Fixed Combination Medicinal Products was referred to and the application is addressed using the framework of the directive. The applicant maintained that there is an enormous amount of clinical experience accumulated that demonstrates the safety and efficacy of the paracetamol/ opiate combinations.
- The provisions of s52E of the Act were listed and arguments for each provision were put forward.

NDPSC evaluation report

The NDPSC evaluation report recommended that a decision to include these compounds in Schedule 3 and Schedule 4 be deferred until further efficacy and safety data of specific agents are provided and safety in OTC/ prescription situations is established. The following points were highlighted in the report:

- The applicant stated that approximately 10% of the population lack capacity to convert codeine to morphine (via CYTP450 2D6) and therefore alternative opiates should be made available OTC. Any evidence that slow codeine metabolisers who receive other opiates have improved analgesia without any compromise in safety is not provided with the submission and is not, to the evaluator's knowledge, present in the literature (following a PubMed search).
- The applicant also suggested that larger doses of the listed opiates with paracetamol be scheduled as Schedule 4 but again, did not provide evidence that these products fulfil Schedule 4 criteria. The applicant argued that access to pain relief should be consistently applied to all citizens. The applicant is quoted: "… we believe that reducing a person's ability to receive pain relief based on genetics including racially distributed genetics is unacceptable".
- The applicant had not provided any specific evidence of independently evaluated efficacy and safety of the proposed formulations. There were no post-marketing data provided for the indications intended, no evidence that slow metabolisers receive more effective analgesia from the alternative formulations and no evidence of these compounds fulfilling Schedule 3 criteria. Limited journal references were provided but no other data supporting efficacy and safety of the proposed OTC compounded formulations were presented.

Pre-meeting response from Sponsor

The applicant has provided a pre-meeting response to the evaluator's report and the following points are made:

- That the evaluator had erred by failing to acknowledge the substantial evidence of the safety and efficacy of the proposed combination analgesics. Such evidence includes that which was part of the submission, that which is referenced in pharmacopoeias and data which a drug regulator would be assumed to be aware of (reference to the ADRAC database is made here).
- The applicant reiterated (as stated in the original submission) that there is overwhelming clinical history and public exposure to the proposed combination of substances. The applicant felt that safety and efficacy had been unambiguously established.
- The applicant stated that the evaluator failed to consider the ethical principles of disallowing clinical trials that evaluate established gold standard treatments.
- The applicant refuted the statement from the evaluator that there is no evidence to demonstrate that slow metabolisers receiving the proposed combination products in fact receive better analgesia without compromise of safety. The applicant referred to TGA guidelines on generic PI statements for products containing codeine which make reference to CYP2D6 poor metabolisers. The applicant argued that inclusion of this statement by TGA demonstrated that it is accepted that slow metabolisers will have reduced benefit from codeine and this fact cannot be disregarded.
- The applicant contested the evaluator's demand for evidence that alternative opiates won't compromise safety. The applicant maintained that post-marketing data is evidence enough. The applicant suggested that the detriment that would result from not having an alternative to codeine should be considered and the path of "inaction" recommended by the evaluator was not supported by any evidence.
- The applicant stated that the evaluator had dismissed more than two million citizens by saying that the only argument provided was with respect to equal access to pain relief. The applicant quoted Human Rights legislation when putting forward a definition of indirect discrimination.
- The applicant concluded by stating that there were distinct disadvantages to the proposed preparations but that widespread clinical use has allowed for monitoring of adverse effects of these combinations to an "unparalleled degree". The applicant pointed out that disregard of precedent leaves open substantial recourse for regulatory and legal review.

The Committee noted that a number of references were submitted in support of the pre-meeting response but, as the guidelines state, a pre-meeting response must not introduce any new data that was not referred to in the original submission.

Pre-Meeting submissions

XXXXX made a pre-meeting submission and noted that while codeine with paracetamol is scheduled as either Schedule 2, Schedule 3 or Schedule 4, hydromorphone, morphine and oxycodone are only Schedule 8. **XXXXX** have reserved the right to comment on the proposal post-meeting

XXXXX made a pre-meeting submission and made the following points:

- The application is "unusual" in that it called for consideration of so many different substances at once.
- **XXXXX** wanted clarification as to whether these products might be restricted to certain clinical situations/ conditions.
- **XXXXX** noted that 10% of the population cannot metabolise codeine.
- **XXXXX** cautioned multiple combination analgesics containing paracetamol as this may increase the likelihood of inadvertent paracetamol overdose.
- **XXXXX** asked if there was evidence to show that misuse/ abuse is less likely with these opiates than with single ingredient products.
- **XXXXX** opposed the Schedule 3 proposal and had concerns regarding the Schedule 4 proposal. **XXXXX** suggested that pharmacies might become targets for ram raids, as was the case at the height of misuse of temazepam capsules. **XXXXX** also opposes Appendix H listing.
- **XXXXX** also stated that inadequate information was provided regarding this proposal in the pre-October 2006 NDPSC Meeting gazette notice.

A pre-meeting submission was received from **XXXXX. XXXXX** recommends that hydromorphone, morphine and oxycodone should remain Schedule 8 poisons, regardless of strength or presence of other actives. The following points were made:

- **XXXXX** referred to abuse/ addiction problems with combination analgesics in the USA, particularly amongst teenagers. **XXXXX** believed that keeping these three opiates as Schedule 8 would allow for proper monitoring of prescribing and dispensing and help to avoid the situation that has occurred in the USA.
- **XXXXX** believed that, although the proposed doses of hydromorphone, morphine & oxycodone may be equianalgesic, the potential for abuse/ misuse with these opiates is far greater. Furthermore, illicit extraction of active from these products would garner a much more potent substance than can be obtained with combination codeine products.
- **XXXXX** referred to a survey of 150 community pharmacies throughout Australia where 70% were concerned about abuse or misuse of Schedule 2 codeine preparations, 86% were concerned about abuse of Schedule 3 preparations and 50% were concerned about abuse of Schedule 4 preparations.
- **XXXXX** aired concerns about the potential for "indiscriminate" prescribing of such low dose opiate analgesics and also stated that the risk of accidental paracetamol overdose may be more likely as tolerance to these products increases (and therefore an increase in frequency of dosing by uninformed individuals).
- **XXXXX** noted that a combination oxycodone/ paracetamol (2.5mg/ 500mg) had been recently discontinued in the US.

- **XXXXX** stated that issues surrounding on-line or interstate prescribing/ supplying may be an issue with these products **XXXXX** could not find reference to any such product being available OTC in any comparably regulated country.
- **XXXXX** quoted guidelines from the BNF regarding prescribing drugs of dependence (Controlled Drugs). It states that a prescriber should avoid creating dependence by introducing drugs to patients without sufficient reason. It also instructs to avoid being used as an unwitting source of supply for addicts ("doctor shopping" etc). With both of these guidelines in mind, **XXXXX** concluded that these three opiates are most appropriately left in Schedule 8.

The Committee noted an online article from Medline Plus in September 2006 which states that sales of opiate painkillers such as oxycodone, hydrocodone, methadone, morphine & fentanyl have increased over the past fifteen years and a parallel increase in numbers of deaths form these drugs has also occurred. The number of all unintentional deaths increased by 5.3 percent each year on average but deaths from prescription opiates increased relatively more than those from cocaine or heroin. The article makes the point that overdose deaths are not necessarily from drugs which were legally prescribed.

Data was submitted by **XXXXX** showing an increase in consumption of all three opiates from 1991 onwards. It was stated in this correspondence that introduction of new formulations of oral morphine preparations coincided with a significant increase in consumption and the same may happen with these three opiates, should they be rescheduled. **XXXXX** stated there are particular concerns with both the prescribing of opiate analgesics and the supply of OTC analgesics through pharmacies. It was further contested that drug users in rural and regional areas are more likely to use licit opiates than illicit ones (report quoted 50% of rural users sourcing licit morphine c.f. 21% of city users).

A report from **XXXXX** on the incidence of conversion of codeine into "homebake" heroin in clandestine laboratories illustrated that the practise of illicit conversion of codeine to heroin may not be widespread but the point was made that the same may not be true, should hydromorphone, morphine and oxycodone become more readily available.

The Committee considered a report from **XXXXX** which showed that 3.1% of the population misuse painkillers/ analgesics (the most common form of misuse of licit substances in the country). A further email from **XXXXX** clarified that the descriptor "painkillers" includes OTC analgesics such as paracetamol, aspirin and stronger combination analgesics like **XXXXX**.

The Committee discussed the lack of evidence provided in the application regarding whether slow metabolisers of codeine would actually be able to metabolise hydromorphone, morphine and oxycodone more effectively than codeine and noted that there were no studies provided that showed this to be the case. A Member noted that comparative trials between the suggested products and products on the market should be conducted before scheduling is considered as this would give the required information about safety and efficacy of the substances in the slow codeine metabolisers. The

Member also noted that the diagnosis of patients as slow metabolisers was difficult and would best be done by their medical practitioner over a period of time and observation of the patient and their experience with opiates.

The Committee noted the small percentage of the population that fall into the slow metaboliser category. Members discussed the fact that only a small proportion of these slow metabolisers would suffer from conditions requiring opioid analgesia and that there was no barrier to these patients, who would be under the management of a medical practitioner, receiving a prescription for the substances from their medical practitioner. A Member noted that titration of dose was important with opioid analgesics as tolerance to opioids may lead to an increase in the frequency of dosing to get the same effect from the medication and this was especially important when in a fixed dose combination with paracetamol. Members discussed that, as these opiates may have a shorter half life than paracetamol, this may lead to patients taking medication more frequently than every four hours which might result in an increase in paracetamol overdose cases.

A Member noted that there was a large amount of regulation on both a federal and State and Territory level to prevent the misuse of opioid analgesics and that such substances are scheduled with a view to their potential for misuse and causing harm. The Committee also discussed the benefit of these substances to patients and the large number of guidelines in place around the management of pain which clearly delineate the place of opiates in treatment. The Committee also discussed that, despite this there is still a substantial harm in society which is caused by the misuse of these substances and noted a number of case studies of abuse of currently available over the counter codeine preparations. The committee also noted that the misuse of hydromorphone, morphine and oxycodone is also well recognised and discussed whether this misuse would increase if these substances became more readily available.

The Committee discussed the large increase in prescribing of these substances over the last decade and also the increase in the misuse of the substances. The Committee also discussed the potential for diversion of hydromorphone, morphine and oxycodone into illicit ‘homebake’ heroin production and noted that the risk of diversion was higher with hydromorphone, morphine and oxycodone than with codeine.

Members further discussed the requirements of the UN Single Convention on Narcotic Drugs 1961 and noted that hydromorphone, morphine and oxycodone do not have the Part 3 exemption which allows combination of the substance in small doses when in combination with other non-opioid agents.

The Committee considered the requirements for inclusion of substances in Schedule 3 and Schedule 8 of the SUSDP. The Committee noted that a requirement for inclusion in Schedule 3 of the SUSDP was the low abuse potential of the substance and the low potential for harm from inappropriate use of the substance. The Committee also noted the guideline that any substance contained in Schedules I or II of the *UN Single Convention on Narcotic Drugs 1961* be classified in Schedule 8 of the SUSDP and further noted the

requirement that any substance which presents a substantial risk of abuse, dependence or misuse for illegal purposes must also be included in Schedule 8.

OUTCOME

The Committee agreed that, due to the lack of evidence provided in the application about both the safety and efficacy specifically in slow metabolisers of codeine, that the current scheduling was appropriate. More importantly, the Committee held concerns regarding the abuse potential of the medications and therefore felt that the current scheduling of hydromorphone, morphine and oxycodone remained appropriate. In reaching this conclusion the Committee also took into account the fact that the NDPSC guidelines require that Schedule 3 substances have a low abuse potential and that substances which present a substantial risk of abuse, dependence or misuse must be included in Schedule 8.

12.1.6 PROCHLORPERAZINE

PURPOSE

The Committee considered restricting the current Schedule 3 prochlorperazine entry to oral use only.

BACKGROUND

Prochlorperazine is a phenothiazine antipsychotic. Prochlorperazine and its salts are widely used in the prevention and treatment of nausea and vomiting including that associated with migraine or drug-induced emesis. They are also used for the short-term symptomatic relief of vertigo and in the management of schizophrenia, mania and other psychoses.

Prochlorperazine was first scheduled following the November 1974 DPSSC Meeting's decision to included a new entry for prochlorperazine in Schedule 4.

The November 1998 and August 1999 NDPSC Meetings considered harmonisation changes to the scheduling of prochlorperazine arising from the TTHWP. At this time New Zealand had a "Restricted" entry reflecting the availability of an OTC product specifically for buccal use. The recommendations from the TTHWP were supported i.e. rescheduling of "tablets when manufactured, packed and labelled for buccal use, only for the treatment of nausea associated with migraine, in packs containing not more than 10 tablets" to Schedule 3 while maintaining a Schedule 4 parent entry for all other uses.

The June 2005 NDPSC Meeting had intended to consider amending the Schedule 3 entry for prochlorperazine to remove reference to "buccal use", but instead decided to defer consideration to allow time to seek comment from the Drafting Advisory Panel (DAP). The October 2005 NDPSC Meeting agreed, in order to harmonise with New Zealand, to amend the Schedule 3 entry for prochlorperazine by removing reference to "buccal use"

to give the current Schedule 3 entry “in divided preparations in packs containing not more than 10 dosage units for the treatment of nausea associated with migraine”.

DISCUSSION

The Committee was advised that following the June 2006 decision several Members raised concerns about the wording of the Schedule 3 prochlorperazine entry. The Committee particularly noted:

- Concern that, while the prochlorperazine entry had gone from specifying a limitation to “buccal use” to no restriction on dosage form, the October 2005 NDPSC Meeting had only intended to broaden allowed usage to oral use.
- Under the interpretation set out in Part 1, "Divided preparation" meant a preparation manufactured and packed as discrete pre-measured dosage units prior to sale or supply, and included tablets, capsules, cachets, single dose powder or single dose sachets of powders or granules. This definition gave a number of inclusions but did not necessarily exclude other presentations (such as suppositories and injections).
- The Member therefore suggested that the Committee consider limiting the Schedule 3 entry to "oral use" or possibly "tablets and capsules".
- In response, **XXXXX** indicated a preference for the addition of the words "oral use" rather than specifying the form of the dosage unit/s.

The Committee recalled that the May 2002 New Zealand MCC Meeting had amended the restricted classification entry for prochlorperazine as the OTC buccal product had been discontinued. The present New Zealand classification for restricted prochlorperazine was “in packs containing not more than 10 tablets for the treatment of nausea associated with migraine”.

The Members also recalled the following from the October 2005 NDPSC Meeting’s attempt to harmonise with New Zealand:

- DAP had suggested that “tablets” be replaced by “dosage units”.
- A Member was of the view that the scheduling amendment was not to create a new entry, but to revise the current entry to accommodate oral use, and thus supported application of the term “dosing units” in the entry.
- Another Member pointed out that in regards to the potential for side effects, administration via the buccal route was no more likely to result in an adverse reaction in comparison to any other route, especially oral. There was no significant safety difference between oral and buccal routes of administration of prochlorperazine.

Members noted that a pre-meeting comment from **XXXXX** supported progress being made toward the ANZTPA and asserted that it was timely that inconsistencies in the scheduling of active ingredients be considered and addressed. It was **XXXXX** position

that any scheduling amendment to prochlorperazine still retain the current availability of buccal prochlorperazine as a Schedule 3 medicine.

Members also noted that the pre-meeting comment from **XXXXX** for item 1.8.1.1 mentioned that it supported an amendment to the Schedule 4 prochlorperazine entry to include "except when in Schedule 3" and harmonization with the current New Zealand Schedule 3 entry "in packs containing not more than 10 tablets for the treatment of nausea associated with migraine".

A Member asked whether there was any particular concern with allowing suppositories to be Schedule 3 instead of Schedule 4. Members noted that a rescheduling consideration of suppository presentations would require data that had yet to be brought to the Committee. In addition, it was noted that the current wording of the Schedule 3 entry would also potentially allow injections, which was not the Committee's intention. Members therefore agreed that the Schedule 3 prochlorperazine entry needed to be amended to specify oral use, and that any consideration of down scheduling suppositories would need to await an application including data addressing the Committee's criteria.

DECISION 2006/48 - 17

The Committee:

- confirmed that the October 2005 NDPSC Meeting intended to broaden the Schedule 3 prochlorperazine entry from buccal use to oral use, but had not intended that this allow formulations such as suppositories or injections to be Schedule 3; and
- agreed, therefore, to reword the Schedule 3 prochlorperazine entry to clarify this intention.

Schedule 3 – Amendment

PROCHLORPERAZINE – amend entry to read:

PROCHLORPERAZINE in divided preparations for oral use in packs containing not more than 10 dosage units for the treatment of nausea associated with migraine.

12.2 SUSDP, PART 5

No items were considered.

13. MATTERS REFERRED BY THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC)

13.1 NEW SUBSTANCES (NOT SEEN BEFORE BY NDPSC)

13.1.1 DEFERASIROX

PURPOSE

The Committee considered the scheduling of a new medicine, deferasirox.

BACKGROUND

The 245th ADEC meeting of March 2006 recommended approval of an application from **XXXXX** to register **XXXXX** containing the new chemical deferasirox. The approved indication is for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in adults, adolescents and in children 6 years and older; and as the second line treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis) in paediatric patients aged 2 to 5 years who are intolerant to desferrioxamine or in whom desferrioxamine has proven ineffective.

DISCUSSION

The Committee noted the Ratified Minutes of the 245th ADEC Meeting. **XXXXX**

The Committee noted that deferasirox was a prescription medicine in New Zealand.

DECISION 2006/48 - 18

The Committee agreed to include deferasirox in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional. The inclusion of deferasirox in Schedule 4 harmonises the scheduling of this substance with New Zealand.

Schedule 4 - New entry

DEFERASIROX.

13.1.2 DULOXETINE

PURPOSE

The Committee considered the scheduling of a new medicine, duloxetine.

BACKGROUND

Duloxetine is a SNRI (serotonin & noradrenaline reuptake inhibitor).

XXXXX

DISCUSSION

The Committee noted the Ratified Minutes of the March 2006 ADEC Meeting, **XXXXX**

XXXXX

The Committee also noted that duloxetine is currently approved overseas for use in the treatment of depression and stress urinary incontinence in women.

- approved by the New Zealand MCC as a prescription medicine in November 2003.
- gazetted in New Zealand as a new medicine **XXXXX** to treat stress urinary incontinence in March 2006.
- approved by the US FDA in August 2004 for major depressive disorder.
- approved by the European Commission in January 2005 for major depressive disorder.
- approved by the European Commission in August 2004 for stress urinary incontinence.

The Committee noted that the June 2006 NDPSC Meeting endorsed the recommendations of the June 2006 TTHWP Meeting to harmonise the remaining unharmonised substances, including duloxetine, and agreed to foreshadow scheduling consideration for the October 2006 NDPSC Meeting.

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

The Committee noted reports of dizziness, fatigue and somnolence as some of duloxetine's main side effects, in particular:

- Martindale records fatigue, somnolence and dizziness as being frequently reported adverse effects;
- Martindale records a caution that, as with other antidepressants, duloxetine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery;
- **XXXXX**
- the Prescribing Information for duloxetine **XXXXX** includes the statement: "Any psychoactive drug may impair judgment, thinking, or motor skills. Although in controlled studies **XXXXX** has not been shown to impair psychomotor performance,

cognitive function, or memory, it may be associated with sedation and dizziness. Therefore, patients should be cautioned about operating hazardous machinery including automobiles, until they are reasonably certain that **XXXXX** therapy does not affect their ability to engage in such activities".

The Committee noted that the February 2002 NDPSC Meeting agreed to undertake a review of the approach taken with SNRI drugs with respect to the need for a sedation warning to ensure consistency, with literature searches at that time yielding six compounds classified as SNRIs, namely venlafaxine, sibutramine, ziprasidone, duloxetine and milnacipran:

- the February 2002 NDPSC Meeting agreed to foreshadow inclusion of ziprasidone in Appendix K on the basis of its potential to cause sedation. The June 2002 NDPSC Meeting agreed to include ziprasidone in Appendix K based on expert advice and information specified in the PI indicating that clinical trials with ziprasidone showed a significantly higher potential to cause drowsiness compared with placebo.
- the February 2002 NDPSC Meeting agreed to foreshadow inclusion of sibutramine in Appendix K on the grounds that as a CNS-active drug it has the potential to cause drowsiness, interact with alcohol and impair judgment, thinking & motor skills; the PI and Martindale monograph included a caution that patients should not drive a vehicle or operate hazardous machinery when taking sibutramine. However, the June 2002 NDPSC Meeting agreed not to include sibutramine in Appendix K as expert advice and data from clinical studies indicated no significant difference in incidence rates for drowsiness between sibutramine and placebo.
- the June 2002 NDPSC Meeting agreed to foreshadow inclusion of fluvoxamine and venlafaxine in Appendix K as the available information indicated significantly higher incidence rates for drowsiness compared with placebo. However, the October 2002 NDPSC Meeting agreed not to include fluvoxamine and venlafaxine in Appendix K on the grounds that the available evidence indicated that these substances had a low potential to cause sedation or affect motor skills at the recommended doses and the inclusion of sedation warnings in the CMI and PI was considered sufficient.

DECISION 2006/48 - 19

The Committee agreed to include duloxetine in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitated appropriate medical diagnosis and the safe use of this medicine required patient management and monitoring by a medical professional. The inclusion of duloxetine in Schedule 4 harmonises the scheduling of this substance with New Zealand.

The Committee also agreed to include duloxetine in Appendix K of the SUSDP based on reports that the drug may impair judgment, thinking, or motor skills, and also that it may be associated with sedation and dizziness.

Schedule 4 - New entry

DULOXETINE.

Appendix K – New entry

Duloxetine

13.1.3 TIGECYCLINE

PURPOSE

The Committee considered the scheduling of the new medicine, tigecycline.

BACKGROUND

Tigecycline is a glycylcycline antibacterial with structural similarity to the tetracyclines. Tigecycline is generally bacteriostatic and acts by binding to the 30S subunit of the ribosome and preventing the binding of aminoacyl transfer RNA, in a similar way to tetracyclines. It has activity against a broad range of Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobic organisms.

The March 2006 ADEC Meeting recommended approval of a submission by **XXXXX** to register **XXXXX** containing tigecycline **XXXXX**, for "the treatment of the following infections in adults: complicated skin and skin structure infections, including those with methicillin-resistant Staphylococcus aureus (MRSA) and complicated intra-abdominal infections". Use in pregnancy recommendation is Category D. Use in patients under 18 years of age is not recommended.

DISCUSSION

The Committee noted the Ratified Minutes of the March 2006 ADEC Meeting, **XXXXX**

- **XXXXX**

The Committee also noted the following from the Micromedex monograph on tigecycline:

- Due to potential for similar adverse effects, precautions similar to those exercised with tetracyclines should be taken with tigecycline. In particular, tigecycline should not be given in pregnancy as it has caused foetal harm in animal studies. It should also not be given during tooth development (up to 8 years of age) as it may cause permanent tooth discoloration.
- Caution should be exercised when using tigecycline in patients with complicated intra-abdominal infections secondary to intestinal perforation. Dosage of tigecycline should be adjusted in patients with severe hepatic impairment.

DECISION 2006/48 - 20

The Committee agreed that tigecycline be included in Schedule 4 of the SUSDP:

- on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional; abd
- to harmonise scheduling with New Zealand.

Schedule 4 - New entry

TIGECYCLINE.

13.1.4 TIPRANAVIR

PURPOSE

The Committee considered the scheduling of the new medicine, tipranavir.

BACKGROUND

Tipranavir is a non-peptidic HIV-1 protease inhibitor that inhibits the virus-specific processing of the viral Gog and Gag-Pol polyproteins in HIV-1 infected cells, thus preventing formation of mature virons. Because tipranavir is a substrate and inducer of Cytochrome P450-3A (CYP3A), co-administration of the antiretroviral, ritonavir inhibits CYP3A activity, thus allowing tipranavir to be minimally metabolized.

The March 2006 ADEC Meeting recommended approval of a submission by **XXXXX** to register **XXXXX** containing tipranavir, co-administered with **XXXXX** ritonavir for "the combination treatment of HIV-1 infection in highly pre-treated adults with evidence of viral replication and HIV-1 strains confirmed resistant to multiple protease inhibitors. This indication is based on the results of analysis of HIV-RNA levels **XXXXX** In deciding to initiate therapy **XXXXX**, careful consideration should be given to treatment history of the individual patient and the patterns of mutations associated with different agents. Genotypic testing should be performed to guide the use of **XXXXX**".

DISCUSSION

The Committee noted the Ratified Minutes of the March 2006 ADEC Meeting, **XXXXX**

- **XXXXX**

The Committee also noted the following from the Micromedex monograph on tigecycline:

- It is contraindicated for co-administration with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
- US Food and Drug Administration placed tipranavir co-administered with ritonavir in Pregnancy Category: Category C.

The Committee noted that tipranavir is in the same class of protease inhibitors as saquinavir which is a Schedule 4 poison.

DECISION 2006/48 - 21

The Committee agreed to include tipranavir in Schedule 4 of the SUSDP on the grounds that the condition being treated necessitates appropriate medical diagnosis and the safe use of this medicine requires patient management and monitoring by a medical professional.

Schedule 4 – New entry

TIPRANAVIR.

13.2 FOR INFORMATION (SUBSTANCES ALREADY SCHEDULED)

No items were considered.

14. OTHER MATTERS FOR CONSIDERATION

14.1 ITEM DELETED

15. MATTERS REFERRED BY THE MEDICINES EVALUATION COMMITTEE (MEC)

No items were considered.

16. MATTERS REFERRED BY THE MEDICINES CLASSIFICATION COMMITTEE (MCC) OF NEW ZEALAND

16.1 SEDATING ANTIHISTAMINES

16.1.1 DAY-NIGHT PACKS CONTAINING SEDATING ANTIHISTAMINES – BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENHYDRAMINE, DOXYLAMINE, PHENIRAMINE, PROMETHAZINE, TRIMEPRAZINE, TRIPROLIDINE

PURPOSE

The Committee considered the scheduling of sedating antihistamines in day-night packs.

BACKGROUND

The October 2003 NDPSC Meeting, when it foreshadowed amendments to sedating antihistamines entries for consideration at the February 2004 NDPSC Meeting, agreed to maintain the status quo of existing day-night cough/cold/flu preparations i.e. allow oral combination preparations containing sedating antihistamines without a sympathomimetic decongestant in Schedule 2 if formulated for the night time dose in a day-night product. Neither this Meeting nor subsequent discussions on sedating antihistamines appeared to have considered the possibility of the day and night doses presenting in separate immediate containers despite being in the same outer pack.

Schedule 2 currently captures both the day and night components of day-night packs of most sedating antihistamines. The night formulation, while needing to be combined with one or more other therapeutically active substances, does not require a sympathomimetic decongestant. This includes solid or liquid preparations of brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine and triprolidine. However, this currently only applies to solid preparations of trimeprazine (all liquid preparations of trimeprazine are Schedule 3 or Schedule 4).

An editorial issue (item 21.1.1) and the scheduling of sedating antihistamines for children < 2 years (item 16.1.2) were dealt with separately.

DISCUSSION

Members were advised that the June 2006 MCC Meeting considered a number of issues of interest to the NDPSC, including diphenhydramine in day-night packs. The Committee particularly noted:

- Medsafe received an application for a day-night pack containing diphenhydramine in the night-time dose. The proposed product was the first in which the sedating antihistamine in the night-time dose was presented in liquid form and in a separate primary container from the day-time dose.
- The concern of both Medsafe and the MCC was that once the night-time dose containing diphenhydramine was removed from the secondary container, it would be inappropriately classified on the primary container as a pharmacy-only medicine.
- The MCC felt that the product did not fulfil the intent of the classification as a pharmacy-only medicine and agreed that Medsafe should be asked to reword the Schedule entry to differentiate between solid dose forms containing day and night doses in the same platform and liquid day and night packs containing two primary containers, one of which contained a sedating antihistamine.
- MCC therefore has made the following recommendations:

- That diphenhydramine and other sedating antihistamines contained in the night time dose of day-night preparations should be pharmacy-only medicines only when in the same primary container.
- That the NDPSC should be recommended to harmonise with this requirement for sedating antihistamines.

The Committee noted an enquiry regarding a diphenhydramine product similar to the one discussed above **XXXXX** in a boxed duo pack. In responding to the enquiry, the Secretariat advised that while the night time **XXXXX** formulation would be Schedule 3 on its own, the boxed duo pack would be correctly labelled as a Schedule 2 product when the duo pack was sold as a single pack (and that the separate component bottles could not be sold separately).

Members also noted the following from the October 2005 NDPSC Meeting:

- It was noted that most of the Schedule 2 sedating antihistamines entries did not allow products intended only for night-time use which are not in a day-night pack. Members were advised that **XXXXX** was unable to find any day-night products where the night dose was labelled for use during the day.
- The Committee reiterated the June 2005 decision to restrict combination products containing a sedating antihistamine to Schedule 3 unless they were a day-night preparation with the sedating antihistamine only in the bed-time dose or if one of the other therapeutically-active substances were a sympathomimetic (other than pseudoephedrine). There was no record of any discussion regarding the possibility of having the day and night doses in separate immediate containers despite being in the same outer pack.

The Members were advised that an additional MCC concern was that both the proposed day and night formulations had the same volume and as a consequence of differing recommended daily dosage for day vs. night use, a consumer would use up the day product while a significant amount of the night-time formulation remained. A Member questioned whether at this stage the night product would revert to Schedule 3 as it was no longer in combination with a day formulation. Members agreed with the MCC that this situation was inappropriate. The Committee also noted that this situation was unlikely to occur with the current solid dose day-night products as these were presented in the same immediate container i.e. blister packaging strips containing a mix of both day and night doses, usually colour coded on the strip.

A Member questioned whether it was fair to limit the formulation type to non-liquids, and asserted that perhaps labelling would be sufficient to distinguish the night-time formulation when it was not in the same immediate container as the day-time formulation.

Another Member asserted that a Schedule 2 entry for day-night packs was only ever intended for products in which the day time and night time doses were in the same immediate container.

The Committee was advised by the Secretariat that due to receipt of the MCC Minutes after the posting of the pre-October 2006 NDPSC Meeting gazette notice, the issue of sedating antihistamines was not gazetted. The Members agreed that foreshadowing consideration at the February 2007 NDPSC Meeting would allow public consultation on limiting the day-night packs allowed in Schedule 2 to those where the day and night time doses are in the same immediate container.

OUTCOME

The Committee agreed to foreshadow an amendment to the Schedule 2 entries for some sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, pheniramine, promethazine, trimeprazine, triprolidine) which would restrict the inclusion of day-night packs by requiring that the day and night doses are in the same immediate container.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 2 - Amendments

BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DOXYLAMINE, TRIPROLIDINE – Amend entries to read:

[SUBSTANCE] when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing [substance] in the bed-time dose where the day and night doses are in the same immediate container,

except in preparations for the treatment of children under 2 years of age.

DIPHENHYDRAMINE, PROMETHAZINE – amend entries to read:

[SUBSTANCE] in oral preparations:

(a) in a primary pack containing ten dosage units or less, for the prevention or treatment of motion sickness; or

(b) when combined with one or more other therapeutically active substances when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing [substance] in the bed-time dose where the day and night doses are in the same immediate container,

except in preparations for the treatment of children under 2 years of age.

PHENIRAMINE – amend entry to read:

PHENIRAMINE:

(a) in eye drops; or

(b) when combined with one or more other therapeutically active substances in oral preparations when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing pheniramine in the bed-time dose where the day and night doses are in the same immediate container,

except in preparations for the treatment of children under 2 years of age.

TRIMEPRAZINE – amend entry to read:

TRIMEPRAZINE when combined with one or more other therapeutically active substances in solid oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing trimeprazine in the bed-time dose where the day and night doses are in the same immediate container,

except in preparations for the treatment of children under 2 years of age.

16.1.2 SEDATING ANTIHISTAMINES IN CHILDREN UNDER 2 YEARS OF AGE

PURPOSE

The Committee considered the outcome of the 34th Meeting of the MCC in respect to antihistamine use in children under 2 years of age.

BACKGROUND

The October 2002 TTHWP Meeting recommended that New Zealand harmonise with Australia the scheduling of antihistamine preparations combined with other active ingredients including codeine, paracetamol and pseudoephedrine using the following broad principles (TTHWP Decision 8/8):

(i) antihistamines and preparations with a significant potential for abuse be included in Schedule 4/Part 1;

(ii) single-active preparations of sedating antihistamines be included in Schedule 3/Part II; and

(iii) single-active preparations of non-sedating antihistamines and specified combination preparations of antihistamines be included in Schedule 2/Part III.

The October 2003 NDPSC Meeting agreed to foreshadow consequential amendments to the SUSDP to align scheduling with the registration status of existing products while maintaining consistency with the recommendations of TTHWP Decision 8/8.

The February 2004 NDPSC Meeting accordingly amended the SUSDP Schedule 2 entries as foreshadowed for sedating antihistamines such that the Schedule 2 entry for diphenhydramine and other oral sedating antihistamines, i.e. brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenylpyraline, doxylamine, pheniramine, promethazine, thenyldiamine, trimeprazine and triprolidine, were amended to address the concerns regarding their sedating effects. Consequently, preparations for the treatment of symptoms of coughs, colds or influenza when combined with a sedating antihistamine were classified as Schedule 2 when at least one of the other therapeutically active substances was a sympathomimetic decongestant or when in a day-night pack with the dose containing the sedating antihistamine was labelled for bed-time dose. This amendment was given effect from 1 September 2004.

The February 2005 NDPSC Meeting considered **XXXXX** proposal to amend the scheduling of diphenhydramine and re-instate in Schedule 2 two of its affected products containing diphenhydramine which were rescheduled to Schedule 3 because they did not contain a sympathomimetic drug. One was a single-active product containing diphenhydramine as cough suppressant and the other was a cough and cold preparation combined with dextromethorphan. **XXXXX** proposed that products for the treatment of

the symptoms of coughs, colds or influenza containing diphenhydramine that did not contain a sympathomimetic decongestant as one of the therapeutically active substances but combined with other active ingredients such as an antitussive or expectorant should remain in Schedule 2 while retaining hypnotic preparations in Schedule 3.

The Committee also noted that the November 2004 MCC Meeting had agreed to accept the broad principles of the NDPSC with regard to the classification of sedating antihistamines but raised a few issues which MCC thought were not considered by the NDPSC. The MCC advised that it had decided to delay the implementation of the scheduling amendments relating to antihistamines to allow a further round of public consultation on the proposed Schedule wording for each individual antihistamine. In light of the submissions received and in anticipation of the outcomes of the May 2005 MCC Meeting, the Committee agreed to review the scheduling of antihistamines at the June 2005 NDPSC Meeting.

The June 2005 NDPSC Meeting noted the outcomes of the June 2005 MCC Meeting when New Zealand agreed to harmonise with Australia on the scheduling of sedating antihistamines except for mepyramine, for which a separate recommendation had been proposed for consideration. On the grounds of harmonisation and public health concerns on the potential risks associated with the sedative effects of the antihistamines, the Committee confirmed that the scheduling of sedating antihistamines amended at the February 2004 NDPSC Meeting remained appropriate.

The October 2005 NDPSC Meeting considered a submission from the TGA's OTC Medicines Section which highlighted that night-time doses containing sedating antihistamines were not combined with a sympathomimetic and as such would not be included in Schedule 2. Furthermore, OTC highlighted that there were a number of combination sedating antihistamine products on the ARTG which contain a sympathomimetic or phenylephrine with or without paracetamol. However, because such products are indicated for the symptomatic treatment of conditions other than coughs, colds or flu, they still fell within Schedule 3 even if they had addressed the Committee's concerns regarding the sedation risks of formulations containing sedating antihistamines. The Committee concurred with points raised in OTC's submission and agreed to foreshadow an amendment to the sedating antihistamine Schedule 2 entries and remove references to indications. This foreshadowed decision would then allow all combination preparations containing a sympathomimetic decongestant (i.e. phenylephrine) to be considered Schedule 2 substances, irrespective of indications. In addition, the NDPSC referred cyclizine for the prevention of travel sickness to the TTHWP in light of MCC's advice that cyclizine has been reclassified to Restricted Medicine in New Zealand (i.e. Schedule 3) because of its sedation potential. Cyclizine is listed as Schedule 4 in Australia.

Furthermore, the October 2005 NDPSC Meeting also agreed to amend the wording of the entries for sedating antihistamines to clarify the Committee's intent in regards to the statement "2 years of age or less" which meant 2 years from the day of birth. This

statement would be replaced with "under two years of age" to avoid further misinterpretations.

DISCUSSION

At its 34th Meeting in June 2006, the MCC noted that it had earlier expressed concern that sedating antihistamines were available over the counter for children under two years of age. MCC had noted that some sedating antihistamines had been implicated in sudden death in this age group. There was also anecdotal and published evidence of misuse and abuse of these medicines in children. The Committee was unanimously of the view that sedating antihistamines should be used in this age group only under medical supervision. Members agreed that the NDPSC should be asked to harmonise on this recommendation, viz

- That sedating antihistamines should be classified as prescription medicines when indicated either singly or in combination for use in children under two years of age.
- That the NDPSC should be asked to harmonise on the above recommendation.

The Committee noted that changes to the scheduling of sedating antihistamines would impact on a range of products in the marketplace. It was also noted that despite many years of use, there had been no adverse incidents reported which might suggest that the current scheduling was not appropriate. Changes to scheduling without adequate evidence was undesirable. On the other hand, a Jurisdictional Member noted that reports of adverse events in regard to the use of promethazine, including reports of death, had only come to light in the last 2 years.

OUTCOME

The Committee agreed that further information should be sought from Medsafe, MEC and ADRAC.

The Committee agreed to foreshadow the consideration of scheduling of sedating antihistamines for use in children under two years of age to Schedule 4.

16.2 OSELTAMIVIR

PURPOSE

The Committee considered harmonising the scheduling of oseltamivir with New Zealand.

BACKGROUND

The October 2004 NDPSC Meeting considered an application that oseltamivir be rescheduled to Schedule 3. The Committee agreed to defer making a decision on this issue until the February 2005 NDPSC Meeting to allow input from **XXXXX** to be received.

The Committee further considered the proposal at the February 2005 NDPSC Meeting with consideration to the comments received from **XXXXX** The Committee considered that further information was required regarding the prophylactic use of oseltamivir and the potential for development of resistance. The Committee thus agreed to defer making a decision on this issue until this data was available and **XXXXX** were able to make a final recommendation.

At the July 2005 NDPSC Meeting the Committee was advised that MCC had received an application for reclassification of oseltamivir from prescription to restricted medicine for the treatment and prophylaxis of influenza in adults and adolescents. The MCC decided to retain the current scheduling for oseltamivir. The Committee agreed to defer the matter until final recommendation from **XXXXX** had been received.

The Committee re-considered the application at the October 2005 NDPSC Meeting with regard to the further information provided by **XXXXX** The Committee agreed that the current scheduling of oseltamivir was appropriate given:

- the concerns relating to the development of resistance to the drug
- concerns regarding the likelihood of misdiagnosis by pharmacists without accurate point-of-care tests or physical examination during non-pandemic periods.

At the February 2006 NDPSC Meeting the Committee considered whether States and Territories had appropriate mechanisms to allow pharmacists to supply Schedule 4 substances without prescription during either a localised outbreak or influenza pandemic. The Committee noted that such powers do exist at State, Territory and Commonwealth levels.

At the 34th MCC Meeting in June 2006, the MCC considered a further application for reclassification of oseltamivir from prescription to restricted medicine. The MCC recommended that pharmacists should be able to sell oseltamivir between the months of May and September for the treatment of influenza but not for prophylaxis

DISCUSSION

The June 2006 MCC Meeting agreed that oseltamivir should be supplied as an over the counter medicine with regard to the following conditions:

- That pharmacists should be able to sell oseltamivir between the months of May and September for the treatment of influenza but not for prophylaxis
- That uncontrolled internet sales of oseltamivir should not be permitted
- That Medsafe be asked to put in place the measures necessary to implement this recommendation

- That the NDPSC should be asked to harmonise on the seasonal availability of oseltamivir
- That the Institute of Environmental Science and Research (ESR) be asked to ensure that pharmacists as well as general practitioners would be advised about the occurrence of seasonal influenza.

During their consideration, MCC considered advice from two virologists who both supported OTC sales of oseltamivir once influenza had manifested in a community and who believed that that there was a very low frequency of resistance developing in response to substantial seasonal oseltamivir use. However, some MCC Members expressed concern regarding the potential overuse of the drug making it less effective in an influenza pandemic.

The MCC also considered the impact of misdiagnosis of influenza and concluded that little harm would come from inappropriate use of the drug.

The MCC also noted the following points:

- The company stated that it would monitor resistance as part of its **XXXXX** package.
- The ESR had expressed a strong desire for the establishment of a national resistance monitoring system. The MCC voiced its support for this.
- Vaccination should be regarded as first-line approach to prevent influenza. The company had agreed that it would not promote the product as an alternative to influenza vaccination. However, Members acknowledged that public perception often differed and this might have to be addressed.
- Availability over the counter during the influenza season would provide considerable consumer convenience.
- There was provision for over-the-counter supplies to be shut down in the case of a pandemic.

The MCC heard from the NDPSC Chair regarding the reasons why the NDPSC had opted not to make oseltamivir available as a Schedule 3 medicine. After discussion the MCC agreed that oseltamivir be made available as an over the counter item for the treatment of seasonal influenza between the months of May and September and that it should not be made available for prophylaxis. The MCC also requested that NDPSC reconsider its Schedule 4 scheduling of oseltamivir to harmonise with New Zealand.

If the Committee decided to foreshadow consideration of oseltamivir for the February 2007 NDPSC Meeting then the Secretariat would seek further advice from **XXXXX** prior to the Meeting.

The Committee was advised that due to the receipt of the MCC Minutes after the posting of the pre-October 2006 NDPSC Meeting gazette notice, the consideration of the scheduling of this item was not gazetted.

XXXXX informed the Committee of the reasons behind the MCC's decision to allow an exemption for the seasonal supply of a prescription only medication. The Member noted that the MCC considered a report on the issue of resistance developing with the use of oseltamivir. The report stated that there was little evidence of such resistance and that the possibility of it developing because of more widespread use of oseltamivir was not supported by the current available data. The Member also stated that New Zealand will be encouraging GPs to send in samples for testing for the development of resistance. The Member stated that, on the issue of misdiagnosis, the MCC was satisfied that a very simple questionnaire being run by pharmacists during the period of the exemption would give a positive predictive value in excess of 70% for the diagnosis of influenza. The MCC also felt that the issue of delayed diagnosis from use of this medication was no different from the delay in diagnosis experienced when a patient was using paracetamol or any over the counter cold and flu preparations. As the MCC was satisfied that safety profile was appropriate and that misdiagnosis was not a problem the MCC felt that the issue came down to how to make sure that the medication was not being imported and then re-exported for inappropriate use via internet sales and the wording of the prescription medicine entry was crafted to avoid this issue.

XXXXX pointed out to the Committee that current scheduling status of oseltamivir in New Zealand is as a prescription medicine but that there were exemptions in place which allow its supply without a prescription as stated in the prescription medicine entry for the substance. The Committee discussed the exemption mechanism by which oseltamivir was being supplied in New Zealand. The Committee also discussed whether any mechanisms existed in Australia to allow an exemption to supply a Schedule 4 medicine without a prescription. The Committee noted that supply of medications was a jurisdictional issue and thus, that the Committee had no role in issues of supply of medications.

The Committee recalled that the legislative mechanisms that exist in each jurisdiction to allow supply of a prescription medicine without a script were discussed at the February 2006 NDPSC Meeting. Members discussed whether, as the New Zealand entry for oseltamivir had not been down-scheduled and was still a prescription medication, the countries were harmonised and that the only difference between the countries was the issue of an exemption for supply which was an issue for the jurisdictions, not the Committee. A Member noted that under the Trans Tasman agency it was envisaged that New Zealand and the jurisdictions would have differences in supply of substances and that the purview of the Committee was to ensure harmonisation in scheduling, not supply. The Member also noted that, as both countries currently list the substance as a prescription only item, they were harmonised.

The Committee discussed whether there was a need to foreshadow consideration of the scheduling of oseltamivir for the February 2007 NDPSC Meeting. However, as the Committee noted that Australia was already harmonised with New Zealand in its scheduling of this substance, the Committee decided that there was no requirement to foreshadow a discussion of the issue.

OUTCOME

The Committee agreed that Australia was currently harmonised with New Zealand on the scheduling of oseltamivir given that the only change to the New Zealand classification was an exemption to do with supply of the medication and that such mechanisms of supply set down by jurisdictions had been duly explored at the February 2006 NDPSC Meeting. Thus it was concluded that the current scheduling of oseltamivir remained appropriate.

16.3 HYDROCORTISONE 0.5% IN COMBINATION WITH A LOCAL ANAESTHETIC

PURPOSE

The Committee considered harmonising the scheduling of hydrocortisone 0.5% with cinchocaine for rectal use with New Zealand.

BACKGROUND

Hydrocortisone and hydrocortisone acetate were first included in Schedule 3 at a concentration of 0.5% or less when present as the only therapeutically active substance at the August 1985 DPSSC Meeting. The August 1994 NDPSC Meeting considered an application that hydrocortisone and cinchocaine preparations for rectal use be rescheduled to Schedule 3.

After due consideration at the May 1995 NDPSC Meeting the Committee recommended that the Schedule 3 entry for hydrocortisone be amended to allow a topical combination containing cinchocaine for rectal use.

At the February 1999 NDPSC Meeting, hydrocortisone and hydrocortisone acetate (dermal use containing 0.5% or less hydrocortisone in packs containing 30 g or less of such preparation, with no other therapeutically active substance or an antifungal as the only other therapeutically active substance) were included in Schedule 2. The Schedule 3 entry was amended to include specific reference to suppositories. The November 1999 NDPSC Meeting included hydrocortisone in Appendix H of the SUSP, permitting the advertising of hydrocortisone for rectal use.

At the October 2005 NDPSC Meeting the Committee considered an application for rescheduling from Schedule 3 to Schedule 2 hydrocortisone acetate (in combination with an anaesthetic) for rectal use. After discussion the Committee agreed that the scheduling of hydrocortisone should not be amended due to concerns that consumers may sometimes have difficulty in differentiating between haemorrhoids and other conditions for which the use of a corticosteroid would be inappropriate. Also, concern was expressed that if used on infected skin, there is potential for any infection to be masked or exacerbated. The Committee also expressed concern that the safety data presented as part of the rescheduling application did not truly reflect the safety of the product for anorectal use as

it included all adverse events relating to hydrocortisone, regardless of route, dose or duration of treatment.

At the June 2006 NDPSC Meeting the Committee considered another application to reschedule hydrocortisone acetate (in combination with an anaesthetic) for rectal use. After due consideration of the new safety data presented the Committee agreed that the current scheduling of hydrocortisone and hydrocortisone acetate remained appropriate. Specifically, it was felt that the sponsor had again not adequately justified exactly what advantage there would be to the consumer, should this product be down-scheduled and therefore accessed without mandatory intervention of the pharmacist.

DISCUSSION

The June 2006 MCC Meeting agreed that hydrocortisone acetate (in combination with an anaesthetic) should be supplied as an over the counter medicine with regard to the following conditions:

- That the restricted medicine entry for hydrocortisone in rectal medicines should be amended to allow these to be sold as pharmacy-only medicines when in medicines containing 0.5% or less of hydrocortisone and when in combination with a local anaesthetic and in a quantity of not more than 30 millilitres per container or 12 suppositories per pack and in packs containing a warning:
    - against use in children
    - against recurrent use and need for medical advice if the condition persists
    - to seek medical advice in the event of rectal bleeding.
- That **XXXXX** be requested to consult with the sponsor company on a training protocol for sale of the product by pharmacy assistants.

During their consideration, MCC noted that both components are available at a lower level of classification when sold individually and only required to be a restricted medicine when sold in combination.

The MCC also considered the possibility of misuse of the product and the impact a change of classification would have on this.

The MCC agreed to ask **XXXXX** to consult with the sponsor company regarding developing a training protocol for the sale of the product by pharmacy assistants.

The MCC requested that the NDPSC reconsider its scheduling of hydrocortisone acetate (in combination with an anaesthetic) to harmonise with New Zealand.

The Committee was advised that due to receipt of the MCC Minutes after the posting of the pre-October 2006 NDPSC Meeting gazette notice, the consideration of the scheduling of this item was not gazetted.

The Committee noted that both of the active ingredients when contained as a single active ingredient in a preparation were scheduled as Schedule 2 medicines. A Member noted that these ingredients were available in the United Kingdom as a General Sales List (GSL) product for external haemorrhoids. Another Member noted that there were other rectal preparations available for sale as general sale items in Australia currently.

The Committee recalled that discussion from the June 2006 NDPSC Meeting had concluded that there was no significant safety issue to prevent down scheduling of the ingredients when in combination but that the Committee had concerns regarding the need for a pharmacist's intervention in the sale of the product. Specifically the concerns related to the storage conditions required for the product and the fact that this necessitated an interaction to access the product and that the sponsor had not adequately justified what advantage there would be to the consumer in this instance.

The Committee discussed the fact that there were no significant safety concerns and discussed the fact that patients would be able to answer questions regarding their condition just as easily from appropriate labelling as from a pharmacist.

OUTCOME

Members discussed the warning statements applied to the product by the MCC and whether these warnings were required to be applied to the Australian product. The committee noted that this issue would have to be referred to RASML. The Committee hence agreed to foreshadow consideration of the down scheduling of hydrocortisone for rectal use in combination with a local anaesthetic given the lack of safety concerns and to harmonise with New Zealand.

FORESHADOWED DECISION (for consideration at the February 2007 meeting)

Schedule 2 – amend entry

HYDROCORTISONE AND HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 0.5 per cent or less hydrocortisone:

(a) for dermal use in packs containing 30 g or less of such preparations; and

(i) Containing no other therapeutically active substance; or

(ii) an antifungal as the only other therapeutically active substance; or

(b) for rectal use, when combined with a local anaesthetic but no other therapeutically active substance **except** unscheduled astringents;

(i) in undivided preparation, in packs of 35 g or less; or

(ii) in packs containing 12 or less suppositories.

Schedule 3 – amend entry

HYDROCORTISONE AND HYDROCORTISONE ACETATE, but excluding other salts and derivatives, in preparations containing 1 per cent or less of hydrocortisone:

(a) for dermal use, in packs containing 30 g or less of such preparations; and

(i) containing no other therapeutically active substance; or

(ii) containing an antifungal but no other therapeutically active substance; or

(b) for rectal use, when combined with a local anaesthetic but no other therapeutically active substance **except** unscheduled astringents:

(i) in undivided preparations, in packs of 35 grams or less; or

(ii) in packs containing 12 or less suppositories,

except when included in Schedule 2.

Schedule 4 – amend entry

HYDROCORTISONE **except** when included in Schedule 2 or 3.

16.4 PARACETAMOL 665 MG TABLETS

PURPOSE

The Committee considered an MCC recommendation to harmonise on the requirement for Schedule 2/pharmacy-only tablets or capsules containing over 500mg and up to 665 mg of paracetamol to be in slow release form only.

BACKGROUND

The October 2001 TTHWP meeting agreed to a process leading to harmonisation of entries for paracetamol in 2004 based on foreshadowing scheduling changes arising from the handover by the NDPSC of Appendix F warning statements for therapeutic goods to the TGA.

The December 2001 MCC Meeting considered the classification of paracetamol 665mg. MCC had agreed to differ on the upper limit for OTC sale and had retained the 500mg per dose form upper limit. They had also agreed to increase pack sizes to 12.5 grams to harmonise with Australia.

New Zealand had advised that it was to review regulatory standards and labelling standards for paracetamol before further addressing the harmonisation of scheduling. In that regard, the TGA OTC Medicines Section advised that revised regulatory guidelines for paracetamol would be developed for the ANZTPA. The 'Required Advisory Statements for Medicine Labels" was issued in July 2004. On this basis, the TTHWP recommended that the scheduling of paracetamol 665mg be referred to MCC for consideration.

The June 2006 MCC Meeting reconsidered the classification of paracetamol 665mg in and agreed to harmonise with Australia for this product.

DISCUSSION

The Committee noted the following points from the Minutes of the June 2006 MCC Meeting:

- The MCC had earlier been concerned that possible confusion of 665mg slow release products with lower dose 500 mg products could result in overdosing. However, Members acknowledged that the 665 mg tablets had been available in Australia for approximately four years and over-dosing did not appear to be a problem.
- An ongoing concern was that emergency rooms might not be aware of slow release paracetamol products and therefore of the need to retest overdose patients with equivocal levels of blood paracetamol. Members agreed that they would like assurance from the company that a protocol for appropriate treatment would be provided for emergency rooms.
- Most Members agreed that there was benefit to consumers in having a slow release product three times daily to provide pain relief throughout the night rather than the usual four doses for 500 mg tablets.
- The MCC agreed to harmonise with Australia on the classification of 665mg paracetamol tablets and that the NDPSC should be asked to harmonise on the requirement for Schedule 2/pharmacy-only medicines over 500 mg and up to 665 mg per tablet or capsule to be in slow release form only.

Members were in favour of harmonising with New Zealand. A Member pointed out that using the term 'modified release' might inadvertently capture fast-releasing dosage forms. It was suggested that the Secretariat should consult the TGA approved terminology for medicines guidelines and find the appropriate wording. The Committee agreed to foreshadow a harmonisation decision on the appropriate wording at the February 2007 NDPSC Meeting. Out of session, the Secretariat consulted the TGA and relevant sources, Members agreed on the term 'slow-release'.

OUTCOME

The Committee agreed to foreshadow a decision to harmonise with the MCC on the requirement for Schedule 2/pharmacy-only tablets or capsules containing over 500 mg and up to 665 mg of paracetamol to be in slow release form only.

FORESHADOWED DECISION (for consideration at the February 2007 meeting)

Schedule 4 – amend entry

PARACETAMOL:

(a) when combined with aspirin, caffeine or salicylamide or any derivative of these substances **except** when separately specified in these Schedules;

(b) in slow release tablets or capsules containing more than 665 mg of paracetamol;

(c) in other tablets or capsules containing more than 500 mg of paracetamol; or

(d) in individually wrapped powders or sachets of granules each containing more than 1000 mg of paracetamol.

16.5 TRANEXAMIC ACID

PURPOSE

The Committee considered the scheduling of tranexamic acid in order to harmonise with New Zealand.

BACKGROUND

The February 2000 NDPSC Meeting:

- supported an application that tranexamic acid for the treatment of menorrhagia be rescheduled to Schedule 3 and that it also be included in Appendix H. This decision was made on the basis that:
- Schedule 3 would allow appropriate monitoring of safety in OTC use;
- that menorrhagia was a condition appropriate for OTC treatment under professional supervision;
- advertising would increase consumer awareness that this was a treatable condition; and
- there was a public health benefit associated with Schedule 3 availability and advertising.
- noted that treatment for menorrhagia could not be advertised under the current Therapeutic Goods Advertising Code, but that the sponsor would seek exemption from this restriction if the Committee approved inclusion in Appendix H;
- agreed also that tranexamic acid be included in Appendix F with Warning Statement 54: Seek medical advice before the first course of treatment.

The June 2006 NDPSC Meeting noted that New Zealand did not support harmonisation with Australia and consideration was deferred pending receipt of the Minutes of the June 2006 MCC Meeting.

DISCUSSION

The October 2006 NDPSC Meeting noted the minutes of the June 2006 MCC Meeting. In particular:

- New Zealand did not agree to harmonise with Australia based on safety concerns surrounding self-diagnosis:
- diagnostic testing (normally by ultrasound) was necessary to determine the cause of menorrhagia, which is not possible for an OTC medicine;
- potential masking of more serious conditions;
- inability to accurately diagnose the underlying cause of menorrhagia within the pharmacy,
- the New Zealand sponsor failed to provide a response during the consultation period regarding MCC's concerns about safety;
- no OTC product for this indication had been marketed in Australia;
- a request that NDPSC reconsider its Schedule 3 scheduling of tranexamic acid to harmonise with New Zealand's prescription only medicine classification.

The October 2006 NDPSC Meeting also noted that:

- **XXXXX**

OUTCOME

Based on New Zealand's safety concerns and the fact that there are no Schedule 3 products marketed in Australia, the Committee agreed to foreshadow harmonisation with New Zealand for consideration at the February 2007 NDPSC Meeting.

FORESHADOWED DECISION (for consideration at the February 2007 Meeting)

Schedule 3 – Delete entry

TRANEXAMIC ACID.

Schedule 4 – Amendment

TRANEXAMIC ACID.

17. MINUTES OF THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE

17.1 ITEM DELETED

18. MINUTES OF THE MEDICAL DEVICE EVALUATION COMMITTEE (MDEC)

No items were considered.

19. INFORMATION ITEMS (PHARMACEUTICALS)

19.1-19.3 ITEMS DELETED

19.4 DICLOFENAC

PURPOSE

The Committee noted a recent paper implicating diclofenac with an increased risk of heart attack.

BACKGROUND

An article "Cardiovascular Risk and Inhibition of Cyclooxygenase – A systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2" published in the *Journal of the American Medical Association* (12 September 2006) has raised questions over the safety of diclofenac and concluded that diclofenac may present similar risks to celecoxib, but unlike celecoxib, may be harmful at commonly used doses. In the article, a review of the regulatory status of diclofenac is suggested.

DISCUSSION

The Committee noted that TGA is currently reviewing the Cox 2 inhibitors and is aware of the recent JAMA article raising possible concerns over diclofenac.

OUTCOME

The Committee noted that the Cox 2 inhibitors were under review by the TGA and agreed to maintain a watching brief in relation to the possible link between cardiovascular risk and inhibition of cyclooxygenase. The Committee also noted that registration and scheduling would be further looked at once the full expert review was complete.

19.5 ORLISTAT

PURPOSE

The Committee considered the current media attention on the direct to consumer advertising of orlistat.

BACKGROUND

Orlistat is a potent, specific and reversible long-acting inhibitor of gastrointestinal lipases which are required for the systemic absorption of dietary triglycerides. It is used in conjunction with dietary modification and physical exercise in the management of obesity.

Orlistat was first considered at the November 1999 NDPSC Meeting, when it was included in Schedule 4 following a recommendation by the TTHWP. The May 2000 NDPSC Meeting noted that the December 1999 ADEC Meeting recommended the registration of **XXXXX** containing orlistat 120 mg for the treatment of obese patients with a body mass index (BMI) > 30, and overweight patients with a BMI > 27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet.

Separate submissions to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3 were considered at both the June 2002 and February 2003 NDPSC Meetings. The February 2003 submission also sought to have orlistat included in Appendix H. On both these occasions, the Committee decided that the information submitted by the sponsor did not provide adequate evidence to address the Committee's concerns in relation to its safety profile; to the necessity for medical assessment to determine a patient's suitability for treatment with orlistat; and to the view that therapeutic intervention should not be the first-line treatment for obesity.

The October 2003 NDPSC Meeting considered a third new submission to reschedule orlistat for the treatment of obesity from Schedule 4 to Schedule 3 without inclusion in Appendix H. The NDPSC agreed to reschedule orlistat from Schedule 4 to Schedule 3

for the treatment of obesity on the basis that the sponsor had provided adequate evidence addressing the Committee's previous concerns.

Both the February 2005 and June 2005 NDPSC Meetings considered two separate proposals to include orlistat in Appendix H of the SUSDP. The Committee did not support the proposal as Members were concerned that omission of information in advertising campaigns about the modest efficacy and reduction of efficacy long-term seen in the clinical trial setting and potential side effects of orlistat could potentially create a consumer demand based on unrealistic expectations of the product's effectiveness. Furthermore, the Committee remained concerned that branded advertising of orlistat would convey an inappropriate public health message that pharmacotherapy is the first-line treatment for obesity. The Committee was also of the view that branded advertising would make consumers less likely to be influenced by the pharmacist's assessment in determining whether the product is suitable for them. The Committee reaffirmed its position that consumers should be encouraged to undertake appropriate lifestyle changes as a first-line option to achieve safe, long-term weight loss.

At the February 2006 NDPSC Meeting, the Committee considered a new application from **XXXXX** The Committee noted additional information on a post-marketing surveillance study, media survey and consumer/market research, as well as the experience gained by pharmacists in screening and consulting patients on the suitability of orlistat for other conditions. The Committee also believed that the newly amended Therapeutic Goods Advertising Code (TGAC) which had been strengthened with regards to the advertising of weight loss products would ensure responsible and appropriate branded advertising of the orlistat product **XXXXX** by the sponsor. The Committee hence agreed to include orlistat in Appendix H on the grounds of potential public health benefit (Decision 2006/46-29). This decision was confirmed at the June 2006 NDPSC Meeting.

DISCUSSION

The Committee recalled that in 2004 **XXXXX** publicly criticised the decision to make **XXXXX** for weight control purposes available on the professional advice of a pharmacist claiming that it would potentially lead to use by inappropriate patients and the likely abuse of the product. **XXXXX** raised concerns about the safety of orlistat and considered that the wider availability of **XXXXX** as a Pharmacist Only Medicine would impart the wrong public health message. It was then **XXXXX** view that orlistat for the treatment of obesity should be available only under the supervision of a medical practitioner in order to ensure it is used appropriately. The NDPSC decided the initial (2004) concerns raised by **XXXXX** could be addressed adequately through the Product Information, Consumer Medicine Information and appropriate labelling. Additionally, pharmacists must comply with professional standards and codes of practice which require medicines to be supplied appropriately.

There had been recent media coverage on the advertising of **XXXXX** during the television programme Australian Idol. Both **XXXXX** and **XXXXX** had criticised the advertising of **XXXXX** during prime time TV. **XXXXX** had stated that advertising

XXXXX direct to consumers gave a misleading message and that it was a medication that shouldn't be allowed to be advertised direct to consumer. **XXXXX** had also commented that the decision to allow direct to consumer advertising needed to be reviewed, as must the decision allowing orlistat to be available without prescription. **XXXXX** believed that the advertising campaign was in breach of the TGAC. **XXXXX** argument was that the code prohibits the advertising of pharmaceuticals to people under the age of 18 and the core audience for the Australian Idol program is girls in the 13-17 year age group. **XXXXX** also expressed concern that the advertisements for **XXXXX** send the message to young women that taking a pill is a solution to weight problems rather than undertaking a balanced diet and exercise regimen.

The Committee noted that **XXXXX** had written to the Chair asking that the Committee reconsider the scheduling and Appendix H listing for orlistat. [**XXXXX** requested that advertising approval be revoked immediately and that orlistat be rescheduled to Schedule 4.

The Complaints Resolution Panel is a committee established to ensure compliance with the TGAC. This panel is part of the co-regulatory system of advertising and its role is to receive and consider complaints about advertisements for therapeutic goods which are published or broadcast in the mainstream print or broadcast media, or via the Internet. As a co-regulatory committee, the Complaints Resolution Panel is representative of peak stakeholder groups and its membership includes representatives from the ASMI and CHC, peak healthcare professional bodies (eg. Pharmacy Guild of Australia), consumer organisations (eg. ACA and Consumers' Health Forum) and government (represented by the TGA). In considering applications for advertising approval and complaints about advertisements, both the delegated approval officers and the CRP assess the advertisements for compliance with the Therapeutic Goods Advertising Code (TGAC).

XXXXX

The Secretariat informed the Committee that it had received a large number of emails from members of the general public asking that the Committee reconsider the scheduling and Appendix H listing for this product.

The Committee noted the role of the TGAC and the Complaints Resolution Panel in the co-regulatory system of advertising regulation and was mindful of not interfering with the activities of the Panel. The Committee also noted that the Complaints Resolution Panel was the body who had the jurisdiction to rule on whether advertisements breached the TGAC or not and to make such rulings was not the purview of this Committee.

The Committee was reminded of the current registered indications for orlistat by the **XXXXX** and that the request received was for the Committee to consider the current Appendix H listing and the current scheduling status of the product.

A Member informed the Committee that there had been a large number of anecdotal reports of patients for whom orlistat is not indicated seeking it from pharmacies and that

this had followed the advertising of the product. Another Member noted that this was anecdotal only and there was no documented evidence of this as a result of the products' inclusion in Appendix H.

A Member commented that, as consideration of Appendix H listing does take into account the wider regulatory system including the TGACC, the TGA registration system and target populations, it is appropriate to reconsider the Appendix H listing for orlistat and that, as the Committee is separate from the Complaints Resolution Panel, it does not need to be informed of the outcome of the Complaints Resolution Panel complaint is before it makes a decision on the appropriateness of the Appendix H listing of this substance. Another Member contended that the fact that a complaint had been made about the advertisement did not mean that there had been a failure in the process of Appendix H listing and thus a review of the Appendix H listing for this item should be considered carefully.

The Committee reviewed and considered the guidelines for Appendix H listing of substances which were disseminated to the Committee by the NCCTG. Members discussed whether the advertising of orlistat may have breached a number of these guidelines, including leading to patterns of inappropriate medication use, and the possibility that the goods may have been advertised for an indication other than that which is included in the Australian Register of Therapeutic Goods (ARTG).

A Member stated that, as the Committee has no new information at this time apart from the submission by **XXXXX** and the advertisement itself, it would not be appropriate for the Committee to review its scheduling decision based solely on these two pieces of information. The Member stated that an opportunity should be given to all interested parties to make submissions regarding this issue.

Members agreed that Appendix H listing for orlistat should be the subject of review and that this discussion should be foreshadowed to allow stakeholders to present new information and have input into the process.

XXXXX

OUTCOME

After discussion, the Committee agreed to foreshadow consideration of the current Appendix H listing of orlistat at the February 2007 NDPSC Meeting in order to give interested parties the opportunity to put forward submissions on the issue. Post-meeting, the Chair decided to also bring consideration of orlistat's current Schedule 3 status to the Committee for consideration at the February 2007 NDPSC Meeting.

19.6 ITEM DELETED

20. ITEM DELETED

21. AMENDMENTS TO THE SUSDP

21.1 EDITORIAL CHANGES & ERRATA

21.1.1 EDITORIAL CHANGES & ERRATA ARISING FROM SUSDP 21 AMENDMENT 1: (AZELASTINE, BROMPHENIRAMINE, CHLORPHENIRAMINE, DEXCHLORPHENIRAMINE, DIPHENHYDRAMINE, DIPHENYLPYRALINE, DOXYLAMINE, PROMETHAZINE, TRIPROLIDINE)

PURPOSE

The Committee considered editorial changes/errata arising from SUSDP 21 Amendment 1 (SUSDP 21/1).

DISCUSSION

Two emails were received from **XXXXX** advising of a number of possible errors in SUSDP 21/1:

Schedule 4 - Azelastine.

- The February 2006 NDPSC Meeting agreed to amend the Schedule 4 entry to read "AZELASTINE except when included in Schedule 3". **XXXXX** noted that there was no reference in this entry to the Schedule 2 entry for azelastine (for nasal use).
- **XXXXX** therefore proposed that the Schedule 4 entry should read "AZELASTINE **except** when included in Schedule 2 or 3".

Schedule 2 – Diphenylpyraline.

- **XXXXX** noted that an amendment to the Schedule 2 entry for diphenylpyraline was included in SUSDP 21/1 as a result of a June 2006 NDPSC Meeting decision. However, there was no Schedule 2 entry to be amended.
- The Committee had previously agreed (at the June 2005 NDPSC Meeting) to delete the Schedule 2 and Schedule 3 entries for diphenylpyraline because there were no Schedule 2 or Schedule 3 products in Australia or New Zealand. There has been no decision to reinstate the Schedule 2 (and/or Schedule 3) entries for diphenylpyraline subsequent to the June 2005 NDPSC Meeting.
- At the June 2005 NDPSC Meeting the Schedule 2 and Schedule 3 entries for another sedating antihistamine, thenyldiamine, were also deleted. **XXXXX** noted that the June 2006 NDPSC Meeting reconsidered a February 2006 decision to amend the Schedule 2 entry for thenyldiamine as part of a broader consideration of sedating

antihistamines. The June 2006 NDPSC Meeting agreed that, as it was not possible to amend a non-existent entry, to not include a Schedule 2 amendment for thenyldiamine in SUSDP 21/1.

- **[XXXXX** therefore enquired whether the Schedule 2 entry for diphenylpyraline in SUSDP 21/1 was a reinstatement or an amendment (i.e. if it was suppose to have been an amendment then by the thenyldiamine precedent it should be considered an error and not a valid entry).

Schedule 2 - Brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, promethazine and triprolidine.

- **XXXXX** advised that the Schedule 2 amendments in SUSDP 21/1 for some of the sedating antihistamines (brompheniramine, chlorpheniramine, dexchlorpheniramine, diphenhydramine, diphenylpyraline {discussed above}, doxylamine, promethazine and triprolidine) contained the generic term [substance] rather than the actual name of the sedating antihistamine. Clause (b) in the entries for these drugs states in a day-night pack containing [substance] in the bed-time dose. The entries for pheniramine and trimeprazine had the name of the drug in this clause of the entry.

Members were advised that an editorial issue for amidopyrine was dealt with separately under item 1.8.1.1.

DECISION 2006/48 - 22

The Committee agreed:

- That, as it was not possible to amend a non-existent entry, the Schedule 2 diphenylpyraline amendment in SUSDP 21 Amendment 1 (part of decision 2006/47 – 25) was not valid. The Members therefore agreed to delete this entry in SUSDP 21 Amendment 2.
- For clarity, to amend the Schedule 4 entry for azelastine in SUSDP 21 Amendment 2 to include a reference to the Schedule 2 azelastine entry.
- To correct the errata in some of the sedating antihistamines entries by replacing the generic term [substance] used in clause (b) of these entries with the specific substance name in SUSDP 21 Amendment 2.

Schedule 2 – Amendments

BROMPHENIRAMINE – amend entry to read:

BROMPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing brompheniramine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

CHLORPHENIRAMINE – amend entry to read:

CHLORPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing chlorpheniramine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

DEXCHLORPHENIRAMINE – amend entry to read:

DEXCHLORPHENIRAMINE when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing dexchlorpheniramine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

DIPHENHYDRAMINE – amend entry to read:

DIPHENHYDRAMINE in oral preparations:

(a) in a primary pack containing ten dosage units or less, for the prevention or treatment of motion sickness; or

(b) when combined with one or more other therapeutically active substances when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing diphenhydramine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

DIPHENYLPYRALINE – delete entry.

DOXYLAMINE – amend entry to read:

DOXYLAMINE when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing doxylamine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

PROMETHAZINE – amend entry to read:

PROMETHAZINE in oral preparations:

(a) in a primary pack containing 10 dosage units or less, for the prevention or treatment of motion sickness; or

(b) when combined with one or more other therapeutically active substances when:

(i) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(ii) in a day-night pack containing promethazine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

TRIPROLIDINE – amend entry to read:

TRIPROLIDINE when combined with one or more other therapeutically active substances in oral preparations when:

(a) at least one of the other therapeutically active substances is a sympathomimetic decongestant; or

(b) in a day-night pack containing triprolidine in the bed-time dose,

except in preparations for the treatment of children under 2 years of age.

Schedule 4 – Amendment

AZELASTINE – amend entry to read:

AZELASTINE **except** when included in Schedule 2 or 3.