The 35th Meeting of the Therapeutic Goods Committee (TGC) was held in Conference Room 1, TGA Building, Narrabundah Lane, Symonston on 14 October 2009, between the hours of 10 am and 4 pm.

Attendance:

Chairperson: Associate Professor Loraine Holley

Members: Mr David Clayton
          Mr Michael Gepp
          Dr Karen Hapgood
          Dr Geoffrey Higgins
          Mr Alan Leslie
          Professor Klaus Schindhelm
          Ms Anthea Steans
          Ms Diane Walsh
          Dr Meera Verma

Apologies: Nil

TGA officers: Ms Vivienne Christ
             Ms Hongxia Jin (part-meeting)
             Ms Libby Kerr (part-meeting)
             Dr Adrian Krauss (part-meeting)
             Mr Michel Lok (part-meeting)
             Dr Ruth Lopert (part-meeting)
             Dr Mark McDonald (part-meeting)
             Mr Andrew Muir (part-meeting)
             Dr David Sinclair (part-meeting)
             Mr Karl Skewes (part-meeting)
             Dr Glenn Smith (part-meeting)

Secretariat: Ms Margaret Joy
             Ms Lyn Lewis (Secretary)
AGENDA AND COMMITTEE ADMINISTRATION

OPENING OF MEETING

The Chairperson opened the Meeting at 10 am and welcomed Members and TGA staff. There were no apologies.

Members noted the Committee’s functions, composition and provisions relating to tenure of office as given in Regulation 34 of the Therapeutic Goods Regulations 1990 (the Regulations), and were reminded of the requirements of Regulation 39 of the Regulations relating to disclosure of interests.

Members submitted their completed Disclosure of Interest Declarations in accordance with Committee procedures. No conflicts of interest relevant to the agenda for this Meeting were declared.

The Committee agreed to vary the order of considerations to allow discussion of all medicine labelling matters in the afternoon session, and to facilitate the attendance of relevant TGA officers. The Agenda, as amended, was adopted.

MINUTES OF THE 34TH MEETING OF THE TGC

The TGC noted that the Resolutions and Minutes from the 34th Meeting of the Committee, held on 13 May 2009, were ratified out-of-session in accordance with usual processes and that key resolutions from that Meeting and a report for stakeholders were subsequently posted on the TGA internet site.

RESOLUTION:

The Therapeutic Goods Committee (TGC) NOTES that:

- the Minutes of the 34th Meeting of the TGC, held on 13 May 2009, were ratified out-of-session in July 2009 as a true and accurate record of that Meeting; and
- the documents Summary of Key Resolutions and Information for Stakeholders – Report on Meeting were published on the TGA website in June and July 2009 respectively,

in accordance with usual practice.

STATUS REPORT OF ACTION ARISING FROM PREVIOUS TGC MEETINGS

Members noted the report summarising the status of action arising from the 34th TGC Meeting. A number of the actions requested by the Committee had resulted in items for consideration at the present Meeting.

SUBCOMMITTEE REPORTS

Subcommittee on Biologicals

The TGC was advised that the second meeting of the Subcommittee on Biologicals was held in Canberra on Thursday 20 August 2009 and the third meeting of the Subcommittee had been held
via video/tele-conference on Tuesday 13 October 2009. Information on those meetings and progress in the development of standards for the new regulatory framework for biologicals would be provided under a later agenda item.

RESOLUTION:

The Therapeutic Goods Committee (TGC) NOTES that the Subcommittee on Biologicals has met twice since the last TGC Meeting, and that the Subcommittee is progressing its Terms of Reference.

Subcommittee on Packaging Requirements for Therapeutic Goods for Human Use

The TGC received the ratified Report of Meeting 2 of the Subcommittee, which had been held on 20 March 2009. It was noted that the TGA was progressing action items identified by the Subcommittee.

RESOLUTION:

The Therapeutic Goods Committee NOTES that:
- the report of Meeting 2 of the Subcommittee on Packaging Requirements for Therapeutic Goods for Human Use, which was held on 20 March 2009, has been ratified by the Subcommittee; and
- the Therapeutic Goods Administration is progressing action items identified by the Subcommittee.

STATUS REPORT ON ADDITIONAL DEFAULT STANDARDS UNDER THE ACT

The TGC was provided with an update on the status of changes to the Therapeutic Goods Act 1989 (the Act) which came into force on 1 July 2009 and gave recognition to the European Pharmacopoeia (Ph. Eur) and the United States Pharmacopeia-National Formulary (USP) as default standards in addition to the British Pharmacopoeia (BP). The TGC noted that the TGA had published a ‘Question and Answers’ document on its website which provided information for stakeholders on the additional default standards and their application by the TGA.

The TGC also noted the publication schedule for the BP, Ph. Eur and USP and the changes to the content of each pharmacopoeia expected as a result of forthcoming new editions or supplements. As recognition under the Act of new editions would now occur automatically, the TGC noted that this advance notice was necessary in order to allow identification of circumstances where a monograph or part thereof may not be suitable for adoption.

RESOLUTION:

The Therapeutic Goods Committee NOTES that amendments to the Therapeutic Goods Act 1989 to adopt the British Pharmacopoeia, the European Pharmacopoeia and the United States Pharmacopoeia-National Formulary as default standards for medicines and other therapeutic goods that are not medical devices took effect on 1 July 2009.
SUMMARY AND STATUS OF THERAPEUTIC GOODS ORDERS

The TGC noted the report on the status of Therapeutic Goods Orders (TGOs) made under the Therapeutic Goods Act 1989 included as a standing item in the agenda. Although no new TGOs had been made since the previous TGC Meeting, three proposed new TGOs were currently undergoing stakeholder consultation.

THERAPEUTIC GOODS ORDER NO. 80 CHILD-RESISTANT PACKAGING REQUIREMENTS FOR MEDICINES - ANNUAL REVIEW OF SCHEDULE 1 (MEDICINES TO WHICH THE ORDER APPLIES)

In recommending the making of Therapeutic Goods Order No. 80 Child-Resistant Packaging for Medicines (TGO 80) in 2008 to specify requirements for child-resistant packaging (CRP) for certain medicines, the TGC accepted the advice of its expert subcommittee that Schedule 1 to TGO 80, which listed those ingredients of medicines that triggered a requirement for CRP, should be reviewed annually.

The TGC was informed that, in order to gather information for the first annual review of Schedule 1 to TGO 80, a notice inviting interested stakeholders to submit relevant information had been posted on the TGA’s internet site on 25 August 2009 and a number of specific stakeholder organisations as well as TGA regulators had been invited to make submissions. The invitation listed a number of substances that had been identified previously by the TGC and/or TGA for inclusion in the first annual review. These included: angiotensin II antagonists, Azadirachta indica, glucosamine sulfate potassium chloride complex (GSPCC), imidazoline decongestants, methyl salicylate, and zolpidem. The invitation also invited stakeholders to identify other substances that may be of concern.

Responses to the invitation were received subsequently from: XXXXX; XXXXX; XXXXX; XXXXX; XXXXX; XXXXX; XXXXX; XXXXX; and Office of Non-Prescription Medicines (ONPM), TGA / Medicines Evaluation Committee (MEC).

The TGC noted:
- the majority of submissions related to the specific substances identified for review, with GSPCC being the focus of a number although no new information on this substance was provided;
- the submission from the XXXXX discussed the difficulties that some consumers experience in accessing medicines with CRP;
- the XXXXX supported the requirement for the proposed substances to require CRP with the possible exception of GSPCC and further discussion was provided in relation to that;
- the XXXXX identified one additional substance of concern for consideration by the TGC. That substance was chloral hydrate;
- the submission from XXXXX provided information on call records relating to the substances listed in the invitation; and
- comments from the pharmaceutical industry relating to GSPCC (XXXXX, XXXXX, XXXXX), imidazoline decongestants (XXXXX, XXXXX) and methyl salicylate (XXXXX).

The TGC also noted:
- the submission from ONPM relating to ingredients used in cough and cold medicines for children, which had resulted from recommendations made by the Medicines Evaluation Committee (MEC) in July 2009 relating to the availability, usage, packaging, scheduling and public awareness of these medicines; and
• a summary of new chemical entities (NCEs) approved by the TGA since Schedule 1 to TGO 80 was finalised in October 2005.

The TGC was requested to consider the information provided by stakeholders and other relevant information, and make an initial assessment of what substances (if any) should be included in a proposed amendment to TGO 80 for full consultation with stakeholders.

The TGC concluded as follows:

- **Angiotensin II antagonists** – although there had been little toxicity data available previously, this may no longer be the case; and as other classes of antihypertensive agent were captured already by TGO 80, there may be little reason to exclude angiotensin II antagonists. Angiotensin II antagonists were proposed as a possible addition to Schedule 1 to TGO 80.

- **Azadirachta indica** – although inclusion of *Azadirachta indica* in Schedule 1 to TGO 80 was largely an administrative action for consistency with the Poisons Standard, this proposal should be included in the stakeholder consultation.

- **Glucosamine sulfate potassium chloride complex (GSPCC)** – at the current time, there was no reason to amend the status of medicines containing GSPCC to require them to be packaged in CRP. The Committee requested however that an ongoing watch be maintained for reports of accidental poisoning with GSPCC.

- **Imidazoline decongestants** – for consistency with the recommendation made by MEC in relation to its review of cough and cold medicines, and the available evidence on toxicity and accidental ingestion by children, a proposal to require CRP on imidazoline decongestants should be included in the stakeholder consultation. The TGA was requested to investigate the availability of child-resistant closures for small volume dropper and spray bottles commonly used for eye drops and nasal decongestants.

- **Methyl salicylate** – a proposal to reduce, from 25 per cent, the concentration cut-off at which liquid preparations containing methyl salicylate required CRP should be included in the stakeholder consultation. For the purposes of the stakeholder consultation, the TGC agreed that no cut-off should be specified. The TGC also requested the TGA investigate the availability of child-resistant closures for tubes commonly used to package creams and other semi-solid preparations.

- **Zolpidem** – this substance, as well as the other “Z drugs” (zopiclone and zaleplon) with similar effects, should also be included in the stakeholder consultation as ‘benzodiazepine related drugs’.

- **Chloral hydrate** – this substance, which had been proposed by XXXXX, should be included in the stakeholder consultation on TGO 80 as a proposed addition to Schedule 1 on the basis of its potential toxicity.

In relation to ingredients of **cough and cold medicines**, the TGC noted that although TGO 80 already required a number of substances used in cough and cold medicines to have CRP, the following ingredients of cough and cold medicines currently did not require CRP:

- antitussives: dextromethorphan, pentoxyverine, pholcodine;
- expectorants/mucolytics: ammonium chloride, bromhexine, guaifenesin, ipecacuanha, senega and ammonia; and
- decongestants: oxymetazoline, xylometazoline.

As the TGA would be undertaking a consolidated consultation on all of the MEC recommendations relating to the regulation of cough and cold medicines, including the recommendation for CRP for these medicines, the TGC requested that it be provided with copies of those stakeholder comments received by the TGA that related to the proposal for CRP for all cough and cold medicines. The TGC advised that in order for it to consider whether amendment to TGO 80 to require CRP for
these substances was justified, the Committee would need to assess each substance against the
criteria given in the ‘Introduction’ to TGO 80. Information on toxicity in overdose would be
particularly relevant.

In relation to New Chemical Entities (NCEs) approved since Schedule 1 to TGO 80 was finalised
in October 2005, the TGC noted that:

- the following were captured by existing class entries in Schedule 1 to TGO 80 and, although
  not named in the Schedule, they would be required to have CRP by virtue of belonging to a
  named class:
    - Dabigatran - Antithrombotic agents,
    - Dasatinib - Antineoplastic agents,
    - Desvenlafaxine – Antidepressants,
    - Duloxetine – Antidepressants,
    - Erlotinib - Antineoplastic agents,
    - Lacosamide – Antiepileptics,
    - Lapatinib - Antineoplastic agents,
    - Levocetirizine – Antihistamines,
    - Nebivolol - Beta blocking agents,
    - Nilotinib - Antineoplastic agents,
    - Paliperidone – Antipsychotics,
    - Rotigotine - Anti-Parkinson drugs,
    - Sitagliptin - Oral blood glucose lowering agents,
    - Sorafenib - Antineoplastic agents,
    - Sunitinib - Antineoplastic agents, and
    - Zonisamide - Antiepileptics.

- inclusion of the following substances in Schedule 1 to TGO 80 did not appear warranted:
  Butoconazole, Darunavir, Entecavir, Etravirine, Maraviroc, Miglustat, Paricalcitol,
  Posaconazole, Raltegravir, Rosuvastatin, Telbivudine, and Tipranavir.

- the information currently available indicated that there may be justification for requiring
  medicines containing any of the following substances to have CRP: Aliskiren, Ambrisentan,
  Bosentan, Cilostazol, Deferasirox, Ivabradine, Lanthanum, Lenalidomide, Prasugrel,
  Sitaxentan, Solifenacin, and Varenicline. These substances should be identified as possible
  additions to Schedule 1 to TGO 80 and undergo consultation to obtain further relevant
  information and stakeholder views on their inclusion.

Noting that regular review of Schedule 1 to TGO 80 was important in ensuring that the Order
remained a useful tool in preventing accidental poisoning in children, the TGC was disappointed
that little substantive information on NCEs and other identified substances had been provided for
consideration. The TGC also noted the scant information provided by XXXXX and the limitations
of the data that was available.

The TGC discussed strategies for obtaining relevant information on NCEs at an early stage in a
medicine’s life, and requested the TGA to explore whether assessment of safety in children
following accidental ingestion could be made in conjunction with the registration evaluation. It also
was suggested that other expert committees, such as the Australian Drug Evaluation Committee and
MEC should be requested to consider the need for CRP for NCEs at the time of consideration for
registration.

In relation to lack of comprehensive data on poisoning incidents, the Committee noted reported
shortcomings in data collection such as the lack of a comprehensive national database with the
ability to integrate data from different sources (e.g. PICs, hospitals, Coroner’s reports). The TGC
considered that it would be worthwhile for the TGA also to explore, with PICs for example, mechanisms for obtaining more comprehensive information.

RESOLUTION:

1. The Therapeutic Goods Committee (TGC) RECOMMENDS that the Therapeutic Goods Administration (TGA) consult with stakeholders on the proposal that Schedule 1 to Therapeutic Goods Order No. 80 Child-Resistant packaging Requirements for Medicines (TGO 80) be amended to:

   (a) include a new class entry for ‘Angiotensin II Antagonists’, with the following substances listed as examples: candesartan, eprosartan, irbesartan, olmesartan, telmisartan, and valsartan;

   (b) include the following additional examples for classes already included in Part 1 to Schedule 1:

      - Antidepressants – desvenlafaxine, duloxetine
      - Antiepileptics – lacosamide, zonisamide
      - Antihistamines – levocetirizine
      - Antineoplastic agents – dasatinib, erlotinib, lapatinib, nilotinib, sorafenib, sunitinib
      - Anti-Parkinson drugs – rotigotine
      - Antipsychotics – paliperidone
      - Antithrombotic agents – dabigatran, rivaroxaban
      - Beta blocking agents – nebivolol
      - Oral blood glucose lowering agents – sitagliptin;

   (c) re-title the existing class entry for ‘Benzodiazepine Derivatives’ as ‘Benzodiazepine Derivatives and Benzodiazepine Related Drugs’ and include the following substances as additional examples: zolpidem, zopiclone and zaleplon;

   (d) include new individual entries for:

      - aliskiren
      - ambrisentan
      - *azadirachta indica* in preparations for human dermal use
      - bosentan
      - chloral hydrate
      - cilostazol
      - deferasirox
      - ivabradine
      - lanthanum
      - lenalidomide
      - prasugrel
      - sitaxentan
      - solifenacin
      - varenicline; and

   (e) amend the existing individual entry for methyl salicylate in liquid preparations to remove the concentration cut-off below which child-resistant packaging is not required.

2. The TGC:

   (a) NOTES:

   (i) the stakeholder consultation soon to be undertaken by the TGA on a series of proposed changes to requirements for medicines for the treatment of the symptoms of cough and cold in children, and that the
proposals on which comment is to be sought in that consultation include a recommendation that, commencing on 1 July 2010, all over-the-counter cough and cold medicines should be marketed in containers with child-resistant closures;

(ii) that TGO 80 already requires a number of substances used in cough and cold medicines to have child-resistant packaging, but the following additional substances may be affected:

- Antitussives - Dextromethorphan, Pentoxyverine, Pholcodine
-Expectorants/Mucolytics - Ammonium chloride, Bromhexine, Guaifenesin, Ipecacuanha, Senega and ammonia
- Decongestants - Oxymetazoline, Xylometazoline; and

(b) REQUESTS that the TGA provide, for consideration by the TGC, responses to the consultation that are relevant to the consideration of requirements for child-resistant packaging of cough and cold medicines, together with supporting data.

3. The TGC REQUESTS that the TGA investigate the availability of child-resistant closures for small volume dropper and spray bottles as commonly used to package eye drops and nasal decongestants, and for tubes commonly used to package creams and other semi-solid preparations.

4. The TGC RECOMMENDS that the TGA explore whether assessments of safety in children following accidental ingestion can be made in conjunction with the evaluation of new chemical entities for registration, in order to allow the TGC to make appropriately informed packaging recommendations at the earliest possible time.

UPDATE ON MEDICINE LABELLING MATTERS PREVIOUSLY CONSIDERED BY TGC

The TGC was provided with advice on the course of action proposed by the TGA to progress amendments to Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) that had been recommended by the Committee at its 34th Meeting (May 2009), as well as any further amendments to TGO 69 recommended at the current Meeting, including the conduct of stakeholder consultation.

The TGC recalled that, at its 34th Meeting, it had considered and made recommendations relating to the labelling of transdermal patches, the inclusion of bar codes on medicine labels, units of potency, declaration of excipients, and prominence of active ingredient names. These recommendations had, in large part, resulted from proposals included in a draft Therapeutic Goods Order on medicine labelling [Draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines - TGO 79 (draft)] which had undergone stakeholder consultation in early 2008 and which, following consideration of stakeholder comments, the TGC had concluded should not be implemented in the proposed form. Instead, the TGC had identified a number of specific initiatives that warranted further consideration for application as possible amendments to TGO 69.

The TGC was now informed that, in view of the number of proposed amendments to TGO 69 that required stakeholder consultation, the TGA considered that the most efficient process for this would be for single stakeholder consultation to be used to seek comment on all labelling proposals. As further labelling matters were yet to be considered, the TGA proposed to hold over the consultation until this had been completed.
The TGC was also informed of the intention of the TGA to develop an industry survey aimed at eliciting information on costs associated with various labelling changes affecting medicines to complement the stakeholder consultation. It was hoped that this survey would assist in the required analysis of the potential impact on business of changes to requirements for the labelling of medicines.

RESOLUTION:

The Therapeutic Goods Committee (TGC):

1. NOTES:
   (a) the intention of the Therapeutic Goods Administration (TGA) to conduct a single stakeholder consultation addressing all proposed amendments to Therapeutic Goods Order No. 69 General requirements for labels for medicines, and
   (b) this consultation will follow finalisation of the TGC’s consideration of labelling matters that were identified by the Committee at its 33rd Meeting during consideration of stakeholder comments on the draft Therapeutic Goods Order on medicine labelling [Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (TGO 79) (draft)].

2. SUPPORTS the conduct by the TGA of an industry survey aimed at developing a schedule of cost estimates associated with various labelling changes affecting medicines.

MEDICINE LABELLING MATTERS REFERRED BY TGA REGULATORS - Vitamin A and Retinol Equivalents

The TGC was requested to consider a proposed amendment to subclause 4(13) of Therapeutic Goods Order No.69 General requirements for labels for medicines (TGO 69) to stipulate that vitamin A should be expressed in terms of “micrograms retinol equivalents” rather than simply “retinol equivalents”, and amendment of subclause 3(1)(c) of TGO 69 to state that the requirements of that subclause did not apply to the expression of vitamin A as outlined in the amended subclause 4(13).

The TGC noted that subclause 4(13) had been amended in April 2009, following an earlier Committee consideration, to change the units of measurement for vitamin A from International Units (IU) to retinol equivalents (R.E.). It had since become apparent to the TGA that the appropriate units specified in subclause 4(13) should have been “micrograms retinol equivalents (R.E.)” as the warning statement required by the document Required Advisory Statements for Medicine Labels (RASML), which advised of the potential for large doses of vitamin A to cause birth defects, referred to micrograms retinol equivalents. Use of different units for the warning statement and the statement of quantity or proportion of active ingredient potentially would be confusing for consumers.

The TGC noted the consequential need for amendment to subclause 3(1)(c) of TGO 69, which otherwise would prevent the use of micrograms to express the quantity of vitamin A in a medicine where the amount exceeded 1000 micrograms, and recommended that the TGA should consult with stakeholders on both proposed amendments to TGO 69.
RESOLUTION:

The Therapeutic Goods Committee RECOMMENDS that Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) be amended in the following manner:

- the term “retinol equivalents” appearing in subclause 4(13) of TGO 69 be amended to read “micrograms retinol equivalents”, and
- subclause 3(1)(c) of TGO 69 be amended to clarify that the requirements of that subclause do not apply to the expression of quantity or proportion of vitamin A as specified in subclause 4(13).

MEDICINE LABELLING MATTERS REFERRED BY TGA REGULATORS - Trace Elements as Mineral Supplements

The TGC was requested to consider a proposed amendment to subclause 4(12) of Therapeutic Goods Order No.69 General requirements for labels for medicines (TGO 69) to clarify requirements relating to the expression of quantity of trace elements present in salt form in supplement preparations.

Subclause 4(12) of TGO 69, dealing with the expression of the quantity or proportion of active ingredient in medicines, was noted to state “for preparations containing trace elements as salts intended as mineral supplements - as the quantity of the element with the name of the salt being indicated”. The TGA’s Office of Complementary Medicines (OCM) had proposed that subclause 4(12) be amended to “for preparations intended as supplements that contain trace elements as salts - as the quantity of the element with the name of the salt being indicated”. This request was a consequence of situations in which labels of listed medicines failed to declare the quantity of trace element present in terms of the element and this had been justified by the sponsor through claims that the trace element was not intended as a mineral supplement despite the overall presentation of the medicine, or explicit label statements, that the medicine was intended for use as a supplement.

The TGC advised that, as there were potentially a number of different salts which could be used as the source of a single element, labels which expressed the quantity of element present in terms of the salt potentially could be confusing for consumers and may lead consumers to believe a medicine contained more of the trace element than it actually did. This would make comparison between medicines difficult.

The TGC supported the proposed amendment and therefore resolved:

RESOLUTION:

The Therapeutic Goods Committee:

1. CONFIRMS that the intention of the requirement given in subclause 4(12) of Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) is that the quantity of trace element present as an active ingredient in any supplement preparation be expressed in terms of the quantity of the element present, with the name of the salt being indicated, irrespective of the intended purpose of the particular trace element.

2. RECOMMENDS that:
   (a) subclause 4(12) of TGO 69 be amended to clarify this intention, and
MEDICINE LABELLING MATTERS REFERRED BY TGA REGULATORS - Expressions of Potency

The TGC was requested to clarify the intention of the recommendation made by the Committee at its 34th Meeting that Therapeutic Goods Order No.69 *General requirements for labels for medicines* (TGO 69) should be amended to require that, where potency units were used on labels as a measure of activity, the potency must be expressed in terms of International Units (IU) as established by the World Health Organization.

This recommendation had resulted from concern held by the TGC over the potential for adoption of multiple default pharmacopoeias to result in some labelling problems. A particular concern related to the possibility of statements of potency appearing on the label of some biological products being expressed in USP Units, rather than metric or IU. The consequence of this could be the labelling of like medicines in different units (USP or IU / metric), which would be confusing for both health professionals and consumers and have adverse outcomes in clinical practice.

The TGC was now advised that the proposed amendment to TGO 69, which had been supported by the Committee at its 34th Meeting, would impact unintentionally on a number of biological products which did not use IU as standard units. These were mostly listable ingredients which used alternate measures of potency such as Acid Lacatase Units (ALU), Cellulase Units (CU) and Hemoglobin Units on the Tyrosine Basis (HUT).

In view of the complexity of expressions of potency, the TGC agreed that there was need for further consideration to be given to the form of an appropriate amendment to TGO 69 that would achieve the outcome sought in previous discussions. In the interim, clarification of the intention of the Committee’s recommendation was suggested as being useful.

The Committee noted that the issue of expression of enzyme activity and conflicts with the current requirements of TGO 69 would need to be further explored by the TGA. Consideration of that matter would need to be undertaken at a later time, separate to the current consideration.

RESOLUTION:

The Therapeutic Goods Committee (TGC):

1. NOTES the recommendation made by the TGC at its 34th Meeting that Therapeutic Goods Order No. 69 *General requirements for labels for medicines* (TGO 69) should be amended to require that, where potency units are used on labels as a measure of activity, the potency must be expressed in terms of International Units (IU) as established by the World Health Organization, and that the Therapeutic Goods Administration should consult with stakeholders on an amendment to TGO 69 that would have this effect.

2. ADVISES that the intention of this recommendation was to ensure that where both International Units (IU) and United States Pharmacopeia Units (USP Units) exist as a measure of potency for a substance then, for patient safety reasons and to ensure consistency in labelling, TGO 69 should require the label to declare the potency in terms of International Units (IU) only.
MEDICINE LABELLING MATTERS REFERRED BY TGA REGULATORS - Update to Edition of Required Advisory Statements for Medicine Labels (RASML) referenced in Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69)

The TGC was requested to note the stakeholder consultation undertaken by the TGA in July-August 2009 on a proposed update to the document Required Advisory Statements for Medicine Labels (RASML), which was defined in Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69), and to advise on whether an amendment should be made to TGO 69 to adopt the updated version of RASML (Update 5.0).

The TGC noted the current legislative requirement for TGO 69 to refer to a defined version of RASML, and hence the repeated need for consideration of an amendment to TGO 69 following publication of each new version. This specific difficulty however would be overcome in the near future as a consequence of the passage by Parliament of the Therapeutic Goods Amendment (2009 Measures No 2) Bill 2009 which was awaiting Royal Assent from the Governor General.

The TGC was informed that although Update 5.0 to RASML had been finalised by the TGA, it had not yet been gazetted or published on the TGA internet site. Rather, the intention of the TGA was to gazette Update 5.0 early in 2010, to coincide with the effective date proclaimed for the related amendments to the Act. That date had not yet been determined.

The TGC noted the advice that the TGA had undertaken the necessary consultation on the proposed revisions to RASML, and that stakeholder comments had been duly considered. It also was noted that the TGC’s role was to consider the principle of whether TGO 69 should be amended to refer to the most recent version of RASML rather than considering or endorsing substance-specific warning statements.

The TGC concluded that the definition of RASML contained in TGO 69 should be amended to refer to the new version of RASML once published, but noted the need for this proposed amendment to TGO 69 to also undergo stakeholder consultation.

RESOLUTION:

The Therapeutic Goods Committee (TGC):

1. NOTES that:
   (a) the definition of Required Advisory Statements for Medicine Labels (RASML) contained in Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) currently refers to the September 2008 version of RASML, and
   (b) the Therapeutic Goods Administration (TGA) undertook stakeholder consultation in July-August 2009 on a proposed update to the September 2008 version of RASML.

2. RECOMMENDS that:
   (a) subject to gazettal by the TGA of the updated version of RASML, the definition of ‘Required Advisory Statements for Medicines’ contained in clause 2 ‘Interpretation’ of TGO 69 should be amended to refer to the updated version of RASML; and
(b) this proposal to amend the definition of ‘Required Advisory Statements for Medicines’ contained in TGO 69 should be included in the stakeholder consultation to be undertaken by the TGA on all proposed amendments to TGO 69 resulting from TGC recommendations.

OTHER MEDICINE LABELLING MATTERS – Batch and Expiry Dating of Plastic Ampoules

Batch and expiry dating of plastic ampoules had been identified by the TGC for further consideration as a result of the proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)].

The TGC noted a comparison of current (TGO 69) and proposed [TGO 79 (draft)] labelling requirements relating to batch and expiry dating of plastic ampoules and the perceived problems with TGO 69 requirements that were being addressed through TGO 79 (draft). These included a difference between requirements for the same size plastic ampoules based on whether or not a connecting strip was broken when an ampoule was detached, and the absence of a requirement for an expiry date on some injections.

The TGC also noted the detailed considerations leading to development of TGO 79 (draft), including the considerations undertaken by the Joint Interim Committee on Trans Tasman Labelling Requirements for Medicines (JECLM). In particular, the JECLM had commented that in relation to plastic ampoules, irrespective of presentation, it was possible to separate ampoules by cutting through connecting strips without breaking the seal, and this was common practice. JECLM therefore advised that the batch number should appear on the individual ampoules rather than the connecting strip. Further to this, JECLM had advised that the expiry date should be required together with the batch number.

The TGC reviewed relevant stakeholder comments, of which there were only two. XXXXX raised the issue of expiry dates for light sensitive products being invalidated if the ampoules were removed from protective intermediate foil packaging and XXXXX commented on the difficulty of including all required information on the label of injections with nominal volume 2 mL or less.

The TGC agreed that there appeared to be justification for amendment to subclause 3(17) of TGO 69 which specified requirements for the labelling of plastic ampoules, and therefore recommended as follows:

RESOLUTION:

The Therapeutic Goods Committee RECOMMENDS that:

1. for safety reasons, the batch number displayed on plastic ampoules which are joined to a connecting strip should appear on the ampoule itself rather than the connecting strip, irrespective of whether the seal on the ampoule is broken when an ampoule is detached.

2. for safety reasons, all plastic ampoules should be required to display the applicable expiry date together with the batch number.

3. subclause 3(17) of Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69), relating to requirements for plastic ampoules, should be amended to adjust the nominal volume at which concessions for ampoules joined
to a connecting strip apply, to extend these to ampoules with a nominal volume of
precisely 5 millilitres.

4. provisions for plastic ampoules with nominal volume of 5mL or less, and which are
not joined by a connecting strip, need not be included in subclause 3(17) of TGO
69.

5. at the present time reformating of subclause 3(17) of TGO 69 to improve clarity,
as proposed in the consultation document Therapeutic Goods Order No. 79
General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)], is
unwarranted.

OTHER MEDICINE LABELLING MATTERS - Expression of Quantity or
Proportion of Active Ingredient in Transdermal Patches

The proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the
Labelling of Medicines [TGO 79 (draft)] relating to the expression of the quantity or proportion of
active ingredients in transdermal patches had previously been identified by the TGC for further
consideration as a potential safety issue.

The Committee noted that TGO 69 currently required the label of transdermal patches to declare the
quantity of the active ingredient released in a stated time, whereas TGO 79 (draft) proposed that this
should be amended to require both the total quantity of the active ingredient in each patch and the
quantity of the active ingredient released in a stated time to be declared.

The TGC noted the detailed considerations leading to development of proposals included in
TGO 79 (draft), including the considerations and consultations undertaken by the Joint Interim
Committee on Trans Tasman Labelling Requirements for Medicines (JECLM). While recognising
that the delivery rate was the important consideration in prescribing transdermal patches, the
JECLM had considered there was a need for information on the total content of active ingredient in
each patch to be given on the label.

The TGC reviewed relevant comments received from stakeholders in response to the consultation
on TGO 79 (draft). Comments from three stakeholders were relevant:

- XXXXXX claimed that inclusion of both the total quantity of active and the quantity of active
  released in a stated time would be confusing for consumers as there may be no direct
  relationship between these expressions;
- XXXXXX responded that inclusion of both the rate of release and the total content would
  potentially cause confusion; and
- XXXXXX supported the proposal in principal but had reservations in relation to transdermal
  patches containing Schedule 8 (Controlled Drugs) medications, such as fentanyl, or
  buprenorphine. As up to 80% of a drug could remain in a transdermal patch after use,
  labelling with the total content of drug would highlight an abuse potential that patients may
  not previously have been aware of.

The TGC considered that the arguments put forward by stakeholders were sound and agreed that,
for transdermal patches, rate of release was the most appropriate way in which to express content of
active ingredient. The Committee considered that there was not sufficient justification at the present
time to amend TGO 69 to require the labels of transdermal patches to also declare the total amount
of active ingredient in each patch.
The TGC also noted that this consideration was separate and distinct from that relating to the inclusion of identifying information on the patch itself, which had been considered at the Committee’s previous Meeting. However the need for consistency between markings indicating strength appearing on the actual patches and the expression of quantity of active ingredient on the container and primary pack labels was stressed.

RESOLUTION:

The Therapeutic Goods Committee:

1. NOTES:
   (a) the proposal included in the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)] for labels of transdermal patches to declare the quantity of active ingredient in each patch both as the total quantity of the active ingredient in each patch, and the quantity of the active ingredient released in a stated time; and
   (b) that this proposal originally arose in the context of the new labelling order being developed for application under the proposed, but now postponed, joint Australia and New Zealand regulatory scheme for therapeutic goods; but

2. RECOMMENDS that, at this time, there is insufficient justification to amend Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) to impose this new requirement for the labelling of transdermal patches.

OTHER MEDICINE LABELLING MATTERS - Expression of Quantity or Proportion where Active Ingredient is a Herbal Extract

The proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)] relating to the expression of content where the active ingredient was an herbal extract had been identified previously by the TGC for further consideration.

Noting now that the TGA was yet to complete its consultation on proposed changes to regulatory arrangements for herbal and homoeopathic medicines, and proposals for label changes would be dependent on that, the TGC concluded that it was premature to implement changes to labelling requirements for medicines containing ingredients derived from herbal extracts at this time. Instead it was agreed that the matter should be set aside for future consideration.

RESOLUTION:

The Therapeutic Goods Committee RECOMMENDS that consideration of proposed amendments to labelling requirements for herbal medicines, as given in the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)], including the expression of quantity where an active ingredient is a herbal extract, should be set aside for future consideration in the broader context of the regulation of herbal medicines.
OTHER MEDICINE LABELLING MATTERS – Route of Administration for Injections and Other Medicines contained in Ampoules

Labelling of injections and other medicines presented in ampoules with the approved route of administration had been identified by the TGC for further consideration as a result of the proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)].

The TGC noted that TGO 69 currently only required the route of administration to be declared on the labels of some ampoules - injections (other than large volume injections), live vaccines and other medicines presented in plastic ampoules. A number of other types of medicines were presented in ampoules (e.g. some homoeopathic medicines for oral administration, and inhalations such as XXXXX) but the labels of these were not required to state the route of administration. This was considered to be a potential safety issue, with the possibility that consumers or health professionals would assume that presentation in an ampoule meant that the medicine was to be injected.

In contrast, TGO 79 (draft) had proposed a requirement for the label of all medicines contained in ampoules, irrespective of whether or not the medicine was an injection, to include a statement of the approved route of administration for the medicine.

The TGC now noted that no specific comments relating to this proposal were received from stakeholders in response to the consultation on TGO 79 (draft). The TGC therefore resolved as follows:

RESOLUTION:

The Therapeutic Goods Committee RECOMMENDS that, for safety reasons, Therapeutic Goods Order No. 69 General requirements for labels for medicines should be amended to require the label on all medicines presented in ampoules to state the approved route(s) of administration for the medicine.

OTHER MEDICINE LABELLING MATTERS – Legibility Requirements including Colour Contrast and Embossing/Debossing

Label presentation and the issue of colour contrast had been identified by the TGC previously for further consideration as a result of the stakeholder consultation on draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)].

Problems with the legibility of embossing/debossing on labels were raised in a number of stakeholder submissions, and also had resulted in a number of complaints to the TGA from consumers and health professionals, particularly in relation to the visibility and legibility of batch and expiry details. The TGC reviewed relevant comments received from stakeholders.

XXXXX suggested that there should be no need for colour contrast to be specified as this would be addressed by the requirement for label particulars to be ‘clearly visible’ and in ‘legible characters’. XXXXXX welcomed clarification relating to colour contrast and durability of labels.

A number of professional organisations (XXXXX, XXXXX, XXXXX, XXXXX) held like views and comments focussed on difficulties that consumers and health professionals have reading embossed/debossed characters unless there was a contrasting colour and the potential for embossing
of expiry and batch details to contribute to the inadvertent supply and consumption of expired medicines and difficulty in identifying recalled products.

The TGC noted that the issue of colour contrast and embossing has been considered previously both by TGC and the Joint Interim Committee on Trans Tasman Labelling Requirements for Medicines (JECLM):

- the TGC, in 2004, as part of the stakeholder consultation on medicine label improvements to assist product recall, with one proposal being that TGO 69 be amended to improve the visibility and legibility of batch numbers and expiry dates by prohibiting the use of embossing and requiring the use of colour contrast for display of this information. Numerous responses from industry had opposed the proposal, with grounds including the world-wide acceptance of this practice by regulatory authorities and technical limitations to printing on some types of packaging. The TGC did not progress the proposal further in view of the imminent formation of the JECLM.

- the JECLM, as part of its discussions in developing a draft labelling Order for the proposed, but subsequently postponed, joint Australia New Zealand regulatory scheme for therapeutic goods. JECLM noted that, for some forms of packaging such as blister trays and tubes, embossing was the only feasible method of including batch and expiry details, and while ink could be used more easily on cartons, legibility was the over-riding consideration. JECLM concluded that, at that time, it was not feasible to prohibit embossing or debossing of batch and expiry details or to mandate inked embossing.

Notwithstanding previous considerations and given that, despite the requirement of TGO 69 for all label information to be clearly visible and legible, the TGA continued to receive complaints from consumers and health professionals concerning the visibility and legibility of batch and expiry details, the TGC agreed that there was justification for a proposal to amend TGO 69 to introduce a mandatory requirement for colour contrast for batch and expiry details. It was proposed that this requirement should apply to all container types, although stakeholder consultation was expected to identify whether any special considerations were needed for particular container types.

RESOLUTION:

The Therapeutic Goods Committee (TGC):

1. NOTES:
   (a) that correspondence received by the Therapeutic Goods Administration (TGA), and responses to the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)], reveal ongoing concerns among consumers and health professionals over the visibility and legibility of batch numbers and expiry dates on the labels of medicines; and
   (b) these concerns exist despite the requirement of Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) for all label particulars to be clearly visible and written in legible characters, and the advice contained in the TGA document Best Practice Guideline on Prescription Medicine Labelling, that ink is preferred over embossing.

2. RECOMMENDS that the Therapeutic Goods Administration develop a proposal, for consultation with stakeholders, for an amendment to TGO 69 that would introduce a mandatory requirement for colour contrast for batch and expiry details on all container types.
OTHER MEDICINE LABELLING MATTERS – Requirements/Concessions for Small and Very Small Containers/Injections

The TGC noted that the proposed changes to labelling requirements for small and very small containers and equivalent size injections included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)] had been developed in recognition of the difficulty sponsors experienced in complying with the requirements of TGO 69 when the container was particularly small and/or there were multiple active ingredients with long names, such as with some vaccine ingredients.

The TGC noted a comparison of current (TGO 69) and proposed [TGO 79 (draft)] labelling requirements relating to the labelling of small and very small containers and injections, and that the proposed changes were complex. The TGC also noted that stakeholder comments on TGO 79 (draft) indicated that the amount of information to be included on labels of these size containers remained problematic and there was issue with the proposed delineation of container sizes at 2 mL and 20 mL.

The following stakeholders had provided relevant comments: XXXXX, XXXXX, XXXXX, XXXXX, XXXXX, XXXXX, and XXXXX. Industry stakeholders in particular raised significant concerns with the amount of information that would be required on the label given the small size of these containers.

The TGC agreed that, given the extent of change to labels that had been proposed and the issues identified by stakeholders in the consultation, there was insufficient justification at the current time to proceed with the proposed amendments to TGO 69 relating to requirements for small and very small volume containers and equivalent size injections. The TGC therefore resolved:

RESOLUTION:

The Therapeutic Goods Committee:

1. NOTES:
   (a) the proposals included in the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)] relating to the labelling of small and very small volume containers and equivalent size injections and the considerations leading to development of those proposals, and
   (b) stakeholder comments received in response to the consultation on TGO 79 (draft) in relation to these proposals.

2. CONCLUDES that amending requirements for the labelling of small and very small volume containers and equivalent size injections as proposed would not have the desired effect of simplifying labelling requirements for medicines packaged in these size containers.

3. RECOMMENDS that amendment to Therapeutic Goods Order No. 69 General requirements for labels for medicines relating to requirements for small and very small volume containers and equivalent size injections (other than where identified in other recommendations) is not justified at this time.
OTHER MEDICINE LABELLING MATTERS – Requirements/Concessions for Strip, Blister and Dial Dispenser Packs and Individually Wrapped Goods

Requirements for strip, blister and dial dispenser packs, and individually wrapped goods, was another matter identified previously by the TGC for further consideration as a result of the stakeholder responses to the proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)].

The TGC noted the apparent problems with current labelling requirements for strip, blister and dial dispenser packs, and individually wrapped goods that were being addressed through TGO 79 (draft), including frequent exemption requests relating to the labelling of listable lozenges and strips and blisters containing medicines with multiple ingredients. The proposed changes also addressed label deficiencies resulting from the common practice of strips and blisters containing tablets or capsules being cut into smaller lots for dispensing, particularly in hospitals. The TGC was requested to consider whether any of these problems were of such significance that amendment of TGO 69 was needed.

A comparison of current (TGO 69) and proposed [TGO 79 (draft)] labelling requirements relating to the labelling of strip, blister and dial dispenser packs, and individually wrapped goods was noted, as were comments received from stakeholders in response to the consultation on TGO 79 (draft) that related to the proposed changes. Relevant comments had been provided by XXXXX, XXXXX, XXXXX, XXXXX, XXXXX, and XXXXX.

The TGC noted the detailed considerations leading to development of TGO 79 (draft), which had in most part been conducted by the Joint Interim Committee on Trans Tasman Labelling Requirements for Medicines (JECLM).

In particular, JECLM had considered that there should be no distinction between requirements applying to blister trays which were designed to allow the detachment of individual dosage units (e.g. through perforations) and those that were not, as it was common practice for blister trays to be cut. JECLM also developed a definition for ‘calendar pack’ (a pack containing medicines that must be taken in a specified sequence to achieve their desired activity) which was intended to differentiate it from a compliance pack (a pack presented with day/date markings simply to aid compliance) and concluded that, where a medicine was presented in a strip, blister or dial dispenser pack, the product name and name and quantity of each active ingredient should be repeated once over each two dosage units irrespective of whether or not the strip or blister foil was perforated, unless the pack was a calendar pack.

The TGC considered the purpose of the proposed changes to labelling requirements and stakeholder comments, and concluded that while repetition of product name and active ingredient details on strip, blister, and dial dispenser packs was a safety issue, and therefore should be progressed, there was insufficient justification to proceed with the remaining changes that had been proposed. The TGC therefore recommended:

RESOLUTION:

The Therapeutic Goods Committee RECOMMENDS that:

1. Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) should be amended to require that, except for calendar packs, the name of the medicine, together with active ingredient details, is repeated on strip, blister
and dial dispenser packs at least once every two dosage units irrespective of whether or not there are perforations between dosage units to facilitate individual segments being detached; and

2. other changes proposed in the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)] for the labelling of individually wrapped goods and strip, blister and dial dispenser packs are not warranted at this time, and difficulties experienced by industry in compliance with the requirements of TGO 69 for medicines packaged in this way should continue to be assessed by the TGA on a case by case basis.

OTHER MEDICINE LABELLING MATTERS – Space Allowance on Prescription Medicines for a Dispensing Label

The TGC noted that currently there was no mandatory requirement in TGO 69 for the labels of any medicines to have a clear space where a dispensing label could be attached, nor had this been proposed in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)]. However, the lack of dedicated space on the labels of prescription medicines for placement of the dispensing label had repeatedly drawn comment in stakeholder consultations on labelling requirements, with many health professionals stressing the need for this. Although space for a dispensing label was recommended in the TGA’s Best Practice Guideline for Prescription Medicine Labelling, these stakeholders considered that the recommendation required further strengthening by inclusion in the labelling Order.

Comments of this nature had been received from the following stakeholders in response to the consultation on TGO 79 (draft): XXXXX, XXXXX, XXXXX, XXXXX, XXXXX, and XXXXX. The TGC noted however that, as no proposal for a clear space for the dispensing label had been included in TGO 79 (draft), there were no industry responses on this issue.

Noting the number of unsolicited requests from health professionals for a mandatory requirement for the labels of prescription medicines, at least, to have a clear space for the attachment of the dispensing label, the TGC considered that it would be appropriate for such a proposal to undergo stakeholder consultation. The TGA was requested to develop, for consultation purposes, an appropriate amendment to TGO 69. The TGC anticipated that this would result in vigorous debate among stakeholders.

RESOLUTION:

The Therapeutic Goods Committee (TGC):

1. NOTES:
   (a) the recommendation, contained in the Therapeutic Goods Administration (TGA) document Best Practice Guideline on Prescription Medicine Labelling, for there to be a clear space on the label of prescription medicines for attachment of the pharmacist’s dispensing label; and
   (b) that a number of unsolicited requests have been received for this recommendation of the Best Practice Guideline on Prescription Medicine Labelling to become a mandatory requirement through amendment to Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 60).
2. **RECOMMENDS** that the TGA develop a proposal, for consultation with stakeholders, for amendment to TGO 69 that would have the effect of requiring that the labels of as many prescription medicines as possible have adequate clear space for attachment of a dispensing label.

**OTHER MEDICINE LABELLING MATTERS – Statement of Volume and Expression of Strength on Injections**

The expression of quantity or proportion of active ingredient for injections with a nominal volume greater than 1 mL had been identified previously by the TGC for further consideration as a result of the proposals included in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)]. Significant issues had been raised by stakeholders, and expression of content/strength was considered to be a safety issue.

The TGC noted that the main change proposed by TGO 79 (draft) was to require medicines for injection with a nominal volume greater than 1 mL, whether intended for multi- or single dose use, to show the content of active ingredient both as the total quantity of active ingredient in the total volume of the injection, and the quantity of the active ingredient in one millilitre of the injection. This proposed change to the labelling of injections had been recommended by the Joint Interim Committee on Trans Tasman Labelling Requirements for Medicines (JECLM) which had been concerned with the potential for dosing errors resulting from misreading of the strength on injections when the strength was expressed as XX mg/mL and the volume was greater than 1 mL. The proposed change was intended to improve the clarity of volume and strength information on the labels of injections, and keep dosing simple by minimising the number of calculations that needed to be made by health professionals.

The TGC noted relevant comments received from stakeholders in response to the consultation on TGO 79 (draft). Comments had been made by XXXXX (regarding insufficient space on labels of ampoules with a nominal volume of 10 mL or less to have both expressions of the amount of active ingredient), XXXXX (regarding impact on products and practical issues relating to label space and printed ampoules) and XXXXX (advising that, from risk management perspective, all injectable drugs should be labelled with the total quantity in the container and not the strength).

The TGC also noted advice received from XXXXX which drew attention to the requirements of TGO 69 for single dose injections having resulted from previous consideration of coronial findings concerning accidental deaths associated with misreading of labels using ‘quantity/mL’ expressions of strength.

Having noted the rationale and background to the proposed change to the expression of strength on injections given in TGO 79 (draft), and the resulting stakeholder comments, the TGC did not support the making of a corresponding amendment to TGO 69 at this time.

**RESOLUTION:**

The Therapeutic Goods Committee:

1. **NOTES** the proposal included in the consultation document Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines (draft) [TGO 79 (draft)] to require the label on injections having a nominal volume greater than 1 milliliter to express the content of active ingredient as both the total quantity of active ingredient in the total volume of the injection, and the quantity of the active ingredient in one milliliter of the injection; but
2. ADVISES that amendment to Therapeutic Goods Order No. 69 General requirements for labels for medicines relating to the expression of content of active ingredient in medicines for injection as proposed in TGO 79 (draft) is not supported at this time.

OTHER MEDICINE LABELLING MATTERS – Expression of Strength on Liquids for Oral Administration

Although the requirements proposed in draft Therapeutic Goods Order No. 79 General Requirements for the Labelling of Medicines [TGO 79 (draft)] for the expression of strength on liquids for oral administration were essentially the same as those currently applied through TGO 69, this issue had been identified by the TGC at its 33rd Meeting (October 2008) for further consideration as a result of a submission from a stakeholder (XXXXX) which advised of a medication overdose resulting from misreading of the strength stated on the label. This stakeholder had recommended that the primary descriptor of strength on the label should be ‘as the quantity of the active ingredient contained in one millilitre of the liquid, and that where there is a series of strengths containing the same active ingredient, then the quantity or proportion of the active ingredient should be expressed consistently across the range in terms of strength per millilitre.’

The TGC noted that the only other comment received from stakeholders in response to the consultation on TGO 79 (draft) that related to the expression of strength on liquids for oral administration had been made by XXXXX. This response advised of concerns over the expression of paediatric doses of some preparations where the dose was not expressed as milligram/millilitre, but rather a larger volume e.g. X mg/25 mL. XXXXX recommended that consideration be given to at least including on the label the number of units (i.e. milligrams, micrograms etc.) per millilitre to facilitate calculations.

The TGC considered the submission received but concluded that, at this time, there was insufficient justification to require such a significant change to the way in which liquids for oral administration were labelled.

RESOLUTION:

The Therapeutic Goods Committee:

1. NOTES the proposal from a stakeholder for an amendment to Therapeutic Goods Order No. 69 General requirements for labels for medicines (TGO 69) to require the label on liquids for ingestion to express the content of active ingredient in terms of the quantity of active ingredient contained in one millilitre of the liquid, but

2. ADVISES that amendment to TGO 69 relating to the expression of content of active ingredient in medicines for ingestion, as proposed, is not supported at this time.

THERAPEUTIC GOODS ORDER NO. 78 STANDARD FOR TABLETS AND CAPSULES – RESPONSE TO THE ADOPTION OF ADDITIONAL DEFAULT STANDARDS

Therapeutic Goods Order No. 78 Standard for tablets and capsules (TGO 78) came into force on 7 November 2008, revoking Therapeutic Goods Order No. 56 General standard for tablets, pills
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and capsules (TGO 56) with effect 1 November 2010. In general, TGO 78 required compliance with a British Pharmacopoeia (BP) monograph as a whole where one existed, and where there was no individual monograph in the BP, TGO 78 set requirements according to whether the medicine was a listed medicine (lower risk) or a registered medicine (higher risk). Members noted that, following amendments to the Therapeutic Goods Act 1989 to adopt multiple default pharmacopoeias, there was now an equity argument that if sponsors were free to choose between equivalent BP, European Pharmacopoeia (Ph. Eur.) and United States Pharmacopoeia-National Formulary (USP) monographs as the standard applicable to other dosage forms, then this approach should also apply to tablets and capsules.

The TGC discussed a range of proposals for possible amendments to TGO 78 to reflect the adoption of additional default standards under the Act and early experiences during the transition period to full compliance with TGO 78.

The Committee recommended that USP and Ph. Eur. individual monographs should be given equal status with BP monographs in TGO 78 as a general principle. The Committee then discussed some implications that flowed from this recommendation.

Scope of USP Dietary Supplement monographs – these often had more flexibility than BP monographs, for example allowing “other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable …”. This would allow the addition of active ingredients other than those stated in the description of the formulation, such as any listable ingredient. The TGC had no objection to the inclusion of this statement in the USP monographs, subject to the medicine also complying with the limits that would otherwise apply to those “other labeled added substances” as active ingredients (e.g. 90 – 120% for listed medicines).

Listed medicines – weight variation – the TGC supported a change to TGO 78 to include the USP’s Dietary Supplements test for weight variation in place of Uniformity of Dosage Units for listed medicines otherwise compliant with a USP monograph, as there was no overwhelming reason to prefer one test over the other.

Listed medicines – dissolution requirements – the Committee noted that although the BP required few (if any) dissolution tests for listable medicines, the USP had numerous individual monographs for vitamin, mineral and herbal medicines that would apply to listed medicines and which included dissolution specifications. The TGC discussed a number of issues resulting from application of the USP monographs, including:

- the impact of this new and unexpected regulation as opposed to any benefit to consumers;
- the desirability for application of pharmacopoeial monographs in full as far as possible and the avoidance/minimisation of redactions or additions to monographs; and
- the technical feasibility of dissolution testing for herbal and multivitamin – multimineral medicines.

Anticipating that public consultation would be undertaken on this and other proposed amendments to TGO 78, the Committee supported compliance with a USP dietary supplement monograph being required in full (except Uniformity of Dosage Units, where applicable) for listed and registered complementary medicines, which would implicitly include any dissolution testing specified in USP monographs applicable to listable medicines.

Registered complementary medicines – content of active ingredient – the TGC noted that by recognising USP monographs for multivitamin and multimineral products as standards, most limits currently included in Schedule 1 to TGO 78 would be able to be applied to registered complementary medicines, which was contrary to the Committee’s previous position. Again
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anticipating that public consultation would be undertaken on proposed amendments to TGO 78, the Committee supported the application of Schedule 1 to both listed and registered complementary medicines, including those that had a USP monograph.

Registered complementary medicines – dissolution testing – the Committee was informed that sponsors considered that the requirement of TGO 78 for a suitable dissolution test for each active ingredient, if either the BP or USP specified that a dissolution test was needed, was too onerous for registered multivitamin and/or multimineral products. Requirements of the USP were preferred, where dissolution testing for such multi-component products only involved folic acid, one water-soluble vitamin and one mineral. The TGC noted that this issue could be addressed by recognising USP monographs for multivitamin and multimineral products as standards, which would bring with it the USP requirement regarding the need to demonstrate the dissolution of three, not all, active ingredients in a registered complementary medicine. The TGC therefore proposed that an amendment to TGO 78 to allow this should undergo stakeholder consultation.

Registered medicines – content of active ingredient – the TGC noted the current trends in BP monographs to set the limits for content of active ingredient at 95-105%, while that for USP monographs was to set the limits at 90-110%. TGO 78 generally specified limits for the content of active ingredients in registered medicines at 92.5-107.5%. At this time, the Committee supported the proposal that 90.0-110.0% limits, in conjunction with Uniformity of Dosage Units requirements, was the appropriate standard for the content of active ingredients in registered medicines not subject to an individual pharmacopoeial monograph.

Chewable tablets – the TGC noted that the USP frequently included dissolution tests for chewable tablets, whereas TGO 78 bracketed together chewable, effervescent and dispersible tablets as dosage forms not requiring dissolution testing. The TGC was advised that the TGA considered the more scientifically valid position to be that the physical disintegration of a chewable tablet would be more variable than that of dispersible or effervescent tablets. Without knowledge of the dissolution characteristics of the particular medicines, it was possible that the absorption profiles may be influenced by particle size. The TGC therefore supported the proposal that chewable registered tablets be required to comply with a dissolution requirement.

Pills – the TGC noted that the scope of TGO 78 currently excluded pills and this had been intentional as the TGA had not yet determined if a standard for pills was required. The TGA now advised that approximately 400 medicines included on the Australian Register of Therapeutic Goods were in a pill dosage form, and all these were listed Chinese medicines. The TGA’s Office of Complementary Medicines therefore considered it appropriate to apply the requirements for physical testing (i.e., weight variation and disintegration) from the Pharmacopoeia of the People’s Republic of China 2005 (Volume 1) to listed medicines in the pill dosage form.

The TGC supported in principle that the scope of TGO 78 should be extended to include standards for the dosage form ‘pills’ and that the requirements of the Pharmacopoeia of the People’s Republic of China (Volume 1) be considered as the standard for listed pills of the types described in that pharmacopoeia.

Concluding the consideration of possible amendments to TGO 78, Members noted that the apparently simple expansion of reference to the BP and Ph. Eur to include the USP had diverse implications. Some of the possible amendments to TGO 78, especially dissolution testing for listed medicines, would be controversial and merited further consideration by the TGA and discussions with the industry sectors in advance of full public consultation. However, the Committee continued to support the approach in TGO 78 that the relevant standards vary according to whether the medicine was a listed medicine (lower risk) or a registered medicine (higher risk).
RESOLUTION:

The Therapeutic Goods Committee:

1. NOTES that:
   (a) Therapeutic Goods Order No 78 Standard for Tablets and Capsules (TGO 78) took effect on 7 November 2008 and medicines within its scope must comply with the Order by 1 November 2010, and
   (b) changes to the Therapeutic Goods Act 1989 to recognise the British Pharmacopoeia (BP), the European Pharmacopoeia (Ph. Eur.) and the United States Pharmacopeia-National Formulary (USP) as default standards took effect on 1 July 2009.

2. RECOMMENDS that TGO 78 be amended such that:
   (a) references to the BP be amended to refer to the BP, Ph. Eur. and/or USP as appropriate;
   (b) the statement in USP Dietary Supplement monographs for multivitamin and multimineral products allowing the inclusion of ‘other labeled added substances that are generally recognized as safe, in amounts that are unobjectionable’ be allowed, subject to compliance with the limits that otherwise apply to listed and registered tablets and capsules for the content of those added active ingredients; and
   (c) the USP’s Dietary Supplement test for weight variation be accepted in place of Uniformity of Dosage Units for listed medicines otherwise compliant with a USP monograph;

3. NOTED the following proposals and SUPPORTED their inclusion as proposed amendments to TGO 78 for stakeholder consultation:
   (a) compliance with a USP Dietary Supplement monograph be required in full (except Uniformity of Dosage Units, where applicable) for listed and registered complementary medicines;
   (b) Schedule 1 be applied to both listed and registered complementary medicines, including those that have a USP monograph;
   (c) registered complementary medicines that are multivitamin and/or multimineral tablets and capsules need not demonstrate dissolution of every active ingredient;
   (d) 90.0-110.% limits be applied for the content of active ingredients in registered medicines not subject to an individual pharmacopoeial monograph, in conjunction with Uniformity of Dosage Units requirements;
   (e) chewable registered tablets be required to comply with a dissolution requirement; and

4. SUPPORTED IN PRINCIPLE, subject to further consultation, that TGO 78 be extended to include standards for the dosage form ‘pills’ and that the requirements of the Pharmacopoeia of the People’s Republic of China, Volume 1 be considered for application to listed pills of the types described in that pharmacopoeia.
ORDERS RELATING TO EXCLUSION OF CERTAIN UNITED STATES PHARMACOPEIA MONOGRAPHS

The TGC was informed of the status of stakeholder consultation on three proposed Orders which would make certain monographs of the United States Pharmacopoeia-National Formulary (USP-NF) ineligible to be considered as a ‘standard’ under the Therapeutic Goods Act 1989 (the Act). The Committee was advised that the TGA had recently commenced consultation with interested parties on the proposals supported by the TGC at its 33rd Meeting that:

- new Therapeutic Goods Order(s) be developed to specify that certain vaccines, toxoids and blood products should comply with the British Pharmacopoeia (BP) or Ph. Eur, and not the USP-NF, in cases where the USP-NF referenced other US documents and requirements, and
- a new Therapeutic Goods Order be developed to specify that water for injection should comply with the BP or Ph. Eur, and not the USP-NF.

RESOLUTION:

The Therapeutic Goods Committee:

1. NOTES that the Therapeutic Goods Administration has commenced public consultation with interested parties on:
   (a) draft Therapeutic Goods Order Standard for human albumin,
   (b) draft Therapeutic Goods Order Standard for water for injection for parenteral medicines, and
   (c) draft Order under section 3C(1) of the Act, and

2. AGREES to consider submissions on the draft Orders at its next meeting.

UPDATE ON THE DEVELOPMENT OF PRODUCT STANDARDS FOR THE NEW REGULATORY FRAMEWORK FOR BIOLOGICALS

The TGC was provided with an update on progress by the TGA in the development of product standards to support the new regulatory framework for biologicals, including a report on the outcomes of the second and third meetings of the TGC’s Subcommittee on Biologicals.

The TGC was advised that the Subcommittee’s second meeting had been held on 20 August 2009 and, at that Meeting, the Subcommittee:

- considered a revised draft of the Infectious Diseases Order, which incorporated suggestions made by Members at the Subcommittee’s first meeting, and recommended further re-formatting to facilitate clarity and understanding;
- considered initial drafts of product type-specific standards for cardiovascular, musculoskeletal and ocular tissues and skin;
- was advised of the progress by the TGA in developing a labelling standard for biological products and standardised terminology; and

The Subcommittee also considered a proposal by the TGA relating to the applicable standards for haematopoietic progenitor cells (HPCs), with the proposal being the revocation of Therapeutic Goods Order No. 75 Standard for Haematopoietic Progenitor Cells derived from Cord Blood (TGO
75), and reliance being placed on the British Pharmacopoeia (BP) monograph for “Human Haematopoietic Stems Cells”.

The TGC was advised also that the third meeting of the Subcommittee had been conducted by video-/teleconference the preceding day, with the primary purpose of reviewing the further revised Infectious Disease Order. Notwithstanding vigorous debate at the Subcommittee meetings, the Subcommittee had been able to provide solid input to the TGA.

RESOLUTION:

The Therapeutic Goods Committee NOTES progress towards the development of standards for human blood and blood components, tissues and cell therapies.

MANUFACTURING PRINCIPLES - GOOD MANUFACTURING PRACTICES FOR MEDICINAL PRODUCTS

The TGC was advised that the TGA had determined a new Manufacturing Principle under Subsection 36(1) of the *Therapeutic Goods Act 1989* (the Act). The new Manufacturing Principle adopted the current Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) *Guide to Good Manufacturing Practice for Medicinal Products*.

In relation to compliance with the requirements of the Manufacturing Principles, the Committee was informed that, where the PIC/S Guide provided that a procedure or requirement ‘should’ be followed, manufacturers of therapeutic goods in Australia ‘must’ follow that procedure or requirement unless it could be demonstrated that the failure (or an alternative procedure) did not:

- increase the risk of harm or injury;
- increase the risk of non-compliance with a standard or listing/registration requirement; or
- compromise record keeping.

A TGC Member reiterated previous concerns with the interpretation of ‘should’ as reflecting mandatory requirements, and the impact of this on manufacturers trying to achieve compliance particularly where new technologies were needed. The Member suggested that it should be emphasised in the various discussions with, and seminars for, stakeholders that the Manufacturing Principles allowed manufacturers to achieve the desired outcome through alternative means.

Further discussion related to the intended new Code of GMP for blood and tissues (*Australian Code of Good Manufacturing Practice – Human Blood and Blood Components, Human Tissues and Cellular Therapies*), a draft of which had been provided to the Biologicals Subcommittee at its second meeting. It was noted that, with the development of product standards for these biological products, the aim was to limit the content of the new GMP Code to manufacturing matters and for manufacturing requirements not to be included in the various product standards. This would reduce any potential for conflict between the GMP Code and product standards.

RESOLUTION:

The Therapeutic Goods Committee NOTES that a new Manufacturing Principle has been determined under Subsection 36(1) of the *Therapeutic Goods Act 1989* to adopt the current Pharmaceutical Inspection Convention and Co-operation Scheme *Guide to Good Manufacturing Practice for Medicinal Products*. 
DRAFT THERAPEUTIC GOODS ORDER - STANDARD FOR HEPARIN

The TGC was advised of progress in the development of a Therapeutic Goods Order (TGO) to specify the required standard for heparin, and that stakeholder consultation on a draft TGO was presently being undertaken. The TGC recalled that the purpose of the proposed TGO was to ensure that heparin used in therapeutic goods was free from contamination with over-sulfated chondroitin sulfate (OSCS).

RESOLUTION:

The Therapeutic Goods Committee:

- NOTES that the Therapeutic Goods Administration has commenced public consultation with interested parties on the draft Therapeutic Goods Order Standard for Heparin, and

- AGREES to consider submissions on the draft Orders out of session.

REGULATORY REFORM AND AMENDMENTS TO THE THERAPEUTIC GOODS ACT 1989 AND REGULATIONS

The TGC noted information on:

- the Therapeutic Goods Amendment (Medical Devices and Other Measures) Act 2009, which had been given Royal Assent on Wednesday 17 June 2009;
- the Therapeutic Goods Amendment (2009 Measures No 1) Act 2009, which had been given Royal Assent on Thursday 27 August 2009;
- the Therapeutic Goods Amendment (2009 Measures No 2) Act 2009, which had been passed by both Houses of Parliament and was awaiting Royal Assent;
- the Therapeutic Goods Amendment Regulations 2009 (No. 5) which had been registered on the Federal Register of Legislative Instrument on 10 September 2009 and commenced on 11 September 2009; and
- future expected amendments to the Therapeutic Goods Regulations 1990 relating to the composition and operation of expert advisory committees, including the TGC.

TGA CONSULTATION PROCESSES

The TGC was informed of a recent TGA initiative to increase the transparency of TGA’s consultation processes. This initiative involved the development of a policy to publish, on the TGA’s website, the names of interested parties who make submissions in response to TGA consultations and the actual submissions unless marked ‘Confidential’ or publication would contravene the Privacy Act 1988.

DATE OF NEXT MEETING

The TGA was requested to canvass Members out-of-session for their availability in April 2010 for the next Meeting of the Committee.

There being no further business, the Chair closed the Meeting at 4:00pm and thanked Members for their attendance.