



Review of Medicines and Medical Devices Regulation

Report on the regulatory
framework for medicines and
medical devices

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March 2015

Expert Panel

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**Report to the Minister for Health on the Regulatory
Framework for Medicines and Medical Devices**

31 March 2015

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INDEPENDENT REVIEW OF MEDICINES AND MEDICAL DEVICES REGULATION

The Hon Sussan Ley MP
Minister for Health
Parliament House
CANBERRA ACT 2600

Dear Minister Ley

The Independent Panel for the Review of Medicines and Medical Devices Regulation is pleased to present its Report on the first stage of the Review. In accordance with the Review's Terms of Reference, this Report examines and makes high level recommendations on the regulatory frameworks for medicines and medical devices, as well as on access to unapproved therapeutic goods in special circumstances. The Report makes recommendations on supporting infrastructure necessary to facilitate the implementation of the recommendations. Further, the Panel has identified and addressed a number of related issues within the text of the Report.

The Panel is mindful of the technological change and innovation that has occurred in the changing health care environment since the regulatory frameworks for medicines and medical devices were conceived. In framing its recommendations, the Panel has endeavoured to ensure that the National Regulatory Authority has the necessary tools, flexibility, and legislative underpinning to respond effectively to future challenges. This will ensure that it can maintain its place as a regulator that is highly regarded both nationally and internationally.

In undertaking the Review, the Panel sought comment regarding the regulation of medicines and medical devices from stakeholders over the November 2014 to January 2015 period, receiving over 100 submissions from consumers, industry and health professionals. In addition, a number of face-to-face and teleconference consultations were held, which were well attended by stakeholders.

The Panel has commenced work on Stage Two of the Review, examining the regulation of complementary medicines, with the release of a supplementary chapter to the Discussion Paper and a call for submissions on 20 February 2015. The Panel will also report on the regulation of advertising of therapeutic goods in Stage Two, to allow a single, whole-of-industry report, to be presented.

The Panel intends to present its Stage Two Report to Government mid-2015.

Yours sincerely

Emeritus Professor Lloyd Sansom /
Chair

Professor John Horvath AO

Mr Will Delaat AM

31 March 2015

cc: The Hon Tony Abbott MP, Prime Minister
The Hon Christian Porter MP, Parliamentary Secretary to the Prime Minister
Senator the Hon Fiona Nash, Assistant Minister for Health

ACKNOWLEDGEMENTS

The Panel would like to acknowledge the following people and organisations for their contribution throughout this process:

Therapeutic Goods Administration

The Panel would like to thank Adjunct Professor John Skerritt and the staff of the TGA for their openness in engaging with the Panel and for their timely responses to the Panel's many requests for information.

Secretariat Services

The Panel wishes to acknowledge the excellent support that it received from the secretariat in the management of the Review and in the preparation of the Review report:

Department of Health - Ms Cheryl Wilson, Ms Michelle Palombi, Ms Fran Verass, Mr Thomas Ashby, Ms Danielle Dalton, Mr Jonathan Ayre and Ms Julie Dennett.

Stakeholders

The Panel would also like to thank all the stakeholders and individuals who provided submissions for the Review, and to all those who attended the consultation forums.

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EXECUTIVE SUMMARY

The Independent Review of Medicines and Medical Devices Regulation commenced in October 2014. The Panel was engaged to assess the current regulatory framework and make recommendations on options to improve the way in which therapeutic goods are regulated in Australia. In undertaking the Review the panel has considered submissions and met with a range of consumer, health professional, and industry stakeholders.

Mindful of the increasing globalisation of the pharmaceutical and medical devices industries and the rapid pace of innovation and change within the health care sector, the Panel has identified opportunities to enhance the regulatory frameworks for medicines and medical devices with a view to positioning the Australian National Regulatory Authority (NRA) for the future. Continuing to harmonise the Australian regulatory system with international regulatory frameworks plays an important role in this regard. In identifying opportunities for reform, the Panel has been conscious of ensuring that there is no diminution of protections for the Australian public.

The Panel identified five core principles which underpinned the Review and provided a lens through which it could view the issues and options brought before it (Chapter One). We were also cognisant of the fact that the Review was only looking at one aspect of a complex regulatory system and that interface issues needed to be carefully managed, as a change at one point has the potential to impact other parts of the health system, such as subsidy programmes (Chapter Two).

Australia's NRA for medicines and medical devices, the Therapeutic Goods Administration (TGA), has an excellent reputation both internationally and domestically for its work in ensuring the availability of high quality, safe, and efficacious therapeutic products on the Australian market. The TGA benchmarks well against comparable overseas NRAs in its regulation of medicines, however its performance in respect of devices is less notable. Retaining Australia's regulatory capacity and decision making authority is critical (Chapter Three).

In undertaking the Review, the Panel has assessed the regulatory frameworks for medicines (Chapter Four) and medical devices (Chapter Five) to ascertain if they are fit-for-purpose and whether processes are adequately streamlined and flexible. The Panel has also looked for opportunities to reduce duplication and inefficiencies. In doing so, it has made recommendations to:

- expand the pathways by which sponsors can seek marketing approval for a medicine or medical device, including making provision for utilisation of assessments conducted by comparable overseas regulators, and for expedited assessments in defined circumstances;

- identify comparable overseas NRAs using transparent criteria;
- enhance post-market monitoring of medicines and medical devices and streamline post-market requirements in respect of products in the Australian Register of Therapeutic Goods; and
- improve transparency and predictability of processes and decisions, to build trust and confidence in the NRA's ability to ensure Australians have timely access to high quality, safe and efficacious products.

The Panel has also made recommendations to streamline access by consumers and health professionals to medicines and medical devices that have not been approved for use in Australia, in certain circumstances (Chapter Six).

Finally, the Panel has identified essential infrastructure to support the implementation of its recommendations (Chapter Seven), including an appropriate legislative framework; revised decision making and organisational structures; and mechanisms to support enhanced post-market monitoring of medicines and medical devices for safety and efficacy.

We invite you to examine the full set of recommendations in the following pages.

RECOMMENDATIONS

RECOMMENDATIONS RELATING TO THE NATIONAL REGULATORY AUTHORITY ROLE

Recommendation One

The Panel recommends that Australia maintain the capacity to undertake assessments of therapeutic goods for safety, quality and efficacy.

Recommendation Two

The Panel recommends that the Australian Government, as a sovereign entity, retain responsibility for approving the inclusion of therapeutic goods in the Australian Register of Therapeutic Goods (ARTG).

REGULATIONS RELATING TO THE MEDICINES REGULATORY FRAMEWORK

Recommendation Three

The Panel recommends that there be three pathways to seek registration of a new chemical entity and its inclusion in the ARTG:

Pathway Option	Description
Pathway One	Submission of a complete dossier for de novo assessment. This assessment may be undertaken in full by the Australian National Regulatory Authority (NRA) or via a work-sharing arrangement between the Australian NRA and a comparable overseas NRA.
Pathway Two	Submission of an un-redacted evaluation report from a comparable overseas NRA, along with a copy of the dossier submitted to that NRA and an Australian specific Module 1, for assessment by the Australian NRA. The Australian NRA to make a recommendation regarding registration of the medicine once it has considered the data within the Australian context.
Pathway Three	Application for expedited approval of a medicine in certain circumstances. Any expedited approval pathway should make provision for submission of data and assessment consistent with requirements of Pathways One and Two as outlined above.

Recommendation Four

The Panel recommends that there be two pathways to seek registration of a generic medicine or biosimilar and its inclusion in the ARTG:

Pathway Option	Description
Pathway One	Submission of a complete dossier for de novo assessment. This assessment may be undertaken in full by the Australian NRA or via

a work-sharing arrangement between the Australian NRA and a comparable overseas NRA.

Pathway Two Submission, to the Australian NRA for assessment, of an un-redacted evaluation report from a comparable overseas NRA, along with a copy of the dossier submitted to that NRA and an Australian specific Module 1, and:

- A. If the product is a generic product, evidence that the reference product used by the comparable overseas NRA when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product; or
- B. If the product is a biosimilar, evidence that the overseas reference product and the Australian reference product are the same.

The Australian NRA to make a recommendation regarding registration of the medicine once it has considered the data within the Australian context.

Recommendation Five

The Panel recommends that the Australian Government develop and apply transparent criteria for identifying comparable overseas NRAs. Such criteria might include that a comparable overseas NRA must:

- A. Regulate for a population demographic that is broadly representative of the Australian population and has similar health outcomes; and
- B. Adopt ICH guidelines; and
- C. Have a credible and consistent track record of approving safe and effective medicines; and
- D. Conduct de novo evaluations of data dossiers for all types of medicines, e.g. new chemical entities, generics and biosimilars; and
- E. Have processes in place that require peer review or independent assessment of the evaluations that they conduct; and
- F. Have evaluators with the necessary technical and clinical capabilities to evaluate the data provided and make an independent regulatory decision in accordance with the ICH guidelines; and
- G. Provide access to un-redacted evaluation reports and, where applicable, individual patient data; and

Communicate and prepare evaluation reports in the English language.

Recommendation Six

The Panel recommends that in circumstances where a sponsor seeks registration of a **new chemical entity** in Australia via Pathway Two and has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA:

1. The Australian NRA makes a recommendation regarding registration of the new chemical entity once it has satisfied itself that:
 - A. The new chemical entity is identical in dosage form, strength, formulation and indications; and
 - B. The new chemical entity will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian NRA has co-recognition); and
 - C. The manufacturing process to produce the new chemical entity will be identical to that assessed by the comparable overseas NRA for the overseas product; and
 - D. There are no specific issues regarding applicability of the submitted data to the Australian context that need to be examined; and
 - E. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements
2. Where the new chemical entity seeking registration in Australia does not meet conditions 1A to 1D above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.
 - A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information, and Consumer Medicine Information is appropriate and consistent with Australian requirements before making a recommendation regarding registration of the new chemical entity in the ARTG.
 - B. Where differences between the new chemical entity seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the new chemical entity in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed and/or taken into consideration in assessing risk and benefit; and
 - II. Assess whether the proposed product labelling, Product Information, and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Recommendation Seven

The Panel recommends that in circumstances where a sponsor seeks registration of a **generic medicine or biosimilar** in Australia via Pathway Two and has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA:

1. The Australian NRA makes a recommendation regarding registration of the generic medicine or biosimilar once it has satisfied itself that:
 - A. The generic medicine or biosimilar is identical in dosage form, strength, and formulation to the product approved by the comparable overseas NRA; and
 - B. The generic medicine or biosimilar will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian authority has co-recognition); and
 - C. The manufacturing process to produce the generic medicine or biosimilar will be identical to that assessed by the comparable overseas NRA for the overseas product; and
 - D. If the product is a generic medicine - the reference product used by the comparable overseas NRA when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product; or
 - E. If the product is a biosimilar - the overseas reference product and the Australian reference product were the same; and
 - F. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.
2. Where the **generic medicine** seeking registration in Australia does not meet conditions 1A to 1D above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.
 - A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements before making a recommendation regarding registration of the generic medicine in the ARTG.
 - B. Where differences between the generic medicine seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the generic medicine in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed; and
 - II. Assess whether the proposed product labelling, Product Information and

Consumer Medicine Information are appropriate and consistent with Australian requirements.

3. Where the **biosimilar** seeking registration in Australia does not meet conditions 1A to 1C and 1E above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.
 - A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements before making a recommendation regarding registration of the biosimilar in the ARTG.
 - B. Where differences between the biosimilar seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the biosimilar in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed; and
 - II. Assess whether the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Recommendation Eight

The Panel recommends that the Australian NRA should develop and apply transparent criteria under which application may be made for accelerated assessment of promising new medicines (Pathway Three). Such criteria should not be inconsistent with those adopted by comparable overseas NRAs for accelerated assessment.

Recommendation Nine

The Panel recommends that in circumstances where the Australian NRA has approved an expedited approval process utilising Pathway Two, and the sponsor has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA, the Australian NRA makes a recommendation regarding registration of the new chemical entity once it has satisfied itself that:

- A. The new chemical entity is identical in dosage form, strength, formulation and indications; and
- B. The new chemical entity will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian regulator has co-recognition); and
- C. The manufacturing process to produce the new chemical entity will be identical

- to that assessed by the comparable overseas NRA for the overseas product; and
- D. There are no specific issues regarding applicability to the Australian context that need to be examined; and
 - E. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements; and
 - F. Any conditions placed on the medicine by the comparable overseas NRA are applicable to the Australian context; and
 - G. Data provided to the comparable overseas NRA under these conditions will be available to the Australian NRA in a timely way.

Recommendation Ten

The Panel recommends that where accelerated approval occurs following evaluation of a more limited data dossier than would be required for a submission under Pathway One, registration of the medicine in the ARTG should be:

1. Provisional and time-limited, with a requirement for the sponsor to collect and submit further data to demonstrate safety, quality and efficacy in order for the product to be granted full registration.
2. Subject to any conditions imposed by the Australian NRA (which should be consistent with those imposed by a comparable overseas NRA if relevant and applicable to the Australian context).
3. Subject to the provision of clear advice to consumers and health practitioners that the medicine has been granted provisional approval and the implications of that for the consumer/health practitioner.

Recommendation Eleven

The Panel recommends that the *Scheduling Policy Framework* be reviewed, in consultation with State and Territory Governments, to provide for:

1. The development and adoption of a formal risk-benefit methodology to assess scheduling applications; and
2. Opportunities to enhance input from interested parties into the scheduling process.

Recommendation Twelve

The Panel recommends that the *Schedule 3 Advertising Guidelines* be reviewed, in consultation with State and Territory Governments, and in concert with the review of the *Scheduling Policy Framework*, to:

1. Provide for the development and adoption of a formal risk-benefit methodology for the assessment of Schedule 3 substances for inclusion on Appendix H of the *Poisons Standard*; and

2. Identify synergies between application requirements for re-scheduling and for inclusion of a Schedule 3 substance on Appendix H, so as to streamline these processes and reduce duplication.

Recommendation Thirteen

The Panel recommends that Australia adopt a risk-based approach to the management of variations to medicines registered in the ARTG. This approach should provide for:

1. Notification of variations to the Australian NRA in circumstances where the variation does not impact the quality, safety or efficacy of the medicine. This approach should be harmonised with that adopted by the EU, unless there is a clear rationale not to do so.
2. Assessment of the variation by the Australian NRA in circumstances where the variation has the potential to impact the safety, quality or efficacy of the medicine. This assessment to be abridged in scope, so that only those aspects of the data dossier that require evaluation in order to establish the continued safety, quality and efficacy of the medicine following implementation of the proposed variation are examined (abridged assessment).
3. Reduced legislative timeframes for abridged assessments.
4. Fees for abridged assessments that reflect cost recovery principles.
5. Electronic submission of data.

Recommendation Fourteen

The Panel recommends that the Australian Government undertake a review of the range of products currently listed in the ARTG (not including complementary medicines) and subject to regulation under the medicines framework, with a view to ensuring that:

1. Products that might best be regulated under other regulatory frameworks, without undermining public health and safety, are removed from the auspices of the Act; and
2. Goods remaining under the auspices of the Act are subject to regulatory requirements that are commensurate with the risk posed by the regulated products.

RECOMMENDATIONS RELATING TO THE MEDICAL DEVICES REGULATORY FRAMEWORK

Recommendation Fifteen

The Panel recommends that:

Class I, non-sterile and non-measuring devices, continue to be included in the ARTG on the basis of a self-assessment by the device manufacturer. NRA communications directed at consumers and health professionals should make it clear that such devices have not been subject to any independent assessment.

In order to provide timely access to devices that are safe, high quality and fit for purpose, there be multiple pathways to seek approval for the inclusion of other classes of medical device in the ARTG. Such pathways to provide for:

Pathway Option	Description
Pathway One	Conformity Assessment to occur within Australia by either: <ul style="list-style-type: none">A. The Australian NRA; orB. A body designated by the Australian NRA to undertake Conformity Assessments of medical devices for the Australian market.
Pathway Two	Utilisation of marketing approval for the device in an overseas market in circumstances where the device has been: <ul style="list-style-type: none">A. Conformity Assessed by a body that has been designated to undertake Conformity Assessments by a comparable overseas <i>Designating Authority</i>; orB. Approved by a comparable overseas NRA.
Pathway Three	Expedited approval of medical devices in certain circumstances.

Recommendation Sixteen

The Panel recommends that the Australian Government develop transparent criteria that it will utilise in order to designate suitably qualified bodies within Australia to undertake Conformity Assessments of medical devices [Recommendation Fifteen, Pathway 1B].

Such criteria to:

1. Include capacity to set specific requirements for different classes of medical devices; and
2. Be developed in consultation with health care consumers, health professionals, the medical devices industry and the NRA.

Recommendation Seventeen

The Panel recommends that:

1. The Australian Government develop and apply transparent criteria for identifying:
 - A. Comparable overseas *Designating Authorities* [Recommendation Fifteen, Pathway 2A]; and
 - B. Comparable overseas NRAs for the evaluation of medical devices [Recommendation Fifteen, Pathway 2B].
2. These criteria are developed in consultation with health care consumers, health professionals, the medical devices industry, and the NRA and give consideration to

factors such as:

- A. Population demographics and health outcomes.
- B. Adoption of International Medical Device Regulators Forum guidelines.
- C. The track record of the organisation in evaluating/assessing medical devices and/or overseeing the evaluation/assessment of medical devices.
- D. Independence and impartiality.
- E. Transparency of systems and processes.
- F. Technical competence.
- G. Utilisation of Quality Management Systems.
- H. Accountability, including independent review/audit.
- I. Reporting and communication.
- J. Timeliness of access to information and data.
- K. Compatibility of evaluation/assessment of medical devices with the Australian *Essential Principles*.

Recommendation Eighteen

The Panel recommends that, where an application for inclusion of a medical device in the ARTG is made utilising Pathway Two, and all necessary documentation is provided to the Australian NRA:

1. The Australian NRA make a recommendation regarding inclusion of the medical device once it has satisfied itself that:
 - A. The device has been correctly classified; and
 - B. The 'marketing approval' documentation is in order and meets Australian requirements; and
 - C. The product is identical to the one assessed by the Notified Body or comparable overseas NRA, having been made in the same manufacturing facility, of the same materials, and for the same intended purpose; and
 - D. There are no specific issues regarding applicability to the Australian context that need to be examined, including in respect to post-market monitoring and risk management; and
 - E. Proposed product labelling and product information/instructions are appropriate and consistent with Australian requirements; and
 - F. Any conditions or provisions that are imposed on the marketing approval of the medical device under the terms of the overseas marketing approval are able to be replicated and complied with in the Australian market.

2. Where the medical device does not meet conditions 1A to 1F above, the Australian NRA should work with the sponsor to correct any deficiencies, or undertake such further assessment as is necessary to satisfy itself that the product is safe and effective, prior to making a recommendation on the inclusion of the medical device in the ARTG.

Recommendation Nineteen

The Panel recommends that:

1. The Australian Government develop transparent criteria under which application may be made for accelerated assessment of novel medical devices for inclusion in the ARTG.
2. In circumstances where accelerated assessment is granted, the Australian NRA have capacity to place conditions on the inclusion of the medical device in the ARTG.

Recommendation Twenty

The Panel recommends that:

1. The regulation of medical devices by the Australian NRA is, wherever possible, aligned with the European Union framework including in respect of the:
 - A. Classification of medical devices;
 - B. *Essential Principles/Requirements*.
 - C. Adoption of a risk-based approach to variations to medical devices.
2. Should the Australian NRA seek to apply specific requirements, there must be a clear rationale to do so.

Recommendation Twenty One

The Panel recommends that the NRA establish target timeframes that reflect international benchmarks and the typical lifecycle of a medical device for:

1. Conformity assessments conducted under Pathway One; and
2. Recommendations about inclusion of a device in the ARTG following submission of an application for inclusion under Pathway 1B or Pathway Two.

Recommendation Twenty Two

The Panel recommends that:

1. All high-risk implantable devices are included in a registry that is compliant with the

requirements for registries established by the Australian Commission on Safety and Quality in Health Care (ACSQHC).

2. Responsibility for ensuring that registries are operated consistent with the ACSQHC requirements should rest with the NRA.
3. Data collected by device registries should be made available to the NRA in a timely manner to inform post-market monitoring.
4. The NRA should implement an active programme of analysis and reporting on adverse events, and associated data, collected through registries or by other means.
5. The NRA should continue collaborative activities with overseas medical device regulators to actively share registry and other monitoring data, with a view to facilitating timely identification of emerging safety concerns and to inform better clinical practice.

Recommendation Twenty Three

The Panel recommends that the Australian Government undertake a review of the range of products currently classified as Class I medical devices, with a view to reclassifying products as consumer goods in circumstances where the product poses little or no risk to consumers should it not perform as specified or malfunction.

RECOMMENDATIONS RELATING TO ACCESS TO UNAPPROVED THERAPEUTIC GOODS

Recommendation Twenty Four

The Panel recommends that:

1. The current criteria and processes for Category A SAS patients remain unchanged.
2. The Australian NRA develop and apply transparent criteria for identifying Category B applications that could be subject to automatic approval. Such criteria might include applications for products that:
 - A. Were previously registered in the ARTG for the proposed indication and were not cancelled or withdrawn for safety reasons;
 - B. Have been approved for the proposed indication by a comparable overseas NRA;
 - C. Have been deemed by the Australian NRA as suitable for automatic approval for treatment of a particular indication; and
 - D. Have been approved by the Australian NRA under Category B in response to a medicine shortage, in circumstances where there is no need to triage the use of the unapproved product.
3. The Australian NRA continue to require individual assessment and approval for certain Category B products, including products that:
 - A. Do not have a history of safe use for the proposed indication through either the SAS scheme or in comparable overseas markets;
 - B. Have not been approved for the proposed indication by a comparable overseas NRA;
 - C. Were cancelled or withdrawn from the ARTG for safety reasons, or had an application for registration rejected by the Australian NRA for safety reasons;
 - D. Were previously approved overseas but were withdrawn or removed from the market for safety reasons; and
 - E. Have been approved by one comparable overseas NRA for an indication but were rejected by another comparable overseas NRA for that indication.

Recommendation Twenty Five

The Panel recommends that the NRA establish an integrated, online system to manage SAS notifications, approvals and reporting requirements. Such a system should have capacity to:

1. Establish a Schedule of Category B Products that are eligible for automatic approval;
2. Allow clinicians to enter a restriction code to auto-populate information relating to SAS notifications, automatic approvals and applications;
3. Utilise smart-forms to reduce unnecessary administrative burden on clinicians and sponsors; and
4. Provide data for real-time monitoring of the SAS by the Australian NRA, to identify potential trends and abuses.

Recommendation Twenty Six

The Panel recommends that the role of the NRA under the Authorised Prescriber Scheme be to authorise a prescriber, and the supply of an unapproved medicine or device to that prescriber, in circumstances where it is satisfied that:

1. Approval for the prescriber to use the unapproved medicine or device in the proposed patient cohort has been provided by a properly constituted ethics committee; and
2. There is no medicine or device available in the ARTG that would be suitable in the proposed circumstances; and
3. There are no emerging safety concerns in respect of the medicine or device that may alter the consideration of risk and benefit.

RECOMMENDATIONS RELATING TO ENABLERS AND FUNCTIONALITY

Recommendation Twenty Seven

The Panel recommends that the Australian government develop a more comprehensive post-market monitoring scheme for medicines and medical devices. Such a scheme to include:

1. Better integration and timely analysis of available datasets, including analysis of matched de-identified data from the Pharmaceutical Benefits Scheme, Medical Benefits Scheme, eHealth records, hospital records, private health insurance records and device and other relevant registries and datasets;
2. Establishment and maintenance of registries for all high-risk implantable devices;
3. Implementation of a scheme to alert practitioners and consumers that a drug is newly registered and to encourage reporting of any adverse events;
4. Provision for electronic reporting of adverse events; and
5. Enhanced collaboration with overseas NRAs to share information relating to safety or efficacy.

Recommendation Twenty Eight

The Panel recommends that:

1. The Australian Government undertake a comprehensive review of the legislative framework underpinning the regulation of therapeutic goods, including a review of the *Therapeutic Goods Act 1989* (the Act) and associated Regulations in their entirety, with a view to simplifying its structure and language to achieve a more user-friendly approach. In doing so:
 - A. the objects clause of the Act should be amended to better reflect the public health and consumer protection outcomes that the Act aims to achieve; and
 - B. the Act should be re-drafted in such a way as to:
 - I. maximise transparency of both policies and processes;
 - II. provide flexibility for the Australian NRA to appropriately modify processes to ensure a thorough analysis of safety, quality and efficacy, while avoiding unnecessary duplication;
 - III. recognise that medicines and medical devices are very different products and should be regulated accordingly;
 - IV. provide for graduated penalties that allow the NRA to respond appropriately to the full range of non-compliance from repeated minor breaches through to serious non-compliance;
 - V. reflect contemporary practice standards for health professionals; and

- VI. maximise the capacity of the Australian NRA to utilise electronic transactions and to collect information once to use for multiple purposes.
2. The Australian Government consider asking the Australian Law Reform Commission to undertake the proposed review and present a report to Government and to the Parliament.

Recommendation Twenty Nine

The Panel recommends that:

1. The decision making process for the inclusion of medicines and medical devices in the ARTG be changed to provide for:
 - A. The Australian Government's Chief Medical Officer to be the delegate for decisions.
 - B. The establishment of a statutory committee to make recommendations to the Chief Medical Officer about registration of a medicine in the ARTG (Advisory Committee on Medicines).
 - C. The establishment of a statutory committee to make recommendations to the Chief Medical Officer about inclusion of a medical device in the ARTG (Advisory Committee on Medical Devices).
2. Both Committees be composed of experts across relevant fields and consumer representation and have the authority to:
 - A. Consider information submitted by the product sponsor.
 - B. Consider evaluation reports prepared by or for the Australian NRA and comparable overseas NRAs.
 - C. Take evidence from sponsors, the Australian NRA, and any other parties which the committees consider may have a reasonable interest in the registration of the medication or medical device.
 - D. Take into account any other information that the committees consider may be material in their deliberations.

Recommendation Thirty

The Panel recommends that the Advisory Committee on Medicines Scheduling (ACMS) become a sub-committee of the Advisory Committee on Medicines and make recommendations to that committee about the:

1. Scheduling of medicines; and
2. Inclusion of medical substances in Appendix H of the *Poisons Standard*.

Recommendation Thirty One

The Panel recommends that the Australian Government give consideration to organisational structures that will facilitate improved integration of:

1. Pre-market regulation of medicines and medical devices with health technology assessment of these products for subsidy and other purposes; and
2. Post-market monitoring of medicines and medical devices for safety, efficacy and cost-effectiveness.

Recommendation Thirty Two

The Panel recommends that the Australian Government review and enhance the NRA's funding model, with a view to providing either a dedicated annual appropriation or other appropriate budgetary arrangements on an 'as-needs' or routine capacity basis, to enable it to more effectively fulfil its mandate to act in the public interest and to ensure that genuine and systemic improvements to its capacity, expertise and operation are achieved.

GLOSSARY OF ABBREVIATIONS

ACCC	Australian Competition and Consumer Commission
ACL	Australian Consumer Law
ACMS	Advisory Committee on Medicines Scheduling
ACSQHC	Australian Commission on Safety and Quality in Health Care
AIMD	Active Implantable Medical Device
ALRC	Australian Law Reform Commission
ARTG	Australian Register of Therapeutic Goods
AusPAR	Australian Public Assessment Report
CAB	Conformity Assessment Body
CTD	Common Technical Document
CIRS	Centre for Innovation in Regulatory Science
CMI	Consumer Medicines Information
CMO	Australian Government's Chief Medical Officer
EAP	Expedited Access Pre-market Assessment (US)
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
GHTF	Global Harmonization Task Force
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMRA	International Coalition of Medicines Regulatory Authorities
IMDRF	International Medical Device Regulators Forum
IVD	<i>In vitro</i> diagnostic
MDD	Medical Devices Directive

MHRA	Medicines and Healthcare Products Regulatory Agency (UK)
MRA	Mutual Recognition Agreement
MTAA	Medical Technology Association of Australia
NASs	New Active Substances
NEHTA	National Electronic Health Transition Authority
NJRR	Australian Orthopaedic Association National Joint Replacement Registry
NCCTG	National Coordinating Committee on Therapeutic Goods
NCE	New Chemical Entity
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NRA	National Regulatory Authority – currently the TGA in Australia
OECD	Organisation for Economic Cooperation and Development
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PDMA	Pharmaceuticals and Medical Devices Agency (Japan)
PI	Product Information
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
RMP	Risk Management Plan
SAS	Special Access Scheme
SMEs	Small to Medium sized Enterprises
TGA	Therapeutic Goods Administration
UDI	Unique Device Identifier
UPI	Unique Product Identifier
WHO	World Health Organization

CHAPTER ONE: BACKGROUND TO THE REVIEW

On 24 October 2014 the then Minister for Health, the Hon Peter Dutton MP and the Assistant Minister for Health, Senator the Hon Fiona Nash, announced the establishment of an expert panel to undertake an independent Review of Medicines and Medical Devices Regulation (the Review). In announcing the Review, Minister Dutton noted that medical technology is constantly evolving and that a modern regulatory framework was required to ensure Australians can access the latest treatments in a timely manner. Senator Nash indicated the Review was a key step in efforts to remove ineffective regulation and encourage greater competition and innovation in the medicines and medical devices sectors and would complement the Government's Innovation and Competitiveness Agenda.

1.1 Objective of the Review

The objective of the Review is to make recommendations to assist the Government to enhance the regulatory framework for medicines and medical devices so that:

- Australia continues to be well positioned to respond effectively to global trends in the development, manufacture, marketing and regulation of therapeutic goods.
- Areas of unnecessary, duplicative or ineffective regulation are removed or streamlined without undermining the safety or quality of therapeutic goods available in Australia.

1.2 Terms of Reference

The Panel was asked to undertake the Review in accordance with the following Terms of Reference.

Background

1. Australia has, by a number of different measures (life expectancy, survival with cardiovascular disease, survival with a range of cancers), amongst the best health outcomes of the OECD countries.
2. The regulatory framework of the Therapeutic Goods Administration (TGA) provides an important protection to the Australian community ensuring only safe and effective medicines and medical devices are granted authority to be marketed and/or exported.
3. The TGA also performs crucial post-market roles including the regulation of advertising for therapeutic products and the monitoring of adverse events to ensure the ongoing safety of therapeutic products.
4. A safe and effective regulatory framework for medicines and medical devices should balance safety and market access priorities to the benefit of patients and industry and align with the government's commitment to increase productivity and competitiveness.

5. It is timely to review the regulatory framework and processes under which the TGA operates, to identify opportunities to improve its operations. This will ensure the TGA is able to operate effectively and efficiently in comparison with high quality international regulators, in respect of regulatory imposts such as timeframes and costs to industry, while also maintaining appropriate public health and safety protections.

Scope of the Review

6. The Review will benchmark TGA regulatory arrangements against trusted international authorities.
7. The Review will make recommendations and related implementation information to:
 - a. Ensure there is an appropriate balance between risk and benefit in the regulation of prescription, over-the-counter, complementary medicines and medical devices, as well as access for individuals to unapproved medicines and medical devices;
 - b. Simplify and streamline the approval processes undertaken by TGA. This will include recommendations on:
 - i. fast tracking approvals processes for medicines and medical devices;
 - ii. opportunities for working together with trusted regulators in other jurisdictions, including the potential for work-sharing assessments for products marketed in multiple countries; and
 - iii. exploring how risk assessments, standards and determinations of trusted regulators can be used more extensively by Australian regulators when approving the supply of medicines and medical devices.
 - c. Ensure regulatory arrangements are sufficiently flexible to accommodate developments in medicines and medical devices, including exploring opportunities to streamline approvals that cross regulatory categories;
 - d. Improve the processes that assist industry, researchers and consumers to navigate the regulatory system for medicines and medical devices;
 - e. Support work underway on medical device reforms and clinical trial approval arrangements in Australia; and
 - f. Any other matters that the review committee regards as important and relevant to the safe and efficient supply of effective medicines and medical devices to the Australian people.

8. The Review will not make recommendations in relation to:
 - a. Any aspect of the Pharmaceutical Benefits Scheme;
 - b. Work by the Department of Health on the reimbursement systems, including reimbursement and or subsidy of medicine and medical devices;
 - c. National Health and Medical Research Council arrangements relating to research and development; or
 - d. Work currently underway by the Department of Health and the Department of Industry on ethics processes for clinical trials.
9. The Review report will be provided to the Minister for Health, copied to the Prime Minister, the Assistant Minister for Health, and the Parliamentary Secretary to the Prime Minister responsible for deregulation, by 31 March 2015.

1.2.1 Additional requirements

In addition to the Terms of Reference the Panel was asked to identify:

- Opportunities for reducing red tape burden in the short and long term.
- Strategies for ensuring red tape reduction can be sustained.
- Issues threatening the achievement of reductions in regulatory burden.

1.3 Timeframe for the Review

The Panel is undertaking the Review in two stages:

Stage one – The first stage of the Review is the subject of this report and focuses on the regulation of prescription medicines, over-the-counter (OTC) medicines and medical devices.

Stage two – The second stage of the Review will focus on the regulatory framework for complementary medicines and for the advertising of therapeutic goods. While the Panel sought comment from stakeholders on the advertising of medicines and medical devices as part of stage one of the Review, it did not consider it appropriate to make recommendations on this issue until it had also considered advertising in the context of complementary medicines. The Panel will provide its stage two report to the Government by mid-2015.

1.4 The Review Panel



Emeritus Professor Lloyd Sansom AO (Chair)

Professor Sansom is a distinguished educator, researcher and policy adviser. He has sat on numerous government and industry advisory groups. He played a major role in the development of Australia's National Medicines Policy and was Chair of the Pharmaceutical Benefits Advisory Committee between 2001 and 2012.



Mr Will Delaat AM

Mr Delaat has over 40 years' experience in the pharmaceuticals industry in a range of roles. He was Managing Director of Merck, Sharp & Dohme (Australia/NZ) for 11 years to 2008 and the Independent Chairman of Medicines Australia until December 2011. Mr Delaat is currently on the boards of a number of pharmaceutical companies including Pharmaxis Pty Ltd and EnGeneIC Ltd.



Professor John Horvath AO

Professor Horvath was the Australian Government's Chief Medical Officer from 2003 to 2009. He continues to advise the Department of Health as principal medical consultant and is on numerous health related boards and committees, including the Prostheses List Advisory Committee, which he chairs.

1.5 Review Secretariat

The Review Panel has been supported by a small Secretariat located within the Best Practice Regulation and Deregulation Division, Australian Government Department of Health.

1.6 Review Methodology

In undertaking the Review the Panel was cognisant of the importance of understanding stakeholder views about the current regulatory framework for medicines and medical devices. In particular, what aspects of the regulatory process were working effectively and where was there room for improvement? The reporting timeframes for the Review were not conducive to the Panel undertaking widespread consultation with stakeholders throughout the Review process. As such, in order to rapidly develop an understanding of what some of the key issues were from the perspective of different stakeholders, the Panel undertook an analysis of stakeholder submissions to previous reviews or consultations. As a

result of that analysis the Panel identified five key themes that highlighted the concerns previously raised by stakeholders about the regulatory framework for medicines and medical devices. These themes were:

1. Duplication of regulatory processes, which was seen as creating unnecessary regulatory burden on industry and undermining timely access to new technologies.
2. Lack of flexibility, which was seen as hindering early access to innovative products.
3. Regulatory requirements were not considered to be commensurate with the risk posed by some regulated products.
4. The regulatory framework was viewed as overly complex and not well understood by those who are required to interact with it.
5. Some regulatory processes were considered to be overly burdensome and out of step with technology.

In addition to identifying these core themes, which assisted the Panel to summarise and categorise the concerns that had previously been expressed by stakeholders about the regulation of medicines and medical devices, the Panel identified five key principles which were considered appropriate to underpin the Review. These principles provided a lens through which the Panel could view the issues and options brought before it.

1.6.1 Principles underpinning the Review

- | | |
|--------------------|--|
| Principle 1 | The role of regulation is to manage risk in order to protect public health and safety. |
| Principle 2 | The level of regulation should be commensurate with the risk posed by the regulated products. |
| Principle 3 | A risk-benefit approach to the regulation of therapeutic goods is appropriate. |
| Principle 4 | The regulation of therapeutic goods should take a whole-of-lifecycle approach. As a result, the regulatory system must: <ul style="list-style-type: none">• Have capacity to source and analyse data as it becomes available.• Recognise and respond, in a timely way, to changes in the risk profile of products across their lifecycle.• Provide for whole of life solutions, from product development to withdrawal/disinvestment.• Be transparent and understood by all stakeholders, including manufacturers and sponsors of therapeutic goods, health professionals, and consumers. |

- Principle 5** The ultimate responsibility for medicines and medical devices regulation should remain with the Commonwealth.
- Australia should maintain its capacity to undertake assessments of medicines and medical devices for safety, quality and efficacy.
 - The role of the regulator undertaking this assessment should be considered in light of approaches taken internationally.

1.6.2 Discussion papers

Having reviewed previous submissions and identified core principles to underpin the Review, the Panel developed two discussion papers that summarised its understanding of the issues and concerns held by stakeholders related to the regulation of medicines and medical devices by the TGA. The first discussion paper, released on 21 November 2014, addressed issues relating to the regulation of prescription and OTC medicines and medical devices. The subsequent discussion paper was released on 20 February 2015 and addressed issues relating to the regulation of complementary medicines.

The discussion papers summarised concerns that had been expressed by stakeholders in the past about the regulation of medicines (including complementary medicines) and medical devices, and some of the options put forward by stakeholders to address these concerns. The Panel included a series of key *questions for consideration* in each discussion paper as a means of encouraging stakeholders to explore each issue further. The intent was to promote a dialogue about the issues raised and assist the Panel form a view about whether stakeholders had a shared understanding of the issues and options for the future.

Both discussion papers were published on the Department of Health's website and accompanied by a call for submissions inviting stakeholders to provide input to the Review. The call for submissions was also emailed to a broad range of consumer, industry and health professional peak bodies, as well as to organisations or individuals who had registered an interest in the Review. Submissions responding to the first discussion paper closed on 5 January 2015, although late submissions were still considered. The submission period for responses to the discussion paper on complementary medicines is ongoing at the time of this report.

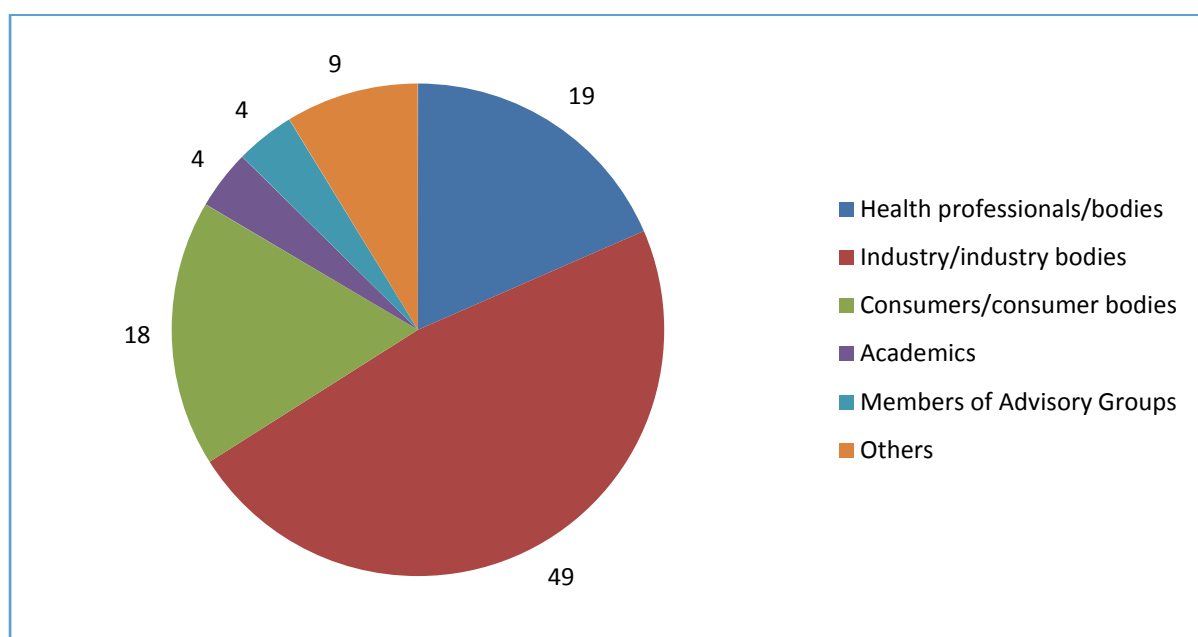
1.6.3 Submissions

In response to the *Review of Medicines and Medical Devices Regulation Discussion Paper*, the Panel received 103 formal submissions from a range of stakeholders (see [Appendix A](#)). As outlined in Figure 1 below, submissions were received from:

- industry, including submissions from both individual companies and peak bodies representing the interests of industry;

- health professionals, including both individuals and representative bodies;
- consumer peak bodies and individual consumers;
- academics;
- members of a number of expert advisory committees, including the Advisory Committee on Prescription Medicines; and
- other groups, such as private health insurers and regulatory advice services.

Figure 1: Submissions received in response to the Panel’s discussion paper



Where consent was provided by the author, submissions received were published on the Department of Health’s website.

The Panel reviewed all submissions. Where submissions raised issues that the Panel wished to further explore or clarify, the Panel sought a meeting with the relevant party. Where possible, all Panel members were present at such meetings, but on occasion meetings were held with the Chair only, or with two members of the Panel.

1.6.4 Consultations

As noted above, the Panel met with a range of stakeholders to discuss their submissions or seek clarification on issues raised. A list of organisations external to the Department of Health with whom the Panel consulted is at [Appendix B](#). Throughout the Review, the Panel also regularly sought information and advice from the TGA or from other relevant officers within the Department of Health.

In addition, the Panel:

- Held a forum in Sydney on Wednesday 12 November 2014 to brief peak consumer, industry and health professional bodies on the terms of reference for the Review and the approach that the Panel planned to take in terms of consultations.
- Attended a meeting of Cancer Australia's Intercollegiate Advisory Group on Thursday 5 February 2015. The Advisory Group has membership from relevant medical specialties, public health organisations, and consumer groups with an interest in the prevention and treatment of cancer.
- Met with a number of public health organisations and consumer groups in Sydney on Friday 13 February 2015 and Melbourne on Thursday 19 February 2015.
- Held a teleconference on Thursday 19 February 2015 with representatives from the Consumers Health Forum of Australia and a number of state and territory peak bodies representing the interests of consumers.

CHAPTER TWO: OVERVIEW

As outlined in its terms of reference, the Panel was asked by the Australian Government to undertake a review of those aspects of medicines and medical devices regulation that are currently administered by the Therapeutic Goods Administration (Therapeutic Goods Regulation). In broad terms, this includes: pre-market assessment of medicines and medical devices for safety, quality and efficacy; post-market monitoring to identify emerging issues and ensure compliance with regulatory requirements relating to, for example, manufacturing practice and promotion; and the oversight of schemes designed to provide consumers access to unapproved products in defined circumstances. These regulatory activities are, however, only one aspect of the regulation of medicines and medical devices. Therapeutic Goods Regulation does not exist in a vacuum in Australia – it is part of a number of interrelated initiatives and strategies that occur across the health system and across levels of government, aimed at achieving broader government objectives related to safety and quality; access and equity; affordability and sustainability; and industry viability and competitiveness, as outlined in the National Medicines Policy.¹

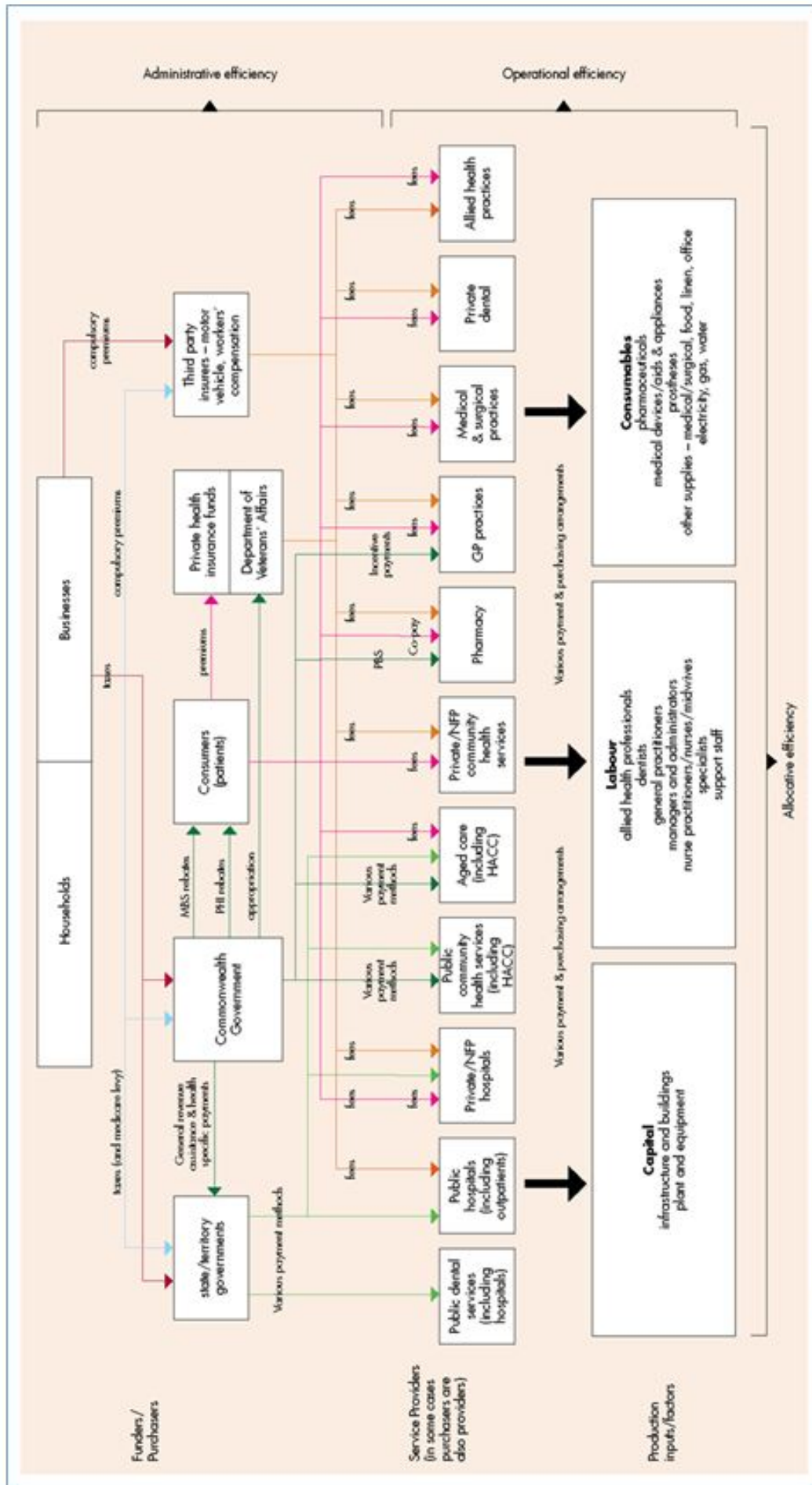
As demonstrated in Figure 2, the Australian health care system is complex, with a myriad of interconnected parts. The regulation of medicines and medical devices occurs across all aspects of the system – through, for example, Australian government regulation of clinical trials and subsidy programmes; or State and Territory Government regulation of the manufacture, distribution, storage and use of medicines under poisons legislations; or management of device procurement and storage under asset management frameworks for medical equipment.ⁱ

There are also interface issues with regulatory regimes for other products, such as food, chemicals and consumer goods. The demarcation line that differentiates a therapeutic good from: a food (regulated by state and territory food authorities); or a chemical (regulated by the National Industrial Chemicals Notification and Assessment Scheme); or a general consumer good (regulated by the Australian Competition and Consumer Commission) is often blurred, adding complexity for industry, consumers and regulators. It also leads to very similar products being subjected to quite diverse regulatory regimes. This issue is discussed further in Chapters Four and Five.

In undertaking the Review the Panel was cognisant of the fact that it was looking at one small part of a complex regulatory system. As with any system, change at one point has the potential to impact on the system as a whole, as well as on its component parts. These impacts may be unpredictable - unforeseen or perverse outcomes are always a risk of reform. **insert descriptor**

ⁱ See for example, State Government of Victoria, Medical Equipment Asset Management Framework FAQ webpage. Accessed on 4 March 2015 at <http://www.health.vic.gov.au/archive/archive2011/med-equip/faq.htm>

Figure 2: Australian health system structure and funding flows*



Source: National Health and Hospitals Reform Commission (2009), *The Australian health care system and the potential for efficiency gains: A review of the literature, Background Paper*.

*Funding flows reflected in this diagram may have changed post implementation of national healthcare reforms.

Where the Panel has identified possible flow-on effects to other parts of the system it has attempted to alert the reader to these. The Panel trusts that the Australian Government will consider how best to mitigate (or exacerbate as the case may be) these flow-on effects in implementing any reforms to the regulatory frameworks for medicines and medical devices.

In addition, Australia is part of a global community, and harmonisation of regulatory practices and the adoption of common processes are being developed with therapeutic goods regulators internationally. Where regulators in different jurisdictions can agree common standards, guidelines and regulatory requirements, the time to market for therapeutic products can be shortened. Better alignment of regulatory requirements directly benefits industry and consumers. From an industry perspective, harmonisation of requirements between regulators can reduce the time taken to develop new medicines and devices, lead to less cumbersome approval processes between countries (including reduced cost and time in preparing different dossiers for different markets) and increase the speed to market, all of which are important to industry.² From a consumer perspective, harmonisation provides more timely access to innovative therapies and may reduce their cost (as costs incurred to achieve market approval are factored into the subsequent price of the medicine or medical device, and increased competition will ultimately reduce prices).

Opportunities to enhance the alignment of Australia's regulatory frameworks for medicines and medical devices with international regulatory practice are discussed throughout this report. In particular, the Panel has considered the Government's policy position that, where a product has been approved under a trusted international risk assessment, Australian regulators should not impose any additional requirements unless there is good reason to do so (discussed in Chapters Three, Four and Five). Regulation, in all its forms, is an important mechanism for governments to achieve strategic policy objectives for the benefit of the community, particularly where the health and safety of Australians is concerned. Good regulation begins with clarity about the problem or risk that needs to be managed and provides for flexibility in how this occurs. As such, in considering these issues the Panel was mindful to ensure that regulatory alignment does not stifle opportunities for regulatory innovation.

A further context for the Review is the Australian Government's desire to promote better regulation, by reducing or eliminating unnecessary, ineffective or inefficient rules or requirements. In the context of the regulation of medicines and medical devices, this does not mean removing requirements that play an important role in protecting Australians from unsafe medicines and medical devices. Rather, it is about questioning why Australia regulates medicines and medical devices in the way it does. What problems are regulatory rules and procedures trying to solve, and how effectively and efficiently do they do this? Does the Australian regulator duplicate the efforts of other Australian or overseas organisations and, if so, does this result in enhanced protections for the Australian community, or does it just slow access by Australian consumers to innovative technologies? Are there opportunities to enhance community protections and reduce inefficient or ineffective regulations?

A critical aspect of the Review has therefore been to examine whether the regulatory frameworks for medicines and medical devices are fit for purpose. These frameworks have been in place for around 25 years and 13 years respectively, so such an examination is timely. In undertaking this examination, the Panel has considered matters such as whether there is an appropriate balance between risk and benefit, and whether processes are adequately streamlined and flexible. The Panel has also reflected on the broader principles of best practice regulation and the extent to which the regulatory frameworks for medicines and medical devices meet these principles. For example, the Panel has considered whether:

- policy objectives of the regulatory frameworks for medicines and medical devices are clear and whether the regulation is achieving its policy objectives in a manner that minimises the cost for government, business and the community;
- regulatory requirements are transparent and well-defined;
- regulatory effort is appropriately matched to the risk posed by the regulated products or processes;
- the regulatory frameworks strike an appropriate balance between principles of outcomes-based regulation and prescriptive regulation;
- the regulatory frameworks include any examples of inconsistencies, overlapping regulation, redundancies, excessive regulatory coverage or excessive reporting or recording requirements; and
- there are transparent and consistent procedures for making decisions under the legislation.

The regulatory frameworks for medicines and medical devices are discussed in Chapters Four and Five respectively, while Chapter Six addresses access to unapproved medicines and medical devices. Given the complexity of the regulatory frameworks and the timeframe for the Review, the Panel has, by necessity, only been able to undertake this assessment at the highest level. Further analysis would form an important part of any reform process.

The Panel is cognisant of the fact that the success of any regulation in achieving Government's objectives depends not just on what the law provides, but also on how the law is interpreted and administered. According to the Centre for Innovation in Regulatory Science, while 'regulatory systems vary across countries as well as over time ... the characteristics that reflect the activities of a well-developed regulatory agency are recognised through four attributes that are embedded into their process and procedures.'³ These enablers are addressed in Chapter Seven and include:

- Transparency – For example, having detailed guidelines and published timeframes, the capacity for sponsors to track the status of applications, and the publication of materials summarising the basis for approvals.
- Timeliness – This includes having defined processes, procedures and project management, and adhering to target timeframes for decision making.

Review of Medicines and Medical Devices Regulation

- Predictability – This includes, for example, the usefulness of published guidelines, dialogue between the regulator and the regulated, and alignment with international requirements.
- Quality – This relates to the competency of staff, the role of experts, the scientific basis for decision making and the scientific and legal consistency of decisions.⁴

Each of these enablers is achieved not by the way in which legislative frameworks are drafted, although that may assist, but rather by how the regulatory authority goes about its work – how it builds the capacity of staff; how it communicates with applicants and sponsors; and how it relates to, and communicates with, the broader community.

Finally, in undertaking this Review, the Panel has been mindful of the regulatory pendulum. That is, the experience in both Australia and internationally, is that the community and governments respond to a negative event or crisis by looking to more stringent regulatory controls as a means of preventing a recurrence of the event. Over time, as things go along smoothly, governments will generally look to loosen the regulatory reins on industry so as to boost competitiveness and productivity. Thus the regulatory pendulum swings back and forth in response to the prevailing conditions. This cycle is a major risk to sustainable regulatory reform. As such, in considering opportunities to reduce regulatory burden, the Panel has taken a conservative approach, developing options for reform that it believes have the capacity to both reduce duplicative, ineffective, or inefficient regulation and enhance consumer protections.

¹ Department of Health and Ageing (1999), *National Medicines Policy*, Commonwealth of Australia, pp. 2-3.

² Weisfeld V. & Lustig T.A. (editors) (2013, October 24), Forum on Drug Discovery, Development, and Translation; Board on Health Sciences Policy; Institute of Medicine (IOM). *International Regulatory Harmonization Amid Globalization of Drug Development: Workshop Summary*. National Academies Press (US), Washington (DC). Available at: <http://www.ncbi.nlm.nih.gov/books/NBK174222/>

³ Centre for Innovation and Regulatory Science (2011), *Emerging Markets focus study - Understanding the enablers of good regulatory process and decision making. What are the features that enable a transparent, timely, predictable and good-quality review?* Accessed online on 3 March 2015 at: <http://cirsci.org/content/november-2011-slide-month>

⁴ Ibid.

CHAPTER THREE: INTRODUCTION

The regulation of medicines and medical devices in Australia plays a critical role in protecting the health and safety of the Australian community. Medicines and medical devices have saved the lives of numerous Australians and have contributed to improved quality of life for many more. But few products are completely safe in all circumstances and use of these products, even as intended, is not without risk.

According to the World Health Organization (WHO):

The use of ineffective, poor quality, harmful medicines can result in therapeutic failure, exacerbation of disease, resistance to medicines and sometimes death. It also undermines confidence in health systems, health professionals, pharmaceutical manufacturers and distributors. Money spent on ineffective, unsafe and poor quality medicines is wasted – whether by consumers or governments. Governments need to establish strong national regulatory authorities (NRAs), to ensure that the manufacture, trade and use of medicines are regulated effectively, to protect and promote public health.¹

Governments need to establish strong national regulatory authorities to ensure that the manufacture, trade and use of medicines are regulated effectively.

WHO

Australian health care consumers and the broader community have a reasonable expectation that medicines and medical devices available on the Australian market will be of high quality, safe to use, and efficacious. Regulation is essential as the potential for serious harm to consumers from medicines and medical devices is high and there is an information asymmetry between those who manufacture or sell medicines and medical devices and those who consume them. That is, health care consumers do not generally have the necessary knowledge and skills to make decisions about the safety, quality, risks and benefits associated with a medicine or medical device themselves. Instead they rely on Government health authorities, together with their clinician, to make this assessment on their behalf. In addition, Australian governments subsidise other aspects of the health system and would therefore incur much of the cost associated with the use of poor quality, ineffective or unsafe medicines and medical devices.

It is, therefore, in the interests of both governments and the community to regulate medicines and medical devices, and to do so effectively and efficiently.

3.1 National Regulatory Authority

The authority responsible for regulating therapeutic goods in Australia is the Therapeutic Goods Administration (TGA), which is part of the Australian Government Department of Health. Throughout this report, when discussing past actions of the authority, the Panel has referred to the TGA. However, to be consistent with the nomenclature used by the World Health Organization, when referring to the Australian regulatory authority in general terms or in future tense, the Panel has used the term 'National Regulatory Authority' (NRA).

The NRA is responsible for regulating a diverse range of therapeutic products, including prescription medicines, vaccines, sunscreens, vitamins and minerals, medical devices, blood and blood products.ⁱ The regulatory framework under which the NRA works is set out in the *Therapeutic Goods Act 1989* (the Act) and related Regulations.

The national system for regulating therapeutic goods focuses on the quality, safety, efficacy and timely availability of therapeutic goods that are used in, or exported from, Australia. Regulatory decisions made by NRA staff are generally made under delegations from the Secretary or Minister. The NRA maintains this system by applying scientific and clinical expertise to assessing the evidence of risks and benefits of use of therapeutic goods. This involves:

- Undertaking assessments of new therapeutic goods before they are released to the market (pre-market).
 - Higher risk (prescription and over-the-counter (OTC)) medicines are 'registered' in the Australian Register of Therapeutic Goods (ARTG) and evaluated for quality, safety and efficacy prior to approval.
 - Lower risk medicines (such as complementary medicines) are 'listed' in the ARTG and must only contain pre-approved, low-risk ingredients. These goods are not independently assessed for quality, safety or efficacy prior to listing.
 - Devices and biologicals are included in the ARTG and are evaluated for quality, safety and performance based on their risk level. For medical devices, this assessment may be undertaken by the manufacturer (self-assessment), an overseas conformity body, and/or by the TGA, depending on the risk level of the device.
- Ongoing monitoring of products already on the market with a view to identifying safety risks and breaches of compliance with regulatory requirements in relation to these products (post-market).
- Assessing the suitability of medicines and medical devices for export.
- Inspecting and licensing manufacturing sites in Australia and assessing the standard of overseas manufacturing sites.

ⁱ Note: The regulation of blood and blood products is not included in the terms of reference for this Review.

- Providing communication and education programmes and partnership activities tailored to consumers, health professionals and industry.

Figure 3 provides an overview of the processes used by the TGA in regulating medicines and medical devices in Australia.

Figure 3: Overview of TGA Regulatory Processes

	Pre-Authorisation	Manufacturers Certification	Authorisation	Monitor	Compliance	Enforcement
Description	The outcome of this step is the approval to access an unapproved product for the purposes of conducting an Australian clinical trial in humans. These trials may form part of an application received by the TGA as part of the Authorisation phase at a later date, but nonetheless support the development of therapeutic products for Australians.	The outcome of this step is that the quality systems and manufactured ingredients or components for use in Therapeutic products comply with GMP or Conformity Assessment standards.	The outcome of this step is to ensure that the benefits of a Therapeutic product at the decision point in time outweighs the risks; and that the appropriate levels of quality, safety and efficacy (if applicable) can be achieved. Also includes consideration of medicines and devices subsidisation.	The outcome of this step is to ensure that TGA's risk based approach to monitoring compliance of registered, listed and unapproved Therapeutic products, will ensure that non-compliance is recognised and an appropriate regulatory response is determined.	The outcome of this step is to ensure that TGA's risk based approach to compliance identifies entities at risk of unintentional or intentional non-compliance and enables the development of appropriate strategies to prevent non-compliance.	The outcome of this step is to ensure that entities who are intentionally non-compliant are managed appropriately in accordance with our compliance framework.
Business Functions	<ul style="list-style-type: none"> - Clinical Trial approval (CTN & CTX) - Access to unapproved products (SAS and Authorised prescriber) - Access to emergency unapproved medicines (s18A) 	<ul style="list-style-type: none"> - Manufacturing Quality Certification (GMP and Conformity Assessment) 	<ul style="list-style-type: none"> - Pre-Market Authorisation - Poisons scheduling - Substance Approval - Access to unapproved products (SAS and Authorised prescriber) 	<ul style="list-style-type: none"> - Market surveillance. - Signal detection (incl. complaints), review and action (proportionate to risk). - Reportable events (adverse & issues). - Audits/ Investigations. - Laboratory Services (Compliance testing). - Product Review. - Sponsor mandatory reporting (safety and PSUR). 	<ul style="list-style-type: none"> - Monitor product compliance. - Undertake communication, education, training and awareness. - Product alerts. - Recalls, suspension & advertising. - Maintain product registers. - Product inspections 	<ul style="list-style-type: none"> - Product Investigations - Laboratory Services (Testing). - Product Enforcement - Civil Penalties - Criminal Penalties - Seizure of Goods

Source: Therapeutic Goods Administration, Half-yearly performance reports: January to June 2014.²

3.1.1 Australian Register of Therapeutic Goods (ARTG)

As at 30 June 2014 there were 78,316 therapeutic products included in the ARTG. Approximately 57 per cent of these products were medical devices (including other therapeutic goods and export only medical devices); 22 per cent were prescription or OTC medicines; and 15 per cent were listed medicines, primarily complementary medicines. The remaining 5-6 per cent of entries related to biologicals, registered complementary medicines, export only medicines or *in-vitro* diagnostic devices (IVDs).

3.1.2 Funding

The TGA is required by government to fully recover the operating costs for all activities that fall within the scope of the Act, including its public health responsibilities, such as communication and education, through the imposition of fees and charges on industry. Fees predominantly cover the costs of pre-market activities, such as the evaluation of data dossiers for the registration of medicines or inclusion of medical devices in the ARTG.

Charges predominately cover the costs of post-market activities such as pharmacovigilance and product recalls, and are applied annually for products included in the ARTG.

A large number of TGA activities are not able to be explicitly cost-recovered. These include activities such as: administrative governance requirements; participation in international collaborative forums; the Special Access and Authorised Prescriber Schemes, which provide access to unapproved medicines; a fee waiver for 'Orphan' drugs; cost of reviews of regulatory decisions provided for under section 60 of the Act; and the cost of legal challenges. These costs can vary between \$10 million and \$20 million per annum and must be factored into overall fees and charges.

The list of fees and charges can be found in the Therapeutic Goods (Charges) Regulations 1990 and are reviewed annually. In 2013-14, TGA revenue was approximately \$132 million and it had expenses totalling around \$133 million.³

3.1.3 TGA performance

The TGA is widely respected internationally and domestically as a regulator of therapeutic goods. In submissions to the Review many stakeholders, across industry, health professional and consumer groups, emphasised the high quality of the assessments undertaken by the TGA, particularly in the medicines space. Nevertheless, the TGA has been subject to criticism about the time it takes to approve medicines and medical devices. A number of stakeholders have asserted that the TGA is slower than its overseas counterparts in providing pre-market approval for medicines and medical devices and have questioned the need for independent evaluation by the TGA of medicines and medical devices that have already been approved by overseas regulators, such as the United States Food and Drug Administration (FDA) or the European Medicines Agency (EMA). They argue that to do so is duplication of effort, which only serves to delay access by Australians to innovative medicines and medical devices.

Indeed, in 2014 the Australian Government adopted the principle that:

....if a system, service or product has been approved under a trusted international standard or risk assessment, Australian regulators should not impose any additional requirements unless it can be demonstrated that there is a good reason to do so. All Commonwealth Government regulatory standards and risk assessment processes will be reviewed against this principle.⁴

Noting this principle, and concerns from some stakeholders about the timeliness of TGA assessments of medicines and medical devices, the Panel considered a number of questions:

1. Is there evidence to support assertions that pre-market assessments by the TGA are less timely than those conducted by comparable overseas NRAs?

2. Would greater use of assessments by ‘trusted’ overseas regulators lead to more timely market access to innovative products by Australian consumers?
3. Would greater use of assessments by ‘trusted’ overseas regulators reduce duplication and cost to industry?

As the nature of the pre-market assessment process is different for medicines and medical devices, the Panel considered these issues in turn for each type of product.

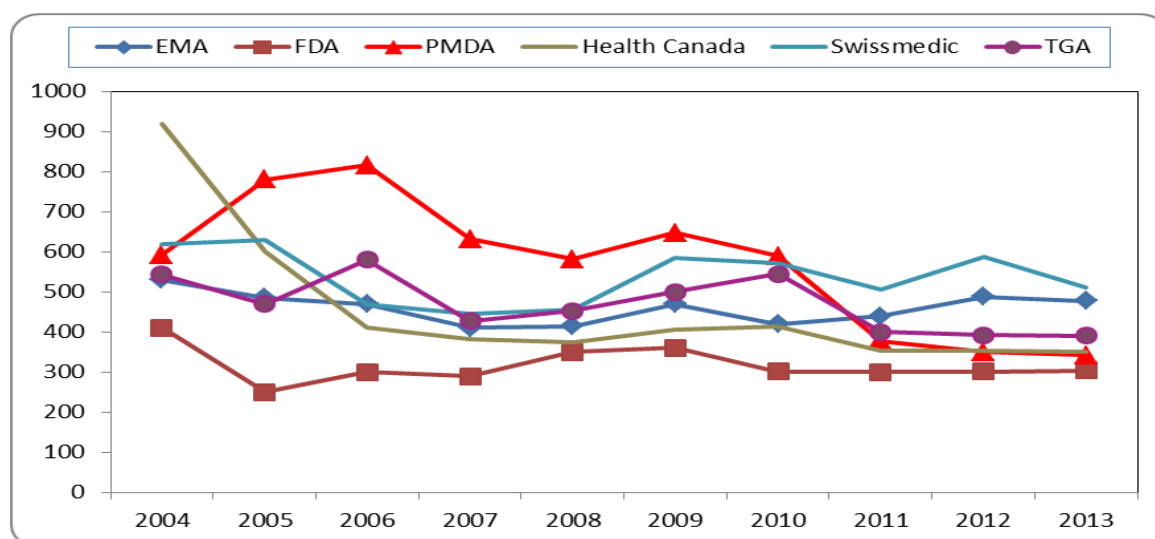
3.2 Medicines

3.2.1 Timeliness of approvals

In respect of the approval of medicines, the Panel examined data produced by the Centre for Innovation in Regulatory Science (CIRS), which benchmarks the performance of major regulators internationally. In its *R&D Briefing 55*, CIRS analysed the approval of new active substances across six NRAs between 2004 and 2013.⁵ The NRAs were the FDA, the EMA, Health Canada, Swissmedic, Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) and the TGA.

The CIRS analysis found that the past decade has seen major improvements in median approval times across all six regulators and there has been a convergence of approval timeframes when compared to the beginning of the decade (see Figure 4). That is, the difference in the median approval time between the fastest and slowest agency has decreased from approximately 500 days in 2004 to 200 days in 2013.⁶ As such, while the TGA’s median approval times have improved markedly over the past decade, particularly following implementation of revised procedures in 2010, overseas regulators have also enjoyed similar improvements. Thus, the data demonstrates that the TGA approves new substances faster than some comparable overseas regulators but slower than others.

Figure 4: New Active Substance median approval time for six NRAs 2004-2013*



*Based on a graph produced by the Centre for Innovation in Regulatory Science.⁷

This is further demonstrated by an analysis of median approval timeframes for new active substances in 2013 (refer Table 1), which indicates that Swissmedic's median approval timeframe is the slowest, at 511 days, while the FDA is the fastest, with a median approval time of 304 days. The TGA ranks in the middle with a median approval time of 391 days, 87 days slower than the FDA, but 87 days faster than the other large regulator, the EMA.

Table 1: Approval of New Active Substances 2013*

Regulator	Total No. of NASs approved	Median approval time (days)
Swissmedic	23	511
EMA	30	478
TGA	25	391
Health Canada	37	350
PMDA	28	342
FDA	29	304

*Table collated from data from the Centre for Innovation in Regulatory Science.⁸

It is important to note, however, that median approval times for new active substances outlined in Table 1 reflect approvals of these substances under both expedited and routine approval pathways. Expedited approvals occurred in all jurisdictions except Australia, as the Act does not provide for the TGA to offer an expedited approval pathway. Expedited approvals comprised between 10 and 39 per cent of all approvals in the five overseas NRAs. Approval times for new active substances assessed via expedited pathways were between 123 and 318 days less than approval times for new active substances assessed through routine approval pathways. If expedited approvals are removed from the data (refer to Table 2), the TGA remains in the middle in terms of median approval times, but the gap between it and Health Canada, which has the fastest median approval time, reduces to 36 days.

Table 2: Approval of New Active Substances via routine approval pathways 2013*

Regulator	Total No. of NASs approved through routine pathways	Median approval time (days)
Swissmedic	19	579
EMA	27	481
TGA	25	391
FDA	18	364
PMDA	17	360
Health Canada	28	355

*Table collated from data from the Centre for Innovation in Regulatory Science.⁹

Based on this analysis, the TGA appears to be performing reasonably well, with a median approval time for new active substances that is around five weeks slower than that achieved

by its most efficient overseas counterpart, Health Canada. Why then the continued perception that the TGA is slow to register new substances?

Availability of a new medicine on the Australian market is determined by both the time that it takes a sponsor to submit a data dossier to the TGA seeking registration, and the time that it takes the TGA to undertake an assessment of the medicine for safety, quality and efficacy. An analysis by the CIRS¹⁰ of the roll out to world markets of new active substances that were launched between 2005 and 2010 (n=146) demonstrates there can be long delays between a company first submitting a data dossier to an overseas regulator and subsequently submitting it to the TGA (or to other medium sized regulators such as Health Canada or Swissmedic). This is particularly the case for small to medium sized companies, who took nearly twice the time to roll out their products internationally when compared to top companies (defined as those with a research and development spend of greater than \$US 3 billion in 2010).¹¹

Availability of a new medicine in Australia is determined by both the time that it takes a sponsor to submit a data dossier and the time that it takes the TGA to undertake an assessment of the medicine for safety, quality and efficacy.

This ‘submission gap’ contributes to the time it takes for new medicines to become available on the Australian market when compared to overseas markets (such as the US and Europe) whose regulators tend to be the first point of submission of data dossiers by both small and large companies. For example, the CIRS analysis identified median submission gaps of between 34 and 467 days for 78 products that were subsequently registered by the TGA, which included anti-cancer medicines (148 day median submission gap); cardiovascular medicines (231 day median submission gap) and nervous system medicines (467 day median submission gap). As at 31 December 2012, only 53 per cent of the medicines launched internationally between 2005 and 2010 were approved for use in Australia, compared to 72 per cent in the US.

These submission gaps may be contributing to a perception that the TGA is slow to approve new drugs for market, as observers will not necessarily be aware the dossier was not submitted in Australia at the same time as it was submitted in, for example, the US. To the observer it will simply appear that a potentially life-saving or life-changing drug is available to patients in the US but not in Australia, as it has not yet been approved by the regulator. This concern may be further exacerbated if the overseas regulator considers the medicine through an expedited approval pathway, which will result in the product being made available in a much shorter timeframe than it can be approved in Australia, which does not have capacity under the current legislative framework to offer expedited approval.

Having analysed the available data, the Panel is of the view that the TGA does have due regard to timeliness when assessing new medicines for the Australian market. Once it

receives an application for the registration of a new active substance in the ARTG, the TGA outperforms the EMA and a number of medium sized regulators in terms of its median approval time and it is only marginally slower (by around five weeks) than Canada, the best performing regulator. That is not to say, however, that there is not room for improvement. As discussed later in this report, it is the Panel's view that increased use of online systems for interacting with sponsors; introduction of expedited approval pathways; and greater engagement of the Australian regulator with pharmaceutical manufacturers and sponsors throughout the lifecycle of a medicine, including prior to the submission of data dossiers for approval; all have the capacity to enhance approval timeframes.

3.2.1.1 Predictability

While timeliness of approvals is important, another common efficiency measure is the predictability of the review process. In particular, adherence by the NRA to its own timing and procedural measures is important to industry, as it allows them to better plan for the release of a product onto the market. In its recent *R&D Briefing 55*, the CIRS noted the six NRAs it examined had all decreased the variability in their approval timeframes over the past decade (thereby increasing predictability). It further noted that the:

*EMA and the TGA had the least variability in approval times over the past decade, and have established even more consistency in review timing in the last five years.*¹²

According to the TGA's key performance indicators report for the period July to December 2014, 100 per cent of new applications were processed within the statutory timeframe of 255 working days.

Thus, in terms of predictability of approval times, the TGA, along with the EMA, is setting the benchmark for other NRAs.

3.2.2 Would use of overseas assessment reports improve timeliness?

The data from the CIRS study suggests that, historically, pharmaceutical companies submit data dossiers for the registration of a new medicine to regulators at different times. But the Panel received anecdotal advice from both industry stakeholders and the TGA that this is changing, and that simultaneous submission of dossiers to multiple regulators is becoming more common. The degree to which use of overseas assessment reports may result in more timely availability of new medicines on the Australian market is, to some extent, dependent on which of these trends continues or, alternatively, on whether sponsors change their submission strategy for the Australian market in response to the availability of a streamlined option to utilise overseas assessments.

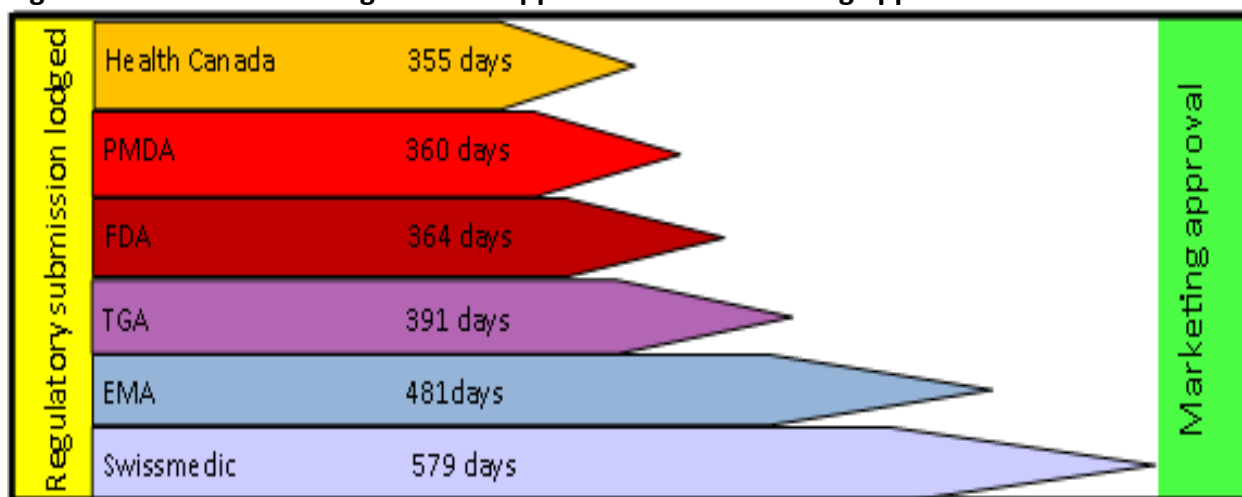
The following examples use:

- the average 2013 median approval times for non-expedited approval of new active substances for the six overseas regulators from the CIRS study into the impact of the changing regulatory environment on the approval of new medicines;¹³ and
- the median ‘submission gap’ for Australia from the CIRS study into the availability of new medicines.¹⁴

Simultaneous Submissions

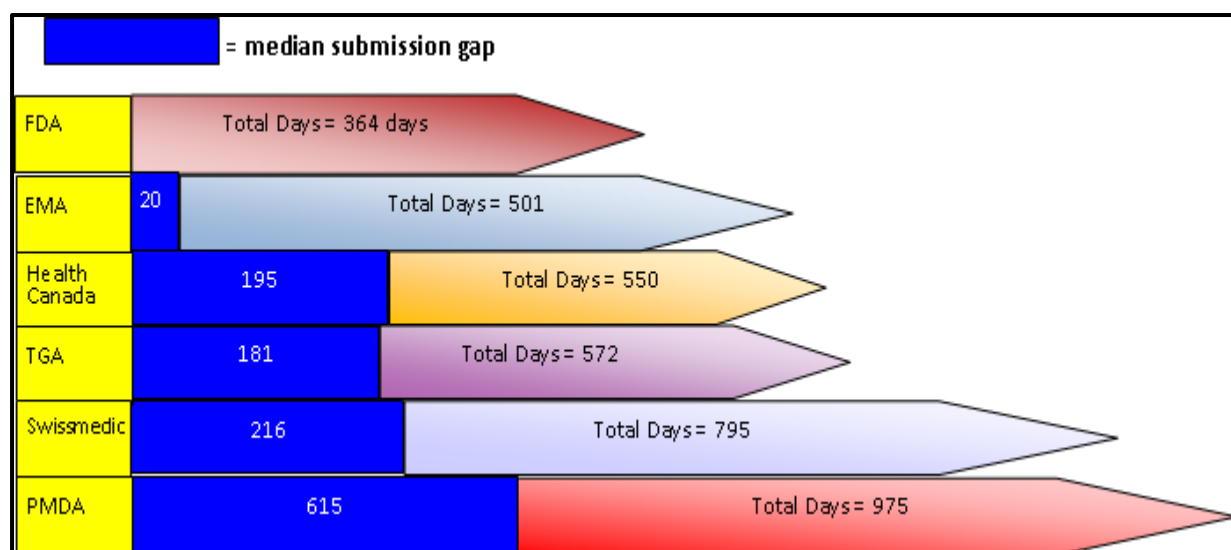
If sponsors submit applications for their new medicines to all jurisdictions simultaneously, then use of overseas assessment reports is likely to slow the availability of new medicines in Australia. As illustrated in Figure 5, Australia’s median approval time in 2013 was only 36 days slower than its most efficient overseas counterpart, Canada. If the Canadian approval was to be used to support approval of the medicine in Australia, then the sponsor would need to submit an application to the Australian regulator, and the regulator would have to do any necessary assessment, within 36 days after the Canadian approval was granted in order to facilitate earlier availability. This is extremely unlikely.

Figure 5: Simultaneous lodgement of applications for marketing approval



Staggered Applications

If pharmaceutical companies were to continue to stagger the submission of their data dossiers to different regulators, then use of overseas assessment reports by the Australian regulator may result in a marginal improvement in the timeframe by which new medicines become available in Australia. That is, in the CIRS study the median submission gap between the FDA and the TGA was 181 days. This, combined with median approval times (based on 2013 data), means that a new medicine would be approved in the US 208 days before it was approved in Australia. If an assessment report from the FDA was to be used to support approval of a medicine in Australia, then theoretically it may facilitate quicker access to the medicine on the Australian market (see Figure 6).

Figure 6: Staggered lodgement of applications for marketing approval

The extent of any improvement in timeliness would depend on:

1. The size of the submission gap. While the CIRS report identifies a median submission gap between lodgement of a submission in the US and its lodgement in Australia of 181 days, the submission gap varied by therapeutic area and company size. The median submission gap for 'top' companies was 132 days and for 'non-top' companies it was 441 days. The median submission gap for different therapeutic types ranged from 34 days for blood and blood forming organs to 467 days for nervous system therapies.¹⁵
2. The time taken by the overseas regulator to approve the new medicine. If the approval times are above the median, then it will cut into any time benefit that might accrue from the Australian regulator utilising an overseas assessment report. The inverse is also true, for example, if an expedited approval pathway is used by the overseas regulator.¹⁶
3. The time it would take the Australian regulator to do any necessary assessment. The Panel is of the view that some additional assessment by the Australian regulator is both necessary and appropriate. This is discussed in some detail later in this report.

Impact on Sponsor's Submission Strategies

If the Australian NRA was to accept an overseas assessment report as the basis for registration of a medicine in the ARTG, this may impact the way in which sponsors view and interact with the Australian market place. For example, it may make the Australian market more appealing as it would reduce both the cost and time involved in having a new medicine included in the ARTG. However, it may also result in sponsors delaying their application for registration while they await the outcome of an overseas assessment.

The Panel notes that the current Therapeutic Goods Act and Regulations define two pathways to registration in the ARTG, known as 'Category 1' and 'Category 2', respectively.

The Category 2 pathway is open to medicines which have been approved in two other acceptable countries and, with a legislative maximum timeframe for determination of 175 working days (compared to 255 working days for Category 1 applications), offers accelerated market entry compared to the Category 1 pathway. Eligibility for the Category 2 pathway is restricted to medicines that have been approved in two other acceptable countries; which have the same formulation, directions for use and indications as approved in those two countries; and for which two independent evaluation reports are available.

Since its introduction in 1992, the Category 2 option has only rarely been used by applicants as a pathway for approval of new medicines. Reasons why this option has not been used more often may include the strict inclusion criteria; the difficulty in the applicant accessing full un-redacted copies of evaluation reports from other regulators (particularly the FDA); and the relatively small number of acceptable overseas regulators currently specified in the Regulations, comprising the FDA, Health Canada, UK's Medicines and Healthcare Products Regulatory Agency (MHRA), Sweden's Medical Products Agency and the Dutch Medicines Evaluation Board. The latter problem is accentuated because over the last decade or so, with the establishment and consolidation of the EMA, the three European regulators undertake relatively few evaluations of new medicines. Taken together, these constraints make the current opportunities for industry sponsors to access the Category 2 route extremely limited. As such, it would be important to ensure that any revised 'Category 2' pathway provided easier access for sponsors who may wish to use it.

Market Access vs Consumer Access

Market access is achieved by the inclusion of a product in the ARTG. But market access does not necessarily translate into consumer access because in practice the cost of the medicine may be prohibitively expensive acting as a barrier to access for most consumers. For example, in December 2014, the Australian media reported that a new medicine for the treatment of non-small-cell lung cancer would cost patients around \$90,000 per annum if it were not subsidised.¹⁷

There is therefore, a further step in providing consumer access to medicines in Australia which involves consideration by the Australian Government about whether or not the medicine should be subsidised. This involves a sponsor, usually the drug company, making application to the Pharmaceutical Benefits Advisory Committee (PBAC) for listing of the medicine on the Pharmaceutical Benefits Scheme (PBS). The PBAC assesses the evidence on the drug's effectiveness, including its cost-effectiveness, compared to other medicines/treatments already available for the treatment of the proposed indication, and makes recommendations to the Australian Government about whether or not the medicine should be subsidised.

Timely access by Australian consumers to new medicines is, therefore, dependent on timely decisions about both product registration and subsidy. To facilitate this, the TGA and the

PBAC currently have parallel processes, whereby a submission to the PBAC may be lodged at any time from the date of lodgement of a TGA registration dossier. It will be important to ensure that any revised approval pathway for medicines which provides for the use of an overseas assessment report does not remove this capacity for parallel processing of applications by the TGA and PBAC.

Given the above, the Panel concluded that it is possible that use of overseas assessment reports may improve the timeliness of access by Australian consumers to innovative medicines.

3.2.3 Would use of overseas assessment reports reduce duplication?

As noted previously, for medicines to be supplied and marketed in Australia they must be included in the ARTG. For all but the lowest risk medicines, the TGA conducts a detailed evaluation of the product for safety, quality and efficacy, in order to determine if, on balance, the benefits of taking the medication outweigh the risks. The TGA undertakes this detailed evaluation irrespective of whether the medicine has already been assessed under ‘a trusted international standard or risk assessment’, such as that conducted by the EMA or the FDA. This necessitates the sponsor of the medicine submitting a comprehensive data dossier and addressing any queries from the TGA, thus duplicating their effort in getting the product approved in other key markets. The sponsor must also pay a fee to the TGA. As at 1 July 2014 a sponsor seeking registration of a ‘new chemical entity’ is required to pay an application fee of \$44,200 and an evaluation fee of \$177,200.

Advocates for greater use of overseas assessment reports argue that very few drugs that are approved by one major regulator are subsequently rejected by another. As such, they assert that once a medicine has been approved by a ‘trusted’ overseas regulator, the TGA assessment is superfluous and imposes an unnecessary regulatory and cost burden on industry.

Use by the Australian NRA of assessment reports from ‘trusted’ overseas regulators would be expected to reduce regulatory burden and costs to sponsors in a number of ways.

1. A reduction in registration fees, as under the Australian Government cost recovery policy such fees are to reflect the efficient unit costs of delivering the specific good or service.¹⁸ As such, if use of an overseas assessment report reduced the time and resources that the Australian NRA needed to commit to the evaluation process, then this would be reflected in the registration fee.
2. Remove the necessity to develop and submit a complete data dossier that is unique to Australia. The Common Technical Document (CTD) is a set of specifications for a dossier for the registration of medicines which is utilised by many regulators internationally. The CTD was developed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and adopted by

the TGA in 2004. The CTD is a harmonised format for applications for registration of new chemical entities, however, actual content requirements may still differ between countries that have adopted the CTD. The CTD is divided into five modules. Module 1 includes administrative information and prescribing information specific to the country in which the application is being lodged. Modules 3 to 5 address quality, safety (non-clinical study reports), and efficacy (clinical study reports) respectively, while Module 2 provides a summary of Modules 3 to 5.

Reliance on an overseas assessment report would mean reliance on the CTD Modules 2 to 5 as submitted by the sponsor to the overseas regulator. The sponsor would, therefore, not have to modify these modules for submission to the Australian NRA. Preparation of a Module 1 that is unique to Australia would, however, still be required.

3. Remove the necessity to respond to as many questions and requests for information from the Australian NRA as would be expected to occur if the Australian NRA were undertaking a de novo assessment. Responding to questions and data requests, while a necessary part of the evaluation process, can be both time consuming and resource intensive for sponsors. Indeed, one of the reasons the CIRS identified that ‘top’ pharmaceutical companies (i.e. those with 2010 R&D budgets >\$US 3 billion) were able to internationalise their medicines quicker than smaller companies was that they ‘are more likely to have the resources to undertake the submission of dossiers and to support their review in multiple jurisdictions.’¹⁹

In addition, where use of an overseas assessment report results in a reduced time to market (and subsidy), this would be of considerable benefit to the sponsor. However, the inverse is also true. That is, should a sponsor choose to delay applying for registration of a medicine in the ARTG until an overseas assessment report is available, and this in turn delays obtaining listing of the medicine on the PBS, then this could result in lost profits.

3.3 Medical Devices

The term ‘medical device’ covers a vast array of products and equipment. A medical device can be a simple, low-risk product such as a tongue depressor or band aid. It can be an implantable device such as a joint replacement, a heart valve, or a coronary artery stent, or it can be a complex piece of equipment, such as a haemodialysis machine. As a result the risk profiles of different medical devices vary significantly. Class I devices generally have risk profiles akin to many consumer goods, while implantable devices have a much higher risk profile. Failure of such devices can result in serious diminution of a person’s quality of life, necessitate surgical intervention, and may even result in death.

Medical devices and the devices industry differ from medicines and the medicines industry in a number of ways. According to the Pan American Health Organization:

...many devices have a considerably shorter useful life than drugs given the high degree of innovation and constant turnover due to technological obsolescence. Unlike the drug industry, which (other than biotechnology) remains relatively static, the device industry is a dynamic one, with a diversity of products that is unparalleled in comparison to the field of pharmaceuticals. In turn, this diversity leads to spirited entrepreneurialism, particularly among small businesses. Thus the composition of the drug industry vis-à-vis the device industry is vastly different. Because the make-up of the device industry is far more heterogeneous, with a large proportion of small companies, special challenges face those tasked with regulating these products.²⁰

The shorter lifecycle of many medical devices and the nature of the industry means it is particularly important for regulatory processes to be timely, simple to navigate, and efficient, if consumers are going to gain access to technology before it becomes obsolete. Submissions to the Review from the medical device industry were, like the industry itself, heterogeneous, but there was a level of concern expressed about the timeliness of evaluations of medical devices by the TGA.

Benchmarking the performance of the TGA against other overseas NRAs with responsibility for the regulation of medical devices is much more difficult than with medicines, however. There is a high level of consistency in the way major NRAs conduct pre-market assessments of medicines, which provides some confidence in the validity of benchmarking data. Regulatory systems for medical devices are less developed²¹ and there is no standard approach internationally to pre-market assessment. The assessment that is undertaken by individual NRAs also differs according to the class or risk profile of the medical device. Thus in trying to undertake benchmarking, the Panel found it difficult to assure itself that the available data was comparing like with like. The following data should be read with these caveats in mind.

3.3.1 Timeliness of approvals

The device consulting company Emergo has produced a series of country specific summary sheets that seek to document the regulatory process for medical devices and associated timeframes, based on its experience with international regulators. Emergo notes that the timeframes provided are ‘typical’, but that submissions may take longer to process depending on the specific circumstances of the product.²² Because classification systems vary between jurisdictions, the data is not directly comparable, but it gives some sense of ‘typical’ timeframes to receive marketing approval for various classes of devices from international regulators.

According to the Emergo summary sheets:

- In the US approval timeframes are typically: 1 month for US Class I devices; 3-6 months for US Class II devices and 18-30 months for US Class III devices.

- In Europe the approval timeframes are typically: <1 month for Class I devices; 3-5 months for Class I Sterile or Measuring devices; 3-5 months for Class IIa devices; 3-6 months for Class IIb devices; and 6-9 months for Class III devices.
- In Canada the approval timeframes are typically: 2-4 months for Canadian Class I devices; 1-2 months for Canadian Class II devices; 4-5 months for Canadian Class III devices; and 6-8 months for Canadian Class IV devices.
- In Japan the approval timeframes are typically: ≤ 1 month for Japanese Class I devices; 3-5 months for Japanese Class II devices; 7-9 months for Japanese Class III devices; and 13-16 months for Japanese Class IV devices.
- In Australia the approval timeframes are typically: <1 month for Class I devices; 2-3 months for Class I Sterile or Measuring devices; 2-3 months for Class IIa devices; 2-3 months for Class IIb devices; and 7-14 months for Class III devices. These timeframes are based on the assumption that the device has already been through a European conformity assessment and has a CE Marking. Emergo further notes that:

...the TGA reserves the right to perform an Application Audit on any submission, regardless of the classification or CE Marking status. A Level 2 Application Audit can lengthen review times by 9-10 months or more. Class III device applications are automatically audited by the TGA.²³

While this data provides a somewhat imperfect basis for comparison, it gives support to industry assertions that the Australian regulatory process for devices lacks timeliness when compared to some of its overseas counterparts, such as Canada and the EU.

3.3.1.1 Predictability

As noted previously in respect to medicines, while timeliness of approvals is important, another common efficiency measure is the predictability of the review process. In discussions with device manufacturers, a number emphasised that predictability was as important, if not more important, than was the actual time taken to approve the device. In the absence of this predictability, and faced with device approval timeframes that can vary from months to years, device manufacturers are unable to plan for the marketing of their device in Australia or in overseas markets that require Country of Origin approval.

The Panel was unable to access any independent benchmarking data in respect of predictability. However, anecdotal reports from industry to the Panel suggest that TGA timeframes are highly unpredictable and this would seem to be borne out by data from the most recent *TGA key performance indicators* report. The report indicates that 100 per cent of conformity assessments were completed within the statutory timeframe of 255 days, but performance in respect of compulsory and non-compulsory audits was variable (see Table 3).

Table 3: Medical Device Application Audits completed within target timeframes - 2014*

	Target (working days)	% completed within target timeframes Jan-Jun	% completed within target timeframes Jul-Dec
Level 1 Compulsory Audit Assessment	30	60	77
Level 2 Compulsory Audit Assessment	60	60	18
Non Compulsory Audit Assessment	30	38	54

*Source: Therapeutic Goods Administration (2015, January) *TGA Key Performance Indicators Version 1.0*. p. 9.

Having reviewed the data available, the Panel concluded that the predictability of the TGA review process for medical devices is problematic.

3.3.2 Would use of overseas assessment reports improve timeliness and reduce duplication?

The regulation of medical devices in Australia differs from that of medicines in that it already makes considerable use of overseas conformity assessments in assessing devices for inclusion in the ARTG. Conformity assessment procedures are the processes undertaken by a manufacturer to ensure a medical device complies with the regulatory requirements for quality, safety and performance, as set out in the Essential Principles.ⁱⁱ A person seeking to include a medical device or IVD in the ARTG must be able to substantiate the application of those conformity assessment procedures to the device, usually relying on certification issued by a 'conformity assessment body' (CAB).

The TGA is the only body that can provide conformity assessment certification for the highest risk medical devices, i.e. those that contain medicines or tissues of animal, biological or microbiological origin, or Class 4 IVDs. For other medical devices and IVDs the TGA may accept certification from certain other CABs as evidence of an appropriate conformity assessment procedure. Given the close parallels between the European and Australian regulatory frameworks for devices, conformity assessment certification is generally accepted from European CABs, which are known as 'notified bodies'.²⁴

Industry stakeholders are broadly supportive of the use of EU conformity assessments and many would like to see their use extended to higher risk medical devices. In addition, concerns were expressed about the additional assessment undertaken by the TGA as part of its 'application audits'. The Act (s 41FH) provides that the TGA may select for an application audit any application for a kind of medical device to be included in the ARTG and must select for audit specific kinds of applications as provided for in the Regulations. An

ⁱⁱ See Schedule 1 of the *Therapeutic Goods (Medical Devices) Regulations 2002*.

application audit involves checking some or all aspects of the application and certification, with the nature of the audit and the documentation required for assessment dependent on the level of risk associated with the medical device.²⁵ Where the audit is mandatory, audit fees apply. This additional layer of assessment is viewed as unnecessary duplication of processes that have already been carried out by an EU notified body, resulting in delayed access by Australian consumers to new technology.

Greater reliance on EU conformity assessments, or those from other comparable CABs, with minimal or no further assessment by the TGA, would undoubtedly result in more timely access to new medical devices by Australian consumers and reduce costs and regulatory burden on device manufacturers. For example, the Emergo data suggests that:

- Reliance on EU certification for the highest risk devices could potentially reduce approval times for these medical devices by up to eight months.
- Removal of the need for assessment audits could reduce approval timeframes by 9-10 months, and reduce industry costs in respect of audit fees and allocation of staff time to respond to questions and provide data.

However, the Panel questions whether such an approach would result in an appropriate balance between safety and timely access.

In recent years the European system has been shown to have systemic weaknesses, which has led to concerns about the quality of conformity assessment undertaken by some EU notified bodies. A series of articles published in the BMJ²⁶ raised a number of issues including:

- The fact that European notified bodies are private commercial entities may create a conflict of interest and brings into question the extent to which the regulatory system prioritises patient health and safety over financial or trade facilitation considerations.
- Lack of transparency about the basis of marketing approvals issued by European notified bodies.
- Concerns that the level of evidence to support the marketing approval of many higher risk devices is insufficient to allow safe widespread use.²⁷

A report produced by the FDA in May 2012 also found concerns with the European conformity assessment system, asserting that it has resulted in harm to patients through the application of less stringent assessment standards than those that apply in the US.

Because of the EU's lower approval standard and degree of oversight, high-risk devices are more often approved first in the EU than in the US. The lack of valid evidence of effectiveness has several negative effects on patients, however. As shown in this report, the EU's reliance on limited testing, generally without significant testing in humans, can fail to predict dangerous risks and ineffective

treatment in actual use. As a result, approval of devices without a valid demonstration of effectiveness has permitted the marketing of products in the EU that turned out to cause severe harm to patients, either because the testing was inadequate to reveal the device's risk or because use of an ineffective device denied patients access to effective treatments for serious diseases. In addition, the lack of valid data on effectiveness has caused some of the biggest EU countries to delay reimbursement for some approved high-risk devices until a second, sometimes lengthy, cost-effectiveness review is completed. In those cases, EU approval of a device does not necessarily mean that it is available to patients there.

The EU system for approving devices has now also come under criticism from the European medical community because of the number of devices that have turned out to be dangerous or ineffective. The medical community has also expressed dissatisfaction with the inconsistent review standards of the private bodies that approve devices in the EU and the secrecy of the approval process there.²⁸

Concerns have also been raised in respect to the regulation of devices by other countries, such as the US. A recent examination of the US regulatory system for devices found issues with the process to list medical devices based on an equivalent approved (predicate) device (i.e. the 510k process), including a lack of scientific data to support the claim of substantial equivalence, particularly clinical data.²⁹

These recent criticisms of EU and US device regulation highlight that, unlike the regulatory framework for medicines, which is relatively mature and stable, the regulation of medical devices is still evolving. The nature and extent of assessment undertaken can vary markedly between countries and this makes dependence on conformity assessments conducted by overseas CABs potentially fraught, particularly in respect of higher risk devices.

3.4 Use of overseas assessments

As outlined above, there is clearly potential for the Australian NRA to make greater use of overseas assessment reports in considering medicines and medical devices for inclusion in the ARTG. To do so will reduce regulatory burden and costs to industry and improve the timeliness of consumer access to innovative medical device technologies and possibly, in a more limited range of circumstances, to medicines. There are, however, risks associated with adopting such reports without any additional oversight or consideration.

In order to manage these risks it is essential that Australia maintain its capacity to undertake assessments of medicines and medical devices for safety quality and efficacy; and continue to make an independent decision about the inclusion of therapeutic goods in the ARTG which has regard to, but is not bound by, decisions of comparable overseas regulators. These issues are discussed below. In addition, appropriate management of risks will necessitate: clear and transparent criteria by which Australia identifies 'trusted' or

comparable overseas NRAs; and the development and implementation of enhanced post-market monitoring of medicines and devices to ensure that any emerging safety concerns are detected as soon as possible. These issues are explored in detail later in this report.

3.4.1 Independent capacity to undertake assessments and make decisions

3.4.1.1 Medicines

In the medicines space many stakeholders, while supportive of the Australian NRA making greater use of overseas assessment reports in certain circumstances, did not want to see any diminution of Australia's capacity to undertake such assessments itself. Australia needs to retain capacity to undertake assessments of new medicines for a number of reasons.

Firstly, full assessment of applications for registration in the ARTG is likely to remain the only viable approach for the market authorisation of vaccines. The difficulty with mutual recognition of other jurisdictions' reports and/or decisions in relation to vaccines includes:

- Alignment with seasonal influenza in the different hemispheres, where Australia can have a different antigenic composition of the product from the Northern Hemisphere, which also varies annually.
- The specific needs and population groups targeted in Australian immunisation programmes, for example, immunisation for Q fever.
- A greater need to consider differences in disease prevalence between the different jurisdictions. Northern Hemisphere regulators encounter a different mix of tropical and subtropical diseases than Australia.

Secondly, given the apparently increasing trend by some major international pharmaceutical companies to make simultaneous applications to first and second-tier regulators, including the TGA, it is important for industry and Australian patients that this pathway remains available.

Finally, even where a medicine has already been approved by a comparable overseas regulator, and the sponsor is seeking to rely on that assessment report for registration of the product in Australia, some further assessment by the Australian NRA is likely to be required. This assessment requires access to the same set of skills and expertise as is required to undertake a de novo assessment of the data dossier. This further assessment may relate to: the need to ensure safety, quality and efficacy where there are differences between the product to be registered in Australia and that assessed overseas; and/or to ensure that Australian contextual issues are addressed.

That is, it is not uncommon for aspects of a new medicine, such as dosage or site of production, to differ in different markets. This may be to ensure the medicine is most appropriate to conditions, such as clinical practice standards or climate, applicable to that market, or to reflect the company's production and distribution strategy. Thus, while it is

unusual, but not unknown, for a new medicine to be approved by one major regulator and be rejected by another, it is quite common for different regulators to approve different dosage regimes, different indications, or different conditions of use for the same medicine. For example: dosage levels for Febuxostat, a drug used to manage gout, are 80-120mg daily in Europe and New Zealand; 80mg daily in Canada; and 40-80mg daily in the US and Australia; while the recommended duration of treatment with Sofosbuvir, for the management of genotype 3 Hepatitis C, in Australia is 16 weeks while the FDA requires 24 weeks treatment. These differences reflect unique conditions within jurisdictions, such as clinical practice standards, which the regulators take into account in making a determination.

Examples of where Australia's demographics, climatic conditions, disease epidemiology, and clinical practice have the potential to impact product safety or analyses of benefit and harm and which, therefore, may necessitate further examination of an application for inclusion of a medicine in the ARTG include:

- Significant climatic variations which, while not unique to Australia, mean that stability, storage and transportation issues need to be closely assessed in the non-clinical evaluation, with cold chain challenges particularly important for vaccines.
- Some quite unique patterns of medicine use when compared to other markets such as the US and Europe. This may impact the analysis of drug interactions and the nature of warnings required in Product Information (PI) and Consumer Medicines Information (CMI).
- Consideration of whether genetic polymorphism or mutation frequency may impact the risk-benefit balance.
- The Australian categorisation system for prescribing medicines in pregnancy differs from the categorisation systems utilised by other regulators, such as the FDA, and almost certainly reinforces a more conservative approach by Australian doctors compared with their colleagues in other jurisdictions.
- Prescribing practices differ between jurisdictions. For example, the synthetic thyroid hormone levothyroxine is the most commonly prescribed medicine in the US and the third most prescribed in the UK, but is not in the top ten prescriptions in Australia. Yet there is no apparent concomitant difference in the prevalence of hypothyroidism between Australia and these other countries.
- Medicines may be used at different stages of treatment of disease in different countries. For example, a medicine that is approved as a first line treatment in the US may be approved as a second or third line treatment in Australia.

These examples reinforce the importance of ensuring that the Australian NRA has both the capacity to undertake assessments of medicines and the capacity to make an independent

decision about the inclusion of a medicine in the ARTG and the terms under which this marketing approval is granted. To abrogate this sovereign right would undermine the Australian regulator's capacity to undertake an independent risk-benefit assessment which takes into account the Australian context, including population parameters and clinical practice settings.

3.4.1.2 Devices

In respect of medical devices, some stakeholders indicated that the Australian regulator should not undertake conformity assessments of medical devices at all. They noted the diversity of devices on the market and the rapid evolution of device technology, and questioned the capacity of the Australian NRA to have ready access to the full range of technical expertise required to undertake device assessments. Difficulty in accessing such expertise was cited as a possible reason that the TGA's approval timeframes lagged behind a number of its international counterparts. Furthermore, these stakeholders raised concerns about a potential conflict of interest in the Australian NRA operating as both a conformity assessment agency and a regulator 'assessing' (through for example, the application audit process) conformity assessments undertaken by other NRAs.

This view was by no means unanimous however. A number of stakeholders, including an industry peak and some local device manufacturers, indicated to the Panel they want to continue to have capacity to seek a conformity assessment domestically, although they wanted this to occur in a timely and predictable manner (with predictability highlighted as being particularly important). They also expressed the view that it was essential to the local industry that health practitioners and consumers had confidence in the quality and safety of medical devices and that, until issues with the EU regulatory system were corrected, there was potential for this to be undermined should Australia transition to total reliance on EU conformity assessments.

Consumers and health practitioners also had a strong interest in ensuring that devices available on the Australian market, particularly high-risk implantable devices, were of high quality, fit for purpose, and adequately assessed in terms of safety. They expressed concern about any diminution of the role of the Australian NRA in this space, in the absence of assurances about the quality of overseas device assessments. They also called for much stronger post-market monitoring of medical devices, noting that there is an element of risk associated with all medical devices and that many problems with medical devices cannot realistically be detected until there has been extensive market experience with the use of the device.

Regardless of whether the Australian NRA undertakes the conformity assessment of a device or devolves this to overseas assessment bodies, a number of stakeholders emphasised the importance of Australia remaining the final arbiter of whether a device is included in the ARTG. It was argued that broader health policy settings differ between

countries and there are circumstances in which this policy context is important in assessing the risk-benefit balance of a new medicine or medical device. For example, Australia's stance on tobacco control is much stronger than that adopted by many countries, and prevalence rates of smoking are lower. These would be relevant consideration in assessing the likely harms and benefits in the Australian context of devices such as e-cigarettes.

Having considered the arguments, and in light of ongoing concerns that have been raised about the regulation of devices in other markets, such as the EU and US, the Panel formed the view that Australia needs ongoing capacity to assess and/or audit devices, particularly high-risk devices. Should confidence building activities currently underway in the EU, and between Australia and the EU, bear fruit, however, greater devolution of these activities might be considered in the future. Regardless of any future devolution of device conformity assessments, the Panel is of the view that Australia should always retain its capacity to make an independent decision about the inclusion of a medical device in the ARTG, rather than simply rely on an overseas assessment.

Recommendation One

The Panel recommends that Australia maintain the capacity to undertake assessments of therapeutic goods for safety, quality and efficacy.

Recommendation Two

The Panel recommends that the Australian Government, as a sovereign entity, retain responsibility for approving the inclusion of therapeutic goods in the Australian Register of Therapeutic Goods (ARTG).

¹ World Health Organization (2003, November), *WHO Policy Perspectives on Medicines - Effective medicines regulation: ensuring safety, efficacy and quality*, Geneva, pp. 1-2

² Therapeutic Goods Administration (2014), Half-yearly performance reports: January to June 2014, version 1.0, October 2014, p. 6.

³ Department of Health (2014), *Annual Report 2013–2014 Volume 2*, Commonwealth of Australia, Canberra, p. 359.

⁴ Australian Government Department of Prime Minister and Cabinet (2014), *Industry Innovation and Competitiveness Agenda*, p. IX. Available at:

https://www.dpmc.gov.au/sites/default/files/publications/industry_innovation_competitiveness_agenda.pdf

⁵ Centre for Innovation in Regulatory Science (2014a), *The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013*, R&D Briefing 55, Centre for Innovation in Regulatory Science Ltd, London, 16 December 2014.

⁶ *Ibid.*, p. 2.

⁷ *Ibid.*, p. 1.

⁸ Ibid., pp. 9-14.

⁹ Ibid.

¹⁰ Centre for Innovation in Regulatory Science (2014b), *Availability of New Medicines. Characterising the factors influencing drug roll out to six mature markets*. R & D Briefing 53, Centre for Innovation in Regulatory Science Ltd, London.

¹¹ Ibid., pp. 5-8.

¹² Centre for Innovation in Regulatory Science (2014a), op.cit., p.2.

¹³ Ibid.

¹⁴ Centre for Innovation in Regulatory Science (2014b), op. cit.

¹⁵ Ibid. (2014b).

¹⁶ Centre for Innovation in Regulatory Science (2014a), op. cit.

¹⁷ Medew, J., (2014, December 4), 'Cost of life under microscope as new cancer drug on wait list,' *Sydney Morning Herald*. Accessed online on 25 February 2015 at: <http://www.smh.com.au/national/health/cost-of-life-under-microscope-as-new-cancer-drug-on-wait-list-20141204-120g70.html>

¹⁸ Australian Government Department of Finance (2014, July), *Australian Government Cost Recovery Guidelines. Resource Management Guide No. 304*, 3rd Edition, Commonwealth of Australia, Canberra, p. 3.

¹⁹ CIRS (2014b), op. cit., p. 17.

²⁰ Pan American Health Organization, (2001), *A Model Regulatory Program For Medical Devices: An International Guide*, PAHO, Washington D.C, p. 11.

²¹ World Health Organization, *Medical devices regulations* webpage. Accessed online on 25 February 2015 at: http://www.who.int/medical_devices/safety/en/

²² Emergo (2014) *Download regulatory Process Charts and Regulatory Timelines*. Available at: <http://www.emergogroup.com/resources/download-regulatory-process-charts>

²³ Ibid.

²⁴ Therapeutic Goods Administration (2014, October 15) *RIS: Premarket assessment requirements for Australian manufactured medical devices*, p. 29.

²⁵ Therapeutic Goods Administration (2013, June), *Regulation Impact Statement: Changes to premarket assessment requirements for medical devices V2.0*. p. 69.

²⁶ See for example: Cohen, D. (2011, May 21), 'Out of Joint', *BMJ* 2011;342:d2905; Cohen, D (2012, October 24), 'EU approval system leaves door open for dangerous Devices', *BMJ* 2012;345:e7173; Storz-Pfennig P., et. al., (2013, May 11) 'Trials are needed before new devices are used in routine practice in Europe', *BMJ* 2013;346:f1646; Cohen, .D (2012, October 23), 'Faulty hip implant shows up failings of EU regulation', *BMJ* 2012;345:e7163. Accessed online on 28 October 2014 at: <http://www.bmj.com/content/345/bmj.e7163>.

²⁷ Therapeutic Goods Administration (2013, June), op. cit., pp. 9-10.

²⁸ Food and Drug Administration (2012, May), *Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US*. Accessed online on 25 February 2015 at: http://www.elsevierbi.com/~media/Supporting%20Documents/The%20Gray%20Sheet/38/20/FDA_EU_Devices_Report.pdf

²⁹ Zuckerman D., Brown P., and Das A., (2014, November 1) 'Lack of publicly available scientific evidence on the safety and effectiveness of implanted medical devices' in *JAMA Internal Medicine*, 174(11):1781-7. Published online September 29, 2014.

CHAPTER FOUR: REGULATORY FRAMEWORK FOR MEDICINES

The *Therapeutic Goods Act 1989* divides therapeutic goods into three broad categories: biologicals, medicines and medical devices. Unless exempt, biologicals and medical devices must be 'included' in the Australian Register of Therapeutic Goods (ARTG) and medicines must be 'registered' or 'listed' in the ARTG before they may be supplied in, or exported from, Australia. The Act defines a medicine as:

- (a) *therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human; and*
- (b) *any other therapeutic goods declared by the Secretary, for the purpose of the definition of therapeutic device, not to be therapeutic devices.*

In general terms, medicines include: drugs that must be prescribed by a doctor, dentist or other approved prescribers (prescription medicines); drugs available without a prescription, which may be purchased from pharmacies or in some cases from other outlets such as supermarkets (over-the-counter (OTC) medicines); and complementary medicines, including vitamins, herbal and traditional medicines. This chapter addresses the regulatory framework for prescription and OTC medicines. The regulatory framework for complementary medicines will be addressed in the Panel's second report.

4.1 Current regulation of medicines

The Australian NRA regulates medicines through three basic procedures:

- Pre-market assessment (before entry of the medicines onto the ARTG).
- Post-market monitoring and enforcement of standards (once the medicine is in the ARTG).
- Licensing of Australian manufacturers and verification of overseas manufacturers' compliance with the same standards as their Australian counterparts.

The balance between the required pre-market assessment and subsequent post-market monitoring depends on what is already known about the particular medicine (or about similar medicines) at the time that the product is assessed by the NRA. Once a medicine is approved and entered in the ARTG, the NRA:

- continues to monitor the product in the market through pharmacovigilance activities, which includes information collection, monitoring, evaluation, and risk management; and
- works with overseas NRAs and conducts regular inspections of manufacturers, both in Australia and overseas, to ensure they continue to meet manufacturing standards.

4.1.1 Risk-based framework

Australia's regulatory framework for medicines is risk-based. That is, differing regulatory standards are adopted in the assessment and management of medicines according to the perceived risk to the public of their use. Products carrying a higher risk, including all prescription medicines, receive a significantly higher degree of pre-market assessment compared to lower risk medicines with well known, and/or tried and tested, ingredients. Higher risk medicines must be registered in the ARTG and this is indicated by the inclusion of an AUST R number on the product label. Lower risk medicines must be listed in the ARTG and are required to display an AUST L number on the product label.

Australia's regulatory framework for medicines is risk-based. That is, differing regulatory standards are adopted in the assessment and management of medicines according to the perceived risk to the public of their use.

Risk assessment of products is also utilised to determine how consumers can gain access to a medicine. For example, a low-risk medicine may be safely sold in a supermarket, whereas a higher risk medicine may only be supplied after consultation with a health professional. Whether a medicine is classified as prescription, OTC, or is available more generally through, for example, supermarkets, is determined by the scheduling of substances on the *Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)*, known as the *Poisons Standard*.

4.1.1.1 Registered medicines

Higher risk medicines, including all prescription medicines and the vast majority of OTC medicines, including commonly used drugs such as aspirin and paracetamol, must be registered in the ARTG following an evaluation by the NRA. A sponsor may apply for registration of a medicine containing a new chemical entity via two pathways, known as 'Category 1' and 'Category 2', respectively. Category 1 is the pathway used in the vast majority of cases and involves the submission of a complete data dossier to the NRA for de novo evaluation. Applications made via the Category 1 route need to be determined within a maximum of 255 working days of receipt of the application. The Category 2 pathway is restricted to medicines that have been approved for general marketing in two other acceptable countries; which have the same formulation, directions for use, and indications as approved in those two countries; and for which two independent evaluation reports are available. The sponsor is required to submit a completed data dossier along with the two un-redacted evaluation reports for evaluation by the NRA. Applications made via the Category 2 route need to be determined within a maximum of 175 working days of receipt of the application.ⁱ

ⁱ Part 3A, s 16C, *Therapeutic Goods Regulations 1990*.

On receipt of an application to register a new chemical entity (NCE), the Australian NRA conducts a detailed evaluation of the data provided in order to establish the quality, safety and efficacy of the proposed product for the proposed usage (indication). This evaluation may include seeking further information or clarification of the data from the sponsor, and/or seeking independent advice from clinical and scientific experts via a number of advisory committees. The purpose of this evaluation is to assist the NRA's delegated decision maker, usually a senior medical officer, to assess the balance between the benefits and the risks of using the medicine, so that (s)he can decide whether or not to grant approval for the product to be registered in the ARTG for its specified use. If the product is accepted for registration in the ARTG it can then be marketed in Australia for the indications included in the ARTG, subject to any conditions specified by the NRA.

Similarly, application must be made to the NRA to register a new indication for a medicine already listed in the ARTG or to register a generic medicine or a biosimilar in the ARTG. In respect to generic medicines, the NRA conducts an evaluation of the bioequivalence of the generic to the originator product, as well as reviewing information concerning the quality of the medicine. In relation to biosimilars, the NRA conducts an evaluation of comparability studies substantiating the similar nature in terms of quality, safety and efficacy of the biosimilar to the reference product. Australia has adopted a number of the EMA's guidelines for assessment of biosimilars, as well as an International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline on the assessment of comparability.¹

4.1.1.2 Listed medicines

Lower risk medicines are listed, rather than registered, in the ARTG before being supplied in Australia. Most listed medicines are complementary medicines, but there are a small number of OTC products, for example menthol throat lozenges and some cough and cold preparations, that are listed in the ARTG. Most sunscreens are also included in the ARTG as listed medicines.

A listed medicine can only be marketed in Australia if:

1. It contains nothing but pre-approved low-risk ingredients. These pre-approved ingredients have been evaluated by the NRA for quality and safety but not for efficacy.
2. The manufacturing site (if in Australia) is inspected and licensed by the NRA or, if manufactured in a facility overseas, the site has been assessed by the NRA and determined as meeting appropriate standards.
3. It does not make claims or imply that it will be useful in the treatment or prevention of serious illnesses that would require the involvement of a health professional.²

Unlike registered medicines, the TGA does not individually evaluate listed medicines before they are entered in the ARTG. Rather, when listing a medicine in the ARTG, the sponsor must make certifications about quality; compliance with labelling, packaging and

Good Manufacturing Practice (GMP) standards; and use of approved ingredients. The sponsor must also certify that they hold evidence to support any therapeutic claims. This allows for early market access, with sponsors of listed medicines generally able to supply their product in Australia within 48 hours of submitting an electronic application.

4.1.1.3 Scheduling

The *Scheduling Policy Framework* is a 'national system for applying access restrictions on all poisons'³, including medicines for human use, veterinary, agricultural, domestic and industrial chemicals where there may be risk to human health and public safety.⁴ Under the *Scheduling Policy Framework*, substances are classified according to the level of regulatory control required to protect public health and safety. As such, scheduling controls how medicines and poisons are made available to the public by considering the active ingredient (substance) contained within the medicine or poisonⁱⁱ and the way in which the medicine is used and packaged. Under the Act, a person may apply to amend the *Poisons Standard* through addition of a new substance or rescheduling of an existing substance.⁵

Medical substances intended for human therapeutic use may be classified as Schedule 8 (controlled drugs), Schedule 4 (prescription medicines), Schedule 3 (pharmacist only) and Schedule 2 (pharmacy only) or may be unscheduled. Medicines containing substances on Schedules 4 and 8 may only be sold with a prescription, whereas medicines on Schedules 3 and 2 may be sold in pharmacies. In some states, Schedule 2 medicines may also be sold by licensed medicine sellers. Unscheduled medicines may be sold generally, for example, through supermarkets. Because the scheduling process considers the way in which the substance is to be sold, as well as the substance itself, a medicine containing the same active substance may appear on several Schedules. For example, ibuprofen solid dosage forms sold in pack sizes of no more than 25, and with a maximum 200mg per dose, are unscheduled and may be sold generally, for example in a supermarket. However, ibuprofen solid dose units at higher dosages (up to 400mg) in pack sizes of up to 50, are included on Schedule 3 and can only be sold with the advice of a pharmacist.

4.1.1.4 Post-Market Monitoring

Once a medicine has been registered or listed in the ARTG, it is subject to monitoring by the NRA. The extent of this monitoring depends on the risk classification of the medicine. Post-market monitoring by the NRA is focused on the safety of the medicine rather than on its efficacy and, as such, generally includes the collection and analysis of adverse event reports from consumers, health professionals and industry. Reports from overseas NRAs or from the medical and scientific literature are also assessed. In addition, sponsors of higher risk prescription medicines may be required to comply with a Risk Management Plan (RMP) which incorporates activities to identify and manage risks relating to the particular

ⁱⁱ Generally combination products are scheduled in line with the substance that is scheduled more restrictively. There are instances, however, where a combination product has been scheduled more restrictively than either of its components (e.g. the combination of ibuprofen and paracetamol).

medicine. For these medicines, compliance with the RMP will be a condition of ongoing registration in the ARTG.

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

WHO (2002)

The aim of these pharmacovigilance activities is to identify any emerging safety problems as quickly as possible so that remedial actions can be taken if necessary. Active pharmacovigilance is particularly important for new medicines, as these have generally only been assessed in clinical trial conditions where the attributes of patients using the product are tightly controlled. When the product is used in the real world, by patients with a range of demographic profiles and with comorbidities, unforeseen adverse events and contraindications for the use of the medicine can emerge. Where problems are detected the NRA is able to take a range of regulatory actions, from continued monitoring through to product withdrawal.

Post-market monitoring also occurs in respect of compliance with regulatory requirements related to, for example, the manufacture and promotion of the medicine.

4.1.1.5 Manufacture of Medicines

Medicines registered or listed in the ARTG in Australia are required to comply with internationally accepted manufacturing principles developed by the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Unless subject to specified exemptions, medicines manufactured in Australia cannot be registered or listed in the ARTG unless each step in their manufacture has been carried out by a licensed manufacturer. If any (or all) of the steps in the manufacture of a medicine have been carried out overseas, listing or registering in the ARTG is subject to those steps being performed to the same standard expected of Australian licensed manufacturers.

In order to satisfy itself, the NRA may inspect the overseas premises or, if the premises have been inspected and authorised by a trusted overseas counterpart, the NRA may accept this authorisation. The TGA has entered into several international agreements with overseas regulators for this purpose, and the vast majority (over 90 per cent) of overseas medicine GMP applications are 'cleared' based on these inspections, rather than requiring the TGA to conduct an on-site inspection.

4.1.1.6 Advertising of Medicines

The regulatory framework for medicines places conditions and limitations on the advertisement of medicines to health professionals and direct-to-consumers. Both

prescription and OTC medicines may be promoted to health professionals. Such promotion must comply with requirements of:

- the *Competition and Consumer Act 2010*;
- section 22(5) of the *Therapeutic Goods Act 1989* (the Act), which establishes an offence where therapeutic goods are advertised with indications other than for which they have been accepted in the Register; and
- any other conditions which may be assigned to the marketing approval of the product.

It is also a condition of registration of medicines in the ARTG that the promotion of all prescription products, whether by a member or non-member of Medicines Australia, complies with the requirements of the Medicines Australia Code of Conduct.⁶

In terms of direct-to-consumer advertising, this is not allowed for prescription medicines and most Schedule 3 (pharmacist only) medicines. Other OTC medicines may be advertised direct-to-consumers but are subject to pre-approval in most circumstances.

4.2 Assessment of current regulatory framework

Submissions to the Review were generally highly supportive of the current risk-based regulatory framework for medicines. The current framework has been in place since 1989, although it has undergone modification from time to time, including to increase harmonisation of Australian requirements with those of overseas NRAs. For example, in 2004 the TGA adopted the Common Technical Document – a set of specifications for a dossier for the registration of medicines developed by the ICH. The regulatory framework is, therefore, well established and appeared to be reasonably well understood by stakeholders.

In terms of implementation of the framework, the consistent view expressed to the Panel by industry, professional and consumer groups was that the TGA was a highly skilled organisation which undertook thorough and sophisticated evaluations of applications for registration of new medicines and which was regarded as a benchmark agency and role model in the Asia-Pacific region. As documented in Chapter Three, the TGA currently performs reasonably well when benchmarked against comparable overseas NRAs on approval timeframes for new medicines and very well when benchmarked against these NRAs on predictability of approval timeframes.

While there was a level of satisfaction with the regulatory framework for medicines, and a sense that the framework had generally served Australia well, there was also recognition that there were opportunities to improve the efficiency and effectiveness of the system in relation to, for example:

- Pre-market assessment of medicines, including opportunities for expedited assessments and greater engagement with the work of overseas NRAs.

- Post-market regulation, including simplified processes for managing variations to ARTG entries and improved post-market monitoring.
- The consistency and transparency of regulatory processes, such as the scheduling of medicines.

In addition, a number of stakeholders commented that a review of the framework was timely, as rapid advancements in the development of medicines and medical technologies necessitate a regulatory system that is flexible and responsive enough to adapt to future trends. Such trends are expected to include: increased ‘personalisation’ of medicine as a result of the identification of biomarkers and other emerging development technologies such as 3D printing; and an increasing development of drug-diagnostic and drug-devices combinations.⁷ These trends pose challenges to the Australian regulatory system, including in terms of the timeliness of assessments where products are subjected to regulation under multiple frameworks (for example, as both a medicine and a device).

Having considered the issues raised, the Panel concluded that, while the regulatory framework for medicines is largely sound, there are a number of areas in which the framework could be improved. These issues are discussed below and can be broadly categorised as:

1. The provision of multiple pathways for pre-market assessment of new chemical entities, and twin pathways for pre-market assessment of generic medicines and biosimilars.
2. Enhanced transparency of scheduling decisions and decisions about advertising Schedule 3 medicines.
3. Changes to post-market regulation with a view to simplifying and streamlining processes, and enhancing post-market monitoring.
4. Threshold issues for ‘therapeutic goods’.

4.3 Proposed reforms to the regulatory framework for medicines

4.3.1 Pre-market assessment of new chemical entities

While stakeholders were generally supportive of the pre-market assessment of medicines in Australia, a number expressed concern about the capacity of the system to provide timely access to novel therapies in all circumstances. In particular it was noted that a number of medicines, including oncology drugs, were available in overseas markets several years before becoming available in Australia. As noted in Chapter Three, a delay in the availability of novel medicines on the Australian market is most likely the result of medicine manufacturers lodging their application for registration later in Australia than in larger markets, such as the US or Europe. The lack of an expedited approval process in Australia may also be a contributing factor. In circumstances where novel medicines were viewed as potentially life-saving or life-changing, further assessment by the NRA of the medicine, which had received registration status from a comparable overseas NRA, was seen by some

consumer and public health groups as unnecessary and a barrier to patients accessing these medicines.

The Panel identified three options to speed market access to novel medicines in Australia. Firstly, pursue work-sharing arrangements with comparable overseas regulators for the assessment of medicines that have been submitted simultaneously to multiple NRAs. Secondly, revisit the Category 2 registration pathway to make it easier for sponsors to utilise an assessment from a comparable overseas regulator. Thirdly, restore capacity for the Australian NRA to undertake an expedited assessment of a new medicine in defined circumstances. Each of these options is discussed below.

4.3.1.1 Work-sharing arrangements

According to the TGA, there has been a trend in recent years for some major international pharmaceutical companies to make simultaneous applications to first and second-tier regulators, including the Australian NRA. Where this occurs, work-sharing between the Australian NRA and a comparable overseas NRA has the potential to reduce approval times in both markets. This approach would allow the two NRAs to work simultaneously on different parts of an evaluation report for a new medicine. For example, one regulator could look at the non-clinical modules of the application (e.g. pharmaceutical chemistry and toxicology) while the other regulator could simultaneously examine the clinical module of the application, which contains the clinical trials data. These would then be combined into a joint evaluation report which would be provided to decision makers in both countries.

A form of work-sharing has been occurring in the EU since 1995, when the EMA was established. Under the European model, while the EMA is a centralised licensing authority for most new active substances for all EU and European Economic Area - European Free Trade Association states, the evaluation work is typically shared between two member regulator countries, such as the UK and Germany.

The broader application of work-sharing is being explored internationally, with interest primarily from medium-sized regulators such as Australia, Canada, Brazil, Singapore and Switzerland. Implementation of work-sharing arrangements is complex, requiring a considerable commitment by each party to: gain an appreciation of each other's legislation, regulatory policy platforms and evaluation processes; and build confidence in each other's capabilities, including the ability to deliver reports in a timely fashion. Generic medicines have been the initial focus of work-sharing arrangements internationally. This is largely because of the high volume of new generic products globally, which has created an urgent need for more efficient evaluation processes. Work-sharing the assessment of generic medicines also provides an opportunity to establish protocols that provide a 'stepping stone' for evaluation of the more complex and lengthy NCE applications.

The Panel is aware that the TGA has been actively engaged in promoting and participating in work-sharing arrangements internationally. In particular the TGA:

- Commenced a joint work-sharing initiative with the Canadian NRA - Health Canada's Health Products and Food Branch (HPFB) - in November 2011. The initiative aims to: enhance regulatory cooperation; reduce duplication of work common to both agencies; increase reliance on work undertaken by each other; and maintain sovereign decision making powers. The first phase of the initiative focused on work-sharing the assessment of generic medicines and demonstrated that cooperation between the TGA and HPFB is possible, realistic and achievable. It also provides a model to expand into other areas of cooperation such as NCEs, and with other comparable overseas NRAs.
- Is an evaluator under an international pilot project that extends the European decentralised process to four regulators outside the EU: Australia, Canada, Chinese Taipei and Switzerland. Under the pilot, on the request of a generic pharmaceutical company, the EMA will share the assessment reports generated, in real time, with all four non-EU countries.
- Is represented on the interim Management Committee for the International Coalition of Medicines Regulatory Authorities (ICMRA), and leads the generic medicines programme. The ICMRA, which was established in December 2013, involves 23 of the main global regulatory agencies and, among other things, is developing processes to support work-sharing more globally.

The Panel supports the continuation of efforts to put in place work-sharing arrangements with comparable overseas NRAs and extending such arrangements as soon as possible to the evaluation of new chemical entities.

4.3.1.2 Category 2 application pathway

There are currently two pathways to registration of a product in the ARTG – Category 1 and Category 2. The Category 2 pathway was introduced in 1992 following the Baume *Report on the Future of Drug Evaluation in Australia*.⁸ In preparing that report, Professor Baume asked much the same question as the Australian Government is asking today by adopting the principle that:

*...if a system, service or product has been approved under a trusted international standard or risk assessment, Australian regulators should not impose any additional requirements unless it can be demonstrated that there is good reason to do so.*⁹

Namely, 'why do we need to re-evaluate drug products which have been approved for marketing in overseas countries which have comparable standards of regulation?'¹⁰

For reasons not dissimilar to those that we have outlined in Chapter Three, Professor Baume concluded that Australia needed to maintain its sovereign decision making capacity. However he went on to argue that this did not mean that 'Australia needed to conduct a completely new and independent evaluation based on unique data requirements' and he recommended that there be a 'simpler and quicker process where drugs have been approved elsewhere.'¹¹ As a result the Category 2 pathway was developed. But since its

inception it has been rarely used and, as such, has failed to facilitate more rapid access by Australians to new medicines as envisioned by Professor Baume.

The current Category 2 pathway presents a number of barriers to its use. Firstly, it requires the provision of two un-redacted overseas assessment reports, which can be difficult for sponsors to obtain, especially from the FDA. Secondly, the assessment reports must be from NRAs of countries specified in the Regulations, namely the US FDA, Health Canada, UK's Medicines and Healthcare Products Regulatory Agency (MHRA), Sweden's Medical Products Agency and the Dutch Medicines Evaluation Board. With the establishment of the EMA in 1995, the number of evaluations by the three European regulators has declined significantly. This effectively leaves, in most instances, only two agencies from which the two assessment reports can be obtained, one of whom (the FDA) does not generally release un-redacted reports. Thirdly, application under the Category 2 pathway is restricted to medicines which have the same formulation, directions for use and indications as approved in those two countries.

*One common question asked in Australia about drug evaluation is 'Why do we need to re-invent the wheel?' That is to say, why do we need to re-evaluate drug products which have been approved for marketing in overseas countries which have comparable standards of regulation?
Professor Peter Baume (1991)*

Given the above, the Panel considers it would be appropriate to replace the existing Category 2 application pathway with a new Pathway Two that provides for:

- a sponsor to request registration utilising one un-redacted de novo evaluation report from a comparable overseas NRA;
- the establishment of a more practicable list of comparable overseas NRAs whose assessment reports may be relied upon; and
- use of an overseas assessment report in circumstances where the medicine the sponsor is seeking to register in the ARTG is highly similar, but not identical, to the product approved by the overseas regulator.

The Panel's proposed approach to implementation of Pathway Two is discussed in section 4.3.3 below.

4.3.1.3 Expedited approval

Across the globe, regulators of therapeutic products are facing increasing consumer demand for early access to novel therapies. In Australia, such advocacy often focuses on subsidised access through the Pharmaceutical Benefits Scheme. However, the timeframes for TGA approval of such therapies and the lack of an expedited route of approval for medicines that are used to treat serious or life-threatening conditions which represent a major

advancement in treatment or are used to treat conditions where there is significant unmet clinical need, have also been a subject of concern. Within this context, the capacity of the regulatory system to appropriately balance the benefits to consumers of having early access to promising new treatments with the risks of accessing therapies, the safety and efficacy of which are still being established, is becoming increasingly important.

As a result of Business Process Reforms implemented by the TGA in 2010, Australia no longer has the capacity to undertake expedited approvals of promising new medicines. In this regard Australia is out of step with comparable overseas NRAs, such as the FDA, EMA or Health Canada, all of whom have capacity to undertake expedited approval in some circumstances. Benchmarking data from the Centre for Innovation in Regulatory Science (CIRS)¹² indicates that expedited approvals represented between 10 and 39 per cent of all approvals of NCEs by overseas NRAsⁱⁱⁱ in 2013 and reduced median approval timeframes by between 123 and 318 days.

The two major regulators, the FDA and the EMA, have taken different approaches to expedited approval. The FDA has implemented four accelerated approval schemes, each of which has its own eligibility criteria and provides for varying intensities of FDA engagement and guidance. Capacity to undertake rolling reviews of data dossiers, which allows the sponsor to submit portions of a marketing application before submitting the complete application, and earlier approval of medicines based on a surrogate endpoint, are features of some of the schemes. As illustrated in Figure 7, two of these schemes – Fast Track and Breakthrough Therapy – seek to both facilitate product development as well as expedite product registration.

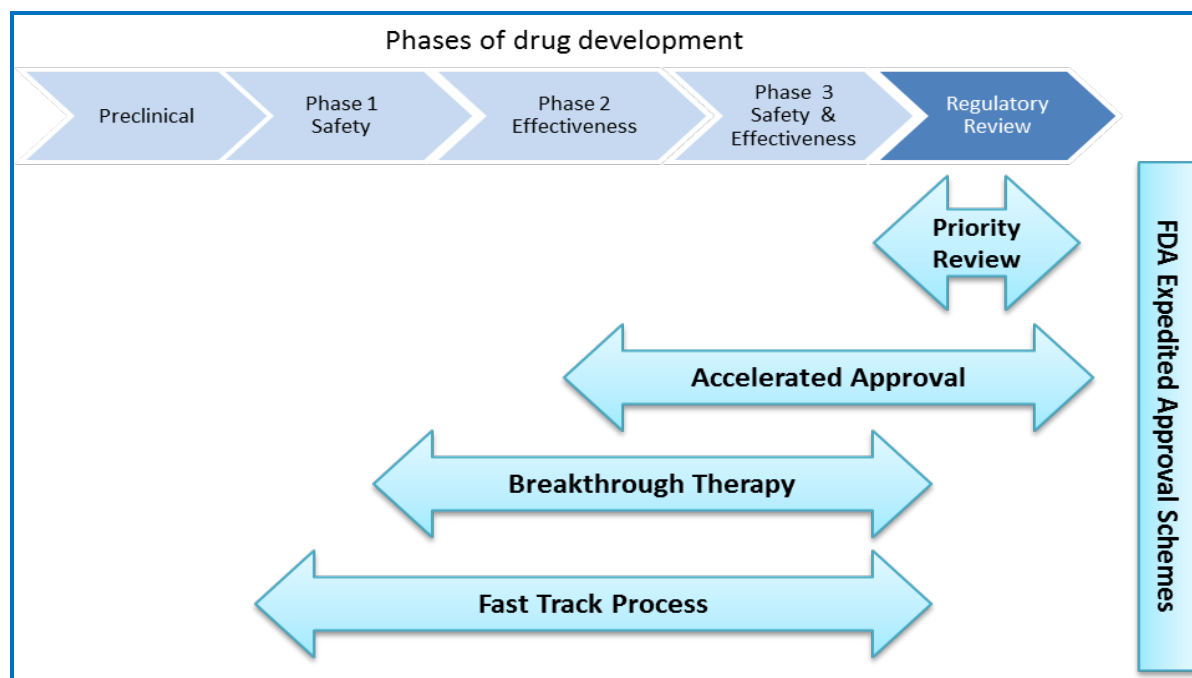
The FDA makes the decision whether to accept applications for these four schemes or alternatively to refer the sponsor back to the standard approval process. The fees payable by the sponsor for fast track approvals reflect the additional FDA effort involved in the schemes. The approval rate is about 50 per cent. While the regulatory consideration phase is accelerated under the four schemes, the main reported advantage to industry is assistance with design and facilitation of clinical trials.

In contrast, the EMA is conducting a pilot project on adaptive licensing, which it defines as:

...a prospectively planned, adaptive approach to bringing drugs to market. Starting from an authorised indication (most likely a 'niche' indication) for a given drug, through iterative phases of evidence gathering and progressive licensing adaptations concerning both the authorised indication and the potential further therapeutic uses of the drug concerned [adaptive licensing] seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms.¹³

ⁱⁱⁱ Based on 2013 approval data from the FDA, EMA, Health Canada, Swissmedic and Japan's PDMA.

Figure 7: FDA expedited development and approval schemes



Adaptive licensing utilises different evidentiary requirements, for example, *Conditional Marketing Authorisation*, based on the results of Phase 2 rather than full Phase 3 trials. This approach recognises the need for ongoing reassessment of the risk-benefit balance throughout the lifecycle of the medicine as experience is obtained with a patient population. It is anticipated that commercial use of the medicine after conditional approval would commence in a small group of patients with a narrowly-defined indication and potentially be expanded as clinical experience with the medicine grows.

The EMA can also undertake an ‘accelerated assessment’ of a new medicine in certain circumstances, which reduces the assessment timeframe from 210 to 150 days.¹⁴

In its *Review of Medicines and Medical Devices Regulation Discussion Paper*, the Panel sought input from stakeholders on whether there was a need in Australia for expedited approval and, if so, what such a programme should look like. There was a high level of support for the development of an expedited approval pathway(s) from both industry and consumers, with submissions noting that earlier access to new medicines can have a positive impact on patient care and patient outcomes.

Expedited approval programmes are offered by all of the major overseas NRAs and there is strong support from industry, professional and consumer stakeholders for the Australian NRA to have capacity to offer such programmes. As such, the Panel recommends that the registration pathways for new medicines include capacity to offer expedited approval. The features of such a pathway are discussed in section 4.3.4 below.

Recommendation Three

The Panel recommends that there be three pathways to seek registration of a new chemical entity and its inclusion in the ARTG:

Pathway Option	Description
Pathway One	Submission of a complete dossier for de novo assessment. This assessment may be undertaken in full by the Australian NRA or via a work-sharing arrangement between the Australian NRA and a comparable overseas NRA.
Pathway Two	Submission of an un-redacted evaluation report from a comparable overseas NRA, along with a copy of the dossier submitted to that NRA and an Australian specific Module 1, for assessment by the Australian NRA. The Australian NRA to make a recommendation regarding registration of the medicine once it has considered the data within the Australian context.
Pathway Three	Application for expedited approval of a medicine in certain circumstances. Any expedited approval pathway should make provision for submission of data and assessment consistent with requirements of Pathways One and Two as outlined above.

4.3.2 Pre-market assessment of generic medicines and biosimilars

Generic medicines

A generic product is a medicine that, in comparison to the originator (sometimes referred to as innovator) product:

- has the same quantitative composition of therapeutically active substances, being substances of similar quality to those in the originator product; and
- has the same pharmaceutical form as the originator product; and
- is bioequivalent to an originator product, or considered to be therapeutically equivalent in the case of topical products; and
- has the same safety and efficacy properties.¹⁵

The NRA will accept applications to register generic products in the ARTG without further safety and efficacy data where the proposed indications and dosage regimen are the same as those of the originator product and where the safety and efficacy data provided with the originator product are not 'protected' (section 25A of the Therapeutic Goods Act 1989 refers).¹⁶ As such, new generic medicines are generally only required to be assessed for quality and for bioequivalence to the original reference product. In respect to bioequivalence, the generic medicine must generally be shown to be bioequivalent to the corresponding strength of a leading brand (normally the originator product) as marketed in

Australia. However, in some circumstances, the NRA may accept bioequivalence studies carried out using samples of the originator product obtained from outside Australia, provided the sponsor can support this with evidence that the formulation of this product is the same as the formulation marketed in Australia.

The volume of applications to register new generic medicines in the ARTG far outweighs those for NCEs. That is, in the 12 months from 1 April 2013 to 31 March 2014, the TGA received 1,257 applications for new generic products, compared to 123 applications for NCEs.¹⁷ Given these volumes, any efficiencies that can be identified in the pre-market assessment process for generic medicines have the potential to be of substantial benefit to industry consumers.

The Panel notes that countries often do not have the same patent expiry and/or data exclusivity provisions for originator medicines and, as such, a generic medicine manufacturer may be able to apply for marketing approval of a generic product at different times in different markets. Australia may, therefore, be the first market for a generic medicine or it may be a subsequent market. Given this, the Panel is of the view that there should be two pathways to registration of a new generic medicine in the ARTG:

1. Pathway One, which would provide for de novo assessment of the data dossier for the generic medicine by the Australian NRA with or without work-sharing with a comparable overseas regulator. As noted in section 4.3.1.1, work-sharing arrangements between regulators, particularly for the assessment of new generic medicines, are being pursued internationally and this option may be worthwhile pursuing where submissions for marketing approval are lodged simultaneously with the Australian NRA and a comparable overseas NRA.
2. Pathway Two, which would provide for the sponsor of a new generic medicine to apply for registration of the medicine in the ARTG utilising one un-redacted de novo evaluation report from a comparable overseas regulator. The Australian sponsor would, however, also need to establish that the reference product used by the comparable overseas regulator when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product.

The Panel's proposed approach to the implementation of Pathway Two is discussed in section 4.3.3 below.

In respect of Pathway One, the Panel notes that the statutory timeframe for assessment of a data dossier for registration of a generic medicine in the ARTG is the same as that for an NCE, namely 255 working days. This is despite the fact that the assessment of a new generic medicine is generally less complex than that required for an NCE, as the safety and efficacy of the active ingredient has already been assessed and its use has been established in clinical practice. The Panel was advised that the TGA has been working with the Generic Medicines Industry Association to examine options to reduce the target timeframe for

assessment of new generic medicines to 180 days. The Panel supports this reduced assessment timeframe and would encourage its implementation as soon as possible.

Biosimilars

A biosimilar, or similar biological medicinal product, is a version of an already registered biological medicine that has a demonstrable similarity in physicochemical, biological and immunological characteristics, efficacy and safety, based on comprehensive comparability studies.¹⁸ Unlike generic medicines which have the same active ingredient as the reference product, biosimilars are complex heterogeneous mixtures of isoforms of the desired substance, meaning that evaluation of biosimilars cannot occur in the same way as evaluation of generic medicines. Instead, comprehensive comparability studies are required to generate evidence substantiating the similar nature in terms of quality, safety and efficacy of the biosimilar to the reference product.

Biosimilars are relatively new products and the approach to assessing them for market is still evolving. For example, the FDA only approved the first biosimilar product for the US market on 6 March 2015.¹⁹ The EMA has had a longer history with biosimilars, having approved 19 products, with the earliest approvals occurring in 2007.²⁰ Australia has adopted a number of the EMA’s guidelines for assessment of biosimilars, as well as an ICH guideline on the assessment of comparability. The Panel is of the view that the Australian NRA should continue to pursue harmonisation of its regulatory requirements for biosimilars with those applying internationally.

While the volume of applications for biosimilars will be smaller than that for generic medicines, applications for marketing would be expected to occur at different times in different markets to coincide with the expiry of patents and/or data exclusivity periods for the originator products. As such, dual pathways for the registration of biosimilars in the ARTG would appear to be appropriate. These should reflect those described above for generic medicines, except in the case of Pathway Two, the sponsor would need to establish that the reference product used by the comparable overseas regulator when assessing the biosimilar and the Australian reference product were the same.

Recommendation Four

The Panel recommends that there be two pathways to seek registration of a generic medicine or biosimilar and its inclusion in the ARTG:

Pathway Option	Description
Pathway One	Submission of a complete dossier for de novo assessment. This assessment may be undertaken in full by the Australian NRA or via a work-sharing arrangement between the Australian NRA and a comparable overseas NRA.
Pathway Two	Submission, to the Australian NRA for assessment, of an un-

Pathway Option	Description
	<p>redacted evaluation report from a comparable overseas NRA, along with a copy of the dossier submitted to that NRA and an Australian specific Module 1, and:</p> <p>A. If the product is a generic product, evidence that the reference product used by the comparable overseas NRA when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product; or</p> <p>B. If the product is a biosimilar, evidence that the overseas reference product and the Australian reference product are the same.</p> <p>The Australian NRA to make a recommendation regarding registration of the medicine once it has considered the data within the Australian context.</p>

4.3.3 Implementation of Pathway Two

The successful implementation of Pathway Two for the registration of new chemical entities, generic medicines, and biosimilars in the ARTG is dependent on a number of factors:

1. The identification of overseas NRAs that the Australian government and Australian consumers feel confident will conduct evaluations of medicines in a manner that is comparable to those conducted by the Australian NRA. This is essential to ensure that there is no diminution of safety standards for the Australian public;
2. The availability of un-redacted evaluation reports written in English from these overseas NRAs;
3. The implementation of enhanced post-market monitoring of medicines; and
4. Implementation of the pathway in a way that minimises regulatory costs and regulatory effort by product sponsors, without undermining public health protections.

4.3.3.1 Recognition of comparable overseas NRAs

If Australia is to base decisions about market access for medicines on an assessment made by an overseas NRA, then it is essential that Australia has confidence in the quality of such assessments. In short, the assessment must be conducted with a level of skill, expertise and rigour that is equal, or superior, to those undertaken by the Australian NRA.

Submissions to the Review provided a number of options for identifying comparable overseas NRAs. Some proposed the establishment of a list (as occurs under section 19A of the Act, which provides for the Secretary to specify ‘trusted’ countries for the purpose of

accessing medicines that are in short supply). Most commonly cited for inclusion on such a list were the two major regulators, the FDA and the EMA.

Other stakeholders considered that the selection of comparable overseas NRAs should be based on an assessment against a transparent set of criteria. This would provide for consistent assessment of overseas NRAs over time and provide a rationale for adding or removing countries from the list should their circumstances change. Within this context stakeholders considered that a range of factors should be taken into consideration including: the regulatory history of the NRA; the demographics and health system performance of the country; the volume of assessments of new chemical entities undertaken by the NRA; the process for review, including engagement of consumers during the assessment process; and adoption of international standards.

The selection of comparable overseas regulators should be based on an assessment against a transparent set of criteria.

The Panel was attracted to a criteria-based approach to the selection of comparable overseas NRAs as it is a more transparent option. Transparency in this regard is important, as Australian health care consumers must have confidence that public health and safety will not be undermined if the Australian NRA utilises assessment reports from comparable overseas NRAs. Being able to see the criteria against which NRAs are assessed may help to provide such reassurance. It also provides the opportunity to differentiate comparable overseas NRAs for different types of medicines. For example, some stakeholders argued that the FDA might not be an appropriate 'comparable overseas NRA' for the purposes of biosimilars at this time because of its limited experience with these products. Transparent criteria against which overseas NRAs are assessed for the purpose of Pathway Two applications should be developed in consultation with consumers, health professionals and industry.

Recommendation Five

The Panel recommends that the Australian Government develop and apply transparent criteria for identifying comparable overseas NRAs. Such criteria might include that a comparable overseas NRA must:

- A. Regulate for a population demographic that is broadly representative of the Australian population and has similar health outcomes; and
- B. Adopt ICH guidelines; and
- C. Have a credible and consistent track record of approving safe and effective medicines; and
- D. Conduct de novo evaluations of data dossiers for all types of medicines, e.g. new chemical entities, generics and biosimilars; and
- E. Have processes in place that require peer review or independent assessment of

Recommendation Five

the evaluations that they conduct; and

- F. Have evaluators with the necessary technical and clinical capabilities to evaluate the data provided and make an independent regulatory decision in accordance with the ICH guidelines; and
- G. Provide access to un-redacted evaluation reports and, where applicable, individual patient data; and
- H. Communicate and prepare evaluation reports in the English language.

4.3.3.2 Availability of un-redacted evaluation reports

Access to un-redacted evaluation reports is critical so that the Australian NRA can obtain a full picture of the efficacy, safety and quality of the medicine. This will inform the delegate's decision to register/not register and also provide the basis of advice to the sponsor, prescribers and the Australian public about the decision. It is also essential in terms of post-market monitoring going forward, including risk management.

It is proposed that it would be the responsibility of the applicant to provide the Australian NRA with the full un-redacted evaluation report(s) prepared by the overseas NRA. As such, to utilise Pathway Two the Australian sponsor would need to be the same commercial/legal entity as the sponsor in the overseas jurisdiction or have a significant contractual arrangement with the overseas sponsor, in order to obtain access to the report.

If it proves difficult for sponsors to access un-redacted evaluation reports from overseas NRAs, the Australian Government might consider pursuing access through diplomatic channels. For example, via the development of Memoranda of Understanding (MOU) with relevant countries that provide for the exchange of un-redacted evaluation reports in circumstances where this is agreed by the sponsor. Such negotiations would need to consider how the un-redacted evaluation report was to be used, noting that the Australian NRA would seek to utilise aspects of the report in its Australian Public Assessment Report (AusPAR) for the medicine. AusPARs are published for all NCEs and it is required to provide detail on efficacy, safety and quality issues so that health care professionals and consumers can take these into account when using particular new medicines for individual patients.

4.3.3.3 Enhanced post-market monitoring of medicines

The lifecycle of a medicine has traditionally been divided by regulators into two stages: pre-market and post-market. During the pre-market stage, access to the medicine is generally limited to patients who are allocated to the treatment arm of a clinical trial. Once the medicine is registered this changes abruptly, as access is expanded 'from a relatively small number of highly selected trial subjects to millions of real-world patients who might not fit treatment eligibility requirements as specified on the label.'²¹ This poses challenges for regulators charged with protecting public health and safety. As noted by Iedema et. al.:

The risk of a drug in ‘real world’ use is often underestimated in clinical trials, as they are often designed to demonstrate efficacy rather than test safety. The trials generally study a highly selected patient group – with a long list of exclusions designed to mitigate risk – and the patients are intensively followed in a manner not typically feasible in routine practice. The true risk of a drug is generally unclear until there is considerable postmarketing experience.²²

As such, clinical trials provide information about many of the possible adverse effects of a medicine, but they do not detect all possible adverse effects because they generally do not:

- Continue for long enough to detect adverse events that may develop over a long period of time.
- Include enough patients to detect adverse events that occur with low incidence.
- Include all of the different types of people who might eventually use the medicine and who might be more susceptible to some adverse events, such as older people, children, pregnant women, or people with comorbidities.²³

As such, it is important for effective post-market monitoring to occur in order to identify possible issues with safety or efficacy that may emerge when the medicine is used in a real world setting. A consistent theme in the Panel’s discussions with stakeholders and in submissions to the Review was that any change in oversight of pre-market assessments by the Australian NRA should be counter-balanced by enhanced post-market monitoring so that emerging problems are detected and addressed promptly. This was considered to be even more important where medicines are approved under expedited approval processes that may rely on more limited clinical data than is traditionally required.

The Panel concurs with this view. The pre-market assessment of medicines for safety, quality and efficacy is essential to protect public health and safety. It would be remiss to make significant changes to the process for such assessments without putting in place safeguards to monitor and detect any adverse outcomes that may result. As such, the Panel recommends that the introduction of Pathways Two and Three go hand-in-hand with enhanced post-market monitoring. As enhanced post-market monitoring is applicable across both the medicines and medical devices frameworks, it is discussed in detail in Chapter Seven.

4.3.3.4 Implementation Strategy

If properly designed and implemented, Pathway Two may be an attractive option, particularly for smaller pharmaceutical companies who have limited capacity to develop, submit and service applications for registration to multiple markets at the same time. As outlined in Chapter Three, a study by the CIRS of 146 new chemical entities that were launched between 2005 and 2010 found that while ‘top’ companies often lodge simultaneous applications with a number of regulators, ‘non-top’ companies staged the

rollout of their product into different markets.^{iv} The CIRS concluded that this was because ‘companies with large R & D budgets are more likely to have the resources to undertake the submission of dossiers and to support their review in multiple jurisdictions’.²⁴

The analysis found that of the 146 new chemical entities launched between 2005 and 2010, only around half (53 per cent) were registered in Australia by 31 December 2012. This represented 80 per cent of the medicines developed by ‘top companies’ and only 32 per cent of those developed by non-top companies. Designing Pathway Two in a manner that provides for more timely assessment, and is both less costly and less resource intensive for sponsors, may encourage these smaller manufacturers to bring their products to the Australian market more quickly.

New Chemical Entities

The Panel proposes that, in order to utilise Pathway Two for a new chemical entity the product sponsor would be required to submit to the Australian NRA:

1. A full application in CTD format including Module 1 of the CTD describing the administrative information and prescribing information (for example, the proposed product information and labelling) for Australia. Modules 2 to 5 would reflect those submitted to the overseas NRA, reducing the need to produce a different set of documents for the Australian market.
2. An un-redacted copy of all evaluation reports, in English, completed by the comparable overseas NRA.
3. Certification/evidence that:
 - A. The medicine is identical to the one approved by the trusted overseas regulator (i.e. same dosage form, strength, formulation and indications); and
 - B. The medicine will be manufactured by the same manufacturer as the medicine approved by the overseas regulator or, if not, that it will be manufactured at a plant that has received applicable GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian NRA has co-recognition); and
 - C. The manufacturing process to produce the medicine will be identical to that assessed by the comparable overseas regulator for the overseas product; and
 - D. There are no specific issues regarding applicability to the Australian context that need to be examined or have been specifically addressed in the submission.
4. Details of the outcomes of the application in all jurisdictions where it has been submitted (this is a current requirement).

^{iv} ‘Top’ companies were defined as those with a research and development spend of greater than \$US 3 billion in 2010.

5. Appropriate certifications and/or authentication of reports, and acknowledgement of penalties for providing false or misleading information.

Evaluation by the NRA

The Australian NRA would evaluate the application in an abbreviated manner to:

1. Verify that the certifications outlined at 3A to 3D above are correct.
2. Ensure that the medicine is fit for the Australian population and conditions, taking into account factors such as demographics, climatic conditions, disease epidemiology, and clinical practice.
3. Verify that the post-market risk management tools proposed for the medicine in Australia are appropriate considering Australia's specific clinical environment.
4. Ensure proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Based on the overseas evaluation report and the above assessment, the Australian NRA would make a decision whether or not to recommend the registration of the medicine in the ARTG. If registered, the NRA would regulate the medicine in the same way as any other medicine, e.g. the sponsor would still need to seek approval from the Australian NRA for later variations to the medicine. The Panel believes that this abbreviated assessment should generally be achievable within 60 working days, once complete and correct documentation is received from the sponsor.

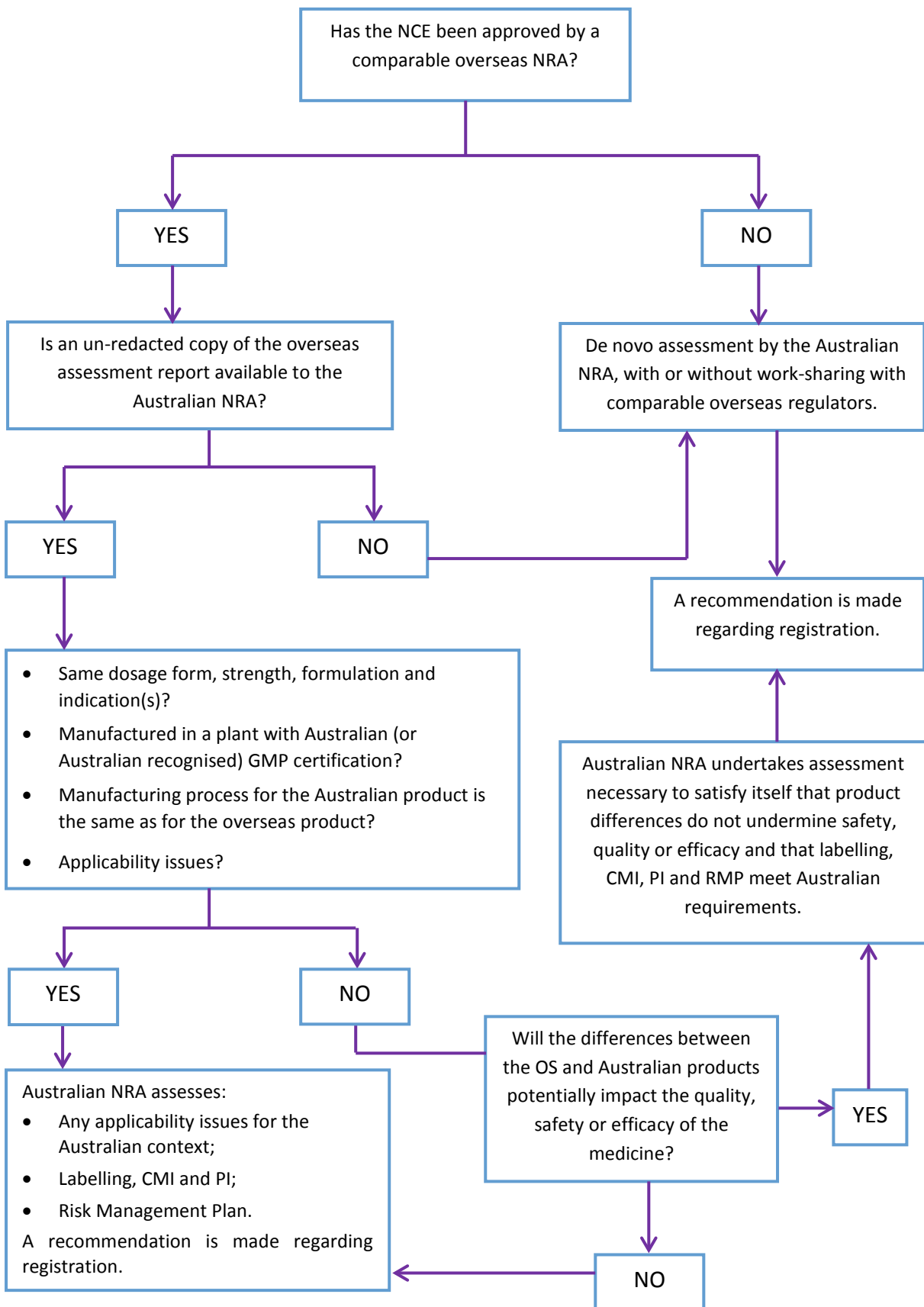
Where a medicine does not meet all of the requirements outlined in 3A to 3D above, this should not preclude it from utilising Pathway Two, but the extent of evaluation that would need to be conducted, and thus the time taken, by the Australian NRA in these circumstances would be greater. For example, where the product is identical but the sponsor is seeking registration for a different indication, the Australian NRA could rely on relevant material, for example pre-clinical, manufacturing, and release specification data, but could undertake its own assessment of clinical efficacy. In these circumstances a longer assessment timeframe would be necessary, depending on the extent of evaluation required by the Australian NRA. An indicative algorithm for the proposed application pathways for non-expedited assessment of new chemical entities is at Figure 8.

Recommendation Six

The Panel recommends that in circumstances where a sponsor seeks registration of a **new chemical entity** in Australia via Pathway Two and has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA:

1. The Australian NRA makes a recommendation regarding registration of the new chemical entity once it has satisfied itself that:
 - A. The new chemical entity is identical in dosage form, strength, formulation and indications; and
 - B. The new chemical entity will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian NRA has co-recognition); and
 - C. The manufacturing process to produce the new chemical entity will be identical to that assessed by the comparable overseas NRA for the overseas product; and
 - D. There are no specific issues regarding applicability of the submitted data to the Australian context that need to be examined; and
 - E. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.
2. Where the new chemical entity seeking registration in Australia does not meet conditions 1A to 1D above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.
 - A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information, and Consumer Medicine Information is appropriate and consistent with Australian requirements before making a recommendation regarding registration of the new chemical entity in the ARTG.
 - B. Where differences between the new chemical entity seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the new chemical entity in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed and/or taken into consideration in assessing risk and benefit; and
 - II. Assess whether the proposed product labelling, Product Information, and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Figure 8: Non-expedited application pathways to registration of a new chemical entity



Generics and Biosimilars

As outlined in section 4.3.2, Pathway Two should also be available for registration of new generic medicines and biosimilars in the ARTG. The Panel proposes that, in order to utilise Pathway Two for a generic medicine or biosimilar, the product sponsor would be required to submit to the Australian NRA:

1. A full application in CTD format including Module 1 of the CTD describing the administrative information and prescribing information (for example, the proposed product information and labelling) for Australia. Modules 2 to 5 would reflect those submitted to the overseas NRA, reducing the need to produce a different set of documents for the Australian market.
2. An un-redacted copy of all evaluation reports completed by the comparable overseas NRA.
3. Certification/evidence that:
 - A. The generic medicine or biosimilar is identical in dosage form, strength and formulation to the product approved by the comparable overseas NRA; and
 - B. The generic medicine or biosimilar will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas regulator with whom the Australian authority has co-recognition); and
 - C. The manufacturing process to produce the generic medicine or biosimilar will be identical to that assessed by the comparable overseas NRA for the overseas product; and
 - D. If the product is a generic medicine – the reference product used by the comparable overseas NRA when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product; or
 - E. If the product is a biosimilar – the overseas product and the Australian reference product were the same.
4. Details of the outcomes of the application in all jurisdictions where it has been submitted.
5. Appropriate certifications and/or authentication of reports, and acknowledgement of penalties for providing false or misleading information.

The Australian NRA would evaluate the application in an abbreviated manner to:

1. Verify that the certifications/evidence outlined at 3A to 3D above are correct (if the product is a generic) or that the certifications/evidence outlined at 3A to 3C and 3E are correct (if the product is a biosimilar).
2. Ensure proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Based on the overseas evaluation report and the above assessment, the Australian NRA would make a recommendation whether or not to register the medicine in the ARTG. If registered, the NRA would regulate the medicine in the same way as any other medicine, e.g. the sponsor would still need to seek approval from the Australian NRA for later variations to the medicine. The Panel believes that this abbreviated assessment should generally be achievable within 60 working days, once complete and correct documentation is received from the sponsor.

Where a generic medicine or biosimilar does not meet all of the requirements outlined in 3A to D (generic) or 3A to C and 3E (biosimilar), this should not preclude it from utilising Pathway Two, but the extent of evaluation that would need to be conducted by the Australian NRA, and thus the time taken, in these circumstances would be greater. An indicative algorithm for the proposed Pathway Two for generic medicines and biosimilars is at Figure 9.

Recommendation Seven

The Panel recommends that in circumstances where a sponsor seeks registration of a **generic medicine or biosimilar** in Australia via Pathway Two and has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA:

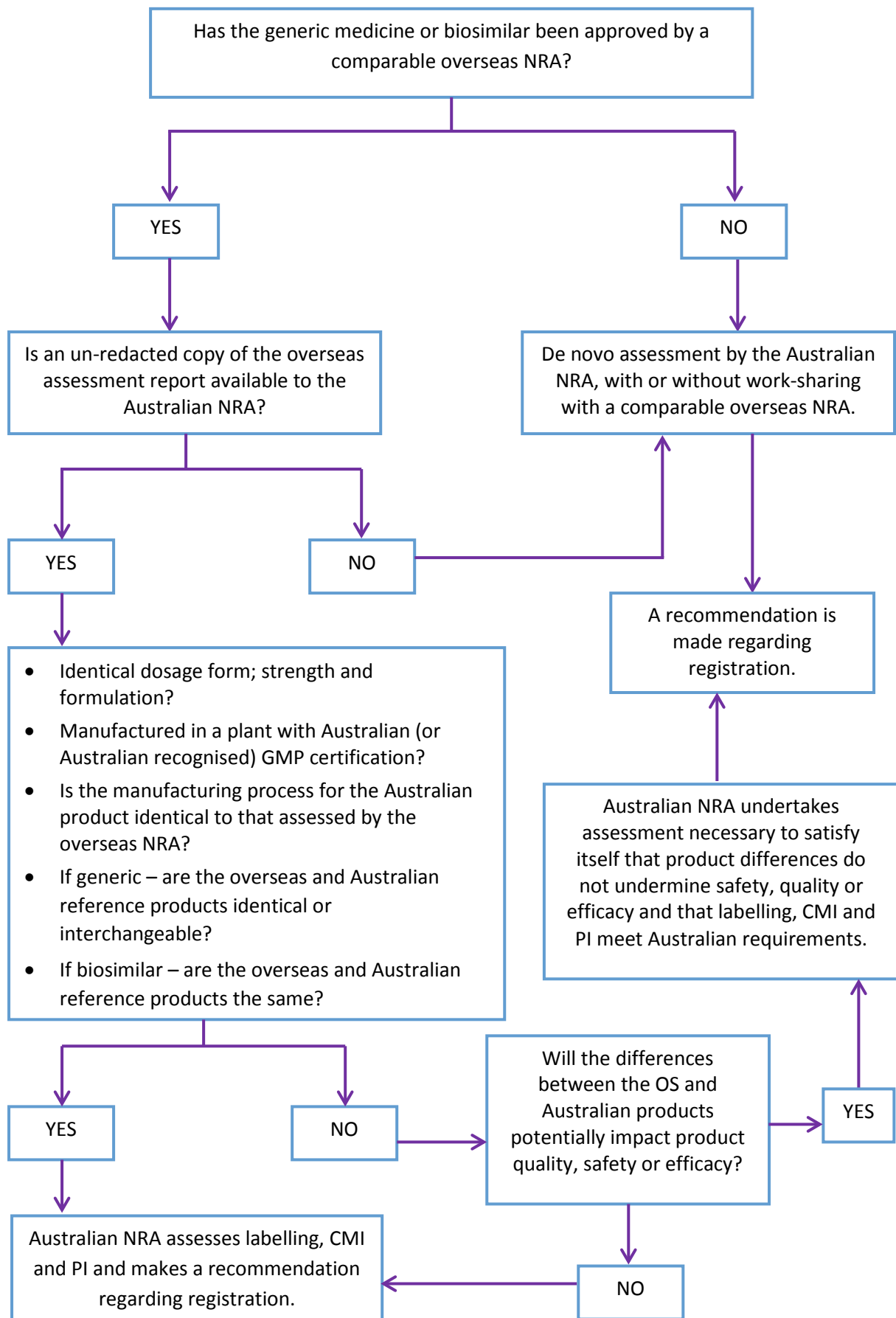
1. The Australian NRA makes a recommendation regarding registration of the generic medicine or biosimilar once it has satisfied itself that:
 - A. The generic medicine or biosimilar is identical in dosage form, strength, and formulation to the product approved by the comparable overseas NRA; and
 - B. The generic medicine or biosimilar will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian authority has co-recognition); and
 - C. The manufacturing process to produce the generic medicine or biosimilar will be identical to that assessed by the comparable overseas NRA for the overseas product; and
 - D. If the product is a generic medicine - the reference product used by the comparable overseas NRA when assessing bioequivalence was identical to, or interchangeable with, the Australian reference product; or
 - E. If the product is a biosimilar - the overseas reference product and the Australian reference product were the same; and
 - F. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.
2. Where the **generic medicine** seeking registration in Australia does not meet conditions 1A to 1D above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or

Recommendation Seven

efficacy of the product.

- A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements before making a recommendation regarding registration of the **generic medicine** in the ARTG.
 - B. Where differences between the **generic medicine** seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the generic medicine in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed; and
 - II. Assess whether the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.
3. Where the **biosimilar** seeking registration in Australia does not meet conditions 1A to 1C and 1E above, the Australian NRA undertakes an assessment of the extent to which the differences have the potential to impact the quality, safety or efficacy of the product.
- A. If the differences are assessed to have minimal impact on product quality, safety or efficacy, the Australian NRA should satisfy itself that the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements before making a recommendation regarding registration of the **biosimilar** in the ARTG.
 - B. Where differences between the **biosimilar** seeking registration in Australia and that approved by the comparable overseas NRA have the potential to impact product quality, safety or efficacy, before making a recommendation regarding registration of the biosimilar in the ARTG, the Australian NRA should:
 - I. Undertake an assessment of the application for registration to the extent necessary to satisfy itself that any potential impact of the differences on quality, safety or efficacy have been addressed; and
 - II. Assess whether the proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements.

Figure 9: Application pathways for registration of a generic medicine or biosimilar



Conflicting decisions by two or more comparable overseas NRAs

Assuming that multiple overseas NRAs are identified as ‘comparable’ to the Australian NRA, there may be occasions where one comparable overseas NRA approves a medicine for certain indications while another rejects the medicine for the same indications. While this situation is only likely to occur infrequently, it is inevitable that it will happen from time to time. Such situations may cause consternation among consumers and health professionals if Australia was to always err on the side of the approving authority.

In its discussion paper, the Panel sought the views of stakeholders as to whether it would be appropriate for the Australian NRA to undertake a de novo assessment of Pathway Two applications if the medicine had been approved by one comparable NRA but rejected by another. There was strong support for some form of additional assessment by the Australian regulator in such circumstances, with some stakeholders expressing concern that manufacturers might ‘NRA shop’ in the absence of any additional review. It was also emphasised that a review was important in terms of protecting public health and safety. However, some stakeholders queried the need to undertake a de novo assessment, arguing that the Australian regulator could limit its review to those aspects of the sponsor’s data dossier that had created the point of conflict.

This approach seems reasonable. For example, if two comparable overseas regulators agree on their toxicology findings but disagree on clinical efficacy grounds, it is difficult to see what value would be added for the Australian NRA to review both the toxicology data and the clinical data. However, it would clearly be essential for the Australian NRA to take a close look at the clinical efficacy data.

A similar situation could also arise where a product that is registered in the ARTG is subsequently rejected for the same indication by a comparable overseas NRA. Were this situation to occur, the Panel proposes that the Australian NRA should implement a review to the extent necessary to assure itself that there are no concerns regarding the safety, quality or efficacy of the medicine. This should occur regardless of whether the medicine was approved following a Pathway One or Pathway Two application.

4.3.4 Features of Pathway Three - expedited approval

As indicated in section 4.3.1.3, there was strong support from stakeholders for the Australian NRA to have capacity to offer expedited assessments of medicines in some circumstances. There was not, however, consensus about the criteria that should apply in order to access an expedited approval pathway or about the form that such a pathway(s) should take.

4.3.4.1 Criteria for expedited approval

There was virtually universal support for expedited approval schemes that provide quicker access to medicines for people with potentially fatal diseases, such as cancer. Where death

was seen as imminent in the absence of treatment, timely access to a potentially efficacious treatment was viewed as a high priority. In such cases the potential benefit of taking the medication was seen to outweigh the risks of accessing a therapy, the safety and efficacy of which is still being established. There was a greater degree of reticence among some stakeholders in circumstances where a novel medicine was considered to be more 'life-changing' than 'life-saving'. In these circumstances the balance of risk and benefit was considered to be less clear. However, some stakeholders argued that it is just as important to have capacity to provide expedited approval of medicines that have the potential to markedly improve quality of life as it is to provide expedited approval of medicines that have the potential to increase the quantity of life. The Panel concurs with this view.

The criteria applied by overseas regulators for expedited approval programmes vary depending on the scheme, but all go beyond life-saving drugs. The following compares the criteria for expedited assessment in three jurisdictions, the US, Europe and Japan.

Europe

In Europe, the EMA will consider accelerated assessment for medicines:

...which are of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation.²⁵

While an application for *Conditional Marketing Authorisation* can be considered if the medicine belongs to one of the following categories:

- *medicinal products that aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases;*
- *medicinal products to be used in emergency situations, in response to public threats duly recognised either by the WHO or by the Community in the framework of Decision (EC) No 2119/98;*
- *medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000.²⁶*

United States

In the US, the four expedited approval schemes offered by the FDA are designed to address an 'unmet medical need in the treatment of a serious condition'. A serious condition is defined as:

. . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that

*the disease, if left untreated, will progress from a less severe condition to a more serious one.*²⁷

Consideration is also given to what other treatments may be available for the serious condition, in terms of identifying whether there is an 'unmet medical need'.

Japan

Japan will consider priority review of medicines based on the following criteria:

(A) Seriousness of indicated diseases:

- (i) Diseases with important effects on patient's survival (fatal diseases).*
- (ii) Progressive and irreversible diseases with marked effects on daily life.*
- (iii) Others.*

(B) Overall assessment of therapeutic usefulness:

- (i) There is no existing method of treatment, prophylaxis, or diagnosis.*
- (ii) Therapeutic usefulness with respect to existing treatment*
 - a) Standpoint of efficacy.*
 - b) Standpoint of safety.*
 - c) Reduction of physical and mental burden on the patient.*²⁸

There are, therefore, no standard criteria for expedited approval programmes used internationally that could be adopted by Australia. However there is some commonality to the factors taken into consideration in determining whether a medicine is suitable for expedited assessment, namely:

1. the seriousness of the disease or condition and its impact on people's daily lives;
2. the existence of effective interventions; and
3. the extent of (potential) innovation offered by the medicine – i.e. will it provide a substantial benefit in some aspect of patient outcomes?

The Panel recommends that the NRA, in consultation with consumers, health professionals and industry, develop transparent criteria against which applications for expedited approval of a medicine may be assessed. Such criteria should not be inconsistent with that adopted by overseas NRAs for accelerated approval and should include consideration of the three factors listed above.

The Panel notes that a further point of consistency between international criteria is that they are qualitative. That is, an assessment of the extent to which the criteria apply to a given medicine requires the exercise of clinical (and some might argue, value) judgement. This provides for maximum flexibility in the application of the criteria, but it may create

confusion and conflict if the approach taken to interpreting each criterion is not consistent across applications.

For this reason the Panel is of the view that, while sponsors should be able to seek assessment of a medicine through the expedited approval pathway the final decision about whether a medicine is eligible for expedited approval should rest with the NRA. In implementing the expedited approval pathway, the NRA should establish and maintain policies and procedures aimed at promoting consistent and transparent decision making in respect of applications for expedited approval. While the Panel notes that some jurisdictions make provision for sponsors to pay an increased evaluation fee in order to obtain a priority review, this approach is not supported. The NRA should make the decision about whether an NCE can access Pathway Three based purely on an assessment against agreed criteria.

Recommendation Eight

The Panel recommends that the Australian NRA should develop and apply transparent criteria under which application may be made for accelerated assessment of promising new medicines (Pathway Three). Such criteria should not be inconsistent with those adopted by comparable overseas NRAs for accelerated assessment.

4.3.4.2 What form should Pathway Three take?

As outlined above, there are a number of different expedited approval schemes operating internationally. Some, such as the FDA's *Fast Track* and *Breakthrough Therapy* programmes, seek to facilitate product development as well as expedite marketing approval for the product. They provide for frequent or intensive engagement between the product sponsor and the FDA to discuss the medicine's development programme so as to ensure the collection of appropriate data to support marketing approvals. Medicines that are accepted for the *Fast Track* and *Breakthrough Therapy* programmes may also be eligible for *Accelerated Approval* or *Priority Review*.

The FDA *Priority Review* is akin to the EMA's *Accelerated Assessment* procedure. Both seek to apply additional resources to the evaluation of an application of a medicine for marketing approval, so as to truncate the period of time required, reducing it to six months in the US and 150 days in the EMA. These programmes are based on the provision of a full data dossier that will allow an assessment of safety, quality and efficacy to be undertaken.

In contrast, the FDA's *Accelerated Approval* programme and the EMA's *Conditional Marketing Authorisation* provide for an assessment of the product for market based on less, or different, clinical data than would be required for a routine assessment. For example, the US *Accelerated Approval* programme allows for an approval based on the

medicine's effect on a surrogate endpoint^v or an intermediate clinical endpoint that is reasonably likely to predict the medicine's clinical benefit.²⁹ Post-marketing confirmatory trials are required to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. The medicine is also subject to expedited withdrawal from the market in certain circumstances, such as: if the sponsor fails to undertake the necessary confirmatory trials; or if the results of such trials fail to demonstrate the predicted clinical benefit; or if other evidence demonstrates that the product is not shown to be safe or effective.³⁰

Similarly, the EMA's *Conditional Marketing Authorisation* may be granted where the Committee for Medicinal Products for Human Use finds that:

...although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- *the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;*
- *it is likely that the applicant will be in a position to provide the comprehensive clinical data;*
- *unmet medical needs will be fulfilled;*
- *the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required...*

*Conditional marketing authorisations are valid for one year, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.*³¹

Based on the above, and an examination of expedited approval options offered by a number of other countries, there appears to be three main approaches to expedited approval:

1. Programmes that commence early in the lifecycle of a medicine and seek to facilitate the development of promising new medicines as well as speed up marketing approval of these drugs.

^v An example of a surrogate endpoint is the effect of a medicine on the viral load of HIV over, for example, a period of six months. In the absence of data on the impact of the medicine on irreversible morbidity or mortality of HIV positive patients, it might be reasonable to predict that a sustained reduction in viral load over a period of six months is likely to predict clinical benefit.

2. Programmes that aim to allow medicines to reach patients with unmet clinical needs earlier than might otherwise be the case, by allowing medicines to be marketed on the basis of surrogate end points or other relevant data, rather than on safety and efficacy data from full Phase III trials.
3. Programmes that seek to provide faster evaluation of full data dossiers for new chemical entities, so that a decision regarding marketing approval can be made more quickly, thus providing for the medicine to be available on the market some months before it would otherwise have been.

The first approach, while supported by some stakeholders, would require a considerable commitment of resources from the Australian NRA over a period of years. The Panel is supportive of the NRA having a role in the provision of information and advice to industry to assist with the development of clinical trials and data dossiers (see Chapter Seven). However, it is concerned that the Australian NRA does not have the human resources or economies of scale of an organisation like the FDA. As such, the Panel questions the Australian NRA's ability to sustain the level of engagement required for the successful implementation of programmes akin to the FDA's *Fast Track* and *Breakthrough Therapy* schemes.

However, the Panel considers that approaches two and three are both viable within the Australian context. The adoption of both approaches under Pathway Three would allow for the Australian NRA to:

1. Prioritise the evaluation of a complete data dossier in certain circumstances, with a view to reducing the target timeframe for a decision regarding registration of the medicine in the ARTG. The Panel would recommend that the target timeframe for such a review be 150 working days, consistent with the benchmarks set by the FDA and EMA for similar programme (Priority Review); or
2. Provide provisional approval for the registration of a medicine in the ARTG, in the absence of full Phase III trial safety and efficacy data, where the benefit to public health of the immediate availability of the medicine outweighs the risk inherent in the fact that additional data is still required (Provisional Approval).

Furthermore, there should be the ability for sponsors to apply for Priority Review or Provisional Approval on the basis of an un-redacted evaluation report from a comparable overseas NRA. This will provide further flexibility and allow Australian consumers even faster access to innovative medicines that have been subject to expedited approval by comparable overseas NRAs. Where application for priority review or provisional approval is made on the basis of an un-redacted evaluation report from a comparable overseas NRA, the Australian NRA would make a recommendation regarding registration of the new chemical entity in the ARTG once it had satisfied itself that:

- A. The new chemical entity is identical in dosage form, strength, formulation and indications; and
- B. The new chemical entity will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian regulator has co-recognition); and
- C. The manufacturing process to produce the new chemical entity will be identical to that assessed by the comparable international regulator for the overseas product; and
- D. There are no specific issues regarding applicability to the Australian context that need to be examined; and
- E. Proposed product labelling, Product Information and Consumer Medicine Information is appropriate and consistent with Australian requirements; and
- F. Any conditions placed on the medicine by the comparable overseas NRA are applicable to the Australian context; and
- G. Data provided to the comparable overseas NRA under these conditions will be available to the Australian NRA in a timely way.

Where a medicine is granted provisional approval by the Australian NRA, whether as a result of an application consistent with Pathway One, requiring a de novo evaluation by the NRA, or with Pathway Two, utilising an un-redacted evaluation report from a comparable overseas NRA, the approval should be:

1. Time-limited, with a requirement for the sponsor to collect and submit further data to demonstrate safety, quality and efficacy in order for the product to be granted full registration.
2. Subject to any conditions imposed by the Australian NRA (which should be consistent with those imposed by a comparable overseas NRA if relevant and applicable to the Australian context). Such conditions might include limiting the use of the medicine to certain populations or as a second or third line treatment.
3. Subject to the provision of clear advice to consumers and health practitioners that the medicine has been granted provisional approval and the implications of that for the consumer/health practitioner. This should include advice about the basis for marketing approval, the time-limited nature of that approval, and the fact that the medicine may be withdrawn with little notice in certain circumstances.

Post-market monitoring in the context of pathway three

Enhanced post-market monitoring will be essential to support the introduction of expedited approval programmes, particularly provisional approvals. If access to promising new medicines is to be expedited on the basis of surrogate endpoints, or other similar data, rather than awaiting the outcomes of full stage III clinical trials, then it is essential that mechanisms be put in place to monitor these medicines in the marketplace. Post-market

monitoring traditionally focuses on safety, but in the case of medicines that have been provisionally approved, efficacy is likely to be more uncertain. As such, post-market monitoring will need to collect and analyse data that goes to both safety and efficacy. In the absence of enhanced post-market monitoring, the Panel has reservations about the Australian NRA offering Provisional Approval, regardless of whether the application for such approval utilises Pathway One or Pathway Two. The Panel's proposed approach to post-market monitoring is discussed in detail in Chapter Seven.

Interface with subsidy schemes

As noted in Chapter Three, market access in Australia is achieved by the inclusion of a product in the ARTG. But market access does not necessarily translate into consumer access because in practice the cost of the medicine may be prohibitively expensive and this acts as a barrier to access for most consumers. There is, therefore, a further step in providing consumer access to medicines in Australia, which involves consideration by the Australian Government about whether or not the medicine should be subsidised. Provisional approval programmes create difficulties in this regard, as the absence of normal efficacy data makes the analysis of comparative effectiveness conducted by the PBAC problematic. As such, in considering the Panel's recommendations in respect of expedited approval, it will be important for the Australian Government to consider the flow on implications for the PBAC and thus for subsidy programmes and how these might be addressed.

Recommendation Nine

The Panel recommends that in circumstances where the Australian NRA has approved an expedited approval process utilising Pathway Two, and the sponsor has submitted all necessary materials, including an un-redacted evaluation report from a comparable overseas NRA, to the Australian NRA, the Australian NRA make a recommendation regarding registration of the new chemical entity once it has satisfied itself that:

- A. The new chemical entity is identical in dosage form, strength, formulation and indications; and
- B. The new chemical entity will be manufactured at a plant that has received GMP certification from the Australian NRA (or from a comparable overseas NRA with whom the Australian regulator has co-recognition); and
- C. The manufacturing process to produce the new chemical entity will be identical to that assessed by the comparable overseas NRA for the overseas product; and
- D. There are no specific issues regarding applicability to the Australian context that need to be examined; and
- E. Proposed product labelling, Product Information and Consumer Medicine Information are appropriate and consistent with Australian requirements; and

- F. Any conditions placed on the medicine by the comparable overseas NRA are applicable to the Australian context; and
- G. Data provided to the comparable overseas NRA under these conditions will be available to the Australian NRA in a timely way.

Recommendation Ten

The Panel recommends that where accelerated approval occurs following evaluation of a more limited data dossier than would be required for a submission under Pathway One, registration of the medicine in the ARTG should be:

1. Provisional and time-limited, with a requirement for the sponsor to collect and submit further data to demonstrate safety, quality and efficacy in order for the product to be granted full registration.
2. Subject to any conditions imposed by the Australian NRA (which should be consistent with those imposed by a comparable overseas NRA if relevant and applicable to the Australian context).
3. Subject to the provision of clear advice to consumers and health practitioners that the medicine has been granted provisional approval and the implications of that for the consumer/health practitioner.

4.3.5 Enhanced transparency of scheduling processes

Whether a medicine is available on prescription only or may be purchased over-the-counter is determined by the scheduling of its active ingredient(s) (referred to as the substance) on the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP), known as the *Poisons Standard*. The scheduling of medicines takes into account both the substance, its use and the way in which the substance is to be sold, for example pack size, in determining the level of health professional intervention required before a consumer can access the medicine, and the sites from which a medicine can be accessed. The scheduling of medicines is designed to: promote the quality use of medicines; and to balance consumer access to medicines with the need to manage risks associated with their use, especially in light of the information asymmetry that exists between consumers and medicines manufacturers.³²

Scheduling decisions are given effect in State and Territory drugs and poisons legislation, with national uniformity in scheduling promoted through the *Scheduling Policy Framework* (SPF). Developed by the now defunct National Coordinating Committee on Therapeutic Goods (NCCTG), the SPF sets out the national system for 'applying access restrictions on all poisons',³³ including medicines for human use. Under the SPF, the active ingredient (substance) of the medicine is classified into one or more of the schedules, depending on

the way in which the product is to be sold, according to the level of regulatory control required to manage risk.

4.3.5.1 Scheduling decisions

Under the Act, a person may apply to amend the *Poisons Standard*.³⁴ Such amendments relate to the addition of a new substance, which occurs at the point of registration of a new chemical entity in the ARTG, or application for rescheduling of an existing substance. Since 1 July 2010, scheduling decisions in respect of medicines have been made by a delegate of the Secretary of the Department of Health, who may receive advice from the Advisory Committee on Medicines Scheduling (ACMS).

When the delegate makes a scheduling decision, (s)he is obliged under the Act to take into consideration:

- the risks and benefits of the use of the substance;
- the purposes for which the substance is to be used and the extent of use of the substance;
- the toxicity of the substance;
- the dosage, formulation, labelling, packaging and presentation of the substance;
- the potential for abuse of the substance; and
- any other matters the delegate considers necessary to protect public health.³⁵

The delegate is also obliged to take into account recommendations from the ACMS and comply with any guidelines of the NCCTG, including the SPF. The panel notes that a new edition of the SPF, endorsed by the Australian Health Ministers' Advisory Council, has been in effect since 1 February 2015.

The SPF sets out a number of scheduling factors which inform the way the ACMS makes recommendations and the delegate makes decisions. The application of these factors embodies a 'cascading principle', in which a substance intended for therapeutic use in humans is first assessed against the factors for Schedule 8 controlled drugs (highest risk), then Schedule 4 prescription only medicines, and if these are not applicable the Schedule 3 factors, and so on and so forth. Table 4 outlines the scheduling factors for medicines, summarised from the *Scheduling Policy Framework*.

The current overarching approach of having four schedules for medicines (Schedules 8 and 4 for prescription medicines and Schedules 3 and 2 for OTC medicines) was supported by stakeholders and the Panel believes it remains appropriate. However, while most stakeholders were supportive of the overarching approach to scheduling, some argued that scheduling policy (including the scheduling factors) could be improved. This was particularly in the context of consideration of applications to down-schedule a substance from, for example, Schedule 4 to Schedule 3.

In particular, some stakeholders argued that the current scheduling framework lacks transparency and places an undue emphasis on risk without proper consideration of the benefits of down-scheduling in terms of greater consumer access and encouraging greater self-management of conditions. Suggestions for improvement included:

- More explicit consideration of the quality use of medicines in scheduling decisions.
- Increasing the capacity of the scheduling process to consider risks in terms of individual patient characteristics (e.g. age, medical history, etc.).
- The adoption of a consistent and transparent methodology for assessing risks and benefits.
- Improved capacity for health professionals, consumer groups, and industry to input to scheduling decisions.

Table 4: Scheduling factors for medicines

Schedule	Scheduling Factors
Schedule 8 (Controlled Drugs)	<ul style="list-style-type: none"> • The substance is included in Schedule I or II of the <i>United Nations Single Convention on Narcotic Drugs 1961</i> or in Schedule II or III of the <i>United Nations Convention on Psychotropic Substances 1971</i>. • The substance has an established therapeutic value but its use, at established therapeutic dosage levels, is recognised to produce dependency and has a high propensity for misuse, abuse or illicit use. • The substance has an established therapeutic value but by reason of its novelty or properties carries a substantially increased risk of producing dependency, misuse, abuse or illicit use.
Schedule 4 (prescription medicines)	<ul style="list-style-type: none"> • The ailments or symptoms that the substance is used for require medical/dental intervention. • The use of the substance requires adjunctive therapy or evaluation. • The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use. • The seriousness, severity and frequency of adverse events are such that monitoring or intervention by a medical/dental practitioner is required to minimise the risk of use. • The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical or dental intervention to minimise the risk of using the substance. • The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, medicine-disease) are such that monitoring or intervention is required by a medical or dental practitioner. • The use of the substance has contributed to, or is likely to contribute to, communal harm (e.g. the development of resistant strains of microorganisms). • The experience of the use of the substance under normal clinical conditions is limited.

Schedule	Scheduling Factors
Schedule 3 (pharmacist only)	<ul style="list-style-type: none"> • The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately. • The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by the pharmacist. • The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are well known, identifiable and manageable by a pharmacist. • The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition.
Schedule 2 (pharmacy medicine)	<ul style="list-style-type: none"> • The quality use of the medicine can be achieved by labelling, packaging, and/or provision of other information; however access to advice from a pharmacist is available to maximise the safe use of the medicine. • The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low. • The use of the medicine at established therapeutic dosage levels is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used. • The risk profile of the medicine is well defined and the risk factors can be identified and managed by a consumer through appropriate packaging and labelling and consultation with a medical practitioner if required. • The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition.

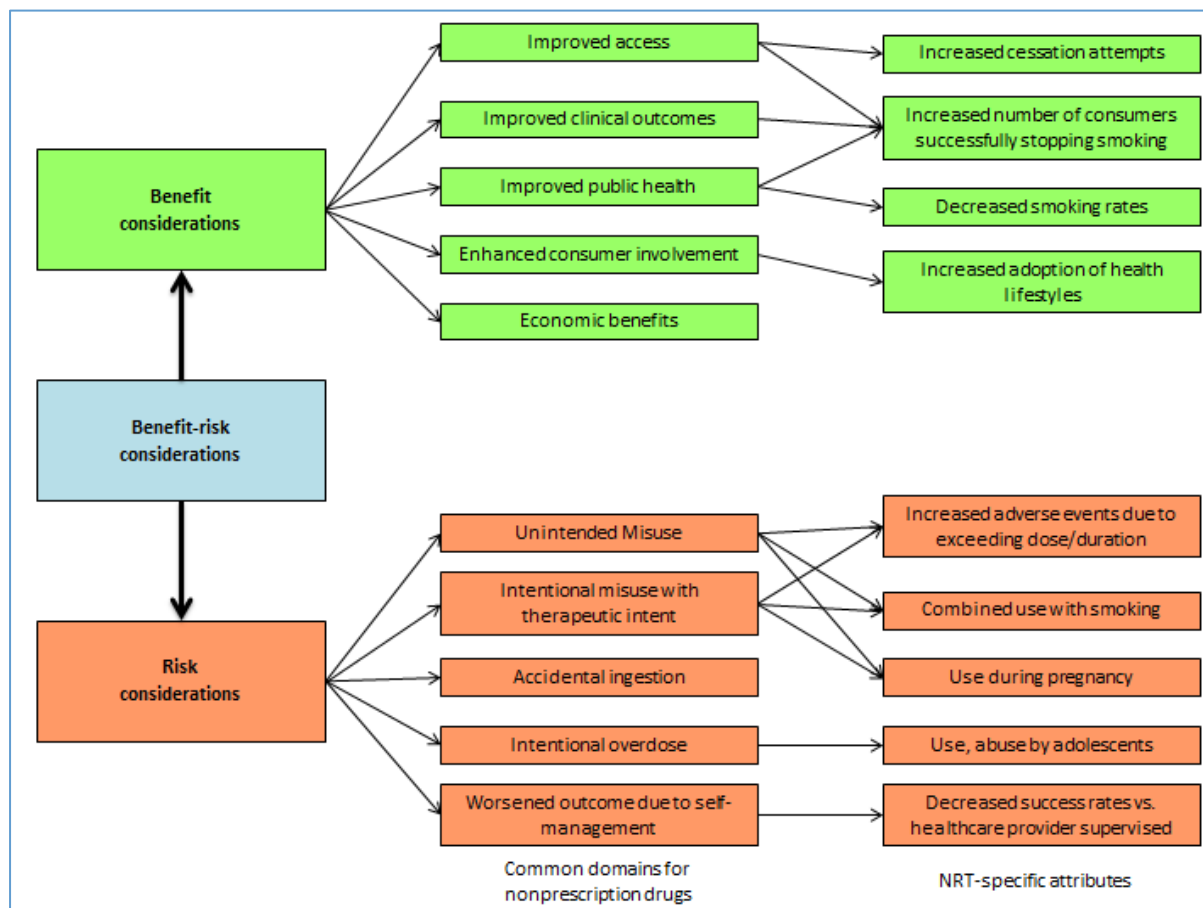
The Panel notes that a 2013 Review of Scheduling recommended that consideration be given to the adoption of a formal methodology for assessing risks and benefits.³⁶ One such approach is the value-tree format, which was developed by Brass et al.³⁷ A number of stakeholders advocated for adoption of this approach and the Panel notes that it is being utilised by both the NZ Medicines Classifications Committee (MCC) and the UK MHRA. The MHRA's guidance on how to reclassify medicines promotes a modified^{vi} value-tree to sponsors as a 'useful tool for conducting the benefit:risk analysis' which must be undertaken by sponsors prior to making an application to have a medicine reclassified.³⁸ An example of how this value-tree framework can be applied to evaluate the benefits and risks of scheduling Nicotine Replacement Therapies (NRTs) such as nicotine-containing gums and patches is provided at Figure 10.

The Panel considers that the adoption of a formalised methodology to inform scheduling decisions has merit. Firstly, it would facilitate a structured and systematic approach to assessing the risks and benefits of re-scheduling a particular substance, ensuring that multiple domains are explored. This should in turn promote consistency of decision making, as it ensures that each domain is explored for each substance. In the absence of a structured methodology there is a risk that the focus of analysis will be driven by the interests and perspectives of the person(s) undertaking the analysis, which may vary over

^{vi} The value-tree utilised in the MHRA's guidance document includes an additional risk domain, 'inherent risks' compared to that put forward by Brass et.al.

time, especially in circumstances where there is turnover in expert advisors and/or NRA staff/delegates.

Figure 10: Value-tree framework of benefits and risks of scheduling Nicotine Replacement Therapies



Source: Brass E. P., Lofstedt R., and Renn O, (2011, December), *Improving the Decision-Making Process for Nonprescription Drugs: A Framework for Benefit-Risk Assessment*, in *Clinical Pharmacology & Therapeutics*, 90(6):791-803.

Secondly, use of a structured methodology would afford a level of transparency to the decision making process that is not provided for under the current SPF. That is, if a formal methodology is adopted, and everyone is aware of what that methodology is, then all parties – the sponsor; consumers; health professionals; other medicines manufacturers with an interest; advisory committees; and the delegate – will be considering the issues within a defined framework. This should make it easier for sponsors or other parties to frame a case for re-scheduling, as the domains that will be considered by the Committee/delegate are clearly articulated. It should also make it easier for other interested parties to input to the process, as they can choose to focus on specific domains or across the value-tree as a whole.

Finally, a structured framework would make the formulation of recommendations and/or statements of reason for a decision easier, as each benefit or risk domain could be

addressed in turn followed by an 'on-balance' summary. It would also provide a consistent format to such documents, making them easy to read, digest and understand.

The Panel notes the concerns expressed by some stakeholders that adoption of a formal methodology for scheduling decisions could introduce additional complexity into the decision making process. The Panel does not concur with this view. Scheduling decisions are, by their very nature, complex, and it is important to get them right, as inappropriate scheduling may have serious consequences for consumers. A structured framework for such decisions has the potential to improve decision making by bringing additional rigour to the analytical process.

In developing a preferred methodology it will, however, be important to consult with a broad range of stakeholders to ensure that the risk and benefit domains are comprehensive and that there is a shared understanding of the issues that each domain is designed to capture. It will also be important to ensure that the methodology is flexible enough to allow consideration of unforeseen issues which may not clearly fall within agreed domains, where such issues may have a material impact on the risk benefit analysis. Such a scenario is unlikely, but should be provided for.

To maximise good decision making in respect of scheduling it will also be important to provide enhanced opportunities for informed input to the process from interested parties. A number of stakeholders, including consumer, professional and some industry bodies, expressed concerns to the Panel about the lack of publicly available information about applications to amend the *Poisons Schedule*. The *Notice inviting public submissions* only provides a brief sentence or paragraph about the proposed change. For example, the March 2015 ACMS meeting included consideration of a proposal to:

*...exempt ranitidine from Schedule 2 when in divided preparations for oral use containing 300 mg or less of ranitidine per dosage unit in the manufacturer's original pack containing not more than 7 dosage units.*³⁹

A number of stakeholders indicated that they would like to have access to the application, so as to inform their submission. This issue was raised by the 2013 Review of Scheduling, which recommended that the 'level of detail, clarity and transparency of the information contained in public notices relating to scheduling proposals' be improved.⁴⁰

The Panel agrees that it is important that information is publicly available about an application to amend the Poisons Schedule, including about the proposed rationale, so that interested parties can make informed submissions to the process. Scheduling decisions may impact health professionals (both doctors and pharmacists), industry, and consumers and, as such, it is important that the process facilitates useful input from these affected parties. If a value-tree tool was adopted for assessing the risks and benefits of rescheduling, publication of the applicant's analysis against each of the domains should be considered, with facility for truly commercial-in-confidence material to be redacted.

Having considered the issues raised, the Panel supports the adoption of a formal risk-benefit methodology for decision making in respect of the scheduling of active substances in medicines. Coupled with enhanced opportunities for informed input from affected parties, such a methodology would, in the Panel's view, provide for more consistent and transparent decision making. It would also create a common understanding of the risk-benefit domains that need to be explored in making such decisions. As such, the Panel recommends that the SPF be reviewed, in consultation with States and Territories, and with industry, professional and consumer stakeholders, to provide for: the adoption of a formal risk-benefit methodology to underpin scheduling decisions; and enhanced opportunities for informed input from affected parties. The NRA and the ACMS should play a key role in the review, particularly given the proposed role of the ACMS as outlined in Chapter Seven.

Recommendation Eleven

The Panel recommends that the *Scheduling Policy Framework* be reviewed, in consultation with State and Territory Governments, to provide for:

1. The development and adoption of a formal risk-benefit methodology to assess scheduling applications; and
2. Opportunities to enhance input from interested parties into the scheduling process.

4.3.6 Scheduling and the advertising of medicines

In addition to regulating the way in which medicines may be supplied, scheduling impacts the way in which medicines may be promoted. Regardless of which schedule a medicine is on, the medicine may be advertised to health professionals. But direct-to-consumer advertising is dependent upon the scheduling decision. If a product is prescription only (Schedules 4 or 8), then advertising is prohibited, whereas if a product is pharmacy only (Schedule 2), advertising to consumers is permissible. For pharmacist only products (Schedule 3), advertising is only permitted if the sponsor successfully applies for the substance to be included in Appendix H to the *Poisons Standard*. Appendix H contains the list of Schedule 3 substances for which direct-to-consumer advertising is permitted. Table 5 provides examples of some common S3 medications, and whether or not they may be advertised direct-to-consumers.

Table 5: Overview of whether a Schedule 3 substance can be advertised

Schedule 3 substance	Can it be advertised?
BUTOCONAZOLE Topical anti-fungal for vaginal candidiasis	✓
DICLOFENAC A non-steroidal anti-inflammatory indicated for short-term relief of acute pain	✓
DIMENHYDRINATE Anti-histamine used to treat motion sickness	✓
HYDROCORTISONE Topical steroid used for eczema and dermatitis	✓
LEVONORGESTREL Morning-after pill	✗
OMEPRAZOLE A proton-pump-inhibitor for oesophageal reflux	✗
PSEUDOEPHEDRINE A sympathomimetic drug often used as a nasal decongestant	✗
SALBUTAMOL inhaler A bronchodilator for prevention of bronchospasms	✗

4.3.6.1 Direct-to-consumer advertising of prescription medicines

Under the Act, promotion of prescription medicines to health professionals is allowed, but it is an offence to advertise such products direct-to-consumers. This approach is based on the view that health professionals have sufficient training, experience and knowledge to properly evaluate the content of promotion/advertising, whereas consumers generally lack the necessary information to do so.⁴¹ Australia's ban on advertising of prescription medicines direct-to-consumers is consistent with international practice, with only the United States and New Zealand permitting such advertisements.

Submissions to the Review were strongly in favour of retaining the current ban on direct-to-consumer advertising of prescription medicines. This view was consistent across consumers, health professionals and industry. Concerns were expressed that allowing direct-to-consumer advertising of prescription medicines could undermine the physician-patient relationship, and would only lead to expensive advertising wars between particular brands of the same product, products within the same therapeutic class, increasing the costs of medicines. Additionally, stakeholders argued that prescription medicines require the involvement of health professionals to determine when their use is appropriate and advertising may lead to pressure being exerted by patients for a prescription drug that is inappropriate to their needs.

Given the broad consensus against relaxing the ban on direct-to-consumer advertising of prescription medicines, the Panel did not consider this issue further. The Panel recommends that the Australian Government retain the status quo in this regard.

4.3.6.2 *Direct-to-consumer advertising of Schedule 3 medicines*

Direct-to-consumer advertising of pharmacist only medicines (Schedule 3) is also banned in Australia.⁴² As noted above, there are some exceptions in respect of active substances currently listed in Appendix H of the *Poisons Standard*. As of March 2015, there were only ten such substances, which means that the vast majority of Schedule 3 medicines are subject to this restriction. Australia's approach to the advertising of Schedule 3 medicines is out of step with many comparable overseas jurisdictions, which allow direct-to-consumer advertising of all medicines, other than prescription medicines. The Panel notes however, that there is disparity in classifications between countries, so medicines that are included in Schedule 3 in Australia may, in fact, be prescription medicines in another jurisdiction.

Appendix H decisions are made by the Secretary of the Department of Health (in practice a delegate) who must take into account matters set out in the 2000 NCCTG Schedule 3 advertising guidelines.⁴³ These guidelines require that the decision maker consider a number of matters, including:

- The potential public health benefit, for example more appropriate use of scarce health resources or a better informed community.^{vii}
- The likelihood of advertising of the substance leading to inappropriate patterns of medication use.
- Whether the application may result in the advertising of goods for an indication other than those included in the ARTG.
- The desire of consumers to manage their own medication and the level of patient education necessary to ensure correct use.⁴⁴

There was no clear consensus among stakeholders about whether or not the restriction on direct-to-consumer advertising of Schedule 3 medicines should be lifted. Some stakeholders argued that the ban on Schedule 3 advertising should be completely relaxed, with Appendix H becoming a list of Schedule 3 substances which cannot be advertised, whereas others argued that the ban should remain in place.

Stakeholders who advocated for the removal of the ban on direct-to-consumer advertising of Schedule 3 medicines made a number of points in support of their position. These included:

^{vii} Where it is not possible to present data to quantify the extent of any claim of public benefit, qualitative data may be acceptable.

- The risk profile of such products is quite different than that of prescription only medicines. That is, Schedule 3 medicines are generally products that have a long history of safe use; their risk profile is generally well-defined; and the risks to patients are manageable through professional intervention by a pharmacist (e.g. the pharmacist can refuse supply and suggest an alternate treatment).
- Relaxing the ban would maximise the public health benefits of down-scheduling of medicines by informing consumers that these products are available in pharmacies. In particular they asserted that the provision of information to consumers about Schedule 3 medicines would increase their health literacy, encourage consumers to become more involved in their treatment, and lead to better disease management.
- That the advertising of Schedule 3 substances listed at Appendix H to the *Poisons Standard* had been allowed for many years and there was no evidence to suggest that this has had a detrimental impact on public health and safety.

Those opposed to any relaxation of the ban on direct-to-consumer advertising of Schedule 3 medicines argued that such advertising may:

- Lead to inappropriate use of medicines, by creating demand for products that may not be medically necessary. Similarly, it was argued that it may undermine the relationship between the pharmacists and their customers, by placing pharmacists in a position of refusing to sell a medicine that the customer has requested.
- Indirectly cause harm by diverting resources from more cost-effective treatment options. For example, by increasing demand for a newer product that may not be clinically superior to older treatments.
- Increase the cost of medicines, as the cost of brand awareness campaigns by pharmaceutical companies would be passed on to consumers.
- Result in the up-scheduling of medicines as evidence of inappropriate use emerges, prompting additional safety concerns. Were this to occur it would undermine the rationale for having a pharmacist only category. That is, to provide easier access by consumers to medicines by managing risk through a pharmacist, rather than requiring a prescription from a clinician.

A number of these stakeholders expressed the view that, if there is a genuine need to increase public awareness of disease states and possible treatment options, it would be better achieved through funding Quality Use of Medicines Programmes, rather than allowing branded direct-to-consumer advertisements.

The evidence evaluated by the Panel from submissions and other sources did not conclusively demonstrate the potential for either widespread harm or widespread benefit from relaxing the ban on direct-to-consumer advertising of Schedule 3 medicines. Indeed, in submissions stakeholders on both sides of this debate noted that most of the research

about the effects of direct-to-consumer advertising has focused on prescription medicines, rather than OTC medicines. Additionally, as was noted in the *Galbally Review*, evidence from overseas jurisdictions may have limited applicability in Australia due to the difference in health systems. For example, at a federal level the US only has two categories: prescription and non-prescription, meaning that some heavily advertised prescription medicines in the US are classified as Schedule 2 medicines in Australia and allowed to be advertised.⁴⁵

Whilst the Panel is not aware of definitive evidence that advertising of substances that have been included in Appendix H has led to harm, there have been instances where substances have been removed from Appendix H due to concerns about their potential to do so. For example, in 2007, orlistat was removed from Appendix H after concerns arose about the potential for inappropriate patterns of use.^{viii} In making the decision, the NDPSC noted:

*...the advice from professionals and consumers that direct-to-consumer advertising increased pressure on pharmacists to provide orlistat to consumers. This in turn had the potential to result in inappropriate patterns of use, in patients for whom orlistat was neither indicated nor appropriate.*⁴⁶

The Panel notes the efforts of industry stakeholders and some professional associations to develop a model for direct-to-consumer advertising of Schedule 3 medicines, whereby the default position would be that Schedule 3 medicines may be advertised, with Appendix H functioning as a 'banned' list. A 'banned' list was considered necessary as it would be inappropriate to advertise some Schedule 3 medicines, such as those containing drugs of misuse/dependence like pseudoephedrine or codeine. For other Schedule 3 products, however, advertising would be permitted provided it met certain requirements, such as a primary focus on disease states rather than on brand identification; and an emphasis on the professional role of the pharmacist.

While this may be a viable approach in the future, the Panel does not believe that there is sufficient evidence available to recommend the adoption of this approach at this point in time. The Panel does, however, support a relaxation of the almost blanket ban on direct-to-consumer advertising of Schedule 3 medicines and proposes a middle ground, which provides for more active utilisation of Appendix H of the *Poisons Standard*.

Under the proposed approach, when a submission is made to down-schedule a medicine, or at some subsequent point, the applicant may also request that the substance be included on Appendix H, allowing it to be advertised direct-to-consumers. This application would be considered by the ACMS, either in parallel with the down-scheduling application or on its own (if submitted at a later date). In recommending inclusion of a Schedule 3 medicine on Appendix H, the ACMS would be able to recommend the imposition of additional conditions,

^{viii} A legal challenge of the decision to remove Orlistat from Appendix H was rejected by the Federal Court in 2007. See *Roche Products Pty Ltd v National Drugs and Poisons Schedule Committee* [2007] FCA 1352.

such as the advertising of a product being dependent on the provision of relevant professional support materials to pharmacies for the supply of the Schedule 3 medicine.

In addition, the Panel recommends that when a medicine is down-scheduled and/or included on Appendix H, post-market monitoring is increased for a period of time, with a view to detecting any increased harm or inappropriate patterns of use as early as possible. This could be achieved through the enhanced post-market monitoring proposed in Chapter Seven.

Implementation of this approach would require revisions to the *Schedule 3 Advertising Guidelines* and the Panel would encourage the adoption of a structured framework (as per Recommendation Eleven in respect of scheduling decisions), to inform risk-benefit considerations in respect of advertising. This will aid consistent and transparent decision making and assist applicants to understand and address the relevant domains. Review of the *Schedule 3 Advertising Guidelines* should logically be conducted in concert with the proposed review of the *Scheduling Policy Framework*, with a view to promoting synergies and reducing duplication in application requirements.

Recommendation Twelve

The Panel recommends that the Schedule 3 Advertising Guidelines be reviewed, in consultation with State and Territory Governments, and in concert with the review of the Scheduling Policy Framework, to:

1. Provide for the development and adoption of a formal risk-benefit methodology for the assessment of Schedule 3 substances for inclusion on Appendix H of the Poisons Standard; and
2. Identify synergies between application requirements for re-scheduling and for inclusion of a Schedule 3 substance on Appendix H, so as to streamline these processes and reduce duplication.

4.3.6.3 Advertising framework

In its *Review of Medicines and Medical Devices Regulation Discussion Paper*, the Panel sought input from stakeholders on the regulatory framework for direct-to-consumer advertising of medicines, including on the processes for pre-approval and complaints management. Whilst the Panel acknowledges the input received on these issues, it has determined that to make recommendations about the advertising framework in this report, ahead of consideration of these issues in respect to complementary medicines, would be inappropriate. As such, the Panel's recommendations about the advertising framework for OTC and complementary medicines and for medical devices will be incorporated into its second report, which is due to Government in mid-2015.

4.3.7 Post-market regulation

The standard conditions of registration that apply to all medicines require the sponsor to notify the NRA of changes or variations in respect of any information about the medicine, and provides that, where necessary, the changes or variation shall not be implemented until approved by the NRA delegate. This means that once a medicine is entered in the ARTG the information cannot be changed without approval. There are some minor exceptions, such as changes to the local handling agent of the active pharmaceutical agent and excipient; or to the supplier or manufacturer of non-sterile containers or container components, but the vast majority of changes relating to a registered medicine must be both notified to, and approved by, the NRA.

The *Therapeutic Goods Act 1989* provides for sponsors to request:

- updates to an ARTG entry that is incomplete or incorrect;
- safety-related variations to an ARTG entry and consequential changes to the Product Information, such as removing an indication or adding a warning or precaution; and
- other variations to an ARTG entry that do not have the effect of creating a separate and distinct good, provided that the change does not reduce the quality, safety or efficacy of the medicine.

If the variation creates a separate and distinct good, sponsors must apply to the TGA for approval of a new registered medicine. Variations that would create a separate and distinct good include new strengths, new dosage forms, different directions for use, formulation changes, changes in trade name, and extensions of indication.

The timeframes for approval of variations by the TGA differ depending on the nature of the variation requested. Major variations which require evaluation of a full dataset, or any combination of quality, nonclinical, clinical and bioequivalence data, have a statutory timeframe of between 175 and 255 working days. Variations that only require evaluation of quality-related data (Category 3 applications) and lower risk variations for which the sponsor can provide an assessment of their own data for the TGA to verify (known as self-assessable requests), have a statutory timeframe of 45 working days. Requests to correct an incorrect or incomplete ARTG entry or to make safety-related variations to the ARTG entry have no statutory timeframes.

The requirement to have virtually every variation approved by the NRA prior to implementation is contrary to the risk-based framework that underpins medicines regulation, in that it adopts a uniform approach to variations rather than one which is nuanced to the risk posed by the variation. The approach is also out of step with international practice. For example, from October 2010 the EU implemented a simpler and more flexible legal framework for variations to marketing approvals aimed at reducing burden on industry and further harmonising requirements across the EU, while maintaining public protections.⁴⁷

Under these reforms, the EU classified variations into a number of categories, based on the level of risk they posed to public health and their impact on the quality, safety and efficacy of the medicinal product concerned. These categories include:

- Minor variations Type IA, covering variations such as:
 - A change to the name and/or address of the marketing authorisation holder.
 - A change in the name of the active substance.
 - A change in the name and/or address of a manufacturer of the finished product.
 - A change to pack size of the finished product that is already within the currently approved range.
 - Minor changes to an approved test procedure.

As long as predefined conditions are met, such changes are subject to a ‘do and tell’ procedure, whereby the sponsor may implement the changes and notify the EMA. In most instances the notification must be within 12 months but a subset of Type IA variations (referred to as Type IA IM), which require continuous supervision, must be notified to the EMA immediately after implementation.

- Minor variations Type IB are defined as a minor variation that is neither a Type IA variation nor a Type II variation nor an Extension. Examples include: minor changes to an approved test procedure for a biological excipient; change in pack size of a finished product that is outside the currently approved range; and addition of new tests and limits applied during the manufacture of the product.

Type IB variations must be notified to the EMA by the sponsor prior to implementation, but do not require a formal approval. Upon acknowledgement of receipt of a valid notification, the sponsor must wait a period of 30 days to ensure that the notification is deemed acceptable before implementing the change (‘Tell, Wait and Do’ procedure).⁴⁸

The EU has also implemented electronic systems to support the lodgement of variations.

Similarly, the FDA allows a range of ‘minor changes’ to be included in a sponsor’s annual report rather than be approved prior to implementation. FDA Guidance⁴⁹ lists examples of variations that they consider to have a minimal potential to have an adverse effect on product quality in areas such as product components and composition; manufacturing sites, process, batch size, and equipment; containers and closures; and labelling. The UK MHRA has also done significant work on variations that only need to be notified rather than approved. There are, therefore, opportunities to learn from international experience in this sphere.

There was strong support from industry stakeholders for the adoption of a risk-based approach to variations to medicines. A number of stakeholders noted that the TGA, until around 2012, had such a scheme which they felt had worked well. The Panel understands

that this scheme was changed not because of any concerns about safety, but because of a reinterpretation of requirements under section 9D of the Act. Some consumer groups were concerned that any notification scheme for variations be limited to minor or cosmetic changes only, with the NRA required to assess other variations and decide what degree of additional scrutiny may be required. Such an approach is not inconsistent with the EU model, whereby some minor variations are simply notified to the regulator under a 'do and tell' approach, while others are subject to a 'tell, wait and do' procedure.

The Panel recommends that the NRA re-implement a risk-based approach to the management of variations that do not have the potential to impact the safety, quality or efficacy of the medicine. Given Australia's increasing alignment with the EU regulatory system, this risk-based approach should harmonise with that adopted by the EU, unless there is good reason for it not to do so. This harmonisation should relate to both policy and documentation as this will further reduce regulatory burden on sponsors by enabling them to use EU submission packages in Australia with minimal reworking. In addition, similar to the EU, the Australian NRA should provide for notifications and applications for variations to be lodged electronically.

In respect to variations that may impact safety, quality and efficacy, a number of stakeholders raised particular concern regarding the process and timeframes for clinical variations, including updates to the PI to reflect the latest pharmacokinetic, clinical data, and side effect profile in approved populations. They indicated that this means that such data is not available in Australia as quickly as in the EU or US. Similarly, concerns were expressed about the process and timeframes for minor variations to export medicines and for the registration of a new trade name.

There are a range of variations, including for an extension of indications or for the registration of a new trade name, that require full Category 1 applications and have a statutory timeframe for evaluation of 255 days. Yet clearly the extent of the evaluation that is required to be conducted by the NRA to assure itself that there is no risk to safety, quality or efficacy is not comparable across all of these. The Panel is aware that the TGA is in discussions with industry about reducing target evaluation timeframes for some variations, such as approval of an additional trade name or the extension of indications for a generic medicine to reflect the indications for the innovator medicine, to 45 days. This process should continue with a view to implementing these changes as quickly as possible.

These examples demonstrate that there is insufficient granularity in the existing legislative framework to allow for modified application and assessment processes for certain types of variations, commensurate with both the risk of the variation and the evaluation effort required by the NRA. In implementing changes to the legislative framework for medicines, consideration should be given to making provision for 'sub-pathways' within Pathway One. These 'sub-pathways' would provide for the NRA to undertake an abridged assessment in certain circumstances, so that only those aspects of the data dossier that require evaluation

in order to establish the continued safety, quality and efficacy of the medicine are examined. Statutory timeframes and fees for these sub-pathways should reflect the abridged nature of the evaluation.

Recommendation Thirteen

The Panel recommends that Australia adopt a risk-based approach to the management of variations to medicines registered in the ARTG. This approach should provide for:

1. Notification of variations to the Australian NRA in circumstances where the variation does not impact the quality, safety or efficacy of the medicine. This approach should be harmonised with that adopted by the EU, unless there is a clear rationale not to do so.
2. Assessment of the variation by the Australian NRA in circumstances where the variation has the potential to impact the safety, quality or efficacy of the medicine. This assessment to be abridged in scope, so that only those aspects of the data dossier that require evaluation in order to establish the continued safety, quality and efficacy of the medicine following implementation of the proposed variation are examined (abridged assessment).
3. Reduced legislative timeframes for abridged assessments.
4. Fees for abridged assessments that reflect cost recovery principles.
5. Electronic submission of data.

4.3.8 Low-risk therapeutic goods

As noted at the beginning of this chapter, the Act defines a medicine as:

- (a) *therapeutic goods (other than biologicals) that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human; and*
- (b) *any other therapeutic goods declared by the Secretary, for the purpose of the definition of therapeutic device, not to be therapeutic devices.*

As such, a range of ‘therapeutic goods’ that most consumers would not traditionally think of as ‘medicines’ are captured within the regulatory framework for medicines. These include products such as some secondary sunscreens, medicated soaps, desensitising toothpastes and gels, lozenges for soothing dry throats, and personal care products such as anti-nappy rash treatments. These products are not individually assessed by the NRA prior to inclusion in the ARTG, but are subject to the self-certification process applicable to all listed medicines.

There are mixed views among stakeholders as to whether or not some types of listed medicines should be regulated as therapeutic goods. Stakeholders who believe that all ‘therapeutic goods’ should remain in the ARTG argue that:

- it is essential that there be a complete listing of all ‘therapeutic goods’ in Australia so the goods can be easily recalled should they prove problematic; and
- where such goods are to be exported and may also be classified as therapeutic goods in overseas markets, they must be in the ARTG in order to meet Country of Origin requirements put in place by some countries.

Others argue that specific products, such as sunscreens, must continue to be regulated by the NRA for safety reasons. That is, in a country like Australia, which has a high rate of melanoma, the potential harm to patients should a sunscreen not function as required is significant. The NRA was viewed by these stakeholders as best placed to manage this risk, given its particular focus on therapeutic goods.

On the other hand, from a safety perspective, many of these goods pose a low risk to consumers and are akin to other types of consumer goods or food. For example, lozenges for soothing dry throats may have a similar safety profile to other food products such as mints, while creams for itchy skin may have a similar safety profile to moisturisers, which are regulated as cosmetics.

The demarcation line that differentiates a therapeutic good from: a food (regulated by state and territory food authorities); or a cosmetic (regulated by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS)); or a general consumer good (regulated by the Australian Competition and Consumer Commission (ACCC)) is often blurred and this adds complexity for industry, consumers and regulators. For example, a menthol throat lozenge that is listed in the ARTG is subject to regulatory requirements applicable to medicines, including compliance with medicinal GMP standards. A similar lozenge, regulated under the food standards, would be subject to a less stringent GMP standard. These higher level standards are not commensurate with the risk posed by the product and meeting these standards adds to the cost of production, which in turn is passed on to the consumer.

For some products, such as sunscreens, it is also argued that their regulation as medicines is out of step with the approach internationally, creating difficulties for manufacturers and sponsors who must comply with different standards in different markets. The application of an AUST L number on the label of listed products is also considered by some stakeholders to provide consumers with a false sense of security, as they assume that it means that the product has undergone some level of independent scrutiny.

Stakeholders that advocated for removal of such products from the auspices of the *Therapeutic Goods Act 1989*, asserted that many of these products could be appropriately regulated under alternative regulatory regimes, depending on their use. For example, a

number of products could potentially be regulated as cosmetics or industrial chemicals by the NICNAS, or as general consumer goods by the ACCC, perhaps under a specific standard.

The Panel is concerned that there are a range of products listed in the ARTG that are subject to a level of regulation which is not commensurate with the risk posed by these products to Australian consumers. This is contrary to the principles underpinning this Review. Options to remedy this would appear to include: excluding such goods from the auspices of the Act and regulating them under other regulatory regimes, such as the NICNAS or ACCC frameworks; or retaining them under the Act but with the application of different regulatory requirements (particularly GMP standards) to those that apply to registered medicines. Which of these options is most appropriate may depend on the specifics of the individual product.

Given the diverse range of products that fall into this category; the time available to the Panel to undertake the Review; and the significant level of disagreement between stakeholders as to how low-risk medicines should be regulated, the Panel does not feel confident in making a recommendation as to its preferred approach. Rather, the Panel recommends that this issue be reviewed by the Australian Government, in consultation with consumers, health professionals and industry, during consideration and/or implementation of the Panel's report. This review should examine three key issues:

- Whether the current definitions of 'therapeutic good' and 'therapeutic use' remain appropriate.
- Whether particular products should be regulated by the NRA or by an alternate body such as the ACCC or NICNAS, taking into consideration factors such as: the risk profile of the product; comparative overseas regulation of the good; and the nature of the product, including its appropriateness for regulation under an alternate regulatory regime.
- Where products are considered to be best regulated by the NRA, whether the regulatory requirements that apply under the medicines framework are commensurate with the risk posed by the regulated products. If not, how might the legislative requirements be amended (or redrafted – Recommendation 28 in Chapter Seven refers) to provide a more suitable regulatory scheme for these products?

Recommendation Fourteen

The Panel recommends that the Australian Government undertake a review of the range of products currently listed in the ARTG (not including complementary medicines) and subject to regulation under the medicines framework, with a view to ensuring that:

1. Products that might best be regulated under other regulatory frameworks, without undermining public health and safety, are removed from the auspices of the Act; and
2. Goods remaining under the auspices of the Act are subject to regulatory requirements that are commensurate with the risk posed by the regulated products.

¹ Therapeutic Goods Administration, (2013, July), *Evaluation of Biosimilars*, Version 1.0, p. 8. Accessed online on 4 November 2014 from: <https://www.tga.gov.au/evaluation-biosimilars>

² Therapeutic Goods Administration, (2013, June 27), *Listed medicines: The role of Australia's medicines regulator* webpage. Accessed online on 7 March 2015 at: <https://www.tga.gov.au/community-qa/listed-medicines-role-australias-medicines-regulator>

³ National Coordinating Committee on Therapeutic Goods (2010, July 1), *Scheduling Policy Framework for Medicines and Chemicals*, p. 1. Accessed online on 21 October 2014 from: <http://www.tga.gov.au/publication/ncctg-scheduling-policy-framework>

⁴ Ibid.

⁵ *Therapeutic Goods Act 1989* (Cth), section 52EAA.

⁶ Therapeutic Goods Administration, (2011, April 8), *Regulation of therapeutic goods advertising in Australia*, p. 2. Accessed online on 16 November 2014 from: <http://www.tga.gov.au/regulation-therapeutic-goods-advertising-australia#presc>

⁷ Centre for Innovation in Regulatory Science (2011), *December 2011 Slide of the Month - Key factors likely to impact medicines development*. Accessed online on 1 March 2015 at: <http://cirsci.org/content/december-2011-slide-month>

⁸ Baume P., (1991, July), *A Question of Balance. Report on the future of Drug Evaluation in Australia*, Commonwealth of Australia, Canberra, p. 17.

⁹ Australian Government (2014, October 14), *Industry Innovation and Competitiveness Agenda. An action plan for a stronger Australia*, p. ix.

¹⁰ Baume P., op. cit., p. 17.

¹¹ Ibid., p.17..

¹² Centre for Innovation in Regulatory Science, (2014a, December 16), *The impact of the changing regulatory environment on the approval of new medicines across six major authorities 2004-2013*, R&D Briefing 55, Centre for Innovation in Regulatory Science Ltd, London.

¹³ European Medicines Agency (2014, March 19), *Pilot project on adaptive licensing*, p. 1. Accessed online on 19 October 2014 at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf

¹⁴ European Medicines Agency (2006, July 17), *Guideline on the procedure for accelerated assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004*, London. Accessed online on 10 March 2015 at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004136.pdf

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- ¹⁵ Therapeutic Goods Administration (2012, October 12), *Australian regulatory guideline for over-the-counter medicines. Appendix 1: Guidelines on efficacy and safety aspects of OTC applications*, Version 1.0, p. 10. Accessed online on 14 March 2015 from: <https://www.tga.gov.au/book/6-generic-products>
- ¹⁶ Ibid.
- ¹⁷ Therapeutic Goods Administration, (2014, October), *Half-yearly performance reports. January to June 2014*, Version 1.0, Commonwealth of Australia, p. 16.
- ¹⁸ Therapeutic Goods Administration, (2013, July), *Evaluation of biosimilars*, Version 1.0, p. 7. Accessed online on 14 March 2015 from: <https://www.tga.gov.au/book/what-biosimilar>
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CHAPTER FIVE: REGULATORY FRAMEWORK FOR MEDICAL DEVICES

All medical devices in Australia are subject to regulation by the NRA, the purpose of which is to protect public health and safety. Section 41BD of the *Therapeutic Goods Act 1989* (the Act) defines a medical device as:

- (a) *any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:*
- i. diagnosis, prevention, monitoring, treatment or alleviation of disease;*
 - ii. diagnosis, monitoring, treatment, alleviation of or compensation for an injury or disability;*
 - iii. investigation, replacement or modification of the anatomy or of a physiological process;*
 - iv. control of conception;*
- and that does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but that may be assisted in its function by such means; or*
- (aa) *any instrument, apparatus, appliance, material or other article specified under subsection (2A); or*
- (ab) *any instrument, apparatus, appliance, material or other article that is included in a class of instruments, apparatus, appliances, materials or other articles specified under subsection (2B); or*
- (b) *an accessory to an instrument, apparatus, appliance, material or other article covered by paragraph (a), (aa) or (ab).*

As such, the number and range of medical devices is vast and includes everything from urinary catheters to ultrasound scanners, incubators to insulin injectors; and sticking plasters to stethoscopes. The diversity of products captured as medical devices and their varying risk profiles pose challenges for regulators.

5.1 Current Regulation of Medical Devices

The regulatory framework for medical devices is set out in the Act, particularly Chapter Four, and associated Regulationsⁱ and guidance documents, including the

ⁱ See also: *Therapeutic Goods Regulations 1990*, Therapeutic Goods Orders, Excluded Goods Orders, Medical Device Standards Orders (MDSOs), and Conformity Assessment Standards Orders (CASOs).

Therapeutic Goods (Medical Devices) Regulations 2002 (the Regulations) and the Australian Regulatory Guidelines for Medical Devices (ARGMD).

The Regulations outline the basic characteristics, such as safety, quality and efficacy that medical devices must demonstrate before they can be lawfully imported, manufactured, supplied or exported. Efficacy in the context of medical devices refers to *'the performance of the device as the manufacturer intended.'*¹ The Act also creates penalties that can be imposed for any breaches of these regulatory requirements.

The Australian medical devices regulatory framework is based on the principles of conformity assessment developed by the Global Harmonization Task Force (GHTF).² The GHTF was created in 1992 with the aim of harmonising medical devices regulation. Australia adopted the GHTF model, which is based on the European regulatory system, in 2002 with a view to providing more opportunities in the global market for Australian manufacturers.³ As a result, the Australian and European systems of device regulation are closely aligned, though not identical.

The Australian NRA undertakes both pre-market and post-market regulation of medical devices. The balance between the required pre-market assessment and subsequent post-market monitoring is determined by the risk profile of the medical device.

5.1.1 Risk-based regulatory framework

The GHTF model that has been adopted by Australia is a risk-based approach to the regulation of medical devices. That is, differing regulatory standards are adopted in the assessment and management of medical devices according to the perceived risk to the public of their use. The level of pre-market assessment performed by the NRA is directly related to the level of potential risk posed by the device.

The three main building blocks for this risk-based approach are the:

1. Essential Principles.
2. Device classification system.
3. Conformity Assessment process.

5.1.1.1 The Essential Principles

The *Essential Principles* set out the requirements relating to the safety and performance characteristics of medical devices. There are six general *Essential Principles* that apply to all devices and a further nine *Essential Principles* about design and construction that apply to devices on a case-by-case basis.

General principles – apply to all devices

1. Use of medical devices not to compromise health and safety.
2. Design and construction of medical devices to conform to safety principles.
3. Medical devices to be suitable for intended purpose.
4. Long-term safety.
5. Medical devices not to be adversely affected by transport or storage.
6. Benefits of medical devices to outweigh any side effects.

Principles about design and construction - apply on a case by case basis

1. Chemical, physical and biological properties.
2. Infection and microbial contamination.
3. Construction and environmental properties.
4. Medical devices with a measuring function.
5. Protection against radiation.
6. Medical devices connected to or equipped with an energy source.
7. Information to be provided with medical devices.
8. Clinical evidence.
9. Principles applying to IVD medical devices only.

For a medical device to be supplied in Australia, the manufacturer must demonstrate compliance with the *Essential Principles* for their medical device.

5.1.1.2 Device Classification System

A fundamental feature of the risk-based approach is the classification system for medical devices. The classification levels are:⁴

Table 6: Classification of Medical Devices

Classification	Level of risk
Class I (non-measuring / non sterile)	low
Class I—supplied sterile Class I—incorporating a measuring function Class IIa	low–medium
Class IIb	medium–high
Class III including Active Implantable Medical Devices (AIMD)	high

In vitro diagnostic medical devices (IVDs) are regulated as a subset of medical devices, and separately categorised in Classes 1 to 4,⁵ with similar risk levels to medical devices, and based on the same GHTF recommendations.⁶

The manufacturer of the medical device is responsible for determining the risk classification of a device using a set of classification rules, outlined in Schedule 2 of the Regulations, that are influenced by the:

- intended use of the device (external versus internal application, measuring, sterile collection);
- length of time of use of the device;
- likelihood of harm from use of the device; and
- inherent risks associated with the device composition, (i.e. a biological or additional medicine delivery function).⁷

All the classification rules must be considered to determine the classification of the medical device and if the device is to be used in combination with another medical device, the classification rules must be applied separately to each device. Where there is any conflict between the classification rules, the higher classification applies. Accessories to a device, for example a remote control for a hearing aid, are classified separately to the medical device they are used with.

Medical devices that are for export only are all classified as Class I devices.

5.1.1.3 Conformity Assessment

Conformity Assessment refers to a systematic examination of evidence generated by a device manufacturer, and procedures undertaken by that device manufacturer, in order to ensure that a medical device is safe and complies with the *Essential Principles*. There are several stages involved in the conformity assessment of a medical device:

Stage	Description
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Stage 1:	<i>Conformity assessment procedures.</i> This refers to how the device manufacturer demonstrates that the device meets the <i>Essential Principles</i> . It involves an assessment of: technical documentation for the design of the device; manufacturing processes used to make the device; risk analysis; clinical evidence; and ongoing monitoring and vigilance procedures that will be in place once the device is available for supply. The manufacturer may choose the appropriate conformity assessment procedures to use, depending on the classification of the device.
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Stage 2:	<i>Issuing conformity assessment evidence.</i> Conformity assessment evidence is the certificate issued to demonstrate that a manufacturer has been assessed and has the appropriate systems in place to manufacture the device. In order to issue this certificate, a conformity assessment body will undertake an
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Stage	Description
	assessment that includes: confirming that the conformity assessment procedures undertaken by the manufacturer are appropriate for the classification of the device and have been applied correctly; systematic examination of the documentation provided and procedures undertaken by the manufacturer; and may include an on-site audit of the manufacturing premises.
Stage 3:	Completion of an <i>Australian Declaration of Conformity</i> (DoC). Once the manufacturer has obtained conformity assessment evidence, they must make an Australian DoC, which declares that the device complies with: applicable provisions of the <i>Essential Principles</i> ; the classification rules; an appropriate conformity assessment procedure. A copy of the DoC must be provided to the NRA if requested and must be maintained and updated when appropriate.
Stage 4:	<i>Ongoing conformity assessment responsibilities</i> , which require the manufacturer to maintain appropriate records relating to the above three stages; along with details of any systemic reviews or of changes to the device and/or to Quality Management Systems. Manufacturers are also required to: notify the NRA about adverse events/malfunctions; take corrective action where necessary; notify the NRA and/or device sponsor about device malfunctions; and systematically review information gained after the device is supplied in Australia.

The classification of a medical device determines the conformity assessment procedures a manufacturer can choose to ensure that the device is adequately assessed. Higher classification devices must undergo more stringent conformity assessment procedures than lower classification devices. For example, a Class III medical device requires a conformity assessment procedure that examines the device design. This requires the submission of a technical design dossier to the body that will issue the conformity assessment certificate (Stage 2), which will be examined to assess the compliance of the device with the *Essential Principles*.

Stage 2 of the conformity assessment process may generally be undertaken by the Australian NRA or by a European Union (EU) Notified Body. The legislation requires that the TGA issue conformity assessment evidence for specific high-risk devices, including Class 4 IVDs, and medical devices that contain:

- materials of animal, microbial or recombinant origin;
- derivatives of human blood or plasma; and/or
- a medicine.

5.1.2 Pre-market assessment of medical devices

5.1.2.1 Australian Register of Therapeutic Goods (ARTG)

To supply a medical device in Australia it must be included in the ARTG. The ARTG provides a record of devices that can be supplied in Australia and a record of all the sponsors who are

legally responsible for the medical devices on the market. The ARTG may contain multiple entries for a device that has more than one Australian sponsor, with each sponsor required to make a separate application for inclusion.⁸ Unlike medicines, where each medicine has a separate entry in the ARTG, if certain criteria are met then devices may be classified as the 'same kind' of device and included in the ARTG as a single entry. There is no record kept in the ARTG of the product family name, model numbers, or catalogue numbers for the separate devices contained with this single ARTG entry.

Inclusion of Medical Devices in the ARTG

As described above, in order to have a device included in the ARTG, the device manufacturer must demonstrate that the device meets the *Essential Principles*. Under the risk-based model, the conformity assessment that is required in order to demonstrate this differs according to the classification of the device.

Self-inclusion of Class I devices

A Class I medical device which is non-measuring and non-sterile may be included in the ARTG on the basis of a conformity assessment procedure that has been self-completed by the device manufacturer. No conformity assessment evidence is required to be submitted to the NRA prior to the inclusion of the device in the ARTG. However, the manufacturer must complete a DoC and retain this, and supporting evidence, and provide a copy to the NRA if requested to do so. Examples of Class I devices include products such as tongue depressors, elastic bandages, and non-sterile sticking plasters.

Inclusion of other Classes

Other classes of medical devices, Class I sterile, Class I measuring, Class IIa, Class IIb, Class III and AIMD, are required to obtain conformity assessment evidence, in the form of a conformity assessment certificate, prior to applying for inclusion of a device in the ARTG. This involves a multistep process:

1. *Conformity Assessment Certificate*: The device manufacturer applies to either the Australian NRA or an EU Notified Body for a Conformity Assessment Certificate. The manufacturer will need to provide all necessary supporting documentation, which will vary depending on the device and device class. Following an assessment, if either the Australian NRA or the EU Notified Body is satisfied that all necessary requirements have been met, it will issue a Conformity Assessment Certificate to the manufacturer.
2. *Submission of Manufacturer's Evidence*: Once the Conformity Assessment Certificate is issued to the manufacturer, the Australian sponsor of the device will be required to register the certificate as Manufacturer's Evidence with the Australian NRA through the e-Business system.

3. *Assessment of Manufacturer's Evidence:* The NRA assesses the Manufacturer's Evidence and decides whether or not to accept it. The TGA has a target timeframe of 15 working days to consider and, where appropriate, accept the Manufacturer's Evidence.
4. *Application for inclusion of a device in the ARTG:* The NRA will notify the sponsor if the Manufacturer's Evidence submission is successful. If it is, the Australian sponsor can proceed with an application to include the medical device in the ARTG.

5.1.2.2 Application Audits

Once a sponsor has lodged an application for inclusion of a device in the ARTG, it may be selected for an application audit. Application audits are compulsory for certain medical devices; however the NRA may also conduct non-compulsory application audits. In undertaking an application audit the NRA may request a range of documentation from the sponsor and may consider two aspects of the application, namely:

1. whether the application complies with the requirements of the Act and the Regulations; and
2. that matters the sponsor has certified in submitting the application are correct.

The TGA has target timeframes for application audits of between 30 and 60 working days, but often exceeds these timeframes.

5.1.2.3 Timeframes

Timeframes for various aspects of device regulation vary, depending on the device. TGA conformity assessments that require a Design Examination have a statutory timeframe of 255 working days. However other types of conformity assessment may include additional activities such as a TGA inspection of production quality or examination of a representative sample of devices. There are no legislated timeframes for the TGA to complete these processes.

According to the TGA, the timeframe for inclusion in the ARTG of a low to medium risk medical device that is accompanied by a valid conformity assessment certificate generally varies from three to eight weeks.⁹ The Regulations do not specify timeframes for inclusion of higher risk devices in the ARTG, but guidance¹⁰ documents produced by the TGA indicate that processing times for such devices may vary depending on the number of applications on hand in the TGA, risk classification of the device, and whether an application audit is required. The Regulations specify that an applicant has 20 working days to provide additional documentation if requested by the TGA to inform an application audit.

5.1.3 Post-Market Monitoring

Once a medical device has been included in the ARTG the device must continue to meet all the regulatory, safety and performance requirements and standards that were required for

the approval. Both the product sponsor and the device manufacturer have ongoing obligations in respect of the device.

In meeting the Australian *Essential Principles*, the NRA requires that a medical device manufacturer must identify any known or foreseeable risks associated with the product use, how those risks are mitigated, and weigh the residual risks against the potential benefits of using the device.¹¹ This process informs risk management and post-market monitoring requirements. For example, if there are risks that the product will be used for a purpose that is inconsistent with its intended purpose, the manufacturer may be required to provide specific warnings in instructions for use and product information. Additionally, the manufacturer and/or sponsor may be required to undertake mandatory reporting of adverse events, submit annual reports to the NRA for a defined term, or collect clinical data (on a registry).

Ongoing monitoring by the NRA also occurs, with a view to identifying emerging safety and performance issues as early as possible so that remedial actions can be taken. This may include: random or targeted review; inspections of manufacturer's or sponsor's records and documentation; and on-site testing of medical devices or taking samples for off-site testing. The NRA also assesses data from reports of adverse events or malfunctions submitted by consumers, health professionals or industry, along with published journal reports, and overseas adverse events data, in order to identify emerging issues. Through various Mutual Recognition Agreements (MRAs) for medical device regulation and its participation in the International Medical Device Regulators Forum (IMDRF), the TGA has an obligation to share vigilance information with overseas NRAs where corrective action, such as a recall, is to be taken, or there is a serious risk to the safety of patients or other users, but where the corrective action is still being determined.

5.1.4 Advertising of Medical Devices

Advertising of medical devices to health professionals and direct to consumers is allowed and does not require pre-approval prior to publication or broadcast. However, the advertisements must comply with:

- the *Competition and Consumer Act 2010*;
- the *Therapeutic Goods Act 1989*, and Regulations which establishes an offence where therapeutic goods are advertised other than for intended purposes as certified in the device application;
- the *Therapeutic Goods Advertising Code* designed to ensure socially responsible marketing and advertising that promotes the quality use of the product and does not mislead or deceive the consumer; and
- any other conditions which may be assigned to the marketing approval of the product.

In addition, members of the Medical Technology Association of Australia are required to comply with the *Medical Technology Industry Code of Practice*. Non-members are not bound by the Code.

5.2 Assessment of Current Regulatory Framework

The current regulatory framework for medical devices was introduced in 2002 and has been fully implemented since 2007. It is, therefore, a less mature framework than that applying to medicines. Since its implementation there have been a number of modifications to the framework, generally in response to: international harmonisation efforts; regulatory failures; and Australian government policy and legislation changes. For example, Australia has up-classified implantable replacement joints; is currently implementing regulation of IVDs; and has implemented additional application audits in response to concerns raised about the EU regulation of devices. These changes have been implemented to manage risks, but have all added additional complexity to the regulatory framework for devices.

The regulation of medical devices will always be complex as a result of the diversity of different technologies that fall within the definition of a medical device; and the fact that ‘adverse events’ may be impacted by a range of factors that are not related to the safety or efficacy of the device itself. This is particularly the case in respect of implantable devices, where the skill of the surgeon and the nature of pre and post-operative care can have a major impact on patient outcomes. However, in the Panel’s view, additional layers of complexity have been added to the regulation of medical devices in Australia as a result of trying to retrofit the regulatory framework for medicines to medical devices. That is, there are features of the regulatory framework that exist not to manage a particular identified risk, but rather to ensure that the system is compliant with the Act, Regulations, and fee structures.

In addition, some statutory timeframes for the regulation of medical devices have been replicated from the medicines framework. For example, conformity assessments that require a Design Examination have a statutory timeframe of 255 working days, the same timeframe as for the assessment of a new chemical entity. But this timeframe has no regard for the fact that the lifecycle of a medical device is much shorter than that of a medicine. Medical devices generally innovate incrementally by improvements to previous generation devices and, as such, a device may only have a lifecycle of around five years. In this context, a regulatory approval timeframe of 255 days is problematic.

The Panel received many more submissions to the Review raising concerns about the regulatory framework for medical devices than it did in respect of medicines. Submissions to the Review were generally supportive of the current risk-based regulatory framework for medical devices, including the classification system, and of Australia’s alignment with the EU. Stakeholders acknowledged that there are flaws in the EU regulatory system for devices,

however, and that these needed to be managed by the Australian NRA, ideally without the imposition of duplicative regulatory processes.

Having said that, major concerns were expressed about the way in which the risk-based framework was being implemented. Many Small to Medium sized Enterprises (SMEs), which make up a significant proportion of the devices market in Australia, described the framework as extremely complex and difficult to navigate. They raised concern at the level of support that was provided by the TGA to assist them to understand regulatory requirements and expressed consternation that when advice was provided it was often in conflict with previous advice or with the TGA's guidelines. Bodies representing larger device manufacturers had fewer issues about the complexity of the framework, but raised major concerns regarding what they viewed as duplication, unnecessary processes, and lack of timeliness. Timeframes and predictability were also identified as significant issues for SMEs and start up enterprises.

Industry stakeholders in particular emphasised that medical devices are different to medicines in terms of the extent to which safety and efficacy can be established through clinical trials. As such, they called for the balance of pre-market assessment and post-market monitoring to be more heavily weighted towards post-market. Consumers and professional groups also favoured a greater emphasis on post-market monitoring of medical devices.

Having considered the issues raised, the Panel concluded that there are a number of areas in which the regulatory framework for medical devices could be improved. These issues are discussed below and can be broadly categorised as:

1. Reducing duplication in the pre-market assessment of medical devices.
2. Enhanced harmonisation of regulatory requirements with the EU.
3. Enhanced transparency of processes and timeframes to manage the complex and poorly understood framework and to assist those who have to interact with it.
4. Enhanced post-market monitoring.
5. Threshold issues for 'devices'.

5.3 Proposed reforms to the regulatory framework for medical devices

As outlined in section 5.1, there are currently several pathways by which a medical device may be included in the ARTG. These pathways provide for:

1. A device manufacturer to undertake a self-assessment of a device's conformity with the *Essential Principles* if the device is Class I and is neither sterile nor has a measuring function. Given the nature of Class I devices that are neither sterile nor have a measuring function, and the low risk that they pose to the Australian public should they malfunction, the Panel considers self-assessment of such devices for inclusion in the ARTG appropriate.

The Panel is, however, concerned that inclusion of such a device in the ARTG may provide consumers and health professionals with a false impression that it has been independently assessed for safety, quality and efficacy. For transparency purposes, the fact that this has not occurred in most instances should be clearly communicated. This could occur in the ARTG entry itself and/or through the inclusion of advice for consumers and health professionals on the NRA's website and in education materials.

2. A sponsor to apply to the TGA for inclusion of a device in the ARTG on the basis of a conformity assessment certificate that the manufacturer has obtained from either:
 - A. the Australian NRA (Pathway One); or
 - B. from an EU Notified Body (Pathway Two). The Australian regulatory system for medical devices is closely aligned with the European system, which has created opportunities for mutual recognition of device assessments undertaken in Australia and in the EU. The EU system is described briefly below.

EU Regulation of medical devices

The EU device regulation system is implemented across 32 participating countries that consist of EU Member States, European Free Trade Area countries and Turkey.¹² The *Medical Devices Directives* (MDD) form the foundation of Europe's regulatory framework for medical devices. The MDD set the safety and performance requirements that must be met by manufacturers in order for their products to be marketed in the EU. These '*Essential Requirements*' are closely aligned to the Australian *Essential Principles*. Like Australia, the EU system also provides for:

- Devices to be classified according to risk. The EU and Australian classification systems are very similar, but there are some differences. These differences add complexity for device manufacturers wishing to supply their product in Australia utilising an EU conformity assessment.
- Medical devices to be assessed for conformity against the *Essential Requirements*, with the level of assessment based on the risk classification of the device.

Whereas in Australia the NRA can undertake conformity assessments, in the EU, neither the EMA nor the NRA within each country undertakes conformity assessments. Rather, conformity assessments are undertaken by commercial third party Conformity Assessment Bodies (CABs), known across the EU as 'notified bodies'. These notified bodies assess medical devices for conformity against the EU *Essential Requirements* and, if satisfied, issue a Conformity Assessment Certificate. The Certificate allows the device to bear a CE Mark which enables the product to be freely traded across EU markets. However, individual EU countries may require local registration of the device with the NRA and may impose requirements regarding the language in which device information is provided. There are around 70 notified bodies across Europe that undertake conformity assessments of medical

devices. Manufacturers are free to choose any notified body that has been designated to carry out the conformity assessment procedure required for their device.

Notified bodies are ‘designated’ to undertake conformity assessments of medical devices by a *Competent Authority* of an EU Member State. The *Competent Authority* is generally the NRA responsible for the regulation of medical devices (and often medicines) within that Member State, commonly Departments of Health. Notified bodies must be able to demonstrate that they have the clinical, scientific and technical competence to assess the technologies for which they are designated and, as such, not all notified bodies will be designated to conformity assess all technologies.

Competent Authorities that designate notified bodies have ongoing responsibilities for oversight of the performance of those notified bodies. This includes conducting surveillance audits, observed audits and spot checks, all of which are designed to assess compliance of aspects of the notified body’s operational activities against the MDD and associated regulations and standards, and against the body’s own procedures.¹³

5.3.1 Multiple Pathways for inclusion of a device in the ARTG

The Panel is supportive of these two pathways continuing, but proposes that they be modified to provide for:

1. More timely market access for devices seeking inclusion in the ARTG utilising Pathway One, by building additional assessment capacity into the Australian system.
2. Implementation of strategies that seek to manage risk systemically, by Australia exerting more control over which notified bodies it will accept conformity assessments from (Pathway Two).
3. Recognition of device assessments from comparable overseas NRAs outside of the EU framework (Pathway Two).

In addition, the Panel recommends that there be a third pathway which provides for expedited assessment of innovative devices in specific circumstances. Each of these proposals is discussed below.

Recommendation Fifteen

The Panel recommends that:

Class I, non-sterile and non-measuring devices, continue to be included in the ARTG on the basis of a self-assessment by the device manufacturer. NRA communications directed at consumers and health professionals should make it clear that such devices have not been subject to any independent assessment.

In order to provide timely access to devices that are safe, high quality and fit for purpose, there be multiple pathways to seek approval for the inclusion of other classes of medical device in the ARTG. Such pathways to provide for:

Pathway One	Conformity Assessment to occur within Australia by either: <ul style="list-style-type: none"> A. The Australian NRA; or B. A body designated by the Australian NRA to undertake Conformity Assessments of medical devices for the Australian market.
Pathway Two	Utilisation of marketing approval for the device in an overseas market in circumstances where the device has been: <ul style="list-style-type: none"> A. Conformity Assessed by a body that has been designated to undertake Conformity Assessments by a comparable overseas <i>Designating Authority</i>; or B. Approved by a comparable overseas NRA.
Pathway Three	Expedited approval of medical devices in certain circumstances.

5.3.1.1 Pathway One

A number of submissions to the Review emphasised the need for Australia to retain its capacity to undertake conformity assessments of medical devices, with some local manufacturers indicating that they want to have capacity to seek a conformity assessment domestically, although they wanted this to occur in a timely and predictable manner. This was particularly important to SMEs, which comprise around 80 per cent of the medical devices industry in Australia.¹⁴ For such companies, long and unpredictable assessment timeframes, delays due to application errors, and/or unanticipated audits are not only costly in terms of the fiscal outlay, but also in terms of lost market opportunity. The impacts on business planning and marketing decisions can be significant, particularly in cases where ‘country of origin’ approval is required before Australian manufacturers can access overseas markets.

Stakeholders generally rated the TGA’s performance unfavourably compared to EU notified bodies in terms of the time it takes to both issue a conformity certificate and to assess an application for inclusion in the ARTG. The predictability of these timeframes was rated particularly poorly. Stakeholders hypothesised that the delays were as a result of:

1. High volumes of device applications coupled with an insufficient number of skilled staff available to undertake the assessments.
2. Lack of available skills in-house to undertake assessments of some medical device technologies, requiring appropriate expertise to be sourced externally.

3. The increased number of application audits conducted by the TGA, which they saw as duplicating conformity assessments undertaken by EU notified bodies.

The Panel notes that the European approach provides for timely assessment of new medical devices as it builds assessment capacity into the system. That is, because medical devices tend to undergo an iterative development process and therefore have short lifecycles, the volume of devices that need to be conformity assessed each year is large. By having multiple bodies who can undertake such assessments, both within a country, but also across Europe more broadly, there is capacity to spread this assessment load, reducing the risk of backlogs and time delays in undertaking assessments. Use of third parties to undertake assessments of medical devices is also common practice in other jurisdictions, including the US and Japan. The Panel considered that this approach may be useful to adopt within the Australian market, reducing the workload on the Australian NRA and providing for more timely assessment of medical devices for the Australian market.

If this approach were adopted, the current Pathway One for inclusion of a device in the ARTG would be expanded to provide for device manufacturers to seek conformity assessments from either:

- A. The NRA; or
- B. A body, or bodies, designated by the Australian NRA to undertake conformity assessments of medical devices for the Australian market.

These designated bodies could be commercial enterprises, academic institutions, or not for profit bodies, and could be designated to undertake conformity assessments for all classes of devices or only for certain devices; and to undertake all conformity assessment pathways or a subset of these. While they would need to be located within Australia, they could potentially be Australian offshoots of European notified bodies. In order to be designated to undertake conformity assessments for the Australian market, such bodies would need to demonstrate that they have the clinical, scientific, and technical competence to assess the technologies for which they are designated. Governance arrangements would also be important to ensure independence and to avoid conflicts of interest.

Implementation issues

There are a range of options for implementing such an approach. Suitable bodies could be identified through a tender process in the first instance, or alternatively a system could be put in place that allows suitable organisations to apply to become a designated body. Either approach would require the establishment of suitable criteria which such bodies would need to meet in order to be considered. Such criteria should be developed in consultation with health care consumers, health professionals, industry and the NRA and address governance and quality management issues as well as technical capacity. Annex VI to the European Medical Devices Directive 93/42/EEC, sets out minimum requirements to be met by EU notified bodies and may provide a useful reference point.

Consideration would also need to be given to ongoing oversight and monitoring of these designated bodies to ensure that they are conducting conformity assessments to the required standard and meeting all other governance and operational requirements. Logically this oversight body, or *Competent Authority* to use the European terminology, would be the NRA, as it would have the necessary technical expertise. Any perceived or actual conflict of interest resulting from the NRA operating as both a *Competent Authority*, overseeing the conduct of conformity assessments by independent third parties, and itself conducting conformity assessments, would need to be appropriately managed.

Recommendation Sixteen

The Panel recommends that the Australian Government develop transparent criteria that it will utilise in order to designate suitably qualified bodies within Australia to undertake Conformity Assessments of medical devices [Recommendation Fifteen, Pathway 1B].

Such criteria to:

1. Include capacity to set specific requirements for different classes of medical devices; and
2. Be developed in consultation with health care consumers, health professionals, the medical devices industry and the NRA.

5.3.1.2 Pathway Two

As noted above, the current regulatory framework for medical devices provides capacity for a sponsor to seek inclusion of a device in the ARTG on the basis of a conformity certificate issued by an EU notified body. Notwithstanding recent concerns about some aspects of the European regulatory system for medical devices, many stakeholders described the EU system as fundamentally sound, and the use of EU conformity certificates was a valued pathway to Australian market authorisation. However a number of stakeholders recommended that, in addition to EU certification, consideration be given to accepting device approvals from other, non-European markets, as the basis for approval of a device in Australia. As outlined in Recommendation Fifteen, the Panel considers both approaches to be viable and each is discussed in turn below.

Pathway 2A - Conformity certificates from EU notified bodies

The Panel formed the view that, given the close alignment that exists between the Australian and European regulatory systems for medical devices, recognition of conformity certificates issued by EU notified bodies was a sensible approach which minimised unnecessary duplication in the pre-market assessment of medical devices. However, the Panel noted that recognition of EU conformity certificates has resulted in the creation of inefficiencies within the Australian regulatory system. Primary among these is the use of application audits to mitigate the risk of poor quality conformity assessments conducted by some EU notified bodies. These inefficiencies impact the timeliness of access by Australian patients to new technologies and impose additional costs on industry. The Panel proposes

that these risks could be more effectively and efficiently mitigated by imposing controls at the front end of the system, through capacity to determine which notified bodies Australia will accept conformity certificates from, rather than through the current system of application audits.

As outlined in Chapter Three, in recent years, the European regulatory system for medical devices has been shown to have systemic weaknesses,¹⁵ which has led to concerns about the quality of conformity assessments undertaken by some EU notified bodies. As a result of these concerns the TGA took a number of actions, including:

- Implementing amendments to the EU-Australia MRA on conformity assessment, with effect from 1 January 2013, to expand:
 - the range of high-risk medical devices (including all Class III devices) that would no longer be able to be assessed under the MRA;ⁱⁱ
 - the range of excluded barrier contraceptives excluded from the agreement; and
 - the scope of medical devices containing medicines or materials of biological origin that will be excluded from the MRA.¹⁶

These exclusions are to remain in place until confidence building activities have been undertaken by Australia and the European Union.

- Auditing all applications for inclusion of medical devices in the ARTG that use supporting evidence from eight EU notified bodies of concern.¹⁷

The European Commission is in the process of reviewing its regulation of medical devices. A proposal is before the European Parliament and Council to agree changes to various aspects of medical device regulation with a view to providing a more robust and transparent regulatory framework, which is supported by sustainable, effective and credible management of the system.¹⁸ Of particular interest in the context of this Review are proposed changes to provide for:

- Stronger supervision of notified bodies by national authorities.
- More powers for notified bodies vis-à-vis manufacturers, to ensure thorough testing and regular checks, including unannounced factory inspections at manufacturing sites.
- Better traceability of devices throughout the supply chain, enabling more timely effective responses to safety concerns (e.g. recalls).

ⁱⁱ The effect of this change was that: (a) manufacturers could no longer get MRA notified bodies to conduct a conformity assessment for these devices to the Australian legislative requirements; and (b) applications for inclusion of a Class III device on the ARTG that utilised an EU conformity certificate would be subject to an application audit.

- Reinforced rules for clinical investigations on devices and the required clinical data for the pre-market and the continuous post-market assessment of medical devices, including *in vitro* diagnostic medical devices.¹⁹

If passed by the European Parliament and Council and implemented effectively, these proposed changes should go a long way towards restoring public confidence in the EU regulatory system for medical devices.

Ahead of these reforms the EU has also implemented joint audits of notified bodies, carried out by audit teams comprised of representatives from the *Competent Authorities* of several countries, together with EU Commission officials. According to industry reports, these audits have resulted in some notified bodies having their authority to undertake conformity assessments under the MDD withdrawn, while others have had their authority suspended or reduced in scope.²⁰

The Panel recommends that the Australian NRA continue to monitor the progress of reforms in the EU. If it is determined that the implementation of reforms has addressed concerns regarding the rigour and effectiveness of conformity assessments undertaken by EU notified bodies, then acceptance by the Australian NRA of EU conformity certificates should be extended to cover high-risk devices. In the interim, the Panel recommends that the Australian NRA implement processes which will allow it to only accept, without additional assessment, conformity certificates from a sub-set of notified bodies, in which it has confidence. The Panel notes that this may require amendments to Australia's MRA with the EU.

Identification of appropriate notified bodies

As noted previously, *Competent Authorities* within EU member states are responsible for designating a conformity assessment body as a notified body under the MDDs. In some cases this function may be delegated to another agency within the member state. For the purposes of this Report, the Panel has adopted the terminology '*Designating Authority*' to refer to the authority within an EU member state that is responsible for assessing, designating, notifying, and monitoring notified bodies within that jurisdiction.

A *Designating Authority* may designate multiple agencies within a jurisdiction to be a notified body for the purposes of the MDDs. Each of these notified bodies will be subject to the same rules and requirements and to the same monitoring and audit regimes. As such, if the Australian NRA has confidence in a *Designating Authority*, this confidence should extend to notified bodies that have been designated by that Authority.

The Panel therefore proposes that the Australian NRA identify *Designating Authorities* within the EU that:

- are comparable to the Australian NRA in terms of the standards that they expect to be applied to the conduct of conformity assessments; and

- have effective systems and processes in place to ensure that these standards are upheld by notified bodies,

with a view to limiting acceptance of conformity certificates, without additional assessment, to only those EU notified bodies that have been designated by one of the comparable *Designating Authorities*. Applications for inclusion of a device in the ARTG that utilise conformity certificates from Notified Bodies that have not been designed by a comparable *Designating Authority* would remain subject to application audits.

A criteria based approach would be the most transparent way of identifying comparable *Designating Authorities*. Such criteria should be developed in consultation with health care consumers, health professionals, the medical devices industry and the Australian NRA and could give consideration to factors such as:

- A. The population demographics and health outcomes of the member state.
- B. Adoption of International Medical Device Regulators Forum guidelines.
- C. The track record of the Authority in overseeing the delivery of medical device conformity assessments by notified bodies, including the outcomes of any joint audits that have been conducted by the EU Commission in respect of notified bodies designated by that Authority.
- D. The independence and impartiality of the Authority.
- E. Transparency of systems and processes.
- F. Technical competence.
- G. Utilisation of Quality Management Systems.
- H. Accountability, including independent review/audit.
- I. Reporting and communication.
- J. Timeliness of access to information and data by the Australian NRA.

If this approach were implemented, the expectation of the Panel is that application audits in respect of devices utilising conformity certificates from notified bodies that have been designated by a comparable *Designating Authority* would cease. Such devices would, however, be subject to post-market reviews, as part of the Australian NRA's ongoing quality assurance procedures.

If it is not possible to adopt the proposed approach within the framework of an EC-Australia MRA the Panel recommends that consideration might be given to separate MRAs with member states that have a comparable *Designating Authority*.

Pathway 2B - Marketing approvals from comparable NRAs

While the existing regulatory framework for medical devices recognises conformity certificates issued by EU notified bodies, it does not recognise device assessments conducted by other jurisdictions. The Panel explored the possible use of device assessments from other jurisdictions, in light of the Australian Government's principle that:

...if a system, service or product has been approved under a trusted international standard or risk assessment, Australian regulators should not impose any additional requirements unless it can be demonstrated that there is a good reason to do so.²¹

A major impediment to the adoption of this principle in respect of medical devices is that there is no single 'trusted international standard or risk assessment' for the assessment of medical devices at this point in time. While the GHTF (now the IMDRF) developed a regulatory model, supported by extensive documentation, which addresses pre-market evaluation, post-market monitoring, quality systems, auditing and clinical safety/performance of devices, different countries adopted different aspects of the model. As a result, the approach to pre-market assessment of medical devices is not consistent across countries.

For example, in the United States (US), there are two ways of obtaining pre-market clearance/approval of a medical device, the 510K process and the Premarket Approval (PMA) process. For medical devices that can demonstrate they have substantial equivalence to medical devices that are already approved, the 510(k) pathway enables faster approval and market access. Following assessment, the US regulator, the Food and Drug Administration (FDA), allows listing of some devices by a pre-market notification, however if a pre-market review is required, there are 12 third party organisations accredited to undertake a 510(k) primary review, and they may charge a fee. On receipt of the review recommendations, the FDA will issue a final determination within 30 days, without additional charge.

Higher risk devices and those that do not have a substantially equivalent predicate that would enable market access through the 510(k) process undergo PMA, which is a process of scientific and regulatory review to evaluate the safety and effectiveness of the device. The process involves the compulsory submission of clinical data to support claims made for the device. In contrast, clinical data is only referred to in about 15 per cent of 510(k) device reviews.²² The US classification system for devices is also different than that used by Australia and Europe.

A recent examination of the US regulatory system for devices raised significant concerns about the 510(k) process, including a lack of scientific data to support the claim of substantial equivalence, particularly clinical data.²³ There is also scope for manufacturers to incorrectly self-classify.

These differences in regulatory systems raise challenges for utilisation of assessments from countries that have not adopted the GHTF model. Certainly, they preclude automatic acceptance of such approvals without further assessment by the Australian NRA. That is, at a minimum the Australian regulator would need to ensure that the device was correctly classified according to the Australian classification system; and that the assessment that was conducted:

- was appropriate for that device classification;
- was at least as rigorous as a comparable conformity assessment conducted by the Australian NRA would have been; and
- provided an evaluation of safety and performance that was equivalent to an assessment against the *Essential Principles* applicable to that device.

These challenges are not insurmountable, however, and as international harmonisation efforts continue, it is likely that we will see greater convergence of international regulatory practice with respect to medical devices in the future. That is, in a presentation to a 2010 workshop on the public health effectiveness of the 510(k) process, Janet Trunzo, a member of the (then) GHTF steering committee, was reported as stating that:

The GHTF founding members [United States, the EU, Canada, Australia, and Japan] are committed to moving their regulatory systems to the GHTF model. The AHWP [Asian Harmonisation Working Party], which has representatives of 20 countries, has developed its regulatory systems on the basis of the GHTF model, and the Association of Southeast Asian Nations (ASEAN), a group of 10 nations, has agreed to adopt the GHTF model. The Latin American Harmonization Working Party also participates actively in the GHTF.²⁴

As such, the Panel was of the view that a forward looking Australian regulatory framework for medical devices should include capacity to recognise approvals of medical devices provided by comparable overseas NRAs, outside of the EU.

There was support from stakeholders for the development of transparent criteria by which comparable NRAs for the purpose of device assessments could be identified. This approach was considered to be a more transparent option than establishing a list. Transparency in this regard is important, as Australian health care consumers must have confidence that public health and safety will not be undermined if the Australian NRA utilises assessment reports from comparable overseas NRAs. Being able to see the criteria against which NRAs are assessed may help to provide this reassurance.

Such criteria should be developed in consultation with health care consumers, health professionals, the medical devices industry and the Australian NRA and could give consideration to factors such as:

- A. Regulates for a population demographic that is broadly representative of the Australian population and has similar health outcomes.
- B. Adopts International Medical Device Regulators Forum (formerly GHTF) guidelines.
- C. The track record of the NRA in undertaking assessments of medical devices for safety and performance.
- D. The independence and impartiality of the NRA.
- E. Transparency of systems and processes.
- F. Technical competence.
- G. Utilisation of Quality Management Systems.
- H. Accountability, including independent review/audit.
- I. Reporting and communication in the English language.
- J. Timeliness of access to information and data by the Australian NRA.
- K. Compatibility of evaluation/assessment of medical devices with the Australian *Essential Principles*.

The Panel notes that the addition of Pathway 2B creates a complexity, in that it is possible that an EU Notified Body may issue a conformity assessment for a device that has been denied marketing approval by a comparable overseas regulator or vice versa. Similarly, assuming that multiple overseas NRAs are identified as ‘comparable’ to the Australian NRA, there may be occasions where one comparable overseas NRA approves a medical device for certain intended uses, while another NRA rejects it. There are certainly documented cases of this occurring in the literature.²⁵

The Panel recommends that a similar approach to managing different regulatory decisions for medicines should apply to medical devices. That is, if the Australian NRA receives an application to include a medical device in the ARTG, or has already approved its inclusion, and it becomes aware that the device has been denied approval by a comparable NRA or EU notified body, it should undertake a review to satisfy itself that there is no risk to public health and safety. In such circumstances, the assessment by the Australian NRA should be limited to those aspects of the medical device technical and design dossier that had created the point of conflict that lead to the different regulatory decisions. Such a review would be particularly important in respect of high-risk implantable devices.

Recommendation Seventeen

The Panel recommends that:

1. The Australian Government develop and apply transparent criteria for identifying:
 - A. Comparable overseas *Designating Authorities* [Recommendation Fifteen, Pathway

Recommendation Seventeen

- 2A.]; and
- B. Comparable overseas NRAs for the evaluation of medical devices [Recommendation Fifteen, Pathway 2B].
2. These criteria are developed in consultation with health care consumers, health professionals, the medical devices industry, and the NRA and give consideration to factors such as:
- A. Population demographics and health outcomes.
 - B. Adoption of International Medical Device Regulators Forum guidelines.
 - C. The track record of the organisation in evaluating/assessing medical devices and/or overseeing the evaluation/assessment of medical devices.
 - D. Independence and impartiality.
 - E. Transparency of systems and processes.
 - F. Technical competence.
 - G. Utilisation of Quality Management Systems.
 - H. Accountability, including independent review/audit.
 - I. Reporting and communication.
 - J. Timeliness of access to information and data.
 - K. Compatibility of evaluation/assessment of medical devices with the Australian *Essential Principles*.

[Use of assessment report/conformity assessments](#)

Consistent with the proposed approach for Pathway 2A, where it is agreed that assessment reports from comparable overseas NRAs can be used to support inclusion of a medical device in the ARTG, the expectation of the Panel is that these applications would not be subject to routine application audits by the Australian NRA. They could, however, still be selected for a post-market review as part of the Australian NRAs ongoing quality assurance procedures. The Panel sees little value in the Australian NRA duplicating assessments of devices conducted by comparable NRAs. That is, an assessment that a body is a comparable overseas NRA or, in the case of EU conformity assessments, a comparable overseas *Designating Authority*, should be sufficient to engender trust in the assessments produced by these regulators, or by the notified bodies designated by these Authorities. If it is not, then the benchmark has been set too low and should be revisited.

While the Panel is of the view that application audits should not be routinely conducted on such device applications, the Australian NRA should undertake a review of the application

and supporting documentation prior to making a recommendation about the inclusion of the device in the ARTG in order to assure itself that:

- A. The device has been correctly classified; and
- B. The 'marketing approval' documentation is in order and meets Australian requirements; and
- C. The product is identical to the one assessed by the Notified Body or comparable overseas NRA, having been made in the same manufacturing facility, of the same materials, and for the same intended purpose; and
- D. There are no specific issues regarding applicability to the Australian context that need to be examined, including in respect to post-market monitoring and risk management; and
- E. Proposed product labelling and product information/instructions are appropriate and consistent with Australian requirements; and
- F. Any conditions or provisions that are imposed on the marketing approval of the medical device under the terms of the overseas marketing approval are able to be replicated and complied with in the Australian market.

In circumstances where the medical device does not meet conditions A to F above, the Australian NRA should: provide clear advice to the sponsor about the nature of any identified deficit in the manufacturer's evidence, or in other aspects of the application; work with the sponsor to correct these deficits; and/or undertake such further assessment as is necessary to satisfy itself that the product is safe and effective, prior to making a recommendation on the inclusion of the medical device in the ARTG.

Recommendation Eighteen

The Panel recommends that, where an application for inclusion of a medical device in the ARTG is made utilising Pathway Two, and all necessary documentation is provided to the Australian NRA:

1. The Australian NRA make a recommendation regarding inclusion of the medical device once it has satisfied itself that:
 - A. The device has been correctly classified; and
 - B. The 'marketing approval' documentation is in order and meets Australian requirements; and
 - C. The product is identical to the one assessed by the Notified Body or comparable overseas NRA, having been made in the same manufacturing facility, of the same materials, and for the same intended purpose; and

- D. There are no specific issues regarding applicability to the Australian context that need to be examined, including in respect to post-market monitoring and risk management; and
 - E. Proposed product labelling and product information/instructions are appropriate and consistent with Australian requirements; and
 - F. Any conditions or provisions that are imposed on the marketing approval of the medical device under the terms of the overseas marketing approval are able to be replicated and complied with in the Australian market.
2. Where the medical device does not meet conditions 1A to 1F above, the Australian NRA should work with the sponsor to correct any deficiencies, or undertake such further assessment as is necessary to satisfy itself that the product is safe and effective, prior to making a recommendation on the inclusion of the medical device in the ARTG.

5.3.1.3 Pathway Three

The Panel notes that the FDA has released guidelines proposing a new expedited access PMA (EAP) process for certain medical devices that demonstrate the potential to address unmet medical needs for life-threatening or irreversibly debilitating diseases or conditions.²⁶ The proposed programme has features similar to that of the Fast Track and Breakthrough Therapy Programs for medicines, in that the intent is for the FDA to engage with sponsors early in the development stage of the device and provide interactive advice throughout the process. As part of the process, consideration will be given to whether certain data may be collected post-market rather than pre-market. The draft guidelines note that:

*FDA intends to work closely with sponsors of EAP Devices to develop a Data Development Plan for the device that provides, among other elements, a description of the premarket and postmarket data collection and an explanation and justification for the proposed balance of premarket and postmarket data collection, with the goal of significantly reducing the time and cost from device development to FDA marketing decision, while still meeting the statutory standard of reasonable assurance of safety and effectiveness.*²⁷

The guidance further notes that getting the balance right between pre-market and post-market data collection ‘*can reduce the extent of premarket data submission and directly impact when patients will have access to high-quality, safe and effective medical devices.*’ This implies that decisions under the programme may be based on less pre-market data than may have traditionally applied.

The introduction of expedited approval processes is not a trend that seems to be being repeated in other markets, possibly because timeframes for approval of devices in the US

can be much more protracted than in markets such as the EU. For example, Emergo reports that 18-30 months is a typical approval timeframe for US Class III devices assessed via the PMA process, whereas typical timeframes for approval of Class III devices in Europe are around 6-9 months.²⁸

Stakeholders expressed mixed views about the need for an expedited approval pathway in Australia, with many indicating that if inefficiencies can be removed from the Australian regulatory system so as to provide for approval timeframes akin to those in the EU, expedited approval would not be necessary. Others thought there may be merit in providing for expedited assessment of a device in defined circumstances, such as for truly innovative device technology that fills a treatment gap. These stakeholders cited the FDA's EAP process as a possible model for Australia to follow.

The Panel has the same concerns with this approach as it has with similar programmes for medicines. Namely, that the NRA may not have the necessary human resources and capacity to support such a programme, as it does not have the economies of scale that an organisation such as the FDA has. As such, the Panel questions the Australian NRA's ability to sustain the level of engagement required for the successful implementation of an expedited approval programme that is akin to the expedited access PMA process.

Having considered the issues, the Panel formed the view that there should be provision for expedited approval within the Australian regulatory framework for medical devices, which should take the form of a priority review process. While this process may not be utilised very often, such a provision will enhance flexibility and avoid the situation that the NRA currently finds itself in with respect to medicines, where it cannot offer expedited assessment even in circumstances where to do so would be appropriate. This has put Australia out of step with international practice.

As such, the Australian NRA should develop criteria, in consultation with health care consumers, health practitioners and industry, under which application may be made for either:

- A priority conformity assessment to be undertaken under Pathway One, and for the expedited assessment of the subsequent application for inclusion of the device in the ARTG; or
- For priority consideration of the manufacturer's evidence supplied under Pathway Two, and for the expedited assessment of the subsequent application for inclusion of the device in the ARTG.

Such criteria should not be inconsistent with that adopted by comparable overseas NRAs for accelerated approval of medical devices.

The Panel notes that if the FDA is identified at some point in the future as a comparable overseas NRA for the purpose of device approvals (or other comparable NRAs introduce expedited approval processes), then there is the potential that sponsors of devices

approved under these new expedited access schemes may seek inclusion of the device in the ARTG on the basis of that approval. Should this occur, and the Australian NRA approves the inclusion of the device in the ARTG, this approval should be subject to:

- Any conditions imposed by the Australian NRA (which should be consistent with those imposed by the comparable overseas NRA if relevant and applicable to the Australian context). Such conditions might include: limiting the use of the device to certain populations; providing intensive education of information to practitioners on the use of the device; or the collection and reporting of specified post-market data. The Australian NRA should have timely access to any such data collections.
- The provision of clear advice to consumers and health practitioners that the medical device has been approved via an expedited process and that it is subject to certain conditions (if any).

Recommendation Nineteen

The Panel recommends that:

3. The Australian Government develop transparent criteria under which application may be made for accelerated assessment of novel medical devices for inclusion in the ARTG.
4. In circumstances where accelerated assessment is granted, the Australian NRA have capacity to place conditions on the inclusion of the medical device in the ARTG.

In addition to providing for additional pathways to inclusion of a device in the ARTG, the Panel identified a number of other opportunities to simplify and enhance the regulation of medical devices. These are discussed below.

5.3.2 Reduced complexity through international harmonisation

As noted in section 5.3, the Australian and EU regulatory frameworks for medical devices are closely aligned, although there are small differences between the two classification systems and the *Essential Principles* and *Essential Requirements* used by Australia and the EU.

5.3.2.1 Classification of medical devices

On the whole, stakeholders indicated that while the Australian classification system was complex, such complexities are necessary to manage the diversity of products and associated risks. However, industry stakeholders indicated that there was insufficient, inconsistent or incomplete guidance and advice, and a lack of opportunities to engage with the TGA to clarify the regulatory requirements. The majority of device manufacturers in Australia are SMEs, with little or no internal regulatory affairs capacity, and a number

expressed concern that the TGA did not provide advice, but instead directed them to consult a commercial regulatory consultant.

Stakeholders advised that simpler, more user-friendly guidance materials, similar to the MHRA or FDA materials, would assist them to properly classify their device and to better understand regulatory requirements. Similarly, a number of stakeholders indicated that an online decision tool that assists manufacturers to correctly classify their device by answering a series of questions, would be useful.

The Panel is of the view that the NRA does not engage enough with manufacturers and/or sponsors (of either medical devices or medicines) and would like to see the NRA strengthen its capacity to provide advice and support, similar to the approach adopted by the FDA. This is discussed further in Chapter Seven.

In respect of the Australian *Essential Principles* and EU *Essential Requirements*, the differences are generally restricted to products that are on the border of medium to high risk classes. These differences can create difficulties for manufacturers seeking Australian market approval, as occasionally they will result in the TGA rejecting an application because the EU conformity certificate does not fully comply with Australian requirements.

There are provisions under the existing EC and EFTA MRAs for manufacturers to obtain EU Conformity Assessment at the Australian classification level and against the Australian *Essential Principles*. If the assessment is not conducted under the auspices of the MRA, the notified body undertaking the assessment is required to do the assessment to the classification legislated in that country and against the European *Essential Requirements*.

Amendments to the MRAs that took effect from 1 January 2013 expanded the range of high-risk medical devices (including all Class III devices) that could no longer be assessed under the MRA. This enabled the TGA to undertake application audits on such devices, as part of confidence building activities implemented in response to concerns about some EU notified bodies.ⁱⁱⁱ However, it created additional difficulties for manufacturers, a number of whom advocated for restoration of the capacity to have a device conformity assessed at the Australian classification level and against the Australian *Essential Principles*.

These difficulties highlight the importance of maintaining harmonisation between the Australian and EU systems where ever possible. Given the Australian market represents around 2 per cent of the global medical devices market, some manufacturers may make a business decision not to seek Australian market access if regulatory requirements are overly burdensome and costly. This will mean that Australian health care consumers are denied access to medical device technologies that may be appropriate and improve health outcomes. It is, therefore, essential to ensure that the Australian regulatory system is as

ⁱⁱⁱ Paragraph 5.3(i) of the Regulations precludes Class III medical devices that are assessed under the EC or EFTA MRA from compulsory application audits under section 41FH of the Act.

streamlined and easy to navigate as possible, for both Australian and overseas manufacturers.

5.3.2.2 Inclusion of medical devices in the ARTG

The Panel received numerous examples from stakeholders of where the requirement to include medical devices in the ARTG led to significant complexities. This is in contrast to the EU, where there is no centralised register of devices. An example included the process to include a ‘family of devices’, which requires the sponsor to submit multiple applications, one relating to each model/iteration. These applications must each be accompanied by a set of supporting information, which is almost identical.

The Panel is concerned that the ARTG process, which works well for medicines, has been retrofitted to apply to devices, without taking account of the distinct differences between these two types of products, not least of which is the sheer number of products that a device sponsor may need to include in the ARTG. Mechanisms put in place to try and mitigate the impact on device sponsors of this retrofitting, have themselves created difficulties, such as not being able to easily trace individual lower risk devices.

Given these concerns, the Panel recommends that the therapeutic goods legislation be redrafted so as to provide for a legislative framework for devices that is fit for purpose (refer Chapter Seven). In doing so, it is recommended that systems and processes are scrutinised individually to ensure that they are appropriate, efficient and effective. This should include a review of the utility of the ARTG for medical devices. In addition, legislative and process reforms should seek to harmonise the Australian and EU systems as much as possible. The Panel is supportive of continued participation by the Australian NRA in international fora designed to progress harmonisation of regulatory requirements.

That is not to say that the Australian NRA should not retain the capacity to act in circumstances where it has concerns about public health and safety. In the Panel’s view, it was appropriate for the Australian NRA to up-classify joint replacement implants from Class IIb to Class III following post-market concerns about these products. So too was the introduction of compulsory application audits in response to concerns about the EU regulatory system. However, where the Australian NRA chooses to diverge from the EU regulatory system for devices, it should provide clear rationale for doing so and implement such measures in a way that minimises any additional impost on industry.

In addition, given the immaturity of regulatory systems for medical devices internationally, there should always be capacity for regulatory innovation. A recent example of this is the implementation of the Australian IVD framework, which will see the full transition of regulatory oversight of IVDs into the medical device regulatory framework by 2017. In contrast, the EU regulates IVDs under a separate IVD Directive, and the classification system does not always align with the Australian IVD classes. However, the current EU medical

device reforms include changes that will bring their classifications and regulatory processes into greater alignment with the Australian practice.

5.3.2.3 Variations

The dynamic nature of many medical devices often gives rise to a number of iterative variations throughout their lifespan. New models, customisations, optimisations and continuous development often lead to the existence of a number of devices that have evolved from an originator device through a series of modifications.

Where a device is included in the ARTG on the basis of an EU conformity certificate or a self-declaration by the device manufacturer, there is no requirement to notify the TGA of design changes. Instead the design changes must be notified to, and assessed by, the EU notified body that issued the conformity certificate before being supplied on the market. This risk-based assessment examines the likely impact of the proposed design changes on the safety, quality and performance of the device.

In circumstances where the TGA has conducted a Design Examination as part of a conformity assessment, the proposed changes must be notified to, and assessed by, the TGA. A number of stakeholders raised concerns that the TGA sometimes undertook de novo Design Examinations, rather than undertaking an abridged evaluation of the possible impact of the proposed design changes on device safety, quality and performance. This had the potential to significantly delay the availability of the new product on the Australian market. Indeed, some Australian manufacturers indicated they had made a business decision not to supply some device iterations in Australia because of the cost and time impost of this requirement. Stakeholders were also concerned that the TGA did not appear to apply any consistent and transparent criteria in determining the extent of assessment required.

There is a lack of transparency and guidance on variation processes. Despite the Australian regulatory framework for devices being fully implemented in 2007, the chapter on variations in the ARGMD is still not available, although there are various cross references within the guidelines and the TGA website that direct people to the undrafted chapter. The Panel recommends that the NRA adopt a risk-based approach to the assessment of variations that is aligned with the EU. This approach should provide for the NRA to undertake an abridged Design Examination that is limited to those aspects of the design that require evaluation in order to establish the continued safety, quality and performance of the device. There should be clear and transparent criteria to determine whether a re-examination is required and the extent of that examination. The Panel also recommends that guidance materials should be completed as a matter of urgency to assist manufacturers and sponsors to understand their obligations.

Recommendation Twenty

The Panel recommends that:

1. The regulation of medical devices by the Australian NRA is, wherever possible, aligned with the European Union framework including in respect of the:
 - A. Classification of medical devices;
 - B. *Essential Principles/Requirements*.
 - C. Adoption of a risk-based approach to variations to medical devices.
2. Should the Australian NRA seek to apply specific requirements, there must be a clear rationale to do so.

5.3.3 Enhanced transparency of processes and timeframes

The Panel heard concerns from numerous stakeholders about the time taken for the TGA to either: undertake a conformity assessment; or assess an application for inclusion of a device in the ARTG utilising an EU conformity certificate. Stakeholders advised that the non-compulsory application audits were particularly problematic, as they could add significant, unexpected, time to the approval process. There was also a view that the lack of TGA familiarity with novel technologies may sometimes be the reason an application is selected for random audit, instead of an identified quality reason. The resulting lack of predictability precluded sponsors from planning for the release of their product onto the Australian and/or overseas markets (where Country of Origin requirements apply).

The Panel understands that it is difficult for the TGA to reject an application for the inclusion of a medical device in the ARTG in the absence of an application audit. As such, if there is missing information on an application, or the TGA wishes to clarify an issue, it will generally instigate an audit. This further delays approval, as it requires formal correspondence to go back and forth. The TGA appears to adopt a formal approach in its liaisons with sponsors, rather than utilising phone calls or emails as a means of resolving minor issues expeditiously. While this may be consistent with legislative requirements, it does not provide for a timely and responsive regulatory system.

Incomplete or inadequate guidance and application forms may also be a factor in delays in the approval processes. SMEs in particular indicated that they found the regulatory system difficult to navigate and understand and that guidance materials and advice from TGA staff sometimes increased their confusion. The Panel recommends that the Australian NRA continue to work towards completing and improving guidance materials and application forms, including the provision of check lists that assist sponsors to understand the steps in the application process and what documents are required for each step.

A further factor impacting timeframes for device approvals is the two-staged application process for inclusion of a device in the ARTG. This requires the sponsor to submit the manufacturer's evidence for assessment; await receipt of an approval notification from the

TGA; and then submit an application for inclusion of the device in the ARTG, at which point it may be subject to an application audit. However, approval of the manufacturer's evidence does not necessarily ensure that the subsequent application will be considered acceptable, because the same manufacturer's evidence may be used for multiple devices. As such, the purpose of the manufacturer's evidence step is unclear.

A more streamlined approach would provide for:

- Medical devices undergoing conformity assessment by the Australian NRA to be included in the ARTG once a conformity certificate is issued and the application fee is paid; and
- Submission of an application for inclusion of a device in the ARTG, along with the manufacturer's evidence and other supporting documents as a single process. To avoid sponsors losing full application fees if manufacturer's evidence is found to be unacceptable, there could be a small, upfront payment and, once the application and supporting evidence is found to be in order, a further payment that allows the application to proceed. This would prevent double handling of manufacturer's evidence and should reduce approval timeframes.

The Act and Regulations are largely silent on timeframes for the assessment of medical devices. TGA conformity assessments that require a Design Examination have a statutory timeframe of 255 working days. This reflects the statutory timeframe for assessment of a new chemical entity under the medicines framework. However, given the significantly shorter lifecycle of a medical device (2-5 years) compared to a medicine, the Panel queries the appropriateness of applying this timeframe to medical devices. There are no statutory timeframes for other processes within the medical devices framework, but the TGA sets target timeframes for: assessment of manufacturer's evidence (15 days); mandatory application audits (30 working days - level 1 audits; 60 working days - level 2 audits) and non-compulsory audits (30 working days). Unfortunately, the TGA frequently fails to meet these target timeframes, further contributing to the lack of predictability of device approval timeframes.²⁹

In redrafting the Act and Regulations, the Panel recommends that the Australian Government give consideration to appropriate statutory timeframes for the conduct of conformity assessments and for consideration of an application for inclusion of a medical device in the ARTG (with and without an application audit). Such timeframes should: reflect international benchmarks; reflect the lifecycle of medical devices; and take account of the different levels of complexity posed by different device Classes.

Recommendation Twenty One

The Panel recommends that the NRA establish target timeframes that reflect international benchmarks and the typical lifecycle of a medical device for:

1. Conformity assessments conducted under Pathway One; and
2. Recommendations about inclusion of a device in the ARTG following submission of an application for inclusion under Pathway 1B or Pathway Two.

5.3.4 Post-market monitoring

No regulatory system can ever be 100 per cent effective for catching all risks and no medical device can be guaranteed to be 100 per cent safe. The iterative nature of medical devices means that many are approved on the basis of their design and the manufacturer's compliance with quality standards, rather than on the basis of detailed clinical trials as are required for medicines. As a result, timely and effective post-market monitoring of the performance of medical devices in the real world is an essential element of an effective regulatory system.

Post-market monitoring of medical devices poses particular challenges compared to medicines due to the greater diversity and complexity of medical devices, the learning curve associated with health practitioners and consumers adopting new technologies, and the short lifecycle and iterative nature of medical devices.³⁰ The Australian NRA has in place a number of strategies for the collection and analysis of post-market data. A requirement of inclusion of a medical device in the ARTG is that the sponsor report adverse events to the TGA that have resulted, or may result, in death or serious injury. Adverse events data may also be submitted by health professionals and/or consumers.

When the TGA receives an adverse event report relating to a device it undertakes an initial risk assessment and logs the report. The report is discussed by an Incident Report Evaluation Committee which can make a decision to investigate or to implement a watching brief. Because there are so many variables that can impact the performance of a device, especially a high-risk implantable device, careful analysis is required in order to tease out the factors that may be contributing to adverse outcomes. These can include faults in the design of the device itself, but may also relate to the proficiency of the user (which may or may not be related to the quality of instructions for use provided by the device manufacturer); and actions or characteristics of the device recipient, such as the extent to which they have complied with pre and post-operative care instructions, or comorbidities.

In addition to adverse event reporting, it is a condition of inclusion in the ARTG that the sponsor of a medical device that is an AIMD, a Class III or an implantable Class IIb device, provides three consecutive annual reports to the TGA following inclusion of the device in the ARTG. These annual reports must include all complaints, including complaints from

overseas markets, received by the manufacturer relating to problems with the use of their device during the reporting period. While such an approach may be valuable, the timeliness of an annual report is questionable.

In light of the Panel's recommendations to: expand the use of overseas device assessment reports as the basis for inclusion of a device in the ARTG; to consider devices for inclusion in the ARTG that have been through an expedited review process; and to remove compulsory application audits of some high-risk devices once confidence in the EU system is restored, the Panel is of the view that Australia should strengthen its post-market monitoring of medical devices. This would include making greater use of device specific registries, accessing and interrogating available datasets, including eHealth, Pharmaceutical Benefits Scheme (PBS) and Medical Benefits Scheme (MBS) data (see Chapter Seven); and adopting the Unique Device Identifier (UDI), consistent with the world's two largest markets, the EU and the US. International post-market vigilance exchanges should also continue to be supported.

Clinical Registries

Device registries play an important role in post-market monitoring as they can provide detailed information about patients, procedures and devices not routinely collected through other means. The Australian Orthopaedic Association National Joint Replacement Registry (NJRR) was cited by stakeholders as an example of an effective registry that enabled the identification of post-market signals, informed clinical practice, and identified better performing devices. It was involved in the identification and later worldwide recall of DePuy ASR hip replacements between 2007 and 2010.³¹

In light of proposed changes to the regulatory framework for medical devices, the Panel recommends that all high-risk (Class III and AIMD and some Class IIb) implantable devices be included on a registry that is compliant with the requirements for registries established by the Australian Commission on Safety and Quality in Health Care (ACSQHC). The ACSQHC has developed a national framework for Australian Clinical Quality Registries (CQR), which details principles for the ethical collection, storage and use of data.

Whilst the Australian NRA should be actively involved in the monitoring and analysis of registry data, it would not necessarily be appropriate for the NRA to manage these registries, given the primary function of the regulator should be to determine market approval and ongoing compliance with that approval. It would however be appropriate for the Australian NRA to actively work with stakeholders and registry providers to ensure that operations support the collection and regular reporting of data that is suitable for post-market monitoring. The Australian NRA would be responsible for monitoring these reports and managing the appropriate risk-based responses to identified issues. The Panel is also of the view that registries should operate on a cost recovery basis, from the range of stakeholders that derive utility/benefits from the data.

Unique Device Identifier (UDI)

The current Australian regulatory framework requires manufacturers to identify most medical devices with a Global Medical Device Nomenclature (GMDN) code, and for high-risk devices an additional Unique Product Identifier (UPI). Another number is provided on acceptance of the Manufacturer's evidence, and again on inclusion in the ARTG. Whilst these identifiers have utility, they do not have the same level of utility as a UDI, and do not allow the efficient tracking of a device across the supply chain and lifecycle.

The UDI consists of internationally recognised data that identifies the specific version or model of a device, and additional conditional and variable information that identifies one or more of the following:

- lot or batch number;
- serial number;
- expiration date;
- manufacturing date; and
- additional information to identify products with human cells, tissues or tissue based products.³²

The US and the EU have both indicated their intention to implement the UDI and it is currently being rolled out in the US. As the majority of devices marketed in Australia are available in the EU and US, they will require a UDI for those markets. Therefore introducing this requirement for the Australian NRA at the beginning of the regulatory process will not present an additional Australian regulatory burden. The Panel supports the Australian NRA in pursuing the adoption of the UDI, in alignment with international practice and data linkage activities.

Active monitoring and international collaboration

To optimise the value of enhanced post-market monitoring, the Australian NRA should actively analyse the data that is supplied from registries, in conjunction with other data sources and international collaborations, and act on it. This will require continued collaboration with international regulators to achieve greater harmonisation of post-market monitoring of medical devices and the continued sharing of data from adverse event reporting and medical device registries.

The Panel supports the continuation of existing activities such as the TGA's responsibilities under the EU and EFTA MRAs. The agreement requires all parties to contribute to post-market monitoring and data sharing, and to communicate any non-compliance, process, or quality defect issues in their jurisdiction that could affect the protection of public health, or require additional controls, in the other Party's jurisdiction.

Publishing regulatory decisions, including recalls

The Australian NRA publishes information related to medical device alerts and recalls, however it does not publish outcomes of regulatory decisions. The EU is implementing this requirement for manufacturers of high-risk medical devices, and published information is to include a summary of the main safety and performance aspects of the device and the outcome of the clinical evaluation. Similarly, the FDA requires manufacturers to publish a 'Summary of Safety and Effectiveness' on the FDA website for devices that have obtained PMA. The published information is reviewed and approved by the FDA, and provides a factual account of the regulatory decision process that preserves commercial confidential data.³³

Stakeholders supported the publishing of medical device regulatory decisions, to assist health professionals and consumers to make decisions about the risk profile and use of the device. However they advised that it would be inappropriate to publish information on rejected or withdrawn applications, or commercially valuable information. Critics of this approach argued that publishing this information would notify competitors of commercial decisions.

The Panel considered that publishing a summary of the basis for the approval of high-risk medical devices in Australian would add value to the post-market use of medical devices, and it would support the Australian NRA in adopting this measure.

Recommendation Twenty Two

The Panel recommends that:

1. All high-risk implantable devices are included in a registry that is compliant with the requirements for registries established by the Australian Commission on Safety and Quality in Health Care (ACSQHC).
2. Responsibility for ensuring that registries are operated consistent with the ACSQHC requirements should rest with the NRA.
3. Data collected by device registries should be made available to the NRA in a timely manner to inform post-market monitoring.
4. The NRA should implement an active programme of analysis and reporting on adverse events, and associated data, collected through registries or by other means.
5. The NRA should continue collaborative activities with overseas medical device regulators to actively share registry and other monitoring data, with a view to facilitating timely identification of emerging safety concerns and to inform better clinical practice.

5.3.5 Threshold issues for 'devices'

The range of products included in the ARTG as Class I medical devices is diverse. It includes products such as dental drill bits, which most Australians would consider to be a medical

device, as well as products such as some toothpastes and liquid soaps, which are more akin to consumer goods. As noted previously, Class I devices are added to the ARTG following a self-assessment by the manufacturer and are not subject to any independent assessment of their safety, quality or performance. As such, it might be argued that their regulation as therapeutic products creates unnecessary burden on industry but does little to manage risk. Their inclusion in the ARTG may also provide false assurance to consumers and health professionals by giving the impression that the product has undergone an independent assessment when in fact this is not the case.

The Panel sought the views of stakeholders regarding whether it was appropriate to manage Class I devices that are akin to consumer goods under the therapeutic goods framework. The majority of stakeholders who expressed a view on this issue argued that such goods should remain in the ARTG as their inclusion provides a number of benefits, namely it:

- Prompts manufacturers to consider their legal responsibilities to comply with manufacturing, quality, performance and safety standards.
- Facilitates post-market monitoring as there is a record of the device and the sponsor.
- Subjects these goods to provisions within the Act that allow the TGA to undertake compliance action, including product recalls, should problems arise.

Requirements under Australian Consumer Law (ACL) also provide for manufacturers to ensure that their goods are safe and fit for purpose and the ACL provides for sanctions and recalls in the event of misadventure. In respect of post-market monitoring, the Panel notes that, due to the process of inclusion and technical structure of the ARTG, which provides for multiple low-risk devices to be grouped as a 'kind' of device, the ARTG does not allow the TGA to easily identify all sponsors supplying a specific Class I device. As such, stakeholders' beliefs that the ARTG allows sponsors and manufacturers of specific Class I medical devices to be easily identified in the event of a problem are unfounded.^{iv}

Given the low-risk nature of Class I devices and the fact that many more closely resemble consumer goods than medical devices, the Panel considers that the regulation and controls available under the ACL would provide adequate protections to the Australian public for many of the lowest risk medical devices. The ACL includes: a national law guaranteeing consumer rights when buying goods and services; a national product safety law and enforcement system; and penalties, enforcement powers and consumer redress options. It is monitored and enforced by the Australian Competition and Consumer Commission (ACCC) and state and territory consumer protection agencies. Many high-risk products, such as child car restraints are successfully regulated under consumer law, and it is considered that it would exert suitable regulatory control of many Class I medical devices.

^{iv} Tracing of individual products by sponsor is possible for higher risk devices.

The Panel notes the concerns of some stakeholders that it is necessary for Class I devices to be included in the ARTG in order for them to meet the country of origin requirements imposed by some overseas markets, such as China. However it is unlikely that products such as toothpastes and liquid soaps are likely to be defined as therapeutic products in such markets. The Panel's proposal is not to remove all Class I products from the ARTG, but rather those that are more akin to consumer goods. Retaining some Class I products within the therapeutic goods framework aligns with international regulatory practice.

The Panel recommends that the Australian Government undertake a review of the range of products currently classified as Class I medical devices, with a view to reclassifying products as consumer goods in circumstances where the product poses little or no risk to consumers should it not perform as specified or malfunctions.

Recommendation Twenty Three

The Panel recommends that the Australian Government undertake a review of the range of products currently classified as Class I medical devices, with a view to reclassifying products as consumer goods in circumstances where the product poses little or no risk to consumers should it not perform as specified or malfunctions.

¹ Therapeutic Goods Act 1989, section 4 – Objects of Act

² International Medical Devices Regulators Forum, *GHTF History* webpage. Accessed online on 21 October 2014 at: <http://www.imdrf.org/ghrf/ghrf-history.asp>

³ Medical Technology Association of Australia (2014, 23 May), *White Paper: Improvements to the Australian Regulatory System for Medical Devices*, p. 3. Accessed online on 1 November 2014 from: <http://www.mtaa.org.au/docs/submissions/improvements-to-regulatory-system-white-paper---23-may-2014--final.pdf>

⁴ Therapeutic Goods Administration (2011a), *Australian regulatory guidelines for medical devices (ARGMD) Version 1.1*, May 2011, Commonwealth of Australia, p. 74. Accessed online on 28 October 2014 from: <http://www.tga.gov.au/sites/default/files/devices-argmd-01.pdf>

⁵ Therapeutic Goods Administration (2011b), *Overview of the regulatory framework for in-vitro diagnostic medical devices*, 6 July 2011. Accessed online on 28 October 2014 at: <http://www.tga.gov.au/overview-regulatory-framework-vitro-diagnostic-medical-devices>

⁶ Ibid.

⁷ Therapeutic Goods Administration (2011a), *op. cit.*, pp. 74-104.

⁸ Therapeutic Goods Administration (2011a), *op. cit.*, p. 22.

⁹ Therapeutic Goods Administration (2006, October 23), *How to make an application through TGA eBusiness services*. Accessed online on 28 October 2014 at: <http://www.tga.gov.au/industry/devices-ebs-application-howto.htm>

¹⁰ Ibid.

¹¹ Therapeutic Goods Administration (2011a), *op. cit.*, pp. 39-73

¹² European Commission (2012a, September 26), *Proposal for a Regulation of the European Parliament And Of The Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009*, available at http://ec.europa.eu/health/medical-devices/files/revision_docs/proposal_2012_542_en.pdf

¹³ European Commission (2001, April), *Medical Devices: Guidance Document. Designation and monitoring of Notified Bodies within the framework of EC Directives on Medical Devices, MEDDEV 2.10-2 Rev. 1*, pp. 17-19. Accessed online on 21 March 2015 at:

http://ec.europa.eu/health/medical-devices/files/meddev/2_10_2date04_2001_en.pdf

¹⁴ Medical Technology Association of Australia (2013), *Medical Technology: Key facts and figures 2013*, p. 5.

¹⁵ Cohen D, Faulty hip implant shows up failings of EU regulation, *BMJ* 2012;345:e7163, published 23 October 2012. Accessed online on 28 October 2014 at: <http://www.bmj.com/content/345/bmj.e7163>

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¹⁷ Therapeutic Goods Administration (2014, September 16), *Increased application audit requirements for some medical devices applications* webpage. Accessed online on 31 October 2014 at:

<http://www.tga.gov.au/increased-application-audit-requirements-some-medical-devices-applications>

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²⁰ Maxwell, A., (2013, October 17), *Notified bodies dropping like flies? New-style authority audits cause near-50% cull*. Accessed online on 12 March 2015 at: <http://www.team-nb.org/documents/2013/Clinica-Notified-bodies-dropping-like-flies-20131017.pdf>

²¹ Australian Government Department of Prime Minister and Cabinet (2014), *Industry Innovation and Competitiveness Agenda*, p. IX. Available at:

https://www.dpmc.gov.au/sites/default/files/publications/industry_innovation_competitiveness_agenda.pdf

²² US Food and Drug Administration, Human Subject Protection; Acceptance of Data from Clinical Studies for Medical Devices; Proposed Rule, Docket No. FDA-2013-N-0080, p. 7. Available at: <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM342236.pdf>

²³ Zuckerman D., et. al. (2014, Nov 1), 'Lack of publicly available scientific evidence on the safety and effectiveness of implanted medical devices' in *JAMA Internal Medicine*, 174(11):1781-7 Published online September 29, 2014. Abstract available at: <http://archinte.jamanetwork.com/article.aspx?articleid=1910556>

²⁴ Institute of Medicine (US) Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process; Wizemann T, editor (2010). *Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report*. Washington (DC): National Academies Press (US), p.45. Accessed online on 22 March 2015 at: <http://www.ncbi.nlm.nih.gov/books/NBK209791/pdf/TOC.pdf>

²⁵ Ibid., p. 49.

²⁶ US Food and Drug Administration (2014, April 23), *Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions - Draft Guidance for Industry and Food and Drug Administration Staff*. Accessed online on 4 November 2014 from: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393879.htm>

²⁷ Ibid., p. 9.

²⁸ Emergo, (2014) *Download Regulatory Process charts and Regulatory Timelines*. Available at: <http://www.emergogroup.com/resources/download-regulatory-process-charts>

²⁹ Therapeutic Goods Administration, TGA key performance indicators: July to December 2014. Accessed online on 19 March 2015 at: <https://www.tga.gov.au/publication/tga-key-performance-indicators-july-december-2014>

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<http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf>

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³³ US Food and Drug Administration, FDA Summary of Safety and Effectiveness Data (SSED) Clinical Section Checklist. Accessed online on 8 March 2015 at: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm220413.htm>

CHAPTER SIX: ACCESS TO UNAPPROVED THERAPEUTIC GOODS

Under the *Therapeutic Goods Act 1989* (the 'Act'), therapeutic goods for human use can only be supplied if they have been evaluated, approved and included on the Australian Register of Therapeutic Goods (ARTG), unless a specific exemption applies. Whilst this requirement provides broad access to therapeutic goods for many patients and promotes the community interest in ensuring therapeutic goods are evaluated for safety, quality and efficacy, there can be particular circumstances in which individual patients and clinicians wish to access unapproved therapeutic goods.

The types of unapproved therapeutic goods sought can cover a wide spectrum, including:

- products that were previously registered in Australia but were withdrawn from the ARTG by the sponsor for non-safety reasons;
- products that were previously registered in Australia but were withdrawn or cancelled for safety reasons;
- products that have been approved overseas but a sponsor has not sought registration in Australia;
- experimental products currently undergoing clinical trials in Australia; and
- experimental products that have not been approved anywhere in the world.

The risk of using these products may vary significantly depending on the nature of the product accessed and the individual characteristics/circumstances of the patient. Recognising the different scenarios under which access to unapproved therapeutic goods is sought, the Act provides a number of mechanisms through which individuals can gain limited access to therapeutic goods that are not in the ARTG, including:

- the Special Access Scheme (SAS);
- the Authorised Prescriber Scheme;
- clinical trials (CTX and CTN Schemes); and
- importation for personal use.

In formulating its recommendations on access to unapproved therapeutic goods, the Panel has examined submissions provided in response to the Review discussion paper, as well as other sources of information, such as previous reviews and inquiries, and information provided to the Panel by the TGA. This chapter analyses the operation of the various schemes for accessing unapproved therapeutic goods, and makes recommendations about how the schemes could be changed to improve access and reduce regulatory burden on patients, clinicians and sponsors, whilst maintaining or strengthening regulatory oversight.

6.1 The Special Access Scheme

The SAS allows a prescriber to provide an unapproved therapeutic good to an individual patient in specific circumstances. Access to unapproved therapeutic goods under the SAS is divided into Category A and Category B. Category A is for patients who are:

... seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.¹

Category B is for all other patients.

The SAS in its present form was introduced in 1991 following recommendations made by Professor Peter Baume in *A Question of Balance: Report on the Future of Drug Evaluation in Australia*. Professor Baume examined the previous arrangements for access to unapproved therapeutic goods, and found that access to unapproved products is ‘morally, socially and ethically justified for the terminally ill and certain seriously ill patients.’² Baume also found that the criteria for accessing unapproved therapeutic goods did not address the needs of people with serious but less immediately life-threatening conditions, and that the high number of Individual Patient Use (IPU) approvals suggested that the scheme was attempting to compensate for a seriously deficient regulatory and approval system.

As such, Baume recommended that a new scheme for special access to unapproved drugs be put in place from 1 January 1992, arguing:

... As already acknowledged, persons with AIDS, cancer and others who are terminally ill need the IPU program for reasons quite different from those, for example, who require a drug not available in Australia and whose lives are not threatened. The level of safety required to be demonstrated before approval is granted for the latter case ought to be greater than for a person with AIDS or cancer whose condition is terminal and who given the seriousness of their condition wishes to accept a greater level of risk in the hope of some benefit. However, most important, the level of safety required before approval ought to be greater for a person expected to live a long life, than for a person who is likely not to live long enough to encounter possible deleterious effects from the usage of a particular drug or drugs...

The existing IPU criteria do not lend themselves well to dealing with these different needs, nor do they recognise the difference between truly experimental drugs and those which have been approved elsewhere for some time. The criteria for approval under the new arrangements should contain a hierarchy of safety and efficacy requirements for approval which differentiates between:

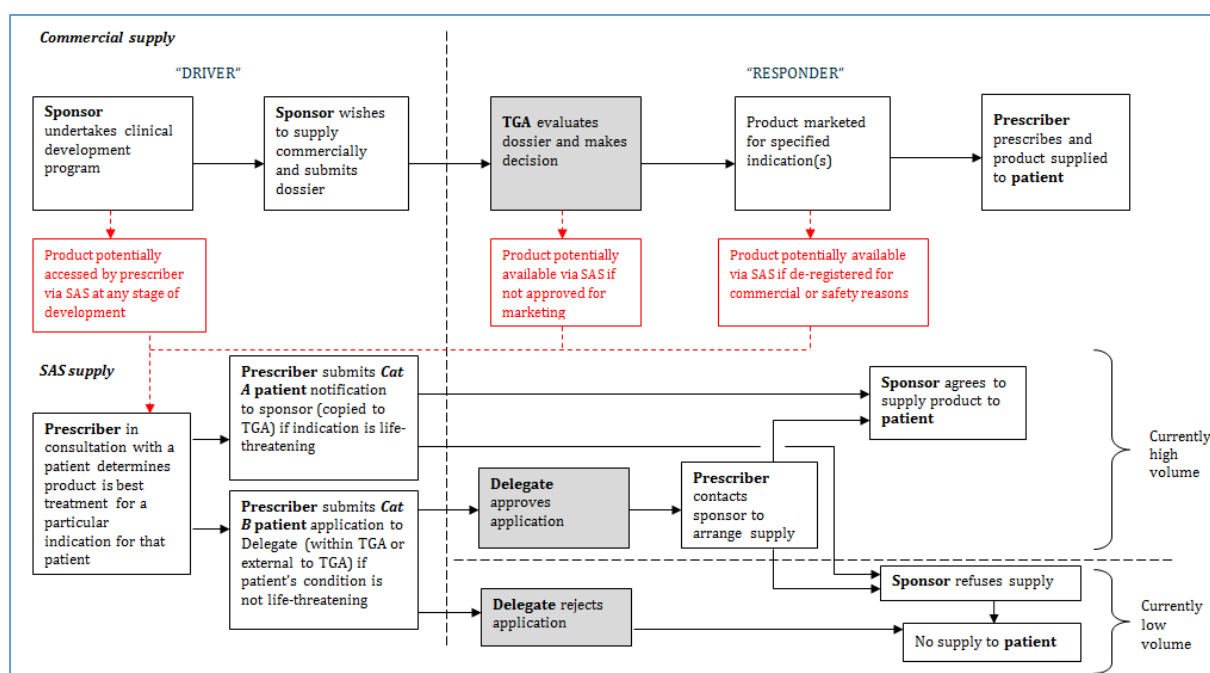
- *drugs which are not approved in Australia but which are approved in comparable countries; and*
- *drugs which are experimental in that they are still undergoing clinical trials and are not approved elsewhere.*³

The current SAS recognises the difference between patients with life-threatening conditions and those without, through the different requirements for Categories A and B.

6.1.1 The process for accessing unapproved therapeutic goods under the Special Access Scheme

As is demonstrated in Figure 11, which outlines the differences between the process for obtaining marketing approval for a therapeutic good in Australia and the process for SAS notification or approval, the SAS is driven by clinicians. This is in contrast to applications for ARTG registration, listing, or inclusion, which are driven by sponsors.

Figure 11: Comparison of SAS supply of therapeutic goods with available commercial supply



This has important implications for the role of clinicians, who under the SAS are responsible for obtaining informed consent from the patient and ensuring the unapproved therapeutic good is appropriate for the patient.⁴ Product sponsors are not under any obligation to supply an unapproved product, but must provide six-monthly tracking reports to the TGA on any products supplied under the SAS (although the Panel notes that this requirement is rarely followed up by the TGA).

Where a medical practitioner believes his or her patient falls within Category A, the practitioner may supply the unapproved therapeutic good without approval from the TGA. Practitioners are required to complete a 'Category A Form - Special Access Scheme' and

send it to the product sponsor. This document constitutes the legal authority for the Australian sponsor to supply the specified product. A copy of the form must be provided by the practitioner to the TGA within four weeks. This is colloquially referred to as a 'do and tell' procedure.

Where a patient falls within Category B, approval by a TGA delegate is required in order to supply the unapproved therapeutic good. There are also a limited number of external delegates who have been appointed to give approvals, however it does not appear that this process has been widely adopted.

Current arrangements for Category B patients require the TGA to provide approval for the supply of an unapproved therapeutic good to a patient, having assessed the merits or otherwise of doing so on a case-by-case basis. In assessing Category B applications the TGA medical officers consider:

- the patient's details, including the adequacy of the clinical justification for the use of the product;
- information on how the product is to be used and an appraisal of the efficacy and safety of the proposed use of the product; and
- information regarding the qualifications and expertise of the prescribing clinician.

The level of evidence required to justify approval will depend on the seriousness of the clinical need, whether the product has been approved overseas, and whether there are alternative treatments, amongst other matters.

There is no statutory timeframe within which the TGA must respond to Category B applications. The TGA website advises that applications are generally responded to within two working days although, in discussions with the Panel, the TGA indicated that turnaround times vary, depending on the volume of applications and available resources. A number of stakeholders advised the Panel that they have experienced turnaround times of three to five days. There is no cost involved in lodging a SAS Category B application.

6.1.2 Issues raised in relation to the Special Access Scheme

A number of issues were raised with the Panel in respect to the SAS, namely:

1. The appropriateness of the current criteria for Category A.
2. Whether the requirement for pre-approval of Category B applications is commensurate with the risk posed by some of the unauthorised medicines and medical devices being accessed through the scheme.
3. The use of the SAS to address medicine shortages.

6.1.2.1 Are the current criteria for Category A appropriate?

As noted above, the SAS allows clinicians to simply notify the TGA of supply of an unapproved product for patients ‘who are seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is reasonably likely to occur in the absence of early treatment.’⁵ Most stakeholders who commented on this issue were supportive of the current Category A arrangements, indicating they were appropriate and working well. However a small number of stakeholders called for an expansion of the criteria for Category A to include a broader range of patients, such as those who may be disadvantaged by any delay in access to an unapproved therapeutic good. Advocates for such an approach argued that expanding the Category A criteria would provide for timelier access to therapies for these patients and reduce the administrative burden on clinicians.

Access to unapproved medicines and medical devices is not without risk. These products may not have been assessed for safety, quality or efficacy by the TGA; their use for the proposed indications may be unproven; or they may be experimental medications, about which there is limited data on risks and benefits of use outside of a defined trial population. Access to such products under Category A, without prior approval by the TGA, is justified on the basis that patients with life-threatening conditions should have the right to ‘accept a greater level of risk in the hope of some prospect of benefit’.⁶ But the use of such products in patients with non-life-threatening conditions, who may have to live with the consequences of an adverse event for a long time should, in the Panel’s view, be subject to a greater level of regulatory scrutiny. The TGA may be able to ‘value add’ to risk-benefit decisions in these circumstances as it will have access to emerging data from both Australia and overseas regulators about adverse events associated with a particular product. It will also be aware if a product has recently been registered in the ARTG, or is about to be registered, that might be more appropriate for use in the patient’s particular circumstances.

In addition, the Panel was concerned that expanding the criteria for Category A may act as a disincentive for sponsors to seek registration of a product in the ARTG, especially in circumstances where the likely market for the product is relatively small. This would potentially undermine the integrity of the regulatory framework, creating a de facto market for certain unapproved products without requiring them to be subject to the raft of regulatory requirements that apply to products that are included in the ARTG. Were this to occur it would undermine the basic premise of the regulatory system, namely to put systems and processes in place that ensure therapeutic goods available to Australian consumers are safe, of high quality, and efficacious.

Given the above, the Panel concluded that the current criteria for SAS Category A are appropriate and should continue.

6.1.2.2 Is the requirement for pre-approval of Category B commensurate with risk?

The current process for Category B requires the clinician to submit an application for use of an unapproved therapeutic good to the TGA for approval prior to accessing or using the unapproved product. The application must include: details about the patient, such as age, gender and diagnosis; and a clinical justification for use of the product, addressing issues such as the seriousness of the patient's condition and details of previous treatment. The clinician is also required to provide efficacy and safety data to support the proposed use of the product and details of intended monitoring.⁷

Each Category B application is assessed by a TGA medical officer, who considers whether there is appropriate clinical justification for approval to supply the unapproved therapeutic good. In practice, very few applications for SAS Category B are rejected by the TGA. For example, in 2013 the TGA approved almost 97 per cent (n= 21,238) of the 21,974 SAS Category B applications for medicines that it received. Of the remaining applications, 271 were cancelled/withdrawn, 399 were pending (as at 31 December 2013, the end of the reporting period) and only 66, or 0.3 per cent, were rejected by the TGA.⁸ Given the very low number of Category B applications that are rejected by the TGA, some stakeholders questioned whether the pre-approval process is adding value or simply acts as a barrier to timely access by patients to unapproved medicines and devices which are clinically appropriate.

The rationale for pre-approval by the TGA of Category B applications is two-fold. Firstly, it aims to protect patients from harm by minimising the risk they will be prescribed unapproved therapeutic goods that are not clinically justified. Secondly, it aims to protect the integrity of the regulatory system by managing the risk that the SAS will create a de facto market for therapeutic goods. That is, the Category B application process allows the TGA to monitor the use of unapproved medicines and devices in Australia for non life-threatening conditions, and to control that use should the TGA become concerned that the scheme is being misused. The Panel considered whether the current pre-approval process for Category B applications was an appropriate way in which to meet these objectives.

Protecting patients from harm

As noted above, the process for accessing unapproved medicines and medical devices under SAS Category B requires the approval of a TGA medical officer prior to the unapproved goods being accessed or prescribed. This minimises the risk that a patient will be prescribed an unapproved therapeutic good that is not clinically justified. However the risk profiles of the unapproved goods that may be accessed under the SAS differ considerably. That is, clinicians may seek access for a patient to:

1. Products that were previously in the ARTG for the proposed indication but were removed by the sponsor for commercial reasons. Such products have undergone an assessment for safety, quality and efficacy by the TGA and there is a history of safe use of the product in Australia.
2. Products previously in the ARTG but withdrawn for safety reasons.
3. Products approved overseas for the proposed indication but not registered in Australia. Where these products have been approved by a comparable overseas regulator they will have been evaluated for safety, quality and efficacy to a standard comparable to that applied by the Australian regulator. They may also have a history of safe use for that indication in the overseas jurisdiction.
4. Products registered overseas by a comparable regulator, but not for the indication requested. However, there is a history of off-label use of the product for the indication requested in the overseas jurisdiction. Because these products have been approved by a comparable overseas regulator they will have been evaluated for quality and for safety in the approved indication.
5. Products that are still experimental and have not yet been approved by a comparable country.

In respect of points 1 and 3, the risk of using these products will be similar to that of using a product that is registered in the ARTG. Similarly, use of a product that is in common off-label use for the indication in countries such as the US, Germany or Canada, is likely to be no more risky than using a registered product off-label in Australia. However, products falling into the remaining two points are clearly higher risk and should be subject to a higher level of scrutiny and a more thorough analysis of risks and benefits prior to their use.

Similarly, some products have a long history of safe use under the SAS. For example, the ten most approved medicines under Category B were largely consistent between 2008 and 2013. In 2013 the ten most approved medicines accounted for 51.7 per cent of all Category B approvals and all but one had been approved (though not necessarily for the relevant indication) in at least one of the United States (US), United Kingdom (UK), New Zealand (NZ) or Canada.ⁱ Commonly, these products: have previously been in the ARTG but were withdrawn for commercial reasons; have been approved overseas for that indication but never brought to Australia; or are used off-label overseas. The case study of preservative-free Triamcinolone (Triesence) demonstrates the use of such medicines under Category B.

Given the varying risk profiles of different therapeutic goods accessed under the SAS, the Panel questioned whether pre-approval of all SAS Category B applications is the most efficient means of achieving the objective of protecting patients from harm. The use of some medicines and devices, especially those that are approved for the intended indication

ⁱ Data provided by TGA to the Review Panel.

by a comparable overseas regulator or that were approved for that indication in Australia but withdrawn for commercial reasons, is unlikely to pose an increased risk to patients that would justify pre-approval by the TGA before the clinician can use the product. The imposition of such a requirement in these circumstances could be seen as delaying access by patients to clinically appropriate treatments and placing an unnecessary burden on clinicians. Pre-approval processes for higher risk products, such as experimental medicines or products that were withdrawn from the Australian market for safety reasons, remain appropriate, however, providing an additional safeguard for patients.

Case Study: Preservative-free Triamcinolone

Preservative-free Triamcinolone (Triesence) is a synthetic corticosteroid in use in ophthalmology that has been approved by the FDA for treatment of sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.⁹ Triesence is also used off-label, including as a treatment for macular degeneration.

Triesence has never been registered for use in Australia, possibly due to the fact that the market for it is not large enough (i.e. it is for a niche indication). The TGA began to receive a large number of SAS requests for Triesence when safety concerns emerged over the use of Triamcinolone with preservative for intravitreal injections.

In 2013 Triesence was the second most requested medicine under Category B, with 2,154 Category B approvals. Additionally, Triesence was in the top ten most requested products in five of the six years between 2008 and 2013.

Protecting the integrity of the regulatory system

As noted previously, a second rationale for requiring pre-approval of Category B applications is to provide the regulator with capacity to monitor the use of unapproved products and prevent the scheme from being used to create a de facto market for therapeutic goods. Therefore it is important that any changes to SAS processes retain the capacity of the regulator to monitor usage of unapproved products by patients with non life-threatening conditions.

6.1.2.3 Proposed approach

The Panel concluded that it would be appropriate to implement changes to the process for accessing unapproved therapeutic goods under SAS Category B, to better align it with the risks posed by various categories of unapproved goods. The proposed approach is to adopt product and indication-based criteria for Category B applications, whereby:

1. Approval by the NRA automatically permits use of unapproved therapeutic goods for certain indications where the use of the product for that indication is considered by the NRA to be of an 'acceptable risk'.
2. Access to unapproved therapeutic goods where the use for a particular indication is considered higher risk continue to be subject to pre-approval by the NRA.

An 'acceptable risk' use of an unapproved therapeutic good might include:

- a. Products previously in the ARTG for the proposed indication that were not cancelled or withdrawn for safety reasons.
- b. Products approved by a comparable overseas regulator for the proposed indication but not registered in Australia.
- c. Products whose use for a particular indication, is deemed by the NRA to be of an 'acceptable risk'. This might include, for example, products that have a long history of safe use under the SAS or products that have a long history of safe use off-label overseas for the proposed indication. This would be determined by the NRA on a case-by-case basis, taking into account the risk profile of the product and the risk of creating a de facto market for the product.

A product, along with proposed indications for use that are considered to represent an 'acceptable risk' could be included on a schedule that states the details of: the sponsor; the product (e.g. dose; route of administration; frequency and duration of administration); and the indications for which the product may be used. If a clinician wishes to use a product from the schedule for the indication listed on the schedule, then they could submit a streamlined application which would be auto-approved by the NRA.

Category B applications for use of a medicine or device that is not on the schedule, or for use of a medicine or device that is on the schedule, but for a different indication, would still be subject to individual assessment by an NRA medical officer. This would include products with known safety concerns and experimental products.

This proposed approach has a number of benefits. Firstly, it would result in more timely access by patients to an unapproved therapeutic good considered to be of an 'acceptable risk' for use for that indication, as clinicians would not have to wait for the approval of the NRA before seeking supply of, and prescribing, the unapproved medicine or medical device. Secondly, it would reduce regulatory burden on clinicians as, while a Category B application would still be required for each individual patient, this could be streamlined since the NRA would have determined the conditions of its use for Category B patients and included the same on a schedule. Finally, the approach would retain the NRA's capacity for real time monitoring of use of unapproved therapeutic goods, but reduce the need to allocate NRA medical staff to assessing each application individually. This would allow these resources to

be redirected to overseeing higher risk activities, such as post-market monitoring or assessments of goods for inclusion in the ARTG.

6.1.2.4 Implementation

To maximise the efficiency of the system, the Panel recommends that SAS procedures be fully automated via an integrated online system that:

- Provides for completion of Category A notifications online and simultaneous submission of the form to the NRA and the sponsor.
- Provides for completion of Category B applications online with automated ‘real time’ approval of Category B applications that meet the criteria for an ‘acceptable risk’ use of a product for an indication.
- Provides for a copy of the automated approval to go to the sponsor, should the clinician so choose.
- Allows the NRA to add products to, or remove products from, the schedule of ‘acceptable risk’ use of unapproved goods in a timely and cost-effective way.
- Allows alerts to be sent to clinicians with current approvals if, for example, a safety concern emerges in respect of the product being used.
- Makes use of ‘smart-form’ technology to pre-populate selected fields.

If such a system were implemented it would both maximise the efficiency gains from the proposed process for ‘acceptable risk’ Category B applications; and provide for further efficiencies and better monitoring of the SAS. For example, the automatic approval process for these Category B applications could be modelled on the Streamlined Authority system in place under the Pharmaceutical Benefits Scheme (PBS), in which prior approval is not required where the patient meets the PBS restriction criteria and the prescriber puts in the relevant streamlined authority code.

Further efficiencies could be gained by providing for Category A applications to be submitted through the online system, with the system providing for automated, real-time approval and simultaneous submission of the application to the sponsor and the NRA. This would be quicker for clinicians who would no longer have to submit a paper based form separately to the NRA and the sponsor and would also eliminate the need for sponsors to complete and submit six-monthly reports. Such an approach would provide for better oversight of the scheme by the NRA and facilitate use of data analytics to identify trends and prevent abuse of the system through auditing.

The Panel notes that online systems have been in place under the PBS and Medical Benefits Scheme for a number of years, and does not see any reason why such a system could not be implemented for the SAS. However, the Panel recognises that it may take some time to develop the IT infrastructure necessary to implement an online SAS system. Rather than

defer the efficiency gains that could be achieved through implementing a risk-based Category B scheme until such time as an electronic approval system is available, the Panel recommends that a ‘tell and do’ procedure be implemented in the interim.

This interim arrangement would involve the clinician submitting a streamlined Category B application to the NRA where they wish to use an unapproved therapeutic good for an indication where the use of the good for an indication has been considered to be of an ‘acceptable risk’ by the NRA. However, the clinician would have to refer to the Schedule of approved medicines/indications, but then would not be required to wait for approval before seeking supply of the product from the sponsor. Rather, this ‘tell and do’ procedure would provide for the clinician to assume that the application has been approved by the NRA unless they hear otherwise and the application would act as legal authority for the sponsor to supply the unapproved therapeutic good.

The NRA would retain the capacity to go back to a clinician if they have any issues or concerns, for example, if on perusing the application they note that the proposed use of the medicine differs from that included on the Schedule. In such situations the NRA could seek further information and, if still not satisfied, rescind the application. To ensure this transitional arrangement was being used appropriately the NRA would need to actively follow up six-monthly tracking reports from sponsors.

6.1.3 The use of the SAS to address medicine shortages

Submissions from stakeholders raised the issue of the use of the SAS to address shortages of medicines (for example, the global medicines shortage of Carbimazole and Carbimazole Neo-Mercazole in 2013). Whilst there is a separate provision in the Act to allow for importation of unapproved therapeutic goods where there is a shortage, it can only be used where the alternative product has marketing approval in at least one of a specified list of foreign countries.¹⁰ Where an alternative with marketing approval in a listed foreign country cannot be located, the SAS has to be used to provide supply of the therapeutic good until an alternative product can be registered in Australia or sourced from a specified country.

Some stakeholders have argued that the SAS is not well-suited to respond to sudden shortages of critical medicines, as processing Category B requests related to medicines shortages can add unexpected additional administrative burden on the TGA and slow approval times for all Category B applications. For example, during the shortage of Neo-Mercazole in 2013, approval of Category B requests was taking the TGA up to 10 working days due to the increased workload.¹¹ Neo-Mercazole was also the most approved Category B medicine in 2013 (n= 2,996).

The Panel considered two options to address this issue. Firstly, the Act could be amended to allow importation of unapproved therapeutic goods that are approved for marketing in non-listed countries in certain circumstances. This could be implemented by granting an NRA delegate the power to sign a legislative instrument authorising supply of a particular

product where there is no product available from a listed country. This instrument could then be revoked once normal supply was restored. However, the process of due diligence may take some time and, as such, this option may not allow an immediate response to a sudden medicines shortage, particularly if it takes some time for the TGA to become aware of this.

Alternatively, short term medicines shortages could continue to be managed via the SAS, utilising the online approval system. Under this approach, once the NRA had located an alternate source of the medicine it could be added to the Schedule of 'acceptable risk' use of the unapproved therapeutic good and applications for its use would be automatically approved for the life of the shortage. The medicine could then be removed from the schedule once the shortage was resolved. In circumstances where supply of the product needs to be triaged for use by patients with the greatest clinical need, a fully automated approval process may not be appropriate. In these circumstances, automated approval might be limited to use in patients who meet defined criteria, with supply for other patients assessed on a case-by-case basis.

Both options may be appropriate depending on the nature of the shortage.

Recommendation Twenty Four

The Panel recommends that:

1. The current criteria and processes for Category A SAS patients remain unchanged.
2. The Australian NRA develop and apply transparent criteria for identifying Category B applications that could be subject to automatic approval. Such criteria might include applications for products that:
 - A. Were previously registered in the ARTG for the proposed indication and were not cancelled or withdrawn for safety reasons;
 - B. Have been approved for the proposed indication by a comparable overseas NRA;
 - C. Have been deemed by the Australian NRA as suitable for automatic approval for treatment of a particular indication; and
 - D. Have been approved by the Australian NRA under Category B in response to a medicine shortage, in circumstances where there is no need to triage the use of the unapproved product.
3. The Australian NRA continue to require individual assessment and approval for certain Category B products, including products that:
 - A. Do not have a history of safe use for the proposed indication through either the SAS scheme or in comparable overseas markets;

Recommendation Twenty Four

- B. Have not been approved for the proposed indication by a comparable overseas NRA;
- C. Were cancelled or withdrawn from the ARTG for safety reasons, or had an application for registration rejected by the Australian NRA for safety reasons;
- D. Were previously approved overseas but were withdrawn or removed from the market for safety reasons; and
- E. Have been approved by one comparable overseas NRA for an indication but were rejected by another comparable overseas NRA for that indication.

Recommendation Twenty Five

The Panel recommends that the NRA establish an integrated, online system to manage SAS notifications, approvals and reporting requirements. Such a system should have capacity to:

1. Establish a Schedule of Category B Products that are eligible for automatic approval;
2. Allow clinicians to enter a restriction code to auto-populate information relating to SAS notifications, automatic approvals and applications;
3. Utilise smart-forms to reduce unnecessary administrative burden on clinicians and sponsors; and
4. Provide data for real-time monitoring of the SAS by the Australian NRA, to identify potential trends and abuses.

6.2 The Authorised Prescriber Scheme

The Authorised Prescriber Scheme allows doctors to supply unapproved therapeutic goods to a class of patients that have either a 'life-threatening or otherwise serious illness or condition'.¹² To become an Authorised Prescriber, a practitioner must be either:

- a medical practitioner engaged in clinical practice in a hospital who has been endorsed by the ethics committee of the hospital; or
- a medical practitioner treating patients outside a hospital setting who has obtained endorsement from an appropriate ethics committee.¹³

Applicants are required to address a number of criteria that relate to the class of recipients, the product and the prescriber. Specifically, the applicant must provide information relating to:

- the clinical justification for the use of the product, including an outline of the seriousness of the medical condition to be treated, the availability of approved

treatments, and an appraisal of the expected benefits from use of the unapproved product;

- the product, including the product details, administration and monitoring regime and efficacy and safety data; and
- the prescriber, including the prescriber's details, the ethics committee endorsement, and the Agreement to Treatment Conditions.

Once an authorisation is granted, the sponsor is able to supply the unapproved therapeutic good and the prescriber is able to prescribe that product to patients in their immediate care. In 2013, the TGA approved 472 applications for medicines and 242 for medical devices under the Authorised Prescriber Scheme.¹⁴

While some stakeholders argued that the Authorised Prescriber Scheme worked well, others indicated that the scheme imposes unnecessary regulatory burden due to the need to apply to the TGA for authorised prescriber status every two years, as well as maintain ethics committee approval. Additionally, it was argued that the requirements for the Authorised Prescriber Scheme have increasingly become analogous to those for clinical trials.

As ethics committees should have considered the clinical justification for use of the product, the risk-benefit of the choice of treatment, informed consent procedures and the prescriber's details, it could be argued that requiring clinicians to provide the same information to the TGA for assessment is unnecessary duplication. The TGA's role should primarily be focused on authorising the supply of the unapproved therapeutic good rather than on further considering issues that have been evaluated by a properly constituted ethics committee.

One way to minimise duplication would be for the clinician to simply submit to the NRA a copy of: the ethics committee application; and the ethics committee approval letter, including any specified conditions of approval; along with a one page application that identifies the practitioner, the sponsor, and the unapproved medicine or device to be used. The role of the NRA would be to:

- check that approval had been provided by a properly constituted ethics committee;
- confirm that there is no medicine or device available in the ARTG that would be suitable in the proposed circumstances; and
- confirm that there are no emerging safety concerns in respect of the unapproved therapeutic good.

Once the NRA has satisfied itself of the above it would authorise the prescriber and the supply of the unapproved therapeutic good.

Furthermore, for renewal of Authorised Prescriber status the clinician could simply provide evidence that they continued to have ethics committee approval. This would avoid

unnecessary duplication whilst ensuring that the TGA had records of Authorised Prescribers and could rescind approvals if appropriate (e.g. if safety concerns arose or an alternative product was registered). Similar to the process recommended for the SAS, the Panel recommends that an online portal be set up to manage this system.

Recommendation Twenty Six

The Panel recommends that the role of the NRA under the Authorised Prescriber Scheme be to authorise a prescriber, and the supply of an unapproved medicine or device to that prescriber, in circumstances where it is satisfied that:

1. Approval for the prescriber to use the unapproved medicine or device in the proposed patient cohort has been provided by a properly constituted ethics committee; and
2. There is no medicine or device available in the ARTG that would be suitable in the proposed circumstances; and
3. There are no emerging safety concerns in respect of the medicine or device that may alter the consideration of risk and benefit.

6.3 Clinical Trials (CTN and CTX)

Clinical trials in Australia operate under either the Clinical Trial Notification (CTN) or Clinical Trial Exemption (CTX) schemes. Under the CTN scheme, the TGA is simply notified that the clinical trial has commenced, whereas under the CTX scheme the trial sponsor submits an application to the TGA for evaluation and comment.¹⁵ Under both schemes Human Research Ethics Committees have the ultimate responsibility for approving the clinical trial.

Stakeholders who commented on the CTN and CTX schemes were generally supportive of them, and argued that the CTN scheme helped reduce unnecessary duplication and encouraged the conduct of clinical trials in Australia. The Panel has not received any evidence to suggest that the operation of both schemes constitutes unnecessary regulatory burden, and accordingly does not believe it is necessary to make any specific recommendations on the CTN and CTX schemes.

6.4 Importation for Personal Use

The Panel did not receive any submissions on the specific issue of importation of therapeutic goods for personal use. However, some submissions did raise the issue of purchasing of therapeutic goods via the internet, and stakeholders expressed concern about the potential impact this may have on the integrity of the regulatory system. The Panel did not have available to it data to suggest that the importation of therapeutic goods for personal use was problematic and no submissions addressed this issue. As such it does not make any recommendations for changes to the framework for importation of therapeutic goods for personal use.

¹ *Therapeutic Goods Regulations 1990* (Cth), Regulation 12A.

² Baume P., (1991, July), *A Question of Balance. Report on the future of Drug Evaluation in Australia*, Commonwealth of Australia, Canberra, p. 98.

³ *Ibid.*, pp. 130-131.

⁴ Therapeutic Goods Administration (2009, November), *Access to unapproved therapeutic goods via the Special Access Scheme*, Commonwealth of Australia, p. 9.

⁵ *Therapeutic Goods Regulations 1990* (Cth), Regulation 12A.

⁶ Baume, P. (1991 July), *op. cit.*, p. 131.

⁷ Therapeutic Goods Administration (2014, September), *Category B form Special Access Scheme*. Accessed online on 3 March 2015 at: <http://www.tga.gov.au/sites/default/files/access-forms-sas-categoryb-140901.pdf>

⁸ Therapeutic Goods Administration (2014), *Half-yearly performance reports: January to June 2014*, version 1.0, October 2014.

⁹ Alcon Reimbursement Systems, *TRIESENCE Coding and Reimbursement Factsheet*, Accessed online on 20 February 2015 from: <https://www.myalcon.com/products/surgical/docs/ars-triesence-fact-sheet-single.pdf>

¹⁰ *Therapeutic Goods Act 1989* (Cth), s 19A.

¹¹ Therapeutic Goods Administration website. *Shortage of Neo-Mercazole (carbimazole)*. Accessed online on 17 February 2015 from: <https://www.tga.gov.au/media-release/shortage-neo-mercazole-carbimazole>

¹² Therapeutic Goods Administration (2004, October), *Access to unapproved therapeutic goods – Authorised Prescribers*, Commonwealth of Australia, p. 12.

¹³ *Ibid.*, p. 16.

¹⁴ Therapeutic Goods Administration (2014), *Half-yearly performance reports: January to June 2014*, version 1.0, October 2014, pp. 50-51.

¹⁵ Therapeutic Goods Administration (2004, October), *Access to unapproved therapeutic goods – Clinical Trials in Australia*, Commonwealth of Australia, p. 13.

CHAPTER SEVEN: IMPLEMENTING A GOOD PRACTICE REGULATORY REGIME

As noted in the preceding chapters of this report, an important part of the Panel's Review has been to examine whether the regulatory frameworks for medicines and medical devices are appropriate, cost-effective, transparent and flexible, and adequately streamlined and balanced. In this context, the Panel has given careful consideration to broader principles of best practice regulation and the extent to which the current regulatory framework in Australia meets such principles. Throughout its Review, the Panel has kept at the forefront the desirability of reducing duplication and inefficiencies to enable timely access to medicines and medical devices in a way that will not undermine public health and safety.

The Panel recognises that there will always be tension between industry, which favours a reduction in regulatory burden in order to promote productivity, innovation and competition; and health professionals and consumer advocates who emphasise the fundamental imperatives of product safety, regulatory rigour and favourable public health outcomes. In undertaking this Review, the Panel has formed the view that these two objectives are not mutually exclusive. If implemented effectively and as a package, the Panel believes that its proposed recommendations will serve to both reduce regulatory burden on industry and increase public health and safety protections. But there will need to be an investment in the reform process if this is to occur.

Good practice regulation is about clearly identifying the problems or risks that regulation is trying to manage; understanding the sources of those problems or risks; and having available to the regulator a range of tools that it can use to address each source of risk effectively and efficiently. As such, good practice regulation is underpinned by:

1. Data and analysis, which allows the regulator to identify emerging problems and, even more importantly, to parse these problems so as to gain an understanding of the factors that may be contributing to them. It is this understanding that allows a regulator to target its interventions effectively, rather than applying sweeping rules that increase burden across the system.
2. A legislative framework that is appropriate, provides the regulator with a diversity of regulatory tools, and entrusts the regulator to use those tools in a flexible and responsive manner.
3. An organisational structure and culture that supports problem solving and innovative regulatory practice, and engagement with stakeholders.
4. Adequate resourcing to ensure that policy and operational objectives are achievable.

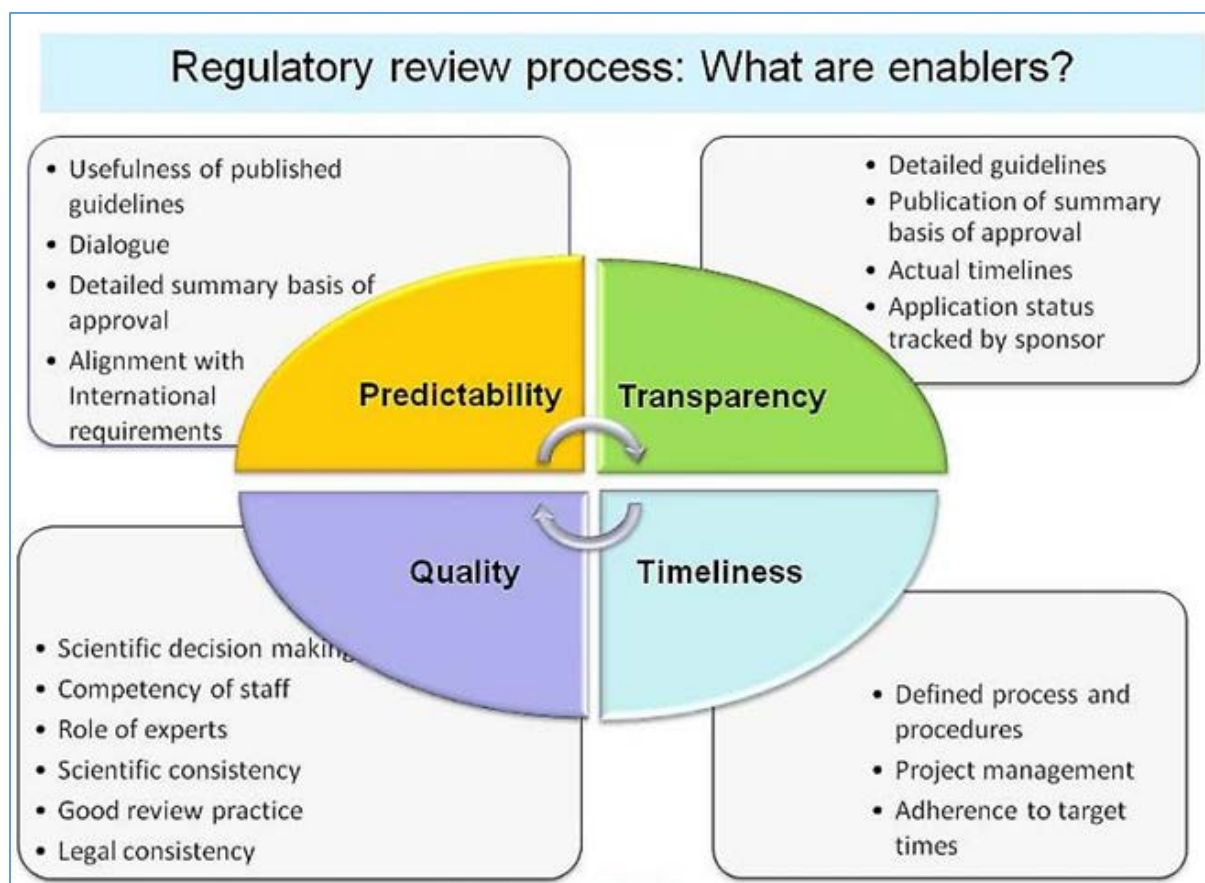
These four core attributes are discussed below. In order to inform this discussion, the Panel undertook an analysis of the performance of the current regulatory frameworks for medicines and medical devices against a number of features of regulatory systems for

therapeutic goods which the Centre for Innovation in Regulatory Science (CIRS) assert enable good quality reviews of medicines. These features were identified through a survey of international NRAs and pharmaceutical companies. While the survey was specific to medicines regulation, the Panel believes that the findings are transferable to other therapeutic goods and that many of the enablers identified are also important in other aspects of the regulatory process.

7.1 Performance against identified enablers

It is generally recognised that an effective and efficient regulatory system will be predictable, transparent, timely and of high quality. Such features have been identified as important in past reviews of therapeutic goods regulation in Australia and are reflected in the principles underpinning this Review. As illustrated in Figure 12, the CIRS study identified practices, processes and procedures that enable the achievement of these outcomes. The extent to which these enablers are in place and/or effectively implemented within the Australian regulatory system varies, particularly between medicines and medical devices.

Figure 12: Enablers of Transparency, Predictability, Timeliness and Quality



Source: Centre for Innovation and Regulatory Science (2011), *Emerging Markets focus study - Understanding the enablers of good regulatory process and decision making. What are the features that enable a transparent, timely, predictable and good-quality review?*¹

The enablers identified by the CIRS can be grouped into a number of areas:

1. **Alignment** of regulatory practice with international requirements.
2. **Timelines** which are documented, understood, and adhered to.
3. **Guidelines** which are detailed, accurate and user-friendly.
4. **Engagement and dialogue** between the regulator and industry.
5. **Tracking** of application progress.
6. **Processes and procedures** which are defined and efficient.
7. **Publication** of basis for approval.
8. **Internal resources**, including staffing and methodologies.

Based on the input that the Panel received during the Review, it has briefly assessed the extent to which each of these enablers is currently supported within the Australian regulatory systems for medicines and medical devices.

7.1.1 Alignment with international requirements

The regulatory framework for medicines is closely aligned with approaches adopted internationally. Provision for expedited approval of medicines and a risk-based approach to variations, as recommended by the Panel, will further align the Australian system with comparable overseas frameworks. Similarly, Australia has adopted the Global Harmonization Task Force (GHTF) model for the regulation of medical devices, which aligns with Europe and is increasingly being adopted in other jurisdictions. As discussed in Chapter Five, a number of inefficiencies have emerged in Australia's implementation of the GHTF model which the Panel believes are primarily the result of trying to retrofit the GHTF model within the provisions of the existing *Therapeutic Goods Act 1989*.

7.1.2 Timelines

The medicines framework provides for legislative timeframes for a number of processes, but lacks granularity. The identification of timelines for different types of reviews, such as abridged reviews, or for different products, such as generic medicines, would enhance transparency and predictability. The TGA consistently adheres to its legislative timeframes.

In respect of the framework for medical devices, timeframes are ill-defined, not fit for purpose, and are poorly adhered to.

7.1.3 Guidelines

With respect to medicines, guidance material is available and well understood by stakeholders. With respect to medical devices, guidance materials are extremely important because the framework is complex and the majority of device manufacturers in Australia are Small to Medium sized Enterprises (SMEs) that do not have internal regulatory affairs capacity. Detailed guidance materials on the regulatory framework for medical devices are

available but are incomplete. However this guidance material is voluminous and is not considered by stakeholders to be particularly user-friendly or easy to navigate and understand. In the Panel's view, this is contributing to elongated timeframes for the inclusion of a device in the Australian Register of Therapeutic Goods (ARTG) as sponsors and manufacturers need to understand requirements and processes in order to prepare high quality applications.

7.1.4 Engagement and dialogue

The CIRS identified the ability for sponsors to engage in dialogue with the regulator throughout the review process as critical. There was a view that such dialogue should occur during the product development and pre-submission stage and should continue throughout the process. In particular, where the regulator has questions or concerns about an application for marketing approval, capacity to discuss these, rather than rely purely on written questions and responses, provides an opportunity to efficiently resolve many matters.

The Panel has concerns about the TGA's willingness to engage not only with sponsors, but with other organisations that may have a legitimate interest, such as public health advocacy or consumer organisations. Certainly in the devices space this was raised as an issue, but it has also been identified as a problem more broadly. In implementing reforms to the regulatory framework it will be important to ensure that this issue is addressed.

7.1.5 Tracking of applications

The TGA's eBusiness Services establishes a base for electronic commerce and electronic lodgement of data packages in support of applications for entry of products onto the ARTG. At this stage the system does not provide capacity for sponsors to track the progress of their application through the system, but the Panel understands that this is the intent as the system is further developed.

7.1.6 Processes and procedures

There are generally clearly defined and transparent processes and procedures in respect to the regulation of medicines although these are still being defined in respect to some aspects of the evaluation of biosimilars. As discussed throughout this report, the efficiency of some processes is questionable, such as those for the approval of Special Access Scheme Category B patient applications or of Authorised Prescribers.

In respect of medical devices, processes and procedures are less clearly defined and transparent. There are significant inefficiencies in the system, with unnecessary procedural steps, some of which appear to have developed as a result of operating within a legislative framework which is not appropriate for medical devices.

In addition, the TGA uses a range of systems in the regulation of medicines and medical devices, but still relies heavily on the submission of a significant amount of paper

documentation for key procedures. The lack of effective IT systems and infrastructure across all aspects of the regulatory system creates significant administrative and time burdens, acts as a barrier to efficient work practices, and contributes to delays in information exchange.

7.1.7 Publication

Since December 2009, the TGA has published an Australian Public Assessment Report (AUSPAR) which provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or reject an application. The AUSPARs are useful documents that are easy to read and readily accessible. There is no equivalent document for high-risk medical devices. The US Food and Drug Administration (FDA) publishes an approval summary for devices approved under the Premarket Approval (PMA) process.

7.1.8 Internal resources

This relates to the regulator: attracting and retaining staff with the appropriate knowledge and skills; developing staff through access to training and professional development activities; having internal standards and operating procedures that are understood and applied by staff and that promote consistent application of the scientific and legal frameworks underpinning these procedures; having quality assurance systems in place, such as peer review; and being adequately resourced to undertake its role.

Stakeholders have confidence in the expertise of the TGA in undertaking pre-market assessments of medicines, describing it as a highly skilled and proficient organisation. It also appears to be sufficiently resourced in this regard, consistently delivering within target timeframes. There is, however, a need for greater investment in post-market monitoring, especially in light of the changes proposed by the Panel regarding use of overseas assessment reports and implementation of an expedited approval pathway.

Stakeholders are less confident in the medical devices space, with some expressing the view that it is difficult for an organisation the size of the TGA to access all of the expertise necessary to assess the diverse range of technologies that apply to medical devices. There were also concerns that the area within the TGA responsible for the regulation of medical devices is under-resourced, resulting in a lack of timeliness and failure to engage effectively with outside stakeholders. Reports of inconsistent advice being provided by different staff within the TGA would also suggest that there is a lack of clear internal documentation to assist staff in undertaking their role. The Panel was left with the impression that the organisation is struggling internally with the complexity and idiosyncrasies of the medical devices framework.

In summary, this analysis suggests that the regulatory framework for medicines and the way in which it is being implemented by the TGA, makes provision for the vast majority of enablers of effective regulatory review. The major exception is in respect to the sufficiency of engagement and dialogue with stakeholders. The situation in respect to medical devices,

however, is not as positive. There are deficiencies across multiple enablers which, in the Panel's view, are primarily related to trying to marry the Act and associated systems and processes, such as the ARTG, with the GHTF regulatory model for medical devices. This has resulted in the creation of a regulatory system that is not fit for purpose. These issues are discussed further below.

7.2 Core attributes of good practice regulatory systems

As noted above, there are a number of core attributes of regulatory systems that promote good practice regulation. These relate to: availability of data and capacity to analyse that data to assist problem solving; a legislative underpinning that is fit for purpose, provides the regulator with a diversity of regulatory tools, and entrusts the regulator to use those tools in a flexible and responsive manner; organisational structures and cultures that support problem solving and innovation; and access to adequate resourcing to ensure that policy and operational objectives are achievable.

7.2.1 Data and analysis – post-market monitoring

The collection, analysis and utilisation of data is fundamental to the effective regulation of medicines and medical devices. Decisions to allow medicines and medical devices access to the Australian market are made on limited data obtained from clinical trials or, in the case of many medium to high-risk medical devices, from consideration of design dossiers. As noted elsewhere in this report, clinical trials of medicines are highly controlled environments which are designed to demonstrate efficacy and are not well suited to identifying likely safety issues of the product in real world use. A 2013 analysis of medicines approved for market in the EU between 2000 and 2010 found that the median number of patients tested in clinical trials for a standard medicineⁱ was 1,708.² It can be concluded from the study that

... although the number of patients studied before approval is sufficient to determine the short-term efficacy of new medicines, it is insufficient to determine safety or long-term efficacy [in chronic conditions].³

As such, effective post-market monitoring of medicines and medical devices is critical to protecting public health and safety.

Australia's current post-market monitoring system is focused on the collection and analysis of adverse events data. It has, therefore, a primary focus on safety. However, the Panel's proposed changes to the pre-market assessment of medicines and medical devices necessitate enhanced post-market monitoring that is focused on both safety and efficacy. In particular, the Panel's recommendations regarding expedited approval of medicines based on early clinical trials data will require post-market collection of data on efficacy as well as safety, to ensure that the approval of the product continues to be justified on a risk-benefit

ⁱ A standard medicine was defined as a non-orphan medicine.

basis. Similarly, the acceptance of EU conformity certificates from notified bodies that have been designated by comparable *Designating Authorities*, without conducting an application audit, will require enhanced post-market monitoring of medical devices so that any concerns regarding safety or performance are identified immediately.

The Panel recommends that post-market monitoring be enhanced to provide for:

1. Timely analysis of data from existing datasets, including analysis of matched de-identified data from the Pharmaceutical Benefits Scheme, Medical Benefits Scheme, eHealth records, hospital records, private health insurance records, and device and other relevant registries and datasets.
2. Establishment and maintenance of registries for all high-risk implantable devices.
3. Implementation of a scheme to alert practitioners and consumers that a medicine is newly registered and to encourage reporting of any adverse events.
4. Provision for enhanced electronic reporting of adverse events.
5. Enhanced collaboration with overseas NRAs to share information relating to safety or efficacy.

7.2.1.1. Utilisation of existing datasets

The Australian Government collects a wealth of data through various means which, if it could be linked and interrogated effectively, could revolutionise post-market monitoring in Australia. This includes claims data from the Pharmaceutical Benefits Scheme (PBS) and Medical Benefits Scheme (MBS); eHealth records; and adverse events data collected by the TGA. However, the Australian Government is generally precluded from linking this data, even in a de-identified form, and utilising it for purposes such as post-market monitoring. This has been identified as an issue previously, with the HTA Review noting that:

‘A reliable assessment of the safety and efficacy of technologies requires data from a range of different systems. The multiplication of data sources within heterogeneous health systems results in both redundant and inaccessible information. The currently fragmented data systems make it difficult, if not impossible to systematically capture these impacts... The existence of these multiple, ‘siloes’ data sources reinforces the need for better data linkage.’⁴

Stakeholders have identified a number of benefits to enabling data linkage and analysis including: improved capacity to monitor risk management plans and facilitate drug utilisation studies; enhanced capacity to monitor rare but serious adverse events; potential to identify possible safety signals in near real-time; and an ability to more rapidly identify factors that may be contributing to adverse events. The latter is particularly important in respect to medical devices, because there are so many factors, other than the device, that could result in adverse outcomes. For example, when drug-eluting stents were introduced into the US market, cases of thrombosis that resulted in death were reported to the FDA

within months, but it was unclear whether this problem was related to the stents or some other variable. Researchers utilised the US Medicare database, which included a unique billing code for drug-eluting stents, to compare the entire stented population before and after the introduction of the drug-eluting products. As a result, they were able to ascertain that the problem was discontinuation of platelet drugs after a year, not in-stent thrombosis at the time of insertion.⁵

The facility of utilising PBS data in Australia for post-market monitoring of medicines has similarly been demonstrated by researchers from South Australia.ⁱⁱ They found that Prescription Sequence Symmetry Analysis, a method that uses prescription dispensing data to detect potential signals of adverse drug events, was valid and performed as well as the TGA's current system for analysing adverse event reports. When utilised in combination with the TGA's existing methods, it led to more adverse events being correctly identified and to earlier identification of adverse events in some cases. If the NRA had access to PBS data they could run such analyses within a day, providing significant improvements in adverse events detection and responsiveness.

Australia is well placed to be a global leader in post-market monitoring of medicines and medical devices, as it already holds existing datasets that cover the entire Australian population. The development of an effective eHealth system in Australia would provide another rich source of de-identified data that could be utilised to monitor the safety and efficacy of medicines and medical devices. The Panel believes that developing a surveillance database that, in the first instance, links the three national data collections, namely the PBS; the MBS and the aged care TRADE database, is critical to enhancing post-market monitoring in Australia. In the longer term it is proposed that Australia work towards linking a range of other data, including:

- personally controlled electronic health record data;
- hospital records (with jurisdictional agreement from States and Territories); and
- clinical registries such as Cancer Registries and the National Joint Replacement Registry and other relevant datasets.

Integrating these datasets would allow the Australian NRA to undertake active monitoring and analysis of these data. It would also provide a rich source of data for other bodies with

ⁱⁱ See for example Pratt NL, et. al. (2014), The performance of prescription sequence symmetry analysis as a tool for active post-market surveillance of newly marketed medicines: a simulation study. *BMC Med Res Methodol* 2014 May 15;14:66. doi: 10.1186/1471-2288-14-66; Wahab IA, et. al. (2013), Sequence Symmetry Analysis and Disproportionality Analyses: What Percentage of Adverse Drug Reaction do they Signal? *Adv Pharmacoepidemiol Drug Saf* 2013;2(140):doi: 10.4172/2167-1052.1000140; Wahab IA, et. al. (2014), Comparing time to adverse drug reaction signals in a spontaneous reporting database and a claims database: a case study of rofecoxib-induced myocardial infarction and rosiglitazone-induced heart failure signals in Australia. *Drug safety : an international journal of medical toxicology and drug experience* 2014;37(1):53-64; Roughead EE, et. al. (2013), Bridging evidence-practice gaps: improving use of medicines in elderly Australian veterans. *BMC Health Serv Res.* 2013 Dec 12;13:514. doi: 10.1186/1472-6963-13-514.

an interest in post-market monitoring (such as the Pharmaceutical Benefits Advisory Committee (PBAC)). Access protocols would need to ensure appropriate protections of patient privacy and ethical governance arrangements. These should be developed in consultation with stakeholders, particularly consumers.

The Panel acknowledges that implementing such a system will require an investment of resources, however the Panel believes that the potential savings to government from avoided morbidity and mortality and reduced health service utilisation would more than offset this investment over time. Furthermore, implementation could leverage off the work of the National E-Health Transition Authority (NEHTA) to build eHealth capacity, such as its work in standardising datasets and building capacity into prescribing and claims software used by clinicians and pharmacists.

Finally, the Panel notes that its proposed approach reflects the direction of post-market monitoring internationally. For example, in 2008 the FDA launched the Sentinel Initiative, which aims to create a linked sustainable system that draws on automated data from multiple sources to conduct post-market monitoring in real-time.⁶ Currently, the FDA is running a pilot programme (known as 'Mini-Sentinel') in partnership with health care providers, which has already undertaken a number of studies looking at post-market safety of medicines.⁷ Similarly, in 2012 the FDA issued a report entitled *Strengthening Our National System for Medical Device Postmarket Surveillance*, which sets out its vision for the future. The Plan proposes using a 'variety of privacy-protected data sources' for the purpose of identifying potential safety signals in near real-time.⁸

7.2.1.2 Improving post-market monitoring of high-risk implantable devices

As noted in Chapter Five, the Panel supports the inclusion of all high-risk implantable devices on a registry. Device registries play an important role in post-market monitoring as they can provide detailed information about patients, procedures and devices not routinely collected through other means. The Australian Orthopaedic Association National Joint Replacement Registry (NJRR) was cited by stakeholders as an example of an effective registry that enabled the identification of post-market signals, informed clinical practice, and identified better performing devices. It was involved in the identification and later worldwide recall of DePuy ASR hip replacements between 2007 and 2010.⁹

Proposed changes to the pre-market assessment of medical devices will result in more timely inclusion of medical devices in the ARTG and reduce regulatory burden on sponsors and manufacturers. However reduced oversight of medical devices at the pre-market stage must be balanced by enhanced post-market monitoring of these products for safety and performance. For implantable devices, the consequences of device failure can be severe, potentially resulting in disability and even death. Removal of such devices will generally require surgery, which brings its own risks and can be costly for patients and the health care system. As such, it is important that any problems with these devices are identified and

remedied as quickly as possible. The inclusion of such devices on a registry will assist to facilitate this.

While there are costs involved in establishing and maintaining device registries, well-designed registries provide valuable, unique insights into device performance and device-associated clinical benefits and risks, which ultimately can create savings for the health system. For example, according to the HTA review, the NJRR 'is estimated to have reduced the number of unnecessary revision operations by 1,200 procedures per year and saved the health sector and consumers around \$44.6 million' in its first ten years of operation.¹⁰

7.2.1.3 Increasing adverse event reporting for new products

Submissions to the Review argued post-market monitoring could be improved by increasing public awareness of new medicines and devices and encouraging greater adverse event reporting, particularly by health practitioners and patients. This issue is particularly important for products that are granted provisional approval based on early datasets, as there will be a greater reliance on post-market monitoring to determine risks and benefits. As such, schemes to increase public awareness and encourage adverse event reporting for newly approved therapeutic goods will be an important component of a robust post-marketing system.

This issue was also considered by the *Review to improve the transparency of the Therapeutic Goods Administration* (the Transparency Review), which considered whether the TGA should adopt a scheme similar to the United Kingdom's black triangle (▼) scheme, which is used to alert consumers and health practitioners to the level of risk in the early post-market period for new products. As the Transparency Review noted, the aim of the scheme is to link risk communication to the public with the TGA's requirement for risk management plans, by indicating which products are associated with a particular uncertainty or risk.¹¹ The Transparency Review took the view that such a scheme could assist in 'linking health practitioners into post-market surveillance activities', and recommended that the TGA conduct a feasibility study into the development of 'an early post marketing risk communication scheme for therapeutic goods'.¹²

Following the Transparency Review the TGA conducted workshops to assess stakeholder views on such a scheme. On the whole, health professionals and industry thought that an early post-marketing risk communication scheme would have some benefit in encouraging adverse event reporting and enable earlier identification of safety issues.¹³ Risks of such a scheme identified by participants included the possibility of the scheme being misinterpreted by consumers and health professionals leading them to think the product was unsafe or should be avoided.¹⁴

The Panel is of the view that an early post-marketing risk communication scheme for therapeutic goods should be implemented to encourage adverse event reporting for new therapeutic goods. The Australian NRA should develop inclusion criteria for which products

should be captured by the scheme in consultation with relevant stakeholders. However, the Panel recommends that the scheme be mandatory for all products granted provisional approval under the new Pathway Three for either medicines or medical devices, as it will be particularly important to encourage adverse event reporting by consumers and health practitioners for these products.

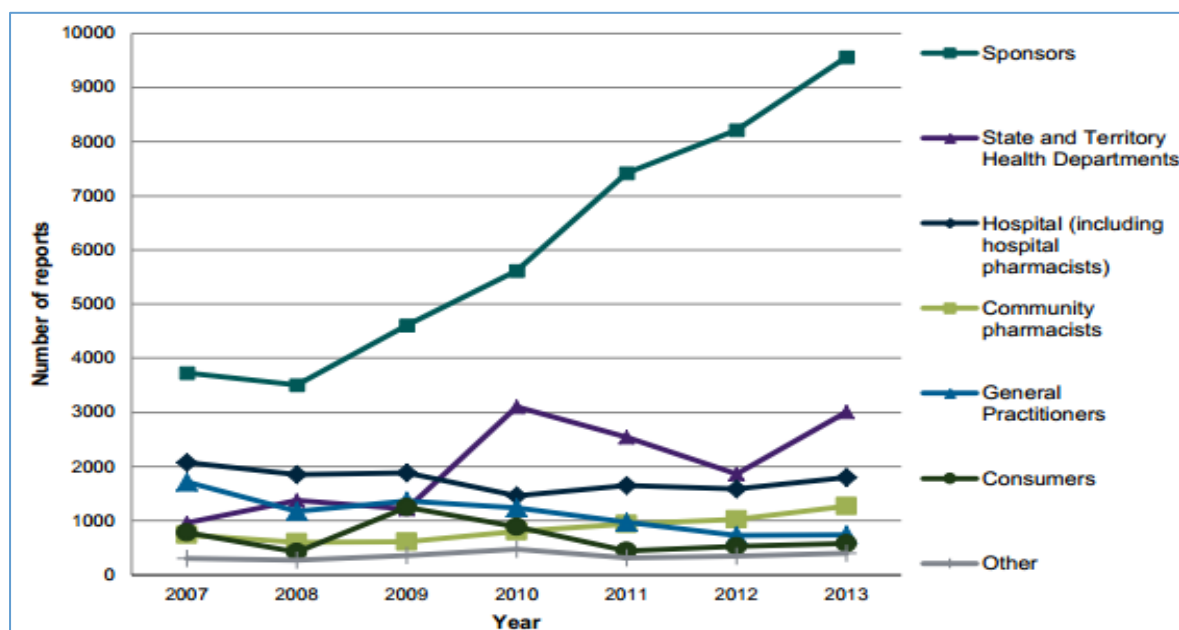
To address possible misinterpretation of the scheme, the Australian NRA should develop a system which is clear and easy to understand, and also provide information for health professionals and consumers explaining the scheme.

7.2.1.4 Enhanced mechanisms for adverse event reporting

The 2009 HTA Review recommended that the TGA take steps to increase the rate of reporting of adverse events, including reporting by health service providers and consumers.¹⁵ Currently, the vast majority of adverse event reports are made by sponsors, with only a small proportion being made by health professionals such as doctors and pharmacists. This is demonstrated by Figure 13, which provides a breakdown of the sources of adverse event reporting to the TGA between 2007 and 2013.

While the smaller numbers of reports by health professionals can be partly explained by the fact that many report adverse events to sponsors who then report them to the TGA, it is clear that there could be greater scope for adverse event reporting by health professionals and consumers. Stakeholder submissions to the Review argued increasing reporting of adverse events by health professionals is necessary to ensure that the Australian NRA receives timely information about possible safety issues.

Whilst the Panel notes that it is currently possible to submit adverse events via the TGA's online e-Business portal, this is time consuming for health professionals who must access the website and enter the relevant data. Consideration should be given to integrating adverse event reporting into pharmacy and medical software, making it easier for practitioners to make a notification. This would also facilitate inclusion of adverse events data in patients' eHealth records. The Panel notes that the FDA is similarly working to link adverse event reporting with hospital incident reporting systems and with hospital electronic health records, with a view to making it part of a clinician's normal workflow. They are also working to develop a mobile app which will allow health professionals and patients to securely report medical device adverse events.

Figure 13: Origin of medicine and vaccine adverse events reported to the TGA (2007-2013)

Source: TGA, Medicines and vaccines adverse event reports: Statistics for 2013.¹⁶

7.2.1.5 International collaboration

Some submissions to the Review argued that Australia has the capacity to participate in greater international collaboration on post-market monitoring. In particular, stakeholders pointed to regional databases such as the Asian Pharmacoepidemiology Network as opportunities for Australia to collaborate in a greater way in post-market monitoring. The Panel also notes that the European Medicines Agency and FDA in 2014 established regular meetings on pharmacovigilance.¹⁷ The Panel is supportive of the Australian NRA taking a leadership role with its overseas counterparts in this regard.

Recommendation Twenty Seven

The Panel recommends that the Australian Government develop a more comprehensive post-market monitoring scheme for medicines and medical devices. Such a scheme to include:

1. Better integration and timely analysis of available datasets, including analysis of matched de-identified data from the Pharmaceutical Benefits Scheme, Medical Benefits Scheme, eHealth records, hospital records, private health insurance records and device and other relevant registries and datasets;
2. Establishment and maintenance of registries for all high-risk implantable devices;
3. Implementation of a scheme to alert practitioners and consumers that a drug is newly registered and to encourage reporting of any adverse events;
4. Provision for electronic reporting of adverse events; and
5. Enhanced collaboration with overseas NRAs to share information relating to safety or efficacy.

7.2.2 Appropriate legislative framework

The Therapeutic Goods Act has been in place for over 25 years and during that period it has been amended frequently, which has resulted in increased complexity. In particular, the inclusion of medical devices under the Act in 2002 has created a very complex and difficult to navigate legislative framework. Stakeholders find the legislative framework inaccessible and rigid and some expressed concerns that it does not adequately convey the important public health and safety function of the legislation, instead focusing more on administrative outcomes. For example, concern was expressed that the *Objects of Act* refer to the ‘establishment and maintenance of a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods’ but fails to articulate that the ultimate purpose is for the protection of public health and safety.

Concerns were also expressed that the Act is now dated and fails to reflect the many technological and health system changes that have occurred since it was drafted. This can have the effect of creating barriers to clinical practice and imposing unnecessary regulatory burden. For example, the legislation fails to recognise the relatively new profession of Nuclear Medicine Technologists. These technologists are required to be registered with the Australian Health Practitioners Regulatory Agency and operate under the supervision of nuclear medicine specialists within a defined scope of practice. However they are precluded from undertaking certain functions (which fall within their scope of practice) by the therapeutic goods legislation. Similar concerns were also expressed about the treatment of ‘reconstitution’ and ‘extemporaneous compounding’ as they relate to the nuclear medicine field. Such legislative anomalies have serious flow-on effects, such as restricting access by patients to the use of some radiopharmaceuticals.

In the coming years there will be a raft of new innovations that challenge the existing framework, for example, personalised medicine and the evolution of 3D printing. The capacity of the current Act and Regulations to accommodate such challenges is questioned by some stakeholders.

In respect of the legislative framework for medical devices, the Panel has serious concerns that it is not fit for purpose. The regulatory framework for medical devices was included under the Act in 2002 and there has been an attempt to align the two frameworks as much as possible. However medicines and medical devices are very different products and the medicines and medical devices industries are very different industries. Attempting to align the way in which these products are regulated has created inefficiencies in the system, added regulatory complexity, and imposed additional burdens on sponsors, manufacturers and the regulator.

The Panel also heard concerns about the prescriptive nature of the legislative framework in terms of the processes that the NRA must follow. This has stifled regulatory innovation and responsiveness and resulted in some perverse outcomes. For example, the TGA stopped applying a risk-based approach to the management of variations to medicines, which was

effective in managing risk, because of advice that it was inconsistent with the legislation. This created additional workload for the TGA and increased regulatory burden on industry, for no apparent reason other than that it complied with the legislation. A legislative framework which is more principles-based would provide greater flexibility for the NRA to respond to emerging issues and exercise its regulatory authority in a targeted and appropriate way.

The NRA's capacity to respond to non-compliance is also an issue of concern. This issue was raised particularly in respect to dealing with advertising breaches, which will be addressed in the Panel's second report, but it also arises with regard to the inclusion of goods in the ARTG. Both low-risk medical devices and listed medicines can be included in the ARTG on the basis of a self-assessment by the manufacturer/sponsor. If a product is included inappropriately and it comes to the attention of the NRA, it may be subject to a review. However, during the review process the sponsor can withdraw the product and the review ceases. There is nothing to stop them including the product again at a later date. While the Panel acknowledges that in many instances products will be inappropriately listed or included in the ARTG in error, in other cases the Panel believes that there is intent involved on the part of the sponsor. The Panel is of the view that the legislative framework should provide a series of graduated penalties that would act as a deterrent for a range of non-compliance.

While it may be possible to implement some of the Panel's recommendations through administrative changes, the majority will require amendments to the Act and/or the Regulations. Given the serious concerns that the Panel has about the existing legislative framework, the Panel recommends that the Act and Regulations be reviewed in their entirety. This would provide an opportunity to: bring the Act into line with current clinical practice; de-couple the regulatory frameworks for medicines and medical devices where it is appropriate to do so; revise the language and structure of the Act to provide for common language and a logical flow; and provide for the NRA to exercise greater flexibility and discretion. Such a review would also provide an opportunity to examine individual processes in detail to ascertain if they are achieving the purpose for which they were designed; if that purpose still exists; and if there are other more effective and efficient means of achieving the desired outcome. The Panel was precluded from undertaking this exercise by the time available for the Review.

The Panel does not underestimate the scale of this task, nor the time and resources it will involve, but considers that it is crucial in ensuring an effective regulatory regime into the future. A possible option to progress reform may be to ask the Australian Law Reform Commission (ALRC) to undertake the review. The Commission is an independent statutory body with responsibility for, and a proven track record in, reviewing areas of Commonwealth law reform as referred by the Attorney-General. In particular, the functions of the ALRC under its governing legislation include: reviewing Commonwealth law with the aim of simplifying the law; removing obsolete or unnecessary laws; and eliminating defects

in the law.¹⁸ The ALRC also has experience in undertaking extensive public consultation with key stakeholders.

Recommendation Twenty Eight

The Panel recommends that:

1. The Australian Government undertake a comprehensive review of the legislative framework underpinning the regulation of therapeutic goods, including a review of the *Therapeutic Goods Act 1989* (the Act) and associated Regulations in their entirety, with a view to simplifying its structure and language to achieve a more user-friendly approach. In doing so:
 - A. the objects clause of the Act should be amended to better reflect the public health and consumer protection outcomes that the Act aims to achieve; and
 - B. the Act should be re-drafted in such a way as to:
 - I. maximise transparency of both policies and processes;
 - II. provide flexibility for the Australian NRA to appropriately modify processes to ensure a thorough analysis of safety, quality and efficacy, while avoiding unnecessary duplication;
 - III. recognise that medicines and medical devices are very different products and should be regulated accordingly;
 - IV. provide for graduated penalties that allow the NRA to respond appropriately to the full range of non-compliance, from repeated minor breaches through to serious non-compliance;
 - V. reflect contemporary practice standards for health professionals; and
 - VI. maximise the capacity of the Australian NRA to utilise electronic transactions and to collect information once to use for multiple purposes.
2. The Australian Government consider asking the Australian Law Reform Commission to undertake the proposed review and present a report to Government and to the Parliament.

7.2.3 Organisational structure and culture

As noted in section 7.1.4 engagement and dialogue is viewed by stakeholders as an important attribute for a regulator. There is a desire for such engagement throughout the lifecycle of a medicine or medical device, with stakeholders asserting that it can enhance timeliness and predictability because:

- It assists manufacturers and sponsors to understand evidence requirements and to ensure that these are collected as part of any clinical trial.
- It helps to ensure that applications for marketing approval of a medicine or medical device are accompanied by the necessary data and information, reducing delays due to the NRA asking questions or seeking additional information.

- This is particularly the case in the devices space where there are a lot of SMEs who struggle with the complexity of classifying their device and understanding what documentation is required by the NRA, resulting in delays and additional effort in order to get their device included in the ARTG.
- During the review process, dialogue can help to resolve issues quickly by assisting both parties to understand where each party is coming from. As one pharmaceutical company executive has stated:
Post-submission, regulator consultation and access facilitates meaningful scientific discussion about questions, issues and data interpretation surrounding a dossier. As an enabler to regulatory review, this interaction can help to ensure understanding of data, allow the most efficient use of the limited number of scientific experts and reduce the bureaucracy of document reviews and quality checks.¹⁹
- Dialogue in the post-market space is also critical, especially where safety concerns emerge.

The Panel heard that in many instances there is reluctance on the part of the TGA to engage in open dialogue with sponsors. There appears to be a preference for formal engagement with sponsors, such as seeking information through letters etc, or through implementing an application audit of a medical device. While this may be a requirement under the Act, it is not necessarily conducive to timely resolution of issues. Similarly, medical device manufacturers/sponsors expressed concern that they were unable to obtain advice about regulatory requirements, instead being referred to regulatory advice agents.

Engagement is not only desired by sponsors, but also by other stakeholders with an interest in the outcomes of NRA processes. For example, the Panel was advised by a number of public health organisations that they were frustrated by the TGA's failure to engage with them on their issues. When engagement did occur it concluded with the provision of somewhat unhelpful advice.

The approach that the Panel has heard is adopted by the TGA in many instances is in distinct contrast to that of some comparable overseas regulators. For example, the FDA is prepared to actively engage with sponsors throughout the lifecycle of a medicine or medical device. It also has mechanisms in place to engage with other stakeholders through public hearings held by the FDA's advisory committees when considering whether a medicine should be approved for market. This process allows interested parties to present information and viewpoints either orally or in writing.

The Panel is unclear what the basis is for the TGA's apparent reluctance to engage with stakeholders. One issue may be concern about perceived or actual regulatory capture if the TGA delegate, or those advising the delegate, are seen to actively engage with sponsors pre and post submission of an application for registration or inclusion of a medicine or device in

the ARTG. Alternatively, it may be the result of limited staff resources, although this may be a false economy, as early engagement could reduce the need for staff to manage issues downstream. If this is an issue, it might be resolved by providing more intensive advice and support on a fee-for-service basis. A further possibility is that it is reflective of a risk-averse culture within the organisation, which has resulted in a sometimes rigid adherence to legislative requirements and a reluctance to exercise discretion.

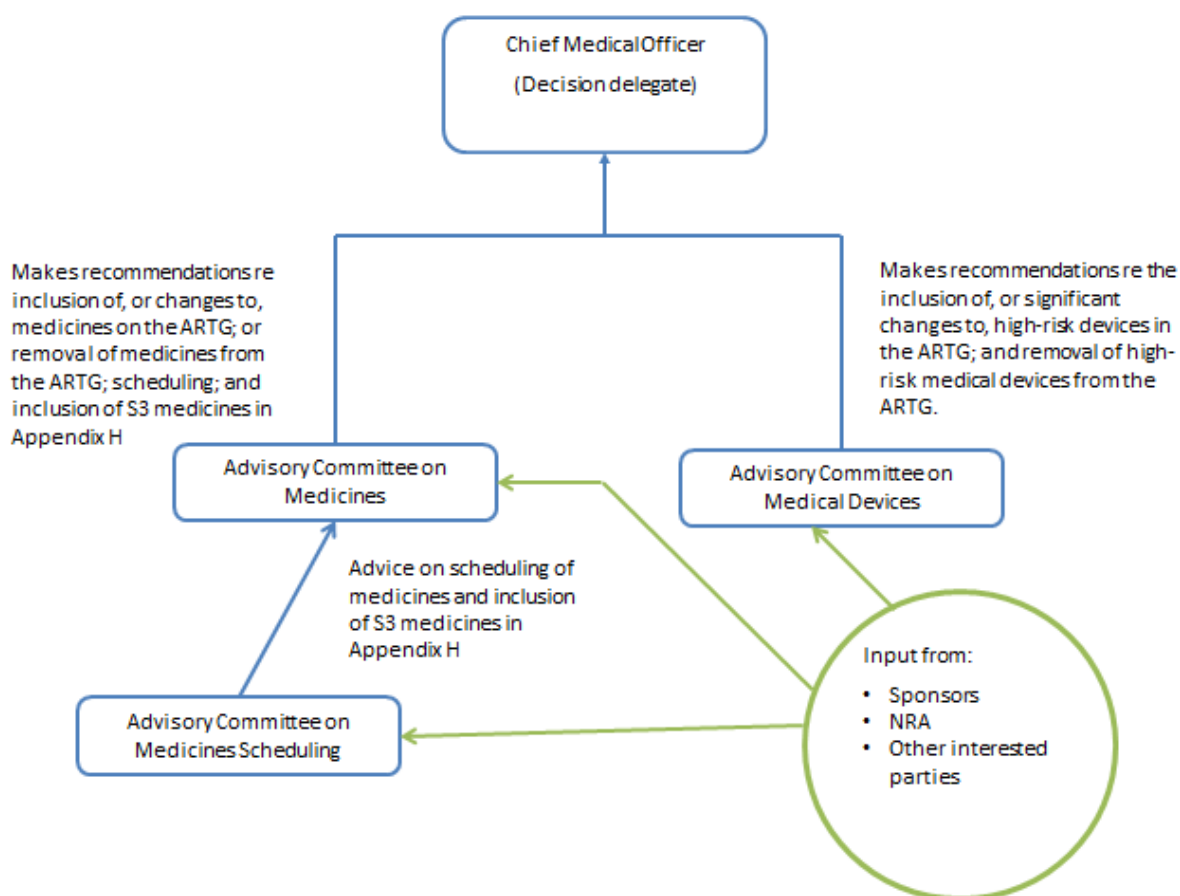
The Panel believes that some of these issues could be addressed through revising decision making arrangements for the approval of medicines and medical devices and through revised organisational structure.

7.2.3.1 Decision making arrangements

The Panel proposes that the NRA implement revised arrangements for the approval of medicines and medical devices for inclusion in the ARTG (Figure 14) which provide for:

- The delegate making decisions about the inclusion of a medicine or medical device in the ARTG to be the Australian Government's Chief Medical Officer (CMO);
- The creation of two Statutory Committees:
 - The Advisory Committee on Medicines (ACM), which will make recommendations to the CMO about: the registration of medicines in the ARTG; significant changes to medicines in the ARTG; and removal of medicines from the ARTG. It will also make recommendations regarding the scheduling of medicines and the inclusion of S3 medicines on Appendix H of the *Poisons Standard*, following consideration of advice from the Advisory Committee on Medicines Scheduling; and
 - The Advisory Committee on Medical Devices (ACMD) – which will make recommendations to the CMO about: the inclusion of high-risk devices in the ARTG; significant changes to high-risk medical devices in the ARTG; and removal of high-risk medical devices from the ARTG.
- The establishment of the Advisory Committee on Medicines Scheduling (ACMS) as a sub-committee of the ACM. The ACMS will provide advice to the ACM on the scheduling of medicines and on the inclusion of S3 medicines in Appendix H of the *Poisons Standard*.

Figure 14: Proposed decision making and advisory structures



It is proposed that the Statutory Committees (and where applicable sub-committee(s)) will be composed of experts across relevant fields and consumer representation with an appropriate skill set. The Panel notes that the FDA has a large number of such committees to provide it with advice, based on clinical specialties. This approach is impractical in the Australian context. However, the Statutory Committees should include members from a diversity of clinical, scientific, and/or engineering practice and have the ability to co-opt additional expertise if required. Discussions and deliberation on a particular medicine for a specific indication(s) should be informed by an expert in the field, who is aware of current best practice and particular management issues in relation to the medicine.

An advantage of the proposed approach is that it separates the function of evaluating applications for registration/inclusion of a medicine or medical device in the ARTG from the final decision making function. This helps to address concerns regarding regulatory capture and frees up the NRA to engage in cooperative interaction with sponsors during the evaluation process. Furthermore, the CMO is an appropriate delegate to make these decisions given his or her expertise and clinical leadership role.

In addition, the Panel proposes that the ACM; ACMD; and the ACMS have the authority to:

- Consider information submitted by the product sponsor.

- Consider evaluation reports prepared by or for the Australian NRA and comparable overseas NRAs.
- Take evidence from sponsors, the Australian NRA, and any other parties which the committees consider may have a reasonable interest in deliberations regarding the medicine or medical device.
- Take into account any other information that the committees consider may be material in their deliberations.

This model is based on the operations of the PBAC and provides an opportunity for the sponsor, the NRA, and other parties that have a legitimate interest, such as public health or consumer health advocacy bodies, to engage with, and input to, the process.

Recommendation Twenty Nine

The Panel recommends that:

1. The decision making process for the inclusion of medicines and medical devices in the ARTG be changed to provide for:
 - A. The Australian Government's Chief Medical Officer to be the delegate for decisions.
 - B. The establishment of a statutory committee to make recommendations to the Chief Medical Officer about registration of a medicine in the ARTG (Advisory Committee on Medicines).
 - C. The establishment of a statutory committee to make recommendations to the Chief Medical Officer about inclusion of a medical device in the ARTG (Advisory Committee on Medical Devices).
2. Both committees be composed of experts across relevant fields and consumer representation and have the authority to:
 - A. Consider information submitted by the product sponsor.
 - B. Consider evaluation reports prepared by or for the Australian NRA and comparable overseas NRAs.
 - C. Take evidence from sponsors, the Australian NRA, and any other parties which the committees consider may have a reasonable interest in the registration of the medication or medical device.
 - D. Take into account any other information that the committees consider may be material in their deliberations.

Scheduling decisions

Since 1 July 2010, scheduling decisions have been made by a delegate of the Secretary of the Department of Health, who may receive advice from the ACMS or the Advisory

Committee on Chemicals Scheduling depending on the type of scheduling decision. The current ACMS is comprised of nominated members from the Commonwealth, states and territories, along with up to six members nominated by the Minister. Each member of the committee has expertise in one of the following areas:

- regulation of scheduled medicines in Australia;
- toxicology or pharmacology;
- clinical pharmacology;
- pharmacy practice;
- medical practice;
- consumer health issues relating to the regulation of therapeutic goods; and
- industry issues relating to regulation of therapeutic goods.²⁰

While a number of stakeholder submissions expressed the view that the new arrangements had improved efficiency, others argued that they had lengthened the process and left a policy vacuum. Further, there remain concerns about the lack of clarity regarding the role of the ACMS, as well as poor integration between scheduling and registration processes.

In order to better integrate these processes the Panel proposes that the ACMS become a sub-committee of the ACM. The ACMS would make recommendations to the ACM about the scheduling of medicines and about the inclusion of an S3 medicine on Appendix H of the *Poisons Standard* (and any conditions on this inclusion). Having considered these recommendations, the ACM would make recommendations to the CMO.

In the Panel's view, this approach will:

- Ensure that decisions on scheduling of medicines and on advertising of S3 medicines are made with proper input from relevant areas of expertise (for example, pharmacy practice, industry, consumers);
- Maintain appropriate representation of states and territories, recognising that scheduling is a multi-jurisdictional area of regulation; and
- Ensure that there is proper integration and harmonisation of scheduling decisions with registration decisions.

In addition, the capacity for the sub-committee to take evidence from interested parties will provide for greater engagement by stakeholders in the scheduling process.

Recommendation Thirty

The Panel recommends that the Advisory Committee on Medicines Scheduling (ACMS) become a subcommittee of the Advisory Committee on Medicines and make recommendations to that Committee about the:

1. Scheduling of medicines; and
2. Inclusion of medical substances in Appendix H of the Poisons Standard.

7.2.3.2 Organisational structure

As discussed in Chapter Two, the regulatory activities that are conducted by the NRA are only one aspect of the regulation of medicines and medical devices. At the Commonwealth level, in addition to the assessment of therapeutic goods for market access by the NRA, health technology assessments are undertaken to inform reimbursement decisions. While the NRA assessment is focused on safety, quality and efficacy, health technology assessments for reimbursement purposes focus on comparative effectiveness (and also cost-effectiveness). These analyses of effectiveness and relative effectiveness draw on similar datasets and are conducted by staff or consultants with the same technical skill sets. There are, therefore, significant synergies between the pre-market regulation of medicines and medical devices and health technology assessment of these products for subsidy purposes.

Similarly the NRA and the subsidy programmes both have an interest in the performance of medicines and medical devices once they are available on the Australian market. Traditionally the NRA has primarily focused its post-market monitoring on safety but, as described in section 7.2.1 provisional approvals of medicines and medical devices will require it to monitor both the safety and efficacy of these products. This will potentially result in duplication, as subsidy programmes undertake activities to examine the efficacy of subsidised medicines.

Given the significant crossover that exists between the health technology assessment activities of the NRA and those associated with Australian Government subsidy programmes, the Panel believes there would be benefits in considering organisational structures that facilitate improved integration of these functions across the lifecycle of medicines and medical devices.

One such approach might be to draw together health technology assessment activities into a single structure, such as a centre for excellence (which could be virtual or actual). This centre would undertake health technology assessments for the Australian Government, which would be nuanced for the particular purpose. For example; it may write an assessment report about the safety, quality and efficacy of a New Chemical Entity (NCE), which the NRA would put before the ACM; and also develop a report on the comparative

efficacy of the NCE compared to the comparative treatment option, which the Department would put before PBAC. Similarly, the centre could undertake post-market monitoring of medicines and medical devices for both safety and efficacy, utilising linked datasets and other data sources as described in section 7.2.1.1.

The Panel sees a number of advantages of such an approach:

- It would create economies of scale and prevent Australian Government bodies competing for the same limited skill set.
- It would provide efficiencies for industry in terms of data submission and utilisation, as data dossiers submitted for pre-market approval processes would be available for other purposes (with the consent of the sponsor), thus reducing the need to submit data on multiple occasions.
- It would create opportunities for industry to engage jointly with staff responsible for both pre-market assessments and subsidy assessments of therapeutic goods. Because the data requirements for these two assessments may differ, advice provided separately may at times appear to be conflicting. Joint dialogue will ensure an alignment between, or better understanding of, requirements of the two assessment processes.²¹
- It would serve to further separate the health technology assessment process from decision making regarding market access and subsidy, reducing any perceived conflict of interest in staff engaging in a cooperative interaction with sponsors during the evaluation process.

Recommendation Thirty One

The Panel recommends that the Australian Government give consideration to organisational structures that will facilitate improved integration of:

1. Pre-market regulation of medicines and medical devices with health technology assessment of these products for subsidy and other purposes; and
2. Post-market monitoring of medicines and medical devices for safety, efficacy and cost-effectiveness.

7.2.4 Future funding models

In implementing reforms to the regulation of medicines and medical devices, it will be essential that the necessary operational and organisational support and resources are available throughout the reform process. In particular, an initial injection of capital to support enhanced post-market monitoring, particularly the development of a linked dataset, will be critical. The potential savings across the health system that can be realised if Australia enhances its capacity to identify safety and efficacy issues quickly are significant. Furthermore, such a dataset would have broader application in terms of the quality use of medicines.

The Panel has particular concerns about the sustainability of the NRA under a full cost recovery model once its recommendations are fully implemented. The operations of the NRA are fully cost recovered from industry, including the activities that it undertakes in the public good. Such activities include programmes designed to improve individual patient outcomes, as well as broader public health. These programmes have flow on effects across the health sector, reducing unnecessary utilisation of the primary and tertiary care sectors. Examples of activities that the Australian NRA undertakes in the public good include:

- Provision of a fee waiver for registration of orphan drugs in Australia. Orphan drugs are medicines, vaccines or *in vivo* diagnostic agents that are intended to treat, prevent or diagnose a rare disease. There are around 8000 known rare diseases, 80 per cent of which affect children. Most start in childhood and continue throughout life and many result in neurological and intellectual disabilities that can result in loss of independence and opportunities.²² As such, access to appropriate diagnosis, prevention and treatment agents is essential.
- The Special Access and Authorised Prescriber schemes, which provide patients with access to medicines and medical devices that are not available in Australia, including potentially life-saving oncology drugs. This includes medicines that are highly appropriate for the patient's needs, but which have been withdrawn from Australia, or never registered in Australia as a result of commercial decisions by the sponsor.
- Provision of information, education and advice to industry, health professionals and consumers about the regulation of medicines and medical devices, including provision of information and advice on adverse events and the management of medicines shortages.

This is a unique situation internationally, with comparable overseas regulators partially funded by their respective governments, in recognition of their critical public health role. The proportion of government funding provided to these organisations varies from around 14 to 50 per cent, depending on the regulator (Table 7 refers).

Table 7: Funding of International Medicines Regulators

Australia (TGA)	United States (FDA)	European Union (EMA)	Canada (Health Canada)
100% cost recovery from industry	Approximately 50 % cost recovered from industry Remaining 50 % funded by government	86% cost recovered from industry Remaining 14% of funding from EU	Approximately 50% cost-recovered from industry (increased in 2011 from 25%) Remaining 50% funded by the Canadian Government

Impact of proposed changes

The Panel is concerned that, in the absence of a commitment of government funds, the changes that it has proposed to the regulatory framework for medicines and medical devices, particularly those relating to use of overseas assessments, may (a) be compromised; and (b) may compromise the capacity of the Australian regulator to continue to undertake activities in the public good.

The Panel's concerns are based on the following:

1. Organisations need a critical mass in order to function efficiently and effectively.
2. Highly expert and technical organisations such as the NRA cannot upsize and downsize quickly.
3. In paying for the NRA's services industry, not unreasonably, has an expectation that, in the face of limited resources, the NRA will prioritise the delivery of the services for which it has been paid.
4. Some of the NRA's costs are relatively fixed, such as those relating to the provision of effective IT and related infrastructure.
5. Cost recovery fees cannot exceed a certain price point without acting as a deterrent to sponsors to register and/or maintain their product in the ARTG.

A number of the Panel's recommendations, such as those related to use of overseas assessment reports and modified fee structures for different types of assessment, have the potential, depending on their uptake, to result in significant reductions in workload and funding of the NRA. The degree of uptake is likely to be highly unpredictable in the first years of implementation.

Reductions in de novo evaluations and introduction of abridged assessments for some variations will result in a reduction in NRA staffing needs, primarily highly skilled medical and scientific staff who will be difficult to replace if the need arises, especially quickly. Such a reduction, if significant enough, may undermine the NRA's capacity to:

- respond to sudden increases in workload, resulting in less timely evaluations of medicines and medical devices, thereby undermining one of the aims of the Review;
- respond to emerging public health issues, such as the need to undertake recalls, manage medicine shortages, or manage major non-compliance. In these instances, resourcing would need to be redirected from other core business, which in turn will translate into reduced timeliness and responsiveness; and
- undertake evaluations of orphan drugs or process applications for access to unregistered medicines in a timely way.

Where capacity issues arise, the focus of the NRA will be on delivering its core regulatory functions and meeting statutory timeframes for these functions. Activities such as guideline

development, horizon scanning, and the provision of education and advice to industry, health professionals and consumers are likely to suffer. As a result inefficiencies within the system will continue.

In addition, the costs of some essential infrastructure are relatively fixed. For example, a well-designed and highly functioning government to business IT infrastructure is critical to the delivery of timely and cost-effective regulatory services, but the costs of such a system remain relatively stable regardless of how many people are utilising the system or for what purposes. As such, if the NRA's income declines, continued investment in such systems will be at the expense of other activities.

One option to address these issues is to increase the fees and charges payable by industry. However, the Australian market is small, representing only two per cent of the global medical devices market. As such, if fees and charges are increased to the point where they are seen as unreasonable or excessive this may deter sponsors from registering and/or maintaining their product in the ARTG. This will be to the detriment of Australian consumers, who will be denied access to these medicines and medical devices.

For these reasons, the Panel is of the view that continuation of a full cost recovery model post implementation of its recommendations has the potential to undermine the Government's policy objectives, both in terms of the NRA's role in promoting the public good, but also in terms of creating a regulatory system that supports competitiveness.

The Panel considers that moving to a partial cost recovery model will ensure a more sustainable, effective and cost-effective NRA into the future. Ideally, this would be in the form of an annual appropriation to support core activities that are not directly associated with the provision of regulatory services to industry, including: activities aimed at promoting the public good, such as the orphan drug and SAS programmes; or activities associated with being a government entity, such as ministerial support and policy development. Such an approach would not be inconsistent with the Australian Government Cost Recovery Guidelines.

Alternatively, rather than an annual appropriation, the NRA could submit a new policy proposal every four years, in line with the budget cycle. This proposal could outline the activities to be funded via the government appropriation over the next four year period, allowing the government to determine its priorities. Such an approach may be appropriate in light of the fact that the impact of the Panel's recommendations on the NRA's workload and budget will not be known for some years. That is, until such time as industry familiarises itself with the proposed system and adjusts its business practices accordingly.

Recommendation Thirty Two

The Panel recommends that the Australian Government review and enhance the NRA's funding model, with a view to providing either a dedicated annual appropriation or other appropriate budgetary arrangements on an 'as-needs' or routine capacity basis, to enable it to more effectively fulfil its mandate to act in the public interest and to ensure that genuine and systemic improvements to its capacity, expertise and operation are achieved.

¹ Centre for Innovation and Regulatory Science (2011), *Emerging Markets focus study - Understanding the enablers of good regulatory process and decision making. What are the features that enable a transparent, timely, predictable and good-quality review?* Accessed online on 3 March 2015 at: <http://cirsci.org/content/november-2011-slide-month>

² Duijnhoven R.G., Straus, S.M.J.M., Raine J.M., de Boer A., Hoes A.W. & De Bruin M.L (2013, March), 'Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis', in *PLoS Med*, 10:3, p. 2.

³ *Ibid.*, Editor's summary, p. 8.

⁴ Review of Health Technology Assessment in Australia (2009, December), *Final Report*, Commonwealth of Australia, p. 102.

⁵ Wizemann T. (Ed), Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report, (2010), Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process; National Academy of Sciences, p. 50.

⁶ Food and Drug Administration Website, *FDA's Sentinel Initiative – Background*. Accessed online on 16 March 2015 from: <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm>

⁷ Psaty, B. and Breckenridge (2014, June), 'A. Mini-Sentinel and Regulatory Science – Big Data Rendered Fit and Functional', in *The New England Journal of Medicine*, 370:23 pp. 2165-2166.

⁸ Food and Drug Administration (2013, April), *Strengthening Our National System for Medical Device Postmarket Surveillance. Update and Next Steps*. Accessed online on 23 March 2015 at: <http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf>

⁹ Therapeutic Goods Administration (2011, 16 May), Recall of DePuy Orthopaedics ASR hip replacement device. Accessed online on 8 March 2015 at: <https://www.tga.gov.au/behind-news/recall-depuy-orthopaedics-asr-hip-replacement-device>

¹⁰ Review of Health Technology Assessment in Australia, op. cit., p. 101.

¹¹ Panel to Review the Transparency of the Therapeutic Goods Administration (2011, June), *Review to improve the transparency of the Therapeutic Goods Administration, Final Report*, Commonwealth of Australia, pp. 46-47. Accessed online on 13 March 2015 from: <http://www.tga.gov.au/sites/default/files/review-tga-transparency-1101-final-report.pdf>.

¹² *Ibid.*, p. 47.

¹³ Therapeutic Goods Administration (2013, July), *Evaluating the feasibility of a new-to-market risk communication scheme: Summary of themes identified by participants at the stakeholder consultation workshops*, p. 5.

¹⁴ *Ibid.*, p. 6.

¹⁵ Review of Health Technology Assessment in Australia, op. cit., p. 99.

¹⁶ Therapeutic Goods Administration, *Australian Statistics on Medicines and Vaccines 2013*, March 2014. Available at: <https://www.tga.gov.au/australian-statistics-medicines-and-vaccines-2013>.

¹⁷ Dal Pan, G and Arlett, P. (2014, December), 'The US Food and Drug Administration-European Medicines Agency Collaboration in Pharmacovigilance: Common Objectives and Common Challenges', in *Drug Safety*, Volume 38, p. 13

¹⁸ *Australian Law Reform Commission Act 1996* (Cth), section 21.

¹⁹ O'Malley P.J., 'Company viewpoint: Examples of practices that have enabled or hindered the review', in Centre for Innovation in Regulatory Science, (2012, April), *Evolving the Regulatory Review Process: What are*

the features that enable a transparent, timely predictable and good-quality review? Workshop Report, 6-7 December 2011, Kuala Lumpur, Malaysia, p. 31.

²⁰ Australian Health Ministers' Advisory Council (2015, 1 February), *Scheduling Policy Framework for Medicines and Chemicals*, p. 8. Accessed online on 5 March 2015 from: <https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals>

²¹ Centre for Innovation in Regulatory Science (2011, March), *Optimal times for between agency dialogue*, Accessed online on 15 March 2015 at: <http://cirsci.org/content/march-2011-optimal-times-between-agency-dialogue>

²² Rare Disease Day Australia website. *What is a rare disease webpage*. Accessed online on 23 March 2015 at: <http://www.rarediseasedayaustralia.com.au/what-is-a-rare-disease/>

APPENDIX A: SUBMISSIONS RECEIVED

AbbVie Pty Ltd
Accord Australasia
ACON
Advertising Standards Bureau
Advisory Committee on Prescription Medicines
Alexion Pharmaceuticals Australasia
Applied Medical
Arnold, Bruce and Bonython, Dr Wendy
Assistive Technology Suppliers Australasia Inc
Astroglide Pty Ltd
AusBiotech
Australasian Association of Nuclear Medicine Specialists
Australasian Health Manufacturers and Development Association Inc
Australasian Sleep Association
Australasian Society for HIV Medicine
Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
Australian Academy of Technological Sciences and Engineering
Australian College of Pharmacy
Australian Dental Association
Australian Dental Industry Association
Australian Federation of AIDS Organisations
Australian Medical Association
Australian Nuclear Science and Technology Organisations
Australian Orthopaedic Association
Australian Red Cross Blood Service
Australian Self Medication Industry

Baxter Healthcare Pty Ltd
Bayer Australia Ltd
Beiersdorf Australia Limited
Biomet Australia
BioPharma Strategic Regulatory Services
Bristol-Myers Squibb Australia Pty Ltd
BSI Group
Bupa

Cancer Drugs Alliance
Chinese Medicine Board of Australia
Cochlear Limited
Commercial Eyes Pty Ltd
Commonwealth Director of Public Prosecutions
Complementary Medicines Australia
ConMed Australia
Consumers Health Forum of Australia
Cook Medical Australia

CSL Limited
Customer Focus Pty Ltd

Diabetes Australia

Edwards Lifesciences Pty Ltd
Ensign Laboratories Pty Ltd

Gardini, Robert
Generic Medicines Industry Association
Global Orthopaedic Technology Pty Ltd

Haemophilia Foundation Australia
Health Consumers' Council of WA
Hospira Pty Ltd

IAA Medical Pty Ltd
IVD Australia

Johnson & Johnson Pty Ltd

Locus Consulting Pty Ltd
Lucire, Dr Yolande
Ludbrook, Professor Guy

Medibank
Medical Device Research Australia Pty Ltd
Medical Oncology Group of Australia Incorporated
Medical Technology Association of Australia
Medicines Australia
Medtronic Australasia
Merck Sharp & Dohme
Montrose Pharma Pty Ltd

National Association of People with HIV Australia
National Committee on Rehabilitation Engineering (Engineers Australia)
National LGBTI Health Alliance
National Tuberculosis Advisory Committee
Novartis Pharmaceuticals Australia Pty Ltd
NSW Therapeutic Advisory Group/The Society of Hospital Pharmacists of Australia

Ong, Dr Keith

Pagram, Ross
Pfizer Australia (non-prescription medicines)
Pfizer Australia (prescription medicines)
Pharmaceutical Society of Australia

Review of Medicines and Medical Devices Regulation

Pharmacy Board of Australia
Phillips, Bianca and Daly, Angela
Private Healthcare Australia
Public Health Association of Australia

Rare Voices Australia Ltd
Reckitt Benckiser Australia Pty Ltd
Ross Cosmetics Aust Pty Ltd
Roughead, Professor Libby

Sless, David
St Jude Medical Australia Pty Limited
Stellar Consulting Pty Ltd
Stryker South Pacific

The Communications Council
The Pharmacy Guild of Australia
The Royal Australasian College of Physicians
The Royal Australian and New Zealand College of Ophthalmologists
The Royal Australian and New Zealand College of Psychiatrists
The Royal College of Pathologists of Australasia
Thomas, Julie

Varian Medical Systems Australasia
Victorian AIDS Council
Vitry, Dr Agnes

Wale, Dr Janet

APPENDIX B: CONSULTATIONS WITH STAKEHOLDERS

6 November 2014

Juliet Seifert

12 November 2014

Stakeholder Forum, Sydney

Accord Australasia

AusBiotech

Australasian Health Manufacturers and Development Association

Australian Commission of Safety and Quality in Health Care

Australian Dental Industry Association

Australian Food & Grocery Council

Australian Nuclear Science and Technology Organisation

Australian Self-Medication Industry

Cancer Voices Australia

Complementary Medicines Australia

Consumers Health Forum of Australia

Generic Medicines Industry Association

Kidney Health Australia

Medical Technology Association of Australia

Medicines Australia

Pharmaceutical Society of Australia

Private Healthcare Australia

Rare Voices Australia

The Pharmacy Guild of Australia

17 November 2014

John Jackson

25 November 2014

Australian Therapeutic Goods Advisory Council

26 November 2014

Generic Medicines Industry Association

12 December 2014

Arthritis Australia

Australian Commission of Safety and Quality in Health Care

Australian Self Medication Industry

Cancer Council Australia

Rare Voices Australia

Rhonda White

18 December 2014

Accord Australasia
Advisory Committee for Prescription Medicines
Medical Technology Association of Australia
Medicines Australia
The Society of Hospital Pharmacists of Australia

22 December 2014

Cancer Australia

19 January 2015

Consumers Health Forum of Australia

28 January 2015

Australian Dental Industry Association
IVD Australia

3 February 2015

Hospira

4 February 2015

Australian Medical Association
National E-Health Transition Authority
Pharmaceutical Society of Australia
The Pharmacy Guild of Australia

5 February 2015

Advisory Committee on the Safety of Medicines
Cancer Australia Intercollegiate Advisory Group
National Industrial Chemicals Notification and Assessment Scheme

13 February 2015

Consumer Forum, Sydney

ACON
Australian Federation of AIDS Organisations
National Association of People with HIV Australia
National LGBTI Health Alliance

19 February 2015

AusBiotech

19 February 2015

Consumer Forum, Melbourne

Consumers Health Forum of Australia

DES Action

Diabetes Australia

Health Issues Centre (Victoria)

Ovarian Cancer Australia

Victorian AIDS Council

19 February 2015

Health Consumer Peak Bodies

Consumers Health Forum of Australia

Health Care Consumers Association of ACT

Health Consumers Alliance of SA

Health Consumers' Council (WA)

Health Issues Centre (Victoria)

23 February 2015

Australasian Association of Nuclear Medicine Specialists

27 February 2015

Cochlear Limited

In addition to these formal consultations, individual Panel members had a number of informal discussions with stakeholders and their representatives.