Mechanisms to maintain the currency of approved Product Information (PI) and Consumer Medicine Information (CMI)

Public consultation paper

Version 1.0, May 2013
About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.

- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.
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Background

In July 2012, the document titled, “Delivering reforms – Implementation plan for TGA Reforms: A blueprint for TGA’s future” was published on the TGA website -

This Blueprint incorporates reforms arising from multiple major reviews of the TGA in 2010 and 2011. The reforms have been grouped into five key themes and will be achieved incrementally over four years, in three phases.

One of the key themes is “communication and stakeholder engagement” and one of the key reviews to which this theme relates is the Report of the Review to improve the transparency of the Therapeutic Goods Administration: Final Report, June 2011” (“the Transparency Review”) - <http://www.tga.gov.au/newsroom/review-tga-transparency-1101.htm>.

In broad terms, the Transparency Review made a range of recommendations aimed at enhancing the amount and accuracy of information available to consumers and other stakeholders once a therapeutic product is available on the Australian market.

This consultation paper relates exclusively to Recommendation 17 of the Transparency Review (TR17) which states -

“This recommendation is that the TGA explore mechanisms to maintain the currency of Consumer Medicines Information (CMI) and Approved Product Information (PI)”,

The Blueprint goes on to state that this recommendation will be progressed in two phases:

July 2012 – June 2013

The TGA will consider processes and regulatory changes that would help ensure that CMI and PI reflect current circumstances. The TGA will also examine options for improving access to and information about CMI and PI. Public consultation will inform the development of these proposals. Advice on any proposals requiring regulatory change will be provided to the Government.

July 2013 – June 2014

The TGA will provide feedback on any proposed changes and the process for their implementation.
About the consultation

Purpose

In order to advance TR17, the TGA wishes to gather information and obtain clarity around some issues relating to the preparation, approval and maintenance of PI and CMI by consulting with interested parties on mechanisms which may be used to maintain the currency of these documents. This consultation also seeks advice on how the community can be assured documents uploaded into the Australian Register of Therapeutic Goods (ARTG) and the PI / CMI search facility are current - \(<\text{https://www.ebs.tga.gov.au/}>.\)

The TGA will also hold consultation workshops in May with peak bodies representing consumers, health professionals and the therapeutic goods industry, and providers of therapeutic goods information. Workshop outcomes will be published on the TGA website. Organisations represented at the stakeholder workshops are not expected to also provide a written submission.

Timetable

Document released for consultation on 13 May 2013.

Interested parties should respond by close of business 13 June 2013.

Feedback will be released following consideration of submissions.

Content of submissions

Submissions may address any issues relating to maintaining the currency of PI and CMI. In particular, the TGA invites comment about:

- the “Questions for Consideration” raised in this paper;
- the possible further options to maintain PI and CMI;
- the possible options to address Recommendation TR17;
- whether or not you support any of these options;
- whether there are other possible options you wish to raise; and
- how any or all of these options will impact on you. That is, what do you see as the likely benefits or costs to you (these may be financial or non-financial). If possible, please attempt to quantify these costs and benefits.

How to respond

All submissions should be accompanied by a TGA submission cover sheet, available from the TGA website. \(<\text{http://www.tga.gov.au/newsroom/consult-opr-currency-pi-cmi-130513.htm#coversheet}>\) Submissions must include full personal or organizational contact details (including address, telephone number and email).

Electronic submissions are preferred and should be emailed to complianceconsultation@tga.gov.au. Please include 'Maintaining the currency of PI/CMI’ in the subject line of the email.

Alternatively, hard copy submissions may be mailed to:
Management and Co-ordination Section  
Office of Product Review  
Therapeutic Goods Administration  
PO Box 100  
WODEN ACT 2606  

What will happen

Submissions will be reviewed by the TGA and feedback on submissions will be provided through the TGA’s Internet site.

Content of submissions will inform the further development of options for maintaining the currency of PI and CMI the evaluation of their feasibility, including impacts on the regulated industry.

The TGA’s evaluation report will be provided to Government by June 2014.

Confidentiality

All submissions will be placed on the TGA website unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked 'IN CONFIDENCE'. Reasons for a claim to confidentiality must be included in the space provided on the TGA submission coversheet.

For submissions made by individuals, all personal details other than your name will be removed from your submission before it is published on the TGA’s website.

In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission coversheet.

Enquiries

Any questions relating to submissions should be directed by email to complianceconsultation@tga.gov.au or by telephone to 02 6232 8660.

What is Product Information?

The Product Information document (PI) is considered by the TGA as a risk minimisation tool to ensure the appropriate prescribing of prescription and some over-the-counter medicines. The purpose of the PI is to ensure that the prescriber is provided with all relevant information on the conditions and populations for which there is evidence of effectiveness, describes those people where the medicine is contra-indicated for use and those where caution in prescribing is required as well as any monitoring of a patient that is required for safe and appropriate use. It reflects the limits of the approval of the medicine by the TGA. For instance, if a particular indication is not included in the PI, the medicine has not been approved for use in Australia for that indication.

The information in a PI is drafted by the pharmaceutical company responsible for the medicine and following evaluation and negotiation, a final PI is approved by the TGA. It provides objective information about the quality, safety and effectiveness of the medicine, as demonstrated in the data provided to the TGA by the pharmaceutical company. It is
important to note that the PI does not, nor is it intended to represent a historical record of all known information or published studies on the particular medicine.

A PI must contain the following information - name of the medicine, description, pharmacology, clinical trials, indications, contraindications, precautions, interactions with other medicines, adverse effects, dosage and administration, overdose, presentation and storage conditions, name and address of the sponsor, poison schedule of the medicine, date of first inclusion in the ARTG and the date of most recent amendment.

What is Consumer Medicine Information?

The Consumer Medicines Information (CMI) (also known as “Patient Information”) is a leaflet that contains information on the safe and effective use of a prescription or pharmacist-only medicine and is written by the pharmaceutical company responsible for the medicine. Part 2A of the Therapeutic Goods Regulations 1990 (“the Regulations”) requires that the CMI be made available to consumers either in the pack or in another manner that will enable the information to be given to the person to whom the medicines are administered or otherwise dispensed. The information it contains must also be consistent with the PI for the medicine.

A CMI includes - name of the medicine, names of the active and inactive ingredients, dosage of the medicine, what the medicine is used for and how it works, contraindications, warnings and precautions, such as when the medicine should not be taken, interactions the medicine might have with food or other medicines, how to use the medicine properly, side effects, what to do in the case of an overdose, how to store the medicine properly, name and address of the sponsor and date the CMI was last updated.

CMI is provided by sponsors and may be reviewed by the TGA to ensure consistency with the PI and that it is in line with the regulatory requirements for the content of CMIs (Schedules 12 and 13 of the Regulations for prescription and over-the-counter medicines respectively). During the evaluation of Risk Management Plans (RMPs) associated with applications for registration of higher risk medicines, the CMI is also considered during the evaluation to ensure it addresses known and potential risks associated with the medicine and makes this information available to consumers.

The regulatory framework: Prescription medicines

Evaluation

All prescription medicines available for general marketing in Australia are registered in the Australian Register of Therapeutic Goods (ARTG). Section 2.5 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) set out the kinds of applications that can be made to enter medicines into the ARTG. Different processes, forms, timeframes and fees apply, depending on the type of application and category.

The legislation mandates that PI and CMI must be made available for prescription medicines being supplied in the Australian market. Section 23(2)(ba) of the Therapeutic Goods Act 1989 (“the Act”) specifies that an application for registration is not effective

2 <http://www.tga.gov.au/industry/pm-argpm.htm>
unless accompanied by a PI and following evaluation, the PI is approved by the TGA under s.25AA(1) of the Act and attached to the letter notifying the sponsor of the decision to approve the registration of the medicine.

Appendix 8 of the ARGPM goes on to describe that a draft PI must be lodged, in a form approved by the Secretary under s.7D of the Act, as part of an application under s. 23 to enter a ‘restricted medicine’ (for example, a prescription medicine) in the ARTG. The form for providing product information3 ("the PI Form") is available on the TGA website. All PI documents must be approved by the TGA before a medicine can be registered.

Sponsors will be advised in the decision letter from the TGA about when changes to the PI will come into effect. Once the product is registered:

- the PI document approved by the TGA must be lodged with the TGA within 2 weeks of the date of registration of the product; and
- the related Consumer Medicine Information (CMI) document must be lodged with the TGA.

For a new product, the CMI must be lodged prior to supply of the product. Both documents are then published on the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Where a change is proposed to be made to a medicine, the sponsor must seek TGA approval which is then reflected in the ARTG entry for the medicine. With some exceptions, variations to existing ARTG entries of medicines can be made under s.9D of the Act or, if the variation will result in the creation of a separate and distinct good, under s.23. Following application by a sponsor, PIs are evaluated as part of the registration or variation process; and recommendations for specific information to be included in the PI are made. This includes information relating to the safety, known and/or potential risks with the use of the medicine, properties of the medicine, dosage instructions, overdosage, identification, etc. In other words, changing or updating a PI will usually be a consequence of applying to vary the ARTG entry for a medicine.

Section 28 of the Act specifies that the registration of therapeutic goods is subject to conditions relating to matters including the manufacture of the goods, the custody, use, supply, disposal or destruction of the goods, the keeping of records, matters dealt with in standards applicable to the goods or such other matters relating to the goods as the Minister thinks appropriate.

One of the standard conditions of registration which apply to all registered prescription medicines states:

Changes or variations in respect of any information concerning the registered or listed therapeutic goods, being information that would have been relevant to a decision to register/list the goods in the ARTG, including information on the formulation of the registered/listed goods or other aspects of their manufacture, and the labelling of the goods, shall forthwith be notified to the Secretary, or the Secretary's delegate appointed for the purposes of section 28 of the Therapeutic Goods Act 1989 and where necessary, the change or variation shall not be implemented until approved by the Secretary.4

Additionally, the following specific conditions which apply to all registered prescription medicines state:

The Product Information (PI) applying to these therapeutic goods must meet the TGA’s approval at all times. Any proposed changes to the approved text of the PI, with the exception of safety related changes, must be submitted to, and be approved by, the TGA prior to distribution. Safety related changes, as defined by section 9D of the Act, must be notified to the TGA within five working days. The PI should conclude with a statement that it has been approved by the TGA, citing the date of the approval letter. (For all injectable products the Product Information must be included with the product as a package insert).

Abridged Product Information must accurately reflect the approved Product Information, including safety-related statements, but may be a paraphrase or precis of the approved Product Information.

Further, the following specific condition has the effect of requiring the sponsors of registered, generic prescription medicines to ensure the PI for their medicines are updated once safety-related changes are made by the sponsor of the innovator medicine:

It is a specific condition of registration that the Product Information and Consumer Medicine Information documents be updated within one month of safety-related changes made by the innovator. It is your responsibility to routinely check the TGA website at [www.ebs.tga.gov.au] for any updates to the innovator Product Information.

These conditions mean that once a medicine is entered in the ARTG, the PI cannot be changed (apart from limited exceptions) without the approval of the Secretary.

Post-market monitoring

Once a product is registered, changes to the PI can then be made when, for example, ongoing use of the product identifies further risk or safety information. When a change is initiated, the PI is evaluated, negotiated and subsequently re-approved by the TGA. Once a product is marketed in Australia, changes to the PI or the need to develop a brand new PI usually result from new dosage instructions and use in populations that differ from the populations studied in clinical trials. These differences may relate to use in populations with co-morbidities or use in conjunction with medicines not used during the clinical trials.

The TGA undertakes monitoring of products once they are marketed. Monitoring includes analysis of adverse event reports sent to the TGA as part of its spontaneous adverse reporting system, evaluation of Periodic Safety Update Reports (PSURs) provided by sponsors and monitoring of published safety information such as the medical literature and the actions of other regulators. This process is further described in the Product Vigilance Framework document available on the TGA website - [http://tga.gov.au/safety/tga-therapeutic-product-vigilance.htm].

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5 Section 9D defines these safety related changes as variations to the ARTG entry which “reduce the class of persons for whom the goods are suitable” or “add a warning, or precaution, that does not include any comparison of the goods with any other therapeutic goods by reference to quality, safety or efficacy”. NB. An alignment of the TGA’s business processes for regulating minor variations to prescription medicines, including safety related changes, will be implemented on 22 May 2013. For further information readers should refer to [http://www.tga.gov.au/industry/pm-notice-minor-variations-120612.htm]
Questions for consideration

To assist with determining the most appropriate manner in which to address recommendation TR17, the following questions are presented for further consideration:

- What is the purpose and function of the PI and CMI?
- Is the purpose and function of the PI and CMI well understood by prescribers and consumers?
- Does the public understand the current mechanisms for reviewing and updating the PI?
- Are these mechanisms adequate or are there any other mechanisms that could be considered?

The regulatory framework: Over-the-counter medicines

The legislation mandates that a PI must be approved (s.25 and s.25AA of the Therapeutic Goods Act 1989 (“the Act”)) and a CMI (Part 2A of the Regulations) be made available for specified over-the-counter (OTC) medicines being supplied in the Australian market.

Approximately 20-25% of OTC medicines registered in the ARTG have a PI. This is primarily because the provision of PIs is mandated for Schedule 3 (S3) (“Pharmacist-only”) medicines and certain other Schedule 2 (S2) (“Pharmacy Medicine”) and unscheduled medicines, where deemed to be necessary by the TGA. The criteria for making such determinations are outlined in Appendix 3 of the Australian Regulatory Guidelines for OTC Medicines (ARGOM).

PI for OTC medicines are evaluated and approved by the TGA, and attached to the letter of marketing authorisation. However, none are currently published in the TGA’s search facility. Sponsors usually arrange for the publication of these PIs in MIMS, but this is not under direction by, or a requirement of the TGA.

These processes raise the question as to whether there should be consistency with the approach taken for prescription medicines. However, given that down scheduling can be a reflection of an ingredient’s improved or better-established safety profile, the counter argument in these circumstances is that there should be no need for a PI to be maintained once an OTC medicine is further down-scheduled since label warnings should be sufficient to ensure ongoing public safety and no CMI should be required.

While there may be no justification for this on safety grounds, some sponsors have indicated their support for the maintenance of existing PI and CMI in the context of enhanced quality use of medicines.

Questions for consideration

To assist with determining the most appropriate manner in which to address
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recommendation TR17, the following questions are presented for further consideration in the context of whether there should be consistency with the approach taken for prescription medicines. Specifically, should the TGA:

- consider publishing PI for OTC medicines in the PI/CMI search facility;
- consider requiring all S3 medicines to publish both the PI and CMI; and /or
- consider requiring CMI to be available to the public for all registered medicines?

Proposed alterations to the PI format

The TGA is seeking comment on proposed changes to the ordering of information in the PI document. The proposed changes will place clinically relevant information about product indication/s, contraindications and, warnings and precautions earlier in the document. The current PI does not highlight this information and therefore the TGA is considering whether re-formatting of the PI would assist healthcare professionals with appropriate prescribing.

Background

The current PI Form requires pharmacology and clinical trial data to be placed before the information on indication/s, contraindications, precautions and adverse reactions. In practice, many PIs have over ten pages of pharmacology and clinical trial data before usage information is presented.

An earlier internal review of the Australian PI identified the following sections of the PI as those considered to be most important by healthcare professionals – warnings, indication/s, adverse reactions, contraindications, precautions and presentation. Pharmacology and clinical trial data, presently located early in the PI, were considered less important. The report proposed a change in the order of items with information on indication/s, adverse reactions and contraindications to be located earlier in the document.

Improved layout of the Australian PI would ease the ability of healthcare professionals to access the information most important to the safe and effective use of a medicine. Despite a recent search of the literature, no specific information on Australian medical practitioner experience of the PI was identified. The TGA has been advised by some stakeholders that the PI in its current format is not user friendly and other sources of information such as MIMs with its abridged PI information, indexing and hyperlinks; and The Australian Medicines Handbook were preferred.

International status

At present, the PI documents for the USA, Canada and European Union are consistent in placing prescriber-relevant information before pharmacology and clinical trial data. Refer to Appendix A for a comparison of the current formats of these and the Australian PI documents.

The proposed rearrangement of information in the Australian PI is consistent with current international practice and would put the Australian PI in line with these overseas
equivalents. The format of PI documents commonly provided in New Zealand is similar to that in Australia and Medsafe advises that this often results in important information being difficult to find.

Prior to the changes to the USA PI (label), extensive consultation was performed by the FDA and found that:

1. the labelling sections physicians read most often and perceive as most important were: Dosage and Administration, Contraindications, Warnings, Adverse Reactions, and Precautions;

2. overall, the Clinical Pharmacology section, and the Abuse and Dependence and Overdose sections, are referred to relatively infrequently [Food and Drug Administration, HHS. Requirements on content and format of labeling for human prescription drugs and biologics Requirements for prescription drug product labels. Proposed rule. FedRegist. 2000 Dec 22;65(247):81082-131].

The current PI formats used in the USA and Canada were developed to allow easy access to relevant clinical information. The US format was developed following consultation with health care practitioners to reduce problems with increasingly lengthy and complicated information presented. The current Canadian and US formats place indication, dosage, contraindications, precautions and adverse reactions in earlier sections of the document, before clinical trial and pharmacology. [Food and Drug Administration, HHS. Requirements on content and format of labeling for human prescription drug and biological products. Final rule. FedRegist. 2006 Jan 24;71(15):3921-97] [Health Canada. Guidance for Industry Product Monograph. 2003 Oct 1. <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/monograph/pm_mp-eng.php>]


Proposed changes

It is proposed the sections of the PI identified by healthcare professionals to be most, such as indication/s, dosage and administration, contraindications and warnings and precautions are placed in an earlier section of the document. The proposed layout is as follows:

1. Name of medicine
2. Description
3. Indications
4. Dosage and administration
5. Contraindications
6. Precautions
   6.1. Effects on fertility
   6.2. Use in pregnancy
   6.3. Use in lactation
6.4. Paediatric use
6.5. Use in the elderly
6.6. Genotoxicity
6.7. Carcinogenicity
6.8. Effects on laboratory tests

7. Adverse Effects
8. Interactions
9. Overdosage
10. Pharmacology
   10.1. Use in pregnancy
   10.2. Use in lactation
11. Clinical Trials
12. Presentation and storage conditions
13. Name and address of the sponsor
14. Poisons Schedule of the medicine
15. Date of first inclusion in the Australian Register of Therapeutic Goods
16. Date of most recent amendment

Question for consideration

To assist with determining the most appropriate manner in which to address recommendation TR17, the following question is presented for further consideration:

- Is the current format for presenting information in PI and CMI relevant and useful to the end user?
- Are there other options for ensuring easier access to the most important information in the PI other than re-formatting?

Currency of PI and CMI

Having summarised the TGA’s current processes for updating the PI above, this section considers submissions made to the Transparency Review in context with these processes, summarises initiatives already being undertaken by the TGA as well as outlining further possible options which may address the issues raised in relation to maintaining the currency of PI across innovator and generic products.
Review of current concerns

A review of the public submissions to the Transparency Review has indicated there is a general view by stakeholders that PI and CMI are not kept up-to-date once the initial approval process has occurred and the medicine has been registered. Submissions also suggested that the TGA needs to put in place formal review mechanisms to ensure the accuracy and currency of PI and CMI documents.

The TGA wishes to further explore the implications of Recommendation TR17, particularly with respect to wording such as "... maintain the currency of CMI and PI". From one of the submissions to the Transparency Review, the following comment is noted:

"It would be excellent to have a system in place for ensuring the information in these leaflets is updated, rather than being the information supplied at the time the product is registered. At present, there is no requirement or incentive for companies to keep the information updated. CMI and PI appear to be updated mainly when the company is making a major marketing push for a new indication or when an adverse effect is serious and TGA requests a change to the information supplied".

Initiatives to maintain PI and CMI

Post transparency review initiatives

Since the Transparency Review was released in November 2010, the TGA has been undertaking numerous activities to provide stakeholders with better access to information about therapeutic goods approved for use in Australia.

The initial release of the ARTG search facility was somewhat limited in its capabilities to identify therapeutic goods entered in the ARTG. In February 2011, changes to the search facility were made to improve selection and searching of the ARTG and to standardise the views of products on it. Other enhancements also allow users to search for new products recently added to the ARTG and to search for products by nominated active ingredient.

Since November 2009, improved access to prescription medicine information for consumers and health professionals has also been achieved by facilitating access to a comprehensive source of up to date PI and CMI. What is provided, through the TGA website <http://www.tga.gov.au/about/ebs-picmi.htm>, is a single trusted source of all PI and CMI documents which support greater transparency of the regulatory process and is consistent with best international regulatory practice.

To further improve public access to this information, in May 2012, the TGA launched an improved interface for the publicly accessible e-Business Services (eBS) website. TGA eBusiness Services is an online portal that provides separate functions for consumers, health professionals and industry. The eBS provides publicly available information about current therapeutic goods by now hosting the Australian Register of Therapeutic Goods (ARTG) and the PI / CMI search facility <http://www.tga.gov.au/about/ebs-picmi.htm>.

The TGA has also recently conducted a review of business processes which apply to making the following kinds of minor variations to an entry of a prescription medicine in the ARTG (which in turn lead to subsequent changes to the medicine’s PI):

- corrections to the entry;
- safety-related requests;
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- 'self-assessable' requests; and
- Category 3 quality-related changes.

Most of these minor variations occur under section 9D of the Act. However, some of these quality-related variations occur by the making of an application under section 23 of the Act because they result in the creation of a 'separate and distinct good' and therefore require the submission and evaluation of data to support that the new good meets the required standards for quality, efficacy and safety.

Section 16 of the Act specifies that therapeutic goods are to be taken to be separate and distinct from other therapeutic goods if they are different in any of the following - formulation, composition, design specification or strength / size or dosage form or name or indications or directions for use or type of container.

The review aimed to clarify the existing administrative and legal processes relating to minor variations and to improve the transparency of the TGA's processes. The scope of the review included the existing processes that both, the TGA and sponsors undertake. These changes follow a previous process of communication and consultation, and will be implemented on Wednesday, 22 May 2013. Full details of the review, including revised guidance documents and new application forms have been published on the TGA website <http://www.tga.gov.au/industry/pm-notice-minor-variations-120612.htm>.

'Business as usual' activities

As noted above, the PI may need to be changed as a result of an application to vary an ARTG entry, or a change to the PI may be the only variation that is requested. The application types which can lead to the evaluation of a new PI or amendment to an existing PI include applications for the registration of a new chemical entity (including the addition of a new salt or ester, similar biological medicinal products and combination products), extension of indications, a variation to an existing registration, the registration of a new generic medicine or the addition of a new trade name to a medicine. The proposed variation determines the data required to be submitted and evaluated by the TGA.

Applications for the registration of new chemical entities, new indications, new strengths, use in new patient populations, new dosage instructions, etc may also require data that supports the efficacy and safety of the medicine or be supported by non-clinical data.

During the period 1 January 2010 – 31 January 2013, the TGA has approved or re-approved approximately 3,600 PIs and this includes approximately 1,550 Safety Related Notifications. (As of 31 March 2013, there were 12,654 ARTG registrations for prescription medicines).

The TGA also currently ensures PIs are kept up-to-date in relation to safety related changes through its safety monitoring activities and this is the highest priority from a risk-based perspective. However, there is no routine mechanism for reviewing each PI although there are processes in place that ensure that safety issues can be identified, reviewed and where needed PIs amended or other appropriate regulatory action undertaken. As noted in the Product Vigilance Framework, the identification of a safety issue can also be dealt with through non-regulatory actions, such as the provision of information and education on the TGA website or publication of articles in the Medicine Safety Update, published on the TGA website and in the Australian Prescriber.

As part of the TGA's post market monitoring program, during the past 12 months approximately 46 PIs for innovator and generic medicines have been updated following
reviews of adverse drug reaction case reports, new safety information (including sponsor initiated notifications to the TGA), literature reports and action initiated by overseas regulators. In addition to these completed PI reviews, as at April 2013, there are approximately 90 other PI reviews in progress.

The TGA has also established mechanisms to ensure that it works closely with the National Prescribing Service (NPS) to ensure timely dissemination of safety information related to the use of medicines on the ARTG to health care professionals.

**Further options to maintain PI and CMI**

*Updating of older PI documents*

There were further views expressed in submissions to the Transparency Review that while there is continual upgrading of recent PIs, this doesn’t occur with older PIs, to the extent that in some cases, even the medicine’s indications are outdated and do not conform with best medical practice.

Older products are subject to the same monitoring as newer products through the spontaneous adverse event reporting system and environmental scanning, including that of the medical literature undertaken by the TGA. Safety related changes to the PI are requested or education/information provided when new information comes to light.

Submissions to the Transparency Review raised the question as to whether PIs for older active ingredients should be updated to reflect the new indications and community practice; since over time and use, practice changes and use may not reflect the original indications sought by the sponsor for the product.

This issue concerns the ‘off label’ prescribing (and subsequent use) of medicines for indications which have not been approved by the TGA. Under the current legislative framework, changes to a medicine’s indication cannot be made by simply updating the PI as this creates a ‘separate and distinct good’ which requires the product sponsor to submit an application to the TGA for the medicine to include a new indication. This requires the submission of data that demonstrate the effectiveness and safety for this new population as well as agreeing to undertake pharmacovigilance activities required to monitor the safety of the product in this new population.

It is recognised that the cost of an application and a lack of data to support the ‘off label’ use may be seen as barriers to achieving this and further, there may be no commercial incentive for the sponsor to do this.

*Identifying changes to the PI*

One of the issues for sponsors of generic medicines (and for healthcare professionals and consumers) is identifying new safety information in the PI or CMI of a product – whether this relates to an innovator or generic product. Currently the PI and CMI documents do not identify where changes have been made and require comparison with previous versions of the documents. Previous PI and CMI documents are also not readily available for comparison and the TGA receives requests for previous PI on a regular basis.

A submission to the Transparency Review stated –

“The current method by which people access PI on the TGA site (and PBS) makes it impossible to know what changes have been made from the previous version(s) and why. This is key information for health professionals. We have to manually track
changes, without always being able to find (from other regulatory agencies or published medical literature) the reasons for them. This history of changes to PI is a useful feature of both EMA and FDA websites, which improves transparency of process and decision making.

A possible option to address this issue is to highlight changes to the PI in the search facility at the time of approval and publication of an updated PI. While this would facilitate the updating of PIs required for the sponsors of generic products, and therefore changes to be made to their own products, it would also clearly identify changes to the PI for prescribers.

A system to ensure that highlighting of changes was removed when new changes were made or a significant period of time had elapsed would also be needed. This could be considered in addition to making previous versions of the PI readily available to the public for comparison. In addition an automated system of notifying changes to sponsors of generic medicines could be developed. Another option would be to maintain archived PI documents for reference.

It should be noted that all of these options would require significant changes to current processes.

Unavailability of PI / CMI

Another issue that has been identified is that a prescription medicine may be on the ARTG but no PI or CMI is available. Current statistics indicate that approximately 12% of the prescription medicines entered in the ARTG do not have a PI lodged with the TGA. This includes products that were “grandfathered” at the time of commencement of the legislation in 1991, those goods that contain excipients only e.g. ‘water for injection’ that fails validation for lodgement into the PI/CMI search facility and those goods that are not currently being marketed in Australia.

To ensure that the public is aware why some products do not have available PI it has been suggested that the TGA should publish information that explains why products may be entered in the ARTG but do not have published or available PI/CMI.

Establishing better linkages between available medicine information

Since 2009 there has been an increased amount of information published on the TGA website about medicines registered on the ARTG. This includes the ARTG search facility, AusPARS (a summary of the evaluation of prescription medicines registered in Australia), PIs and CMIs. The TGA has been advised that some stakeholders encounter difficulties in locating all three repositories or are not aware that it is important to review the information in all of them in order to obtain the most complete set of information about the medicine of interest to them.

To assist with addressing these difficulties, information has recently been included on the TGA website which provides details and weblinks to all three search facilities from the one webpage - <http://www.tga.gov.au/consumers/information-public-tg.htm>.

Notwithstanding these details, it is suggested that it would be ideal if users could access all three search facilities from the one location of the TGA website, rather than having to search for, and access multiple pages. This would ensure the public is aware of all available information on the prescription medicine of interest.

The inclusion of conditions of registration as part of the ARTG entry could also be considered for addition to the search facility, as these conditions include information on
what additional activities (either pharmacovigilance or risk minimisation) a sponsor may be required to undertake to market a product in Australia.

The TGA will examine the practicality and resource implications of including hyperlinks from the publicly viewed entries in the ARTG search facility to the PI/CMI and AusPAR repositories for each specific Register entry that is selected by the external user. To achieve this, consideration also needs to be given to the difficulty of linking PI/CMI to multiple ARTG entries eg. for the same medicine registered with different strengths and the resources and IT capability to achieve this outcome and the overall benefit to prescribers and consumers.

Cancelled ARTG entries could automatically be archived or remain available to the public although this would need to be developed separately and may be technically difficult to achieve.

**Question for consideration**

To assist with determining the most appropriate manner in which to address recommendation TR17, the following question is presented for further consideration:

- Is there consensus on what is understood by maintaining the currency of the PI and CMI?
Some options to address recommendation TR17

In order to comprehensively address Recommendation TR17,

"The TGA explore mechanisms to maintain the currency of Consumer Medicines Information (CMI) and Approved Product Information (PI),"

the TGA will implement a range of mechanisms which aim to provide -

- an educational focus for consumers and healthcare professionals;
- evidence of updating and a process for ensuring the currency of PI and CMI; and
- provide clear public access to all relevant information.

These aims may be achieved by further developing or examining the feasibility of the following proposed options -

1. ease the ability of healthcare professionals to access the information which is most important to the safe and effective use of medicines by re-formatting the PI document;
2. identify changes made to PIs / CMIs by including the archive of previous versions in the public search facility and / or highlighting any changes in the current versions;
3. address the unavailability of some PIs / CMIs by publishing information that explains why products may be entered in the ARTG but do not have published or available PI/CMI;
4. ensure clearer public access to relevant information by examining the practicality of establishing linkages between the ARTG, PI/CMI and AusPar search facilities; and
5. publishing PI for OTC medicines in the search facility and whether CMI should be made available for all registered medicines.
### Appendix A: International comparison of PI formats

<table>
<thead>
<tr>
<th>Australia</th>
<th>European Medicines Agency</th>
<th>United States of America</th>
<th>Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name of the medicine</strong></td>
<td>Name of the medicinal product</td>
<td>Highlights: Recent major changes (with dates)</td>
<td>Part I: Health professional Information</td>
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<tr>
<td><strong>Description</strong></td>
<td>Qualitative and Quantitative composition</td>
<td>Indications and usage</td>
<td>Summary product information, route of administration, Dosage form/quantity, strength, clinically relevant non-medicinal ingredients</td>
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<tr>
<td><strong>Pharmacology</strong></td>
<td>Pharmaceutical Form</td>
<td>Dosage and administration</td>
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<tr>
<td><strong>Clinical Trials</strong></td>
<td>Clinical Particulars</td>
<td>Dosage forms and strengths</td>
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<tr>
<td><strong>Indications</strong></td>
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<td>Contraindications</td>
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<tr>
<td><strong>Contraindications</strong></td>
<td>4.2 Posology and method of administration</td>
<td>Warnings and precautions</td>
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<tr>
<td><strong>Precautions</strong></td>
<td>4.3 Contraindications</td>
<td>Adverse reactions</td>
<td></td>
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<tr>
<td><strong>Effects on fertility</strong></td>
<td>4.4 Special warnings and precautions for use</td>
<td>Use in specific populations: pregnancy, lactation, paediatrics, renal impairment</td>
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<tr>
<td><strong>Use in pregnancy</strong></td>
<td>4.5 Interaction with other medicines, products and other forms of interaction</td>
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<td></td>
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<tr>
<td><strong>Use in lactation</strong></td>
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<tr>
<td><strong>Paediatric use</strong></td>
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<tr>
<td><strong>Use in the elderly</strong></td>
<td>4.8 Undesirable effects</td>
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<tr>
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<tr>
<td><strong>Carcinogenicity</strong></td>
<td>Pharmacological properties</td>
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<td><strong>Effects on laboratory tests</strong></td>
<td>5.1 Pharmacodynamic properties</td>
<td>Warnings and precautions</td>
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<tr>
<td><strong>Interactions with other medicines</strong></td>
<td>5.2 Pharmacokinetic properties</td>
<td>Adverse Reactions</td>
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<td><strong>Adverse Effects</strong></td>
<td>5.3 Preclinical safety</td>
<td>Drug Interactions</td>
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<td>Drug interactions</td>
<td>Special handling instructions</td>
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<td>paediatrics, geriatrics, renal impairment</td>
<td>Dosage forms, composition and packaging</td>
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<td>Pharmaceutical particulars</td>
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<td>6.1 List of excipients</td>
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<td>Presentation and storage conditions</td>
<td>6.2 Incompatibilities</td>
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<td>6.4 Special precautions for storage</td>
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<td>6.5 Nature and contents of container</td>
<td>Description</td>
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<td>6.6 Special precautions for disposal</td>
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<td>Non-clinical toxicology</td>
<td>Clinical trials</td>
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<td>Clinical studies</td>
<td>Detailed Pharmacology</td>
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<td>How supplied/storage and handling</td>
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