Australian Government

Australian Pesticides and Veterinary Medicines Authority

REPORT 1: EMPLOYMENT OF RISK PROPORTIONATE CHEMICAL REGULATORY REGIMES IN AUSTRALIA AND SELECTED INTERNATIONAL JURISICTIONS

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First Draft (for comment)

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Employment Of Risk Proportionate Chemical Regulatory Regimes in Australia and Selected International Jurisdictions

February 2015

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Abbreviations

Abbreviation	Expansion
ACERA	Australian Centre of Excellence for Risk Assessment
AI	Active Ingredient
ARTG	Australian Register of Therapeutic Goods
CAB	Conformity Assessment Body
CSP	Continuous Sampling Plan
EC	European Council
EMA	European Medicines Agency
FDA	Food and Drug Administration of the United States of America
FICA	Food Import Compliance Agreement
FSANZ	Food Standards Australia New Zealand
GAP	Good Agricultural Practice
GHS	Globally Harmonised System (of hazard classification)
HHRA	Human Health Risk Assessment
IFIS	Imported Food Inspection Scheme
MRL	Maximum Residue Level
NAMW	Number Average Molecular Weight
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
OECD TG	Test Guidelines of the Chemicals program of the Organisation for Economic Cooperation and Development
OTC	Over the Counter Medicine
PBT	Persistent, Bio-accumulative and Toxic
PCP	Pest Control Product
PLC	Polymer of Low Concern
PMRA	Pest Management Regulatory Agency
PPP	Plant Protection Product
QMS	Quality Management System
QSAR	Quantitative Structure Activity Relationship
RM	Risk Management
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
TGA	Therapeutic Goods Administration
TSE	Transmissible Spongiform Encephalopathy
URMULE	User Registered Minor Use Label Expansion
VOI	Value of information
vPvB	very Persistent, very Bioaccumulative

1 Executive Summary

- This paper provides an overview of the application of risk proportionate regulatory processes for chemicals regulated in Australia and provides a high level review of regulatory risk stratification in Canada, the USA and EU, focussed primarily on agricultural products, with a brief overview of the NZ approach.
- For Australia, the overview covers the approach taken by the Therapeutic Goods Administration (TGA), National Industrial Chemicals Notification and Assessment Authority (NICNAS) and Food Standards Australia New Zealand (FSANZ). The medical devices regulatory regime of the TGA is also described as it provides a range of examples of a risk proportionate regulatory approach and the use of the output of international regulatory agencies to streamline regulatory processes.
- Although there are substantial conceptual, and legislative, differences between the structure and scope of the various regulatory regimes for chemicals in Australia, and none of the other regulatory systems reviewed is directly equivalent to that of the APVMA, all have elements, or cover products &/or ingredients, that are similar to a greater or lesser degree.
- The establishment of a risk proportionate regulatory framework involves the consideration of a number of sources of risk including that arising from; the capabilities of the applicant(s), the nature of the regulated commodity, and the intended end user. Each of these sources of risk require consideration in the design of proportionate regulatory structures.
- An outline of the risk based approach of the Imported Food Inspection Scheme (IFIS) and the underlying basis for that approach is also provided. The relevance of the IFIS is that it provides a strategy to establish trust and confidence in individual importers, with regulatory intervention decreased, or increased, based on the outcomes of that confidence building (the results of inspections and testing).
- The principle conclusion of the review of the Australian agencies is that each has developed regulatory pathways for what they deem to be low risk, or well characterised, products &/or substances they regulate, with the intention of reducing the time, cost and data required for their regulation. These pathways and concessions include:
    - Exclusion of substances/products or classes of substances/products from regulation by that regulator,
    - Exemptions from some or all otherwise applicable regulations or regulatory requirements for assessment and approval, but retention of the product or substance within the scope of that regulators oversight,

    - Self-assessment of products or ingredients by the applicant/sponsor/notifier or supplier/manufacturer/importer
        - With scope for random or targeted compliance audits,
    - Desk audit, without technical assessment, of the compliance with specific regulatory requirements,
    - Graduated risk based regulatory requirements and technical assessment for higher risk products/ingredients,
    - A fee and assessment time proportionate to the level of regulatory oversight and risk applicable to classes of products/ingredients,
    - Various levels of recognition, and use, of international assessments for a subset of products/ingredients covered by the regulator.
- A range of options and opportunities potentially available to the APVMA for reducing the regulatory burden on sponsors by improving risk proportionality of regulatory requirements are identified and presented for consideration including:
    - Exemptions, self-assessment and listing
        - For classes of products that are either inherently low risk or which have extensively characterised and well defined risks and use patterns.
    - A Product Monograph approach
        - Where a large number of products with similar or identical actives and approvals for use are, or are likely to become, available.
    - Recognition and use of existing approvals in other Australian or International regulatory schemes
        - Where high quality technical assessments are available from trusted National and/or international authorities.
- The efficient and effective operation of a streamlined and risk proportionate regulatory framework is likely to require the development of a mechanism for building and maintaining confidence in the technical capacity, and willingness, of applicants and/or their advisors to reliably comply with their obligations under a risk proportionate model.

Employment of Risk Proportionate Chemical Regulatory Regimes in Australia and Selected International Jurisdictions

2 Introduction

The APVMA has initiated a series of projects to support a review and modernisation of its regulatory processes. A key aspect of this process is a consideration of the strategies available for allocating resources to aspects of their regulatory roles and responsibilities in a manner that achieves the greatest benefit for stakeholders and best fulfils its mission "To protect the health and safety of people, animals and crops, the environment, and trade, and support Australian primary industries through evidence-based, effective and efficient regulation of pesticides and veterinary medicines".

As one component of this series of projects BartCrofts Scientific Services Pty Ltd was commissioned to provide an overview of the application of risk proportionate approaches in the regulation of chemicals, and related products and substances, by Australian and selected international regulators, as described by those regulators, and identification of potential approaches that might be usefully considered by the APVMA for application in its regulatory roles. Risk proportionate approaches in this context includes the level of regulatory evaluation, data requirements, time lines for evaluations and fees charged to applicants. The APVMA has established procedures for monitoring adverse outcomes from the range of products it regulates and is well positioned to assess the relative risks of the various types of products, arising under its current regulatory approach and to monitor changes in the risk profile following implementation of any changes in its regulatory approach flowing from the review of its current processes. Similarly the risk assessment practices of the APVMA and supporting agencies is under constant review and benchmarking against international best practice. Consequently, the scope for this review does not include an independent assessment of the magnitude or nature of the risks regulated by the agencies reviewed, the success, limitations or proportionality of the approaches employed in terms of managing those risks, except where issues of implementation are known, or an evaluation of the hazard or risk assessment processes themselves.

The stratification of risk and the application of regulatory regimes intended to be proportionate to those risks is a common attribute of a broad range of Australian regulatory systems. This approach applies to medicines and medical devices within the Therapeutic Goods Agency (TGA), industrial chemicals and cosmetics within the National Industrial

Chemicals and Assessment Scheme (NICNAS), food ingredients under Food Standards Australia New Zealand (FSANZ), and inspections of food at the border by customs, as examples. The procedures and requirements associated with the various risk categories established by each agency can be quite complex, to ensure precision of capture and exclusion within those categories. Consequently, the overview which follows is necessarily high level in nature, although including sufficient detail and depth to enable a consideration of the potential suitability of the approaches discussed to the regulatory model of the APVMA.

3 Regulatory Overlap

Although not covered in detail in this review, regulatory overlap is an important consideration when designing a risk proportionate, and efficient, regulatory system. The regulatory system for chemicals in Australia and internationally is based on a somewhat facile division of chemicals into regulatory categories; as medicines for human use, medicines for veterinary use, industrial chemicals & cosmetics, agricultural chemicals and food chemicals. In practice chemicals do not fall neatly into such categories and the same substance is likely to be captured under multiple schemes. Triclosan, an antiseptic and disinfectant finds, or has found, use in such widely divergent applications as an industrial antimicrobial, a cleansing or preserving agent in cosmetics, a disinfectant in medical soaps and in a range of consumer goods such as clothing and bedding (NICNAS 2009). Many cosmetic ingredients are used in topical pharmaceuticals and many surfactants are used in a wide range of cosmetic, agricultural, pharmaceutical, veterinary and industrial applications. Flavouring, sweetening and colouring ingredients are used in pharmaceuticals, foods, and veterinary applications to identify but a few of the myriad examples.

A consequence of this overlap is the asymmetric availability of safety data across the regulatory agencies and a largely haphazard and ad hoc sharing of that information. Opportunities exist for a more streamlined approach to overlap substances that avoids repetitive, duplicative, and often incomplete evaluation of these substances. As an initial step, an IT solution that at the least provides visibility of assessments and data sets available across the regulatory divisions, would be valuable. Implementation of a system that ensures all chemicals regulators have visibility of previously submitted human and environmental safety data has the potential to support a reduction of regulatory burdens and resource requirements across the chemicals regulators collectively while opening opportunities to reduce duplicative regulatory requirements on industry.

4 Therapeutic Goods Administration (TGA)

The TGA regulates therapeutic goods through a combination of pre-market assessment, post-market monitoring, enforcement of published standards, licensing of Australian manufacturers and verification of overseas manufacturers' compliance with Australian requirements.

Therapeutic goods are traditionally divided broadly into two classes, medicines and medical devices, with a third category of biologicals (goods made from or containing human cells or human tissues), a more recent addition that is not considered in this review. Medicines must be entered as either 'registered' or 'listed' medicines and medical devices must be 'included' on the Australian Register of Therapeutic Goods (ARTG) before they may be supplied in or exported from Australia, unless explicitly exempted. As discussed further below the terms “listed”, “registered”, “included” and “exempt” have quite specific regulatory meanings and represent clear differentiation of, and regulatory imposts on, categories of therapeutic goods on the basis of anticipated risk. Because both the risks and the benefits associated with the use of therapeutic goods accrue to the same individual and are essentially inseparable, the TGA regulates therapeutic goods on the basis of a risk benefit paradigm.

4.1 Environmental Risk Assessment

Although various groups have raised concern over the potential environmental risks posed by pharmaceuticals, and agencies such as the European Medicines Agency (EMA) (EMA, 2006) and the US Food and Drug Administration (FDA) (FDA, 1998) have guidance on environmental risk assessment of Pharmaceuticals, the environmental risk management options are essentially limited to rejection or labelling advice on responsible disposal. Given the limited range of risk management options and recognising that rejection of applications for new pharmaceuticals for individual human or animal use on the basis of environmental risk is unlikely to be defensible the FDA has implemented a range of explicit (categorical) exclusions from the requirements of environmental risk assessment for a range of veterinary pharmaceuticals including all veterinary drugs for individual animals provided under prescription, 21CFR25.33 (FDA, 2014).

To maintain consistency with international standards, and to reduce the resource requirements necessary for the development of comprehensive medicines guidelines, the TGA adopts where appropriate the European guidelines of the European Medicines Agency (EMA). Those guidelines not adopted are identified on the TGAs web site. With respect to

environmental risk assessment **the TGA has explicitly not adopted the EMA** "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use". Similarly the TGA also not perform environmental risk assessment on products regulated as medical devices.

4.2 Risk Proportionate Regulation

Therapeutic goods are broadly divided into medicines and devices, although this distinction may be blurred where devices incorporate one or more medicines, or where medicines are supplied in conjunction with a device for administration. Risk stratification for regulatory purposes occurs within each of these broad divisions as discussed under those headings below. Conceptually, two further risk based categories can be identified as exempt and excluded goods which are explained immediately below.

4.2.1 Exempt and Excluded Goods

Exempt Goods The TGA has the power to exempt therapeutic goods from the requirement for premarket assessment and inclusion on the ARTG, and other aspects of the Act and Regulations, where it believes such goods are of low risk both in terms of safety and efficacy/indication. Exempt goods remain subject to other aspects of the Therapeutic Goods Act as specified by the TGA. Examples of exempt therapeutic goods include some disinfectants, some orthopaedic devices and prostheses, extemporaneously dispensed medicines, antidandruff shampoos and many homeopathic medicines. See for example http://www.tga.gov.au/pdf/dr4-appendix-08.pdf and http://www.tga.gov.au/industry/cm-argcm-part-a-05.htm#homoeopathic-medicines

For all exempt goods the TGA remains the responsible regulator. Consequently the exemption of goods from aspects of the act and regulations may carry some organisational and reputational risks which require careful management and consideration of those potential risks prior to the granting of exemptions.

Excluded Goods The TGA has the power to exclude goods from the operation of the Therapeutic Goods Act and regulations by declaring them not to be therapeutic goods for the purposes of the ACT. Examples of goods that have been so declared are:

- hair bleaches, hair dyes, hair-colorants or hair-perming preparations;
- household and personal aids, or furniture and utensils, for people with disabilities;
- menstrual pads other than tampons;
- incontinence pads, mattress overlays or mattress protectors;
- dental bleaches or dental whiteners;
- preparations that are applied topically to the nails to harden, or to deter biting of, the nails;

- compressed gases when supplied for use as a power source for medical devices;
- piped medical gas systems installed to comply with AS 2896-1998/Amdt No. 1-1999 : Medical gas systems - Installation and testing of non-flammable medical gas pipeline systems;
- disinfectant and sterilant gases;
- equipment for use in the purification or treatment of drinking water;
- sanitation, environmental control or environmental detoxification equipment;
- goods for the measurement of alcohol level either in body fluids or exhaled air;
- goods related to colostomy and ileostomy that are adhesive removers or non-medicated skin cleansers;
- goods for retail sale to the ultimate consumer for retention, cushioning or repairing of dentures;
- fresh viable human organs, or parts of human organs, for direct donor-to- host transplantation and used in accordance with applicable laws and standards;
- fresh viable human haematopoietic progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution;
- human tissue and cells that are:
    i. collected from a patient who is under the clinical care and treatment of a medical practitioner registered under a law of a State or an internal Territory; and
    ii. manufactured by that medical practitioner, or by a person or persons under the professional supervision of that medical practitioner, for therapeutic application in the treatment of a single indication and in a single course of treatment of that patient by the same medical practitioner, or by a person or persons under the professional supervision of the same medical practitioner;
    iii. reproductive tissue for use in assisted reproductive therapy

Goods may also be conditionally excluded, for example;

- Deodorant preparations
    - Use for dermal application or with therapeutic devices
- Unmedicated dental chewing gums
    - If benefits claimed to result for the use of the goods are restricted to those consequential on improvements to oral hygiene
- Soap and detergent, other than medicated soap and medicated detergent
    - Use for skin cleansing or hair cleansing
- Non-sterile protective or safety apparel or equipment
    - Use in the home or for occupational or recreational use
- Anti-acne skin care products (including spot treatments, cleansers, face scrubs and masks
    - If presented as controlling or preventing acne only through cleansing, moisturizing, exfoliating or drying the skin

Goods excluded from the operation of the Act cease to be the regulatory responsibility of the TGA. (Although in practice this tends to be correct there are exceptions such as the case of tampons where incidents of toxic shock syndrome associated with tampons resulted in their re-regulation.) Where another regulator has appropriate jurisdiction, excluded goods then become that regulators responsibility. Hair dyes for example, once excluded by the TGA become subject to regulation by NICNAS. **Because excluded goods become subject to other regulatory regimes the process of exclusion may not necessarily reduce the regulatory burden on manufacturers/suppliers of those goods.**

4.3 Medicines

Medicines that are neither exempt nor excluded are regulated as either "listed" or "registered" dependent on the assessed level of risk the medicine presents to consumers. Risk in this context includes risks related to safety, those related to therapeutic failure, and those associated with the seriousness of the condition being treated. The level of regulatory control applied by the TGA increases with the level of risk associated with the use of the medicine, Figure 1.

Risk management options available to the TGA include restrictions on supply and point of sale (eg prescription only, pharmacy only, general sale), labelling (including the detailed prescriber information), restriction of therapeutic indications, identification of contraindications, and ongoing monitoring and reviewing of risks over time.

4.3.1 Recognition of international assessments

Under section 16C(4) of the therapeutic goods regulations, for a product containing a new chemical entity, where an applicant is able to provide evaluation reports from 2 countries, that have been assessed by the TGA as suitable, on the same product as that to be registered in Australia a reduced evaluation time line of 175 days (compared to 225 days) applies. In practice applicants are rarely able to obtain complete evaluation reports from 2 agencies partly because applications tend to be made simultaneously across major regulatory jurisdictions and partly because some agencies such as the FDA do not provide these to applicants.

4.3.2 Self-Assessable variations.

Some minor, low risk, variations to the ARTG entry are self-assessable by the sponsor of the goods. Examples of self-assessable variations include changes to; the manufacturing site for an active ingredient, assay & test methods, narrowing the limits for purity etc of actives or excipients, packaging materials and pack sizes, shelf life variations. Various conditions and limits are placed on the allowable self-assessable variations.

4.3.3 Harmonised data Requirements

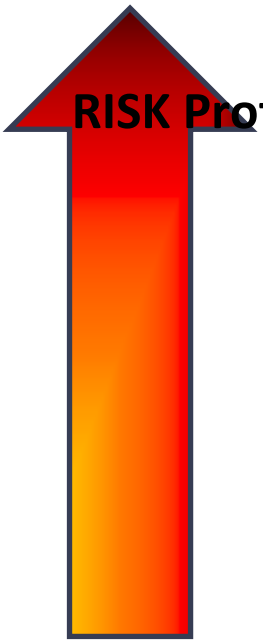
The TGA has largely harmonised its data requirements for specific categories of registered medicines with those of the EMA with some variations as documented on its web site.

4.3.4 Registered Medicines

Registered medicines are higher risk medicines that require rigorous evaluation of quality, safety and efficacy of each product individually. Sponsors are required to provide comprehensive data sets to support these evaluations. All prescription medicines, most over the counter medicines (OTCs) and some complimentary medicines are registered. Once approved these medicines are entered onto the ARTG and are assigned an "Aust R number" which must be shown on the label of the product. Registered medicines are further divided through the use of scheduling mechanisms into higher risk medicines which are prescription only and lower risk medicines which are non-prescription. Non-prescription medicines may be further risk categorised as Pharmacy Only, Pharmacist Only or general supply, through the medicines Scheduling mechanism. Over time, as clinical experience is obtained and confidence in the safety of prescription medicines is increased, some may be rescheduled to non-prescription or even to general sale, eg dermal antifungal creams and antibiotic eye ointments, and some oral analgesics such as naproxen.

Data Requirements, processing times and fees may vary according to the nature of a registered product and the availability of credible international assessments although, with the exception of orphan drugs, variation from the default requirement for a full data set is minimal for most registered, prescription medicines.

Figure 1 TGA Risk Based Regulation of Medicines and ARTG Entry



ARTG Entry	Designated Risk Category	Product types	Exceptions	Product Markings
Registered	High risk	Prescription medicines Most OTC medicines Biologicals (blood and tissue products)		AUST R Number on packaging
Listed	Low risk	Most complementary medicines Most sunscreens	unless, the product Contains scheduled substance/s, is a Sterile preparation or is Intended for substantial therapeutic indications	AUST L Number on packaging
Not on the ARTG	Negligible risk	Certain homeopathic preparations Some anti-dandruff products, antiperspirants and medicated insect repellents. Cosmetics type products		No indication on packaging

The TGA has a necessarily complex and detailed fee structure which recognises the various levels of assessment required for the multiple levels of applications it processes ranging from minor alterations to non-active ingredients (excipients), inclusion of additional therapeutic indications for existing medicines, registration of generic products etc.

Orphan drugs are medicines intended to treat rare medical conditions where there are insufficient patients to sustain a commercially viable research program that would yield the full data set normally required for a new chemical entity. Reduced data requirements and fees apply to these applications provided the TGA supports the orphan designation and is a means of managing the risk that therapies for rare conditions might otherwise be unavailable.

4.3.5 Registered Over The Counter Medicines (OTC)

The TGA applies a risk based approach to the regulation of therapeutic goods including OTC medicines based on the principles of ISO 31000:2009. OTC medicines are those that are available to the public without prescription. For OTC medicines the TGA applies five risk levels for new OTC products, designated N1 through N5, and for changes to an existing medicine four risk levels are applied, designated C1 through C5, Table 1. Data requirements and evaluation time lines are determined by the risk categorisation, as shown in the following tables. Total fees are made up of a series of components the largest of which is based on the page count of the application, which in turn is determined by the data that is required to be submitted. As the data requirements are determined by the risk categorisation, the fees are also broadly proportionate to the risk categorisation.

Table 1 New OTC Product Risk Categories for Assessment.

Application level		Target* evaluation time	# Requests for Information (RFI)	Sponsors respond to the RFI	Conditions
N1	Clones (a product that is identical in all safety and efficacy respects to an existing fully evaluated medicine) flavour/fragrance/colour variants	45	1	5	Parent product fully evaluated for safety, efficacy and quality [ie not 'grandfathered'] Parent product must comply with current standards, Full access to the rights of the parent product is provided.
N2	Generic medicines that fully meet a specific OTC monograph and all of the general requirements.	75	1	15	Product complies fully with the requirements of a specific OTC Medicine Monograph
N3	Generic medicines that do not require data to support the safety or efficacy of the product (eg identical to existing product)	150	2	1st – 43 2nd – 21	safety and efficacy data not required Does not include applications included in Appendix X. Quality (CTD module 3) data are evaluated in full, unless all quality aspects of the product are identical to a product which has previously been fully evaluated by the regulator - abbreviated data & assessment.
N4	Generic medicines that: – require safety and/or efficacy data or a justification for not providing data. (eg bioequivalence, safety to support a new excipient, or to support a new label claim.) - have not been previously evaluated as an OTC medicine following down-scheduling. – require a higher level assessment due to the umbrella segment of the product name.	170	2	1st – 43 2nd – 21	Quality (CTD module 3) data are evaluated in full, unless all quality aspects of the product are identical to a product which has previously been fully evaluated by the regulator - abbreviated data & assessment.
N5	New medicines that are not generics (e.g. new chemical entities, new indications).	210	2	1st – 43 2nd – 21	Safety and/or efficacy data or justification for not providing such data are required. Quality (CTD module 3) data are evaluated in full. - unless all quality aspects of the product are identical to a product which has previously been fully evaluated by the regulator - abbreviated data & assessment.

* All time lines are in working days

Table 2Risk Categories for changes to existing products

Application level		Target* evaluation time	# Requests for Information (RFI)	Sponsors respond to the RFI
C1	Minor changes (self-assessable requests and safety related requests)	20	1	5
C2	Changes to quality aspects and non-quality aspects where no safety and efficacy data are required.	64	1	15
C3	Changes to the product name where a higher level of assessment is required due to umbrella branding (use of a common component within the brand name of a number of different products). Non-quality changes where some safety and efficacy data may be required, other than C4 changes.	120	2	1st – 43 2nd – 21
C4	Changes to the indications or directions for use where safety and efficacy data are required.	170	2	1st – 43 2nd – 21

4.3.5.1 Over The Counter (OTC) N2 Applications and OTC Medicine Monographs - A recent innovation

From October 2013 the TGA has been trialing a new application route for common OTC medicines that typically have many sponsors – known as 'N2' applications (TGA, 2013a). From that date applications were able to be submitted for products that fully comply with specific monographs and with a range of associated general requirements including that all excipients in the products must be established pharmaceutical excipients common for the proposed dosage form, already present in other products on the ARTG with the same route of administration, and at doses that do not exceed those for existing products. See for example the monograph for topical nasal decongestants (TGA, 2014b). N2 applications involve reduced requirements for data assessment by the TGA and consequently shorter evaluation timelines, although fees are unchanged during the trial. Sponsors are required to complete a list of assurances (TGA, 2013b) confirming that the product meets the specified requirements of the monograph and those of the general requirements document. Post-market monitoring of products approved through this route will be conducted to ensure compliance

4.3.6 Listed Medicines

Low risk medicines that contain only ingredients that have been pre-approved (TGA, 2007), Table 3, below any applicable concentration limits, for the applicable route of administration, and which make only limited therapeutic claims can be listed on the ARTG. Listed medicines are entered on the ARTG via a streamlined electronic listing facility, which allows for low application fees and early market access for complementary and some other medicines. A sponsor completing an electronic listing is self-assessing the product, the label and the therapeutic claims being made for the product and is required to "make a statutory declaration stating that the information submitted is true, the final products contains only permitted ingredients, the label complies with all regulatory requirements and the company has the necessary evidence to support the claims being made". Unlike registered medicines, there is no evaluation of the product prior to listing on the ARTG. The TGA therefore uses a variety of mechanisms to assure the safety and quality of the ingredients used, as well as the resultant medicinal products.

Listed medicine ingredients are assessed by the TGA for quality and, with some caveats, safety but are not assessed for efficacy. For most listed medicines the assessment is ingredient based rather than product based, with products being self-assessed by applicants. All listed medicines contain unscheduled ingredients usually, but not exclusively, with a long history of safe use (generally centuries). The evaluation of safety is based principally on the history of use, what is known of the biological activity and "the likelihood

of the ingredient being harmful based on **available published evidence** and any **reported** adverse reactions". Specific toxicological data is not necessarily required.

Although the TG Act requires that sponsors hold information to substantiate all of their product's claims for therapeutic efficacy the scientific validity of that evidence is highly variable ranging from robust evidence of efficacy for sunscreens by demonstrating compliance with the relevant Australian Standard, to the facile demonstration of a tradition of use for a complimentary medicine. Consequently some listed medicines may legally contain statements such as *"Traditionally used in Ayurvedic medicine to support healthy immune function"* (TGA, 2014b) without a requirement for credible scientific support for that claim provided evidence of the historical use of that medicine for that purpose can be demonstrated. Similarly therapeutic claims can be made for scientifically unrecognised conditions provided they are also traditional, for example *'Trichosanthis kirilowii (tian hua fen) is traditionally used in Chinese medicine to 'clear and drain lung heat' to help relieve chest congestion'*

Table 3 Examples of entries for ingredients permitted in listable products (TGA 2007)

Ingredient	Use	Restriction
Coconut oil - hydrogenated	E	
Cocos nucifera	A, E	
Cod-liver oil	A, E	If vitamin A is claimed as a component then it must conform to the BP monograph for cod-liver oil.
Methyl isobutyl ketone	E	Concentration must not exceed 0.5%. Residual solvent limit is 50 mg per MDD. Product must contain 25% or less of designated solvents as defined in Part 1 of the SUSMP.
Methyl methacrylate	E	
Methyl salicylate	E, C	Approved for topical use only. In liquid preparations, the concentration must be less than 25%.
Menthyl anthranilate	A	Sunscreen active permitted only in topical products. Concentration must not exceed 5%
Melaleuca alternifolia	A, E	Permitted without restriction in preparations containing 25% or less of melaleuca oil. When the concentration of melaleuca oil is greater than 25% and the nominal capacity of the container is 15 mL or less, a RFI must be fitted on the container and the product label must include the statements CHILD and NTAKEN. When the concentration of melaleuca oil is greater than 25% and the nominal capacity of the container is greater than 15 mL but less than or equal to 25 mL, a CRC and RFI must be fitted on the container and the product label must include the statements CHILD and NTAKEN. Melaleuca oil, Cajuput oil and Cineole are mandatory components of this ingredient (see separate entries). Native species – if exporting this product (excluding oil) please contact the DSEWPC.

Bergamot oil cold pressed	A, E	Permitted when: a) steam distilled or rectified; b) in preparations for internal use; c) in preparations containing 0.4% or less of bergamot oil; d) in soaps or bath and shower gels that are washed off the skin; or e) packed in containers labelled with the statement SENS. Oxedrine is a mandatory component of this ingredient when used for internal use (see separate entry).
Ascorbic acid	A, E, C	When used as an active in oral or sublingual products, the label must include the statement VIT.

A = active; E = excipient; C = component

Compliance. The TGA reports that on average, sponsors list 1800 new complimentary medicines on the ARTG each year through the self-assessment electronic listing facility. To maintain some oversight and to provide some assurance of compliance by sponsors with the conditions applicable to product listing, the TGA conducts both random and targeted compliance audits. The TGA has indicated that it intends to strengthen its post market review activities by using its audit experience to support a more targeted, risk-based and resource efficient approach to compliance monitoring. Risk profiles will be developed for both the medicines and sponsors likely to be associated with low compliance.

For **random audits** the TGA reviews;

1. Labels used for the product as supplied in Australia,
2. finished product specifications,
3. a certificate of analysis for the last released batch,
4. Manufacturing formula,
5. a summary of the evidence held by the sponsor that supports the indications and claims, and
6. copies of completed Transmissible Spongiform Encephalopathy (TSE) questionnaire/s and data, if applicable,
7. websites to ensure advertising complies with the Therapeutic Goods Advertising Code.

Targeted audits may result from information provided in a complaint or referral, information from other sources and/or information included on the ARTG. In addition to the information required for a random review the TGA may require a diverse range of additional information including:

- raw material specifications and certificates of analysis,
- methodology and results in relation to a specific test,
- copies of permits and/or licences allowing the importation of the medicine,
- promotional and advertising material, and
- detailed evidence to support the indications and claims made in relation to the product.

4.4 Medical device Regulation

Although medical devices do not generally have a direct parallel within the APVMA regulatory environment, other than for biocides and some veterinary drug/device combinations, their regulation provides an additional example of a health, safety and efficacy focused regulatory regime that includes risk proportionate requirements. The key elements of this regime are briefly reviewed here with a high level focus on the risk stratification and resource husbandry strategies that underpin the regime.

4.4.1 Regulatory Framework

Medical devices in Australia are regulated under the *Therapeutic Goods Act 1989,* the Therapeutic Goods Regulations 1990, and the Therapeutic Goods (Medical Devices) Regulations 2002.

Medical devices are classified as **Included**, **Exempt**, or declared not to be Therapeutic Goods (ie **excluded** goods). All medical devices must be included on the Australian Register of Therapeutic Goods (ARTG) prior to supply unless they have been exempted from that requirement. As for medicines there is scope to exempt or exclude devices from the Therapeutic Goods Act. For example there are a range of exemptions related to individual patient usage, experimental use and transit through an Australian port, which are not directly relevant to the objectives of this review. There are also a few very low risk medical devices that are exempt from the requirement to be assessed and included on the ARTG. These include manufacturing, laboratory and dispensary equipment used in the preparation of therapeutic goods and some disinfectants. If a medical device does not fit into the definition of a medical device then it is excluded from the requirements of the Act. There is also provision within the Act to declare something Not to be a Therapeutic Good if there is a need.

An application for inclusion of a device on the ARTG must be accompanied by a declaration of conformity of their safety and quality, and that they perform as claimed/ intended. The level of assessment conducted by the TGA is proportionate to the risk categorisation of the device type and function, whether the TGA or an overseas body issued the conformity assessment certificate, whether the certificate was issued under the provisions of trade facilitation agreements in place with European countries (EC - Australia, n.d.), and whether there are any concerns with the application that would require the TGA to request further information for review prior to inclusion.

Conformity assessment is conceptually somewhat different to the process of safety assessment applied to chemicals and includes both evidence generated by the manufacturer against guidelines similar to that for chemicals, and also the procedures undertaken, by the manufacturer to determine that a medical device is safe and performs as intended, and therefore conforms to what are known as 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 that 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; and

6. benefits of medical devices to outweigh any side effects.

Principles about design and construction:

7. chemical, physical and biological properties;

8. infection and microbial contamination;

9. construction and environmental properties;

10. medical devices with a measuring function;

11. protection against radiation;

12. medical devices connected to or equipped with an energy source;

13. information to be provided with medical devices;

14. clinical evidence; and

15. principles applying to In Vitro Diagnostic (IVD) medical devices only.

4.4.2 The Nature of conformity assessment

A manufacturer must be able to demonstrate that both the device and the manufacturing processes used to make the device conform to the requirements of the therapeutic goods legislation as set out in the Act and Regulations. Conformity assessment is the systematic and ongoing examination of evidence and procedures to ensure that a medical device complies with the Essential Principles. This process provides objective evidence of the

safety, performance, benefits and risks for a specific medical device and enables the TGA to ensure that products placed on the market conform to the applicable regulatory requirements

The Australian Regulatory Guidelines for Medical Devices (ARGMD) (TGA, n.d.) provides the following table to explain the process involved in the conformity assessment of a medical device:

Table 4 Conformity Assessment Process

Activity	Description	Who is responsible?

Conformity assessment procedures	• How a manufacturer demonstrates that they have met the Essential Principles for a particular medical devices
	• Manufacturers can choose the appropriate procedures to use, depending on the classification of the device
	• Involves assessment of the:
	  • Technical documentation for the design of the devices
	  • Manufacturing processes used to make the devices
	  • Risk analysis
	  • Clinical evidence
	  • Ongoing monitoring and vigilance procedures that will be in place once the device is available for supply
		Manufacturer

Issuing conformity assessment evidence	Conformity assessment evidence is the certificate issued by a regulatory body to demonstrate a manufacturer has been assessed and has the appropriate systems in place to manufacture the devices. Assessment includes: • confirming that the conformity assessment procedures 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 • may include an on-site audit of the manufacturing premises • assessment processes will vary according to the conformity assessment procedures selected by the manufacturer • re-certification of conformity assessment evidence that is due to expire	the TGA or an European Union (EU) Notified Body
Australian	Once the manufacturer has obtained conformity	Manufacturer

Activity	Description	Who is responsible?
Declaration of Conformity (DoC)	assessment evidence, they must make an Australian DoC The DoC declares that the device complies with: • the applicable provisions of the Essential Principles • the classification rules • an appropriate conformity assessment procedure • if requested, the TGA must be provided with a copy of the DoC • the DoC must be maintained and updated when appropriate	
Ongoing conformity assessment responsibilities	Maintain appropriate records, including: • technical documentation • evidence that an appropriate conformity assessment procedure has been applied • the Australian Declaration of Conformity • details of any systematic reviews undertaken • details of any changes to the device and/or quality management system • implement appropriate means to apply any necessary corrective action in relation to the design or production of a device • notify the TGA and/or the sponsor as soon as practicable after becoming aware of information relating to any malfunction or adverse event • systematically review information gained after the device is supplied in Australia • apply for re-certification prior to the expiry of existing conformity assessment evidence	Manufacturer

The classification of a medical device determines the range of 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

4.4.3 Risk Proportionate Regulation

The risks associated with using medical devices can range from low potential risk to patients and users to high potential risks. The device classes encompass devices of similar assessed risk,Risk categories for medical devicesFigure 2, with the assessed risk increasing progressively across the class designations. The nature and quantum of data, and assessment, required also increases with increased assessed risk, Figure 3. Thus, regulatory requirements of the TGA, before the device is able to be supplied in Australia, directly relates to the designated level of potential risk.

Figure 2 Risk categories for medical devices

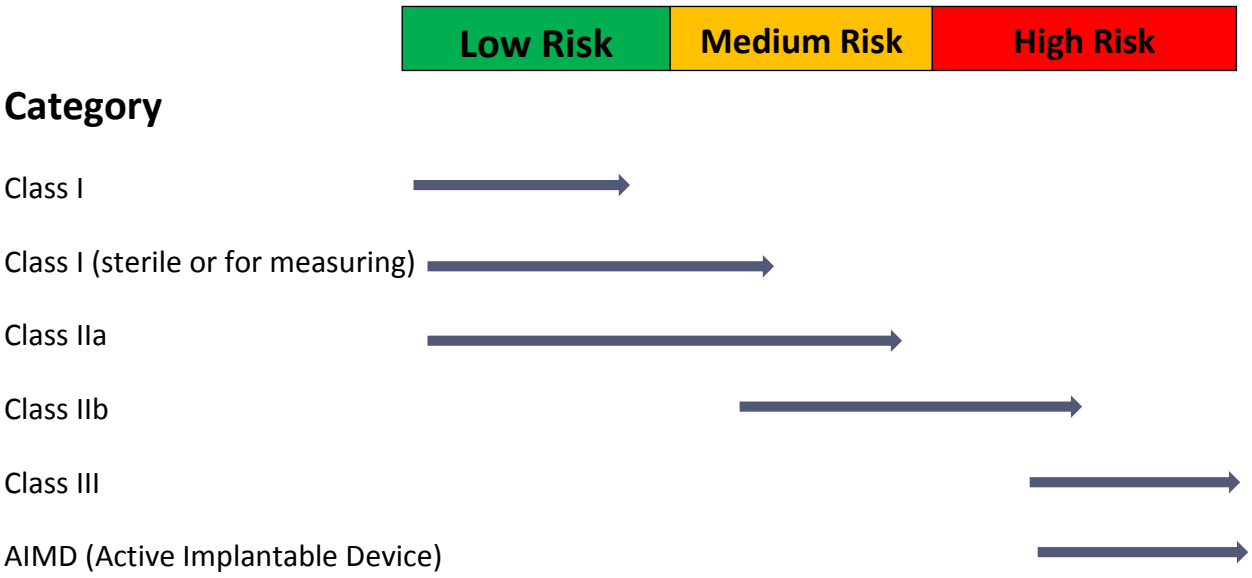
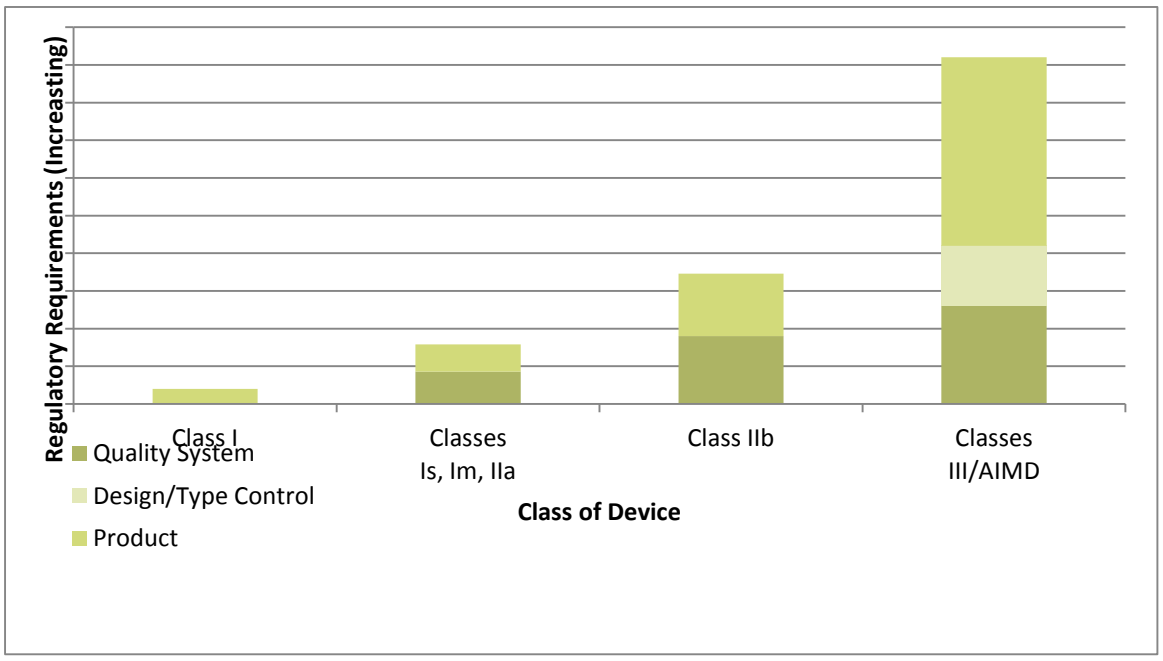


Figure 3 Risk vs Regulatory Requirements for Medical Devices



4.4.3.1 Class I Medical Devices – Self-Assessed

Class I medical devices are defined as low risk. These goods are not therefore subject to formal evaluation by the TGA. These products are **self-assessed** by the manufacturer. The manufacturer must follow a conformity assessment procedure and prepare an "Australian Declaration of Conformity" but this does not need to be submitted to the TGA. Quality assurance of this process is achieved through a programme of audits where the manufacturer can be compelled to provide the evidence relied upon by the manufacturer, to the TGA on request. The audit process consists of a random selection process, with 10 % of new listings selected for review, and targeted reviews of specific devices or manufacturers, where the TGA considers there is a need to confirm compliance. Examples of Class I devices include Surgical retractors, tongue depressors , Sterile bandages, drainage bags.

4.4.3.2 Class I measuring, Class I sterile, Class IIa and Class IIb medical devices

For medical devices classified as Class I measuring, Class I sterile, Class IIa or IIb, the Manufacturer's Evidence of conformity must have been accepted by the TGA prior to inclusion on the ARTG. Through an **administrative review** process the details of the device application is compared with the details on the Manufacturer's evidence, to ensure that the device is appropriately covered by conformity assessment certification, is appropriately classified and has an appropriate intended purpose for that class of good. A technical assessment is not conducted unless the application is required to be audited under the Regulations or the application is selected for a random application audit. Additionally an initial and **ongoing review** of the manufacturer's quality management system (QMS) by a Conformity Assessment Body (CAB)- usually a European Notified Body, or the TGA, is required.

4.4.3.3 Class III and active implantable medical devices (AIMD) – High Risk Devices

These are high risk medical devices, such as heart valves or intraocular lenses, and generally require a comprehensive pre-market assessment before inclusion on the ARTG. Conformity assessment for high risk medical devices consists of a review, by a CAB, of the manufacturer's quality management system (QMS) and the design of the device. The design review involves an examination of the design dossier to assess compliance with the Essential Principles. The design dossier includes technical documentation, design files and risk analysis. The examination by the CAB **may include testing of a representative sample** of the device.

The quality management system (QMS) must ensure appropriate control over the design, production, packaging, labelling and final inspection of the device, and implementation of an appropriate ongoing monitoring system.

The current legislation requires that the TGA conduct an evaluation of the conformity assessment documentation that demonstrates compliance with the Essential Principles for: Australian manufacturers, specific high-risk devices, including devices that contain materials of animal, microbial or recombinant origin, derivatives of human blood or plasma, or a medicine.

4.4.4 Recognition of International Assessments & Mutual Recognition Treaty

One of the TGA's strategies to reduce the regulatory burden on industry is to negotiate agreements with other international regulators. These agreements can range from recognition and acceptance of regulatory decisions on specific products to the sharing of information about regulatory processes, such as what pre-market assessments occur before a product is able to be supplied.

In Australia the TGA is the only conformity Assessment Body (CAB) allowed to perform conformity assessments. However, under mutual recognition treaties with Europe, certification issued by European CABs (also known as Notified Bodies), which are often commercial, non-government certifying bodies, may be accepted by the TGA for most medical devices. Exceptions to this provision are a subset of high risk devices such as those containing tissues of animal origin or medicines, and medical devices made by Australian manufacturers which must go through the TGA.

4.4.5 Post Market Surveillance

The TGA conducts post market surveillance of medical devices to ensure the ongoing regulatory compliance and safety of medical devices in Australia. This is a shared responsibility of the regulator and the manufacturer. In addition to the random and targeted audits, manufacturers are obliged to report adverse incidents involving their medical devices (within 2 to 30 days depending on the seriousness of the incident), any overseas regulatory actions, and the results of any investigations undertaken by the manufacturer. Under the QMS, manufacturers are required to have a procedure for gathering, investigating and acting on information on the performance and safety of their device throughout its marketed life and are required to perform regular reviews of the ongoing safety and benefit-risk assessment of their product(s).

4.4.6 Flexibility

The medical device regulatory framework provides manufacturers with some degree of flexibility to allow for technological advances and changes in the development of new medical devices. The framework does not for example mandate the means by which a manufacturer must prove that they have met the Essential Principles. The responsibility for determining, and generating, the evidence required to demonstrate compliance with the Essential Principles rests with the manufacturer. To assist manufacturers a minimum set of conformity assessment procedures are defined in legislation, and these are based on the

designated level of risk of the device.

5 Food standards Australia New Zealand (FSANZ)

FSANZ is a Bi-National Authority that regulates food in Australia and New Zealand through the establishment of Standards in the Food Standards Code (the Code). The Agency has no enforcement role, the constitutional authority and responsibility for which rests with the States, Territories and New Zealand. The Food Standards Code is divided into 4 chapters each of which reflects some differentiation of regulatory focus and approach. The chapters of the Code are:

- Chapter 1 – General food standards, contains standards that are generally applicable to all foods or classes of foods, or specific aspects of the composition, production and presentation for sale of foods, largely independent of specific food products or product types. including;
    - labelling
    - permissions for the addition of substances to food (food additives, processing aids)
    - Contaminants and residues
    - Foods requiring premarket clearance
    - Microbiological and processing requirements
- Chapter 2 Food product standards, contains standards specific to a type of food or food product, many of which are very brief and may only contain one or two specific requirements such as a specified maximum pH for pickled or canned vegetables, or may provide quite extensive compositional boundaries and other requirements for specific product types, eg
    - Individual foods - Cereals, meat, eggs and fish, Edible oils, dairy products
    - Food products – beverages, infant formula, food for medical purposes
- Chapter 3 Food safety standards (Australia Only) contains standards on general food safety practices at food production and retail facilities, including, Food Safety Programs, Food safety Practices and general Requirements, food premises and equipment
- Chapter 4 Primary Production Standards (Australia Only) which contains standards on primary food production including meat, poultry, seafood, dairy products and seed sprouts and provides general guidance on practices, procedures, health and hygiene requirements.

In terms of the focus of this review chapters 3 and 4 are of limited relevance and are not discussed further. Chapters 1 and 2 reflect risk based approaches that may be of relevance to a consideration of alternative approaches to the regulation of agricultural and veterinary products. In terms of regulatory philosophy and approach FSANZ sits somewhere between NICNAS, which is almost entirely substance focused, and the TGA which is predominantly product focused.

Unlike the APVMA, TGA and NICNAS which are primarily funded through cost recovery mechanisms, FSANZ is primarily funded by appropriation and only a small component of its work plan is cost recovered. Applications to the code are made free of charge unless the applicant wishes to fast track the application or has an exclusive capturable benefit, in which case a cost recovery fee is applied. Where fees are payable they are based on an estimate of the work hours required to complete assessment as provided in the table below.

Table 5 FSANZ Fee Structure for Cost Recovered Applications

Procedure	Hours	Time based Charge	Admin Charge	Total Fees $AUD
Minor Procedure	Maximum of 100 hours	11,500	10,000	21,500
General Procedure	Maximum of 350 hours	40,250	10,000	50,250
	Maximum of 650 hours	74,750	10,000	84,750
	Maximum of 1000 hours	115,000	10,000	125,000
	More than 1000 hours	115,000+	10,000	125,000+
Major Procedure	1200 hours or more	138,000	10,000	148,000+

Within the FSANZ regulatory framework, risk stratification is primarily achieved through a combination of risk proportionate data requirements, recognition of international evaluations and self-assessment by the industry. Applications are divided into Minor, General and Major procedures with further divisions within General procedures to ensure fees are proportionate to the work required. The levels of procedure apply to both paid and unpaid applications and to work initiated by FSANZ and has implications for the work of FSANZ beyond the determination of fees, as specified in the Act, such as the number of rounds of public consultation required for example. Statutory time lines for the completion of procedures begin on the payment of fees where cost recovery is applicable, or on commencement of work. FSANZ maintains a publicly available work-plan indicating the intended start date for self-initiated procedures and unpaid procedures, which must await available resources before commencement and initiation of the clock (ie the start of the

process time line). Requirements for applications to change the code are laid out in the Application Handbook (FSANZ, n.d.).

The **General Procedure** is the default assessment process and involves one round of public comment. General Procedure applications are required to be completed within 9 months of commencement (or of the payment of fees where cost recovery applies). For the purposes of cost-recovery under the Regulations, the General Procedure is split into four levels as shown in the Table above. The types of assessments that are likely to fall into the levels of the General Procedure is provided in Table 6.

A Minor Procedure covers activity such as correcting a typographical error, updating a reference to another document, amending a cross-reference within a food regulatory measure, omitting provisions of a food regulatory measure that has ceased to have effect, any other matter of similar complexity. Minor procedures are required to be completed within 3 months of the commencement of assessment.

A major Procedure applies to activities such as the development of a new food regulatory measure or the variation of a food regulatory measure that involves either complex scientific or technical issues or an especially significant change to the scope of a food regulatory measure. A minimum of two rounds of public comment is required and consultation might also require the establishment of external working parties or advisory groups to assist with the assessment. Examples of Major procedures might include developing a new standard, adding a new substance affecting a wide range of foods, a pre-market approval, with no similar previous approvals, or making a change that affects a wide range of foods. These types of procedures may involve especially complex considerations or activities related to one or more of the assessment components such as; risk assessment, risk management, social and economic analysis, communication or stakeholder engagements.

Table 6 Assessment Levels for General Procedures

Level	Time	Example	Range of Possible Assessments Required
1	< 350 hrs	extending the use of a food or food additive that is permitted under a standard	Less complex assessment of the risk to public health and safety
		a new source organism for an enzyme	limited, or no, social or economic impact
		a minor change to a labelling requirement	Less complex assessment of toxicology, nutrition, food technology, dietary modelling or microbiology
		a minor change to a compositional requirement for a food	Less complex risk management measures
		reducing a maximum residue limit	basic community communications
2	>350 hrs, < 650 hrs	extending the use of a substance to a specific food	Average assessment of the risk to public health and safety
		a pre-market approval similar to a previous approval	low social or economic impact
		a new microorganism	Average toxicological, nutritional, food technology, dietary modelling or microbiological assessment of
		changing a compositional requirement for a food	risk management measures of average complexity
		inserting or increasing a maximum residue limit	development of a community communications strategy
3	>650 hrs <1000 hrs	extending the use of a substance to a range of foods	Average assessment of the risk to public health and safety
		changing a labelling requirement for a food	broad social or economic impact
		a pre-market approval	toxicological, nutritional, food technology, dietary modelling or microbiological assessment of greater than average complexity
		establishing or increasing a maximum permitted concentration for an environmental contaminant or heavy metal	risk management measures of greater than average complexity
			a complex community communications
			targeted consultation with key stakeholders or special interest groups
4	>1000 hrs	adding a new substance to a limited range of foods	extensive and complex assessment of the risk to public health and safety
		changing a labelling requirement for a limited range of foods	broad and significant social or economic impact
		a complex pre-market approval	extensive and complex toxicological, nutritional, food technology, dietary modelling or microbiological assessment
			extensive and complex assessment of risk management measures
			extensive and complex community

	communications strategy
	targeted consultation with key stakeholders or special interest groups
	development and distribution of community education material
	establishment of external working groups to discuss and interpret scientific evidence and social perceptions

5.1 Environmental Risk Assessment

FSANZ does not conduct, require or commission environmental risk assessments for substances added to food.

5.2 Risk Proportionate Regulation

FSANZ employs a range of strategies to adjust the regulatory resources and burden applicable to applications and procedures to reflect the level or nature of risk, and complexity, the agency assigns to the issue being addressed. These strategies include:

- Industry Self-Assessment
- Development of product class Monographs
- Pre-market assessment
- Use or Recognition of International assessments and approvals

5.3 Self-Assessment

In general FSANZ does not approve specific products and manufacturers and importers are required to self-assess their compliance with the code. Partial exceptions to this generalization include the introduction of a novel food or a new genetically modified food. In these cases, permission for the new food type is required although specific products are not assessed as such. In the case of a novel food, the introducer of that food must self-assess the food against the novel foods standard in order to determine if an application and approval is required prior to sale.

Compliance with the Code is determined through self-assessment by the manufacturer of a new food product. New Zealand and the States and Territories provide an enforcement role where breaches come to their attention or are detected by inspection officers. Where a manufacturer wishes to develop a food product that uses a new food additive or processing technology or they wish to make label claims not previously approved, an application to change the relevant aspect of the code to permit that change is required.

5.3.1 Novel Food

The Standard for **Novel Foods** is an example of a clear intention with unclear implementation. The regulatory capture of a novel food is reliant on 2 defined concepts,

that of a history of safe use in Australia and New Zealand and that of novelty (in the sense of public health and safety). In order for a food supplier or manufacture to determine if a product they wish to market contains a novel food they are required to self-assess whether that food falls within those 2 defined concepts. Under the Food Standards Australia New Zealand Act 1991, FSANZ is not permitted to provide interpretations of the code so at least in theory FSANZ is unable to provide a definitive opinion on this matter.

Non Traditional is defined as

> **non-traditional food** means –
> (a) a food that does not have a history of human consumption in Australia or New Zealand; or
> (b) a substance derived from a food, where that substance does not have a history of human consumption in Australia or New Zealand other than as a component of that food; or
> (c) any other substance, where that substance, or the source from which it is derived, does not have a history of human consumption as a food in Australia or New Zealand.
>
> **novel food** means a non-traditional food and the food requires an assessment of the public health and safety considerations having regard to -
>
> (a) the potential for adverse effects in humans; or
> (b) the composition or structure of the food; or
> (c) the process by which the food has been prepared; or
> (d) the source from which it is derived; or
> (e) patterns and levels of consumption of the food; or
> (f) any other relevant matters.

Thus, the responsibility for determining whether a new food is novel falls to the supplier or manufacturer who must determine whether the food is traditional or non-traditional and whether FSANZ would believe it requires a safety assessment based on a number of considerations including “any other relevant matters”. In practice this requirement has proved sufficiently problematic to the food industry and to the Jurisdictions that must enforce the code, that a quasi-official committee consisting of FSANZ and representatives of the States and Territories, was established to provide an opinion on the capture or otherwise of potentially novel foods.

5.3.2 General level health Claims

For general level health claims food businesses may apply to FSANZ for approval or they have the option of self-substantiating the food-health relationship and are then obliged only to notify FSANZ of the relationship before making the claim on food labels or in advertisements for food.

5.3.3 Food Packaging

For Food packaging in contact with food, Standard 1.4.3, places responsibility for safety entirely in the hands of manufacturers.

> Permission for articles and materials
>
> Articles and materials may be placed in contact with food, provided such articles or materials, if taken into the mouth, are not -
>
> (a) capable of being swallowed or of obstructing any alimentary or respiratory passage; and
>
> (b) otherwise likely to cause bodily harm, distress or discomfort.

5.4 Product Monograph Style Approach

The operation of a number of food standards are somewhat analogous to the N2 monograph approach for registered OTC medicines within the TGA. Infant formula and foods for special medical purposes for example provide compositional limits for key nutrients and other ingredients. These may be either or both upper and lower limits. Manufacturers are only required to make an application to FSANZ where those limits would need to be altered in order to for their product to be compliant with the Code.

Table 7 Example of "Monograph Style" Product Composition Specification

Minimum and maximum content of vitamins, minerals and electrolytes in food for special medical purposes (Std 2.9.5) represented as being suitable for use as a sole source of nutrition.

Column 1	Column 2	Column 3
Nutrient	Minimum Amount per MJ	Maximum Amount per MJ
Vitamins		
Vitamin A	84 µg retinol equivalents[1]	430 µg retinol equivalents[1]
Thiamin	0.15 mg	No maximum set
Riboflavin	0.2 mg	No maximum set
Niacin	2.2 mg niacin equivalents[2]	No maximum set
Vitamin B_6	0.2 mg	1.2 mg
Folate	25 µg	No maximum set
Vitamin B_{12}	0.17 µg	No maximum set
Vitamin C	5.4 mg	No maximum set
Vitamin D	1.2 µg	6.5 µg or 7.5 µg[3]
Vitamin E	1 mg alpha-tocopherol equivalents[4]	No maximum set
Biotin	1.8 µg	No maximum set
Pantothenic Acid	0.35 mg	No maximum set
Vitamin K	8.5 µg	No maximum set
Minerals		
Calcium	84 mg or 120 mg[3]	420 mg or 600 mg[3]
Magnesium	18 mg	No maximum set
Iron	1.2 mg	No maximum set
Phosphorus	72 mg	No maximum set
Zinc	1.2 mg	3.6 mg
Manganese	0.12 mg	1.2 mg
Copper	0.15 mg	1.25 mg
Iodine	15.5 µg	84 µg
Chromium	3 µg	No maximum set
Molybdenum	7 µg	No maximum set
Selenium	6 µg	25 µg
Electrolytes		
Sodium	72 mg	No maximum set
Potassium	190 mg	No maximum set
Chloride	72 mg	No maximum set

5.5 Pre Market Assessment

Pre-Market assessment and approval is required for new food additives or processing aids, novel, irradiated or genetically modified food, and for new high level health claims.

5.5.1 Individual Chemical/Substance Approvals

As the basis of food regulation in Australia is the establishment of standards and the creation of permissions to use specific ingredients in food products, rather than a product by product approval, the scope for reductions in the regulatory imposts for permissions to use new ingredients is somewhat limited. Nonetheless FSANZ has implemented a range of risk proportionate regulatory requirements for the range of chemicals and substances it regulates. Some pertinent examples are discussed further below.

5.5.1.1 Processing aids

Processing aids are substances used in the production of food which do not have a function in the final food as consumed, and in most cases is not present, or not present in an active form in the case of enzymes, or present only at trace levels in the final food as consumed. Processing aids are broadly divided into chemicals and enzymes. Because of the pattern and nature of their use, processing aids have reduced safety data requirements in comparison to most other food additives confined largely to the provision of acute and short term toxicity studies but with provision of any additional information that may be available on;

a. long-term toxicity and carcinogenicity
b. reproductive toxicity
c. developmental toxicity
d. genotoxicity
e. special studies such as neurotoxicity or immunotoxicity.

Where data are not available or not considered relevant the applicant is required to provide an explanatory statement that outlines the rationale for their absence.

For Processing aids that are enzymes there is no requirement to routinely conduct acute or short term oral toxicity studies or genotoxicity studies, however, if such data already exists it should also be provided. The primary safety related data required for enzymes includes that necessary to preclude allergenicity or potential relationship to known protein toxins;

a. Information on the enzyme's prior history of human consumption and/or its similarity to proteins with a history of safe human consumption.
b. Information on any significant similarity between the amino acid sequence of the enzyme and that of known protein toxins
c. an analysis of similarity between the amino acid sequence of the enzyme and that of known allergens.
d. information on the stability of the enzyme to degradation in appropriate gastric and, if applicable, intestinal model digestion systems. In the case that the enzyme is tested for stability and found to be stable, the following data will also be needed:
e. specific serum screening.

Other information for enzymes may be required regarding the nature of the source organism, its taxonomy, genetic stability and pathogenicity.

Thus the data requirements are tailored to the specific risks that need to be managed, the pattern of use and the potential for exposure.

5.5.2 Recognition of International Assessments

When preparing food standards FSANZ will often consider relevant international standards and actively seek to establish a harmonized position where that is practicable or desirable. In developing the standard for Foods for Special Medical Purposes for example FSANZ was cognisant of the fact that such foods are largely imported into Australia from Europe or Nth America and therefore sought to establish a range of permissions and requirements for nutrients that was aligned with the requirements of those countries. Similarly FSANZ actively considers changes to MRLs in the Code to harmonise with MRLs established by Codex or by a regulatory authority in a recognised jurisdiction. This process may occur with or without a formal application.

Similarly in developing the standard for Nutrition, Health and Related claims, FSANZ populated the standard with claims that had previously been approved in the EU, after a high level screening exercise, to ensure their appropriateness in the Australian context.

For issues relating to contaminants FSANZ routinely considers reports prepared by JECFA or other suitable regulatory or scientific body as the first iteration of their assessment. In many cases no further assessment is required and risk management decisions can be based on the international document. In other cases the safety assessment is focused on specific aspects either not addressed or not sufficiently addressed in the international report, substantially reducing resource cost of such assessments and allowing a considerably faster reaction time to contaminant incidents.

5.5.2.1 Food Additives – Flavours

Flavouring substances generally have intense flavour and are therefore used in small quantities resulting in low levels of exposure to consumers. These substances are used widely in the food industry across the world and various systems are in place internationally to assess their safety. Food Standard 1.3.1 Food Additives includes a provision that permits the use of flavouring substances that are approved for use in the USA and Europe, specifically;

a. Flavouring substances which are listed in at least one of the following publications –
    i. Generally Recognised as Safe (GRAS) lists of flavouring substances published by the Flavour and Extract Manufacturers' Association of the United States from 1960 to 2011 (edition 25); or

ii. Chemically-defined flavouring substances, Council of Europe, November 2000; or
iii. 21 CFR § 172.515; or

b. Flavouring substances obtained by physical, microbiological, enzymatic, or chemical processes from material of vegetable or animal origin either in its raw state or after processing by a traditional preparation process including drying, roasting and fermentation; or
c. Flavouring substances obtained by synthetic means which are identical to any of the flavouring substances described in subparagraph (b).

6 National Industrial Chemicals Notification and Assessment Scheme

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) was established in July 1990 under the Industrial Chemicals (Notification and Assessment) Act 1989. NICNAS regulates the importation, manufacture and use of industrial chemicals including cosmetic ingredients with the objective of protecting public and occupational health, and the environment. This scheme is substance focused rather than product focused and in simple terms has jurisdiction over all chemicals not covered by other regulatory regimes (eg TGA – medicines, FSANZ – food ingredients, APVMA – pesticides and veterinary medicines). NICNAS does not approve new industrial chemicals *per se*, and does not regulate products, but rather assesses each new chemical that importers notify to the agency, and issues an assessment report that details the various hazards associated with it, and may recommend further regulatory controls such as poisons scheduling or work health and safety or environmental controls. Following assessment, NICNAS issues a permit or assessment certificate to the introducer of the chemical which then allows the chemical to be brought into the country. The agency has powers under their act to conduct reviews of existing industrial chemicals of concern either as priority existing chemicals, secondary notifications (reassessment of an existing chemical) or targeted assessments addressing specific health and environmental concerns .

Risk is a function of both hazard and exposure and the exposure to a chemical is dependent on its concentration in a product and the nature, use and composition of products it is within. Risk in that sense relates to the product as opposed to the individual ingredient. Because NICNAS does not regulate products as such it has minimal visibility of the nature, composition and use patterns of finished products, it is therefore necessarily limited in the extent to which it can assess risk in the broader sense. The NICNAS scheme is, consequently, principally hazard based with some exposure based aspects, related to volumes of production or importation, and is therefore philosophically different to the risk based regulatory paradigm applying to food, therapeutic goods and agricultural and veterinary chemicals. To a large extent this is necessitated by the substance based NICNAS regulatory regime, as opposed to the more commodity or product based foundations of the other regulators considered here. The distinction between hazard based and risk based regulatory frameworks is relative rather than absolute or dichotomous, however and all schemes share some elements of the broader risk assessment paradigms.

NICNAS maintains the Australian Inventory of Chemical Substances (AICS) which provides a publicly accessible record of chemicals that have been assessed by NICNAS or were in use prior to the introduction of the NICNAS Act (grandfathered chemicals). A small proportion of notified chemicals are retained on a confidential section of the AICS where publication of the chemical name and structure would substantially prejudice the commercial interests of interested persons dealing in those chemicals. Once a chemical is on the AICS it is available

for importation and use by any industrial user. If the use pattern or volume changes markedly from that set out in the initial assessment certificate, users of the chemical are required to notify NICNAS of the nature of the changes and NICNAS may then require a secondary notification.

A notification generally includes the provision of predefined data to support a risk assessment of the notified chemical. In essence a notification to NICNAS is analogous to an application to the APVMA.

Annual reporting involves provision of information to NICNAS on the volumes and uses of chemicals and of any OH&S or environmental effects observed to have resulted from the use of the chemical.

6.1 Environmental Risk Assessment

Unlike the TGA and FSANZ, environmental risk assessment is an integral component of the NICNAS process. These assessments are performed by the Department of the Environment as is also true for Agricultural chemicals. Requirements for environmental risk assessment are included in the overall risk stratified approach to industrial chemicals described below.

6.2 Risk Proportionate Regulation

The NICNAS regulatory regime is primarily composed of exemptions, permits and notifications, and includes a self-assessment category where notifiers complete a new chemical assessment themselves and submit the completed assessment to NICNAS for review. Within this structure there are a number of hazard/exposure based regulatory strata that require different levels of data, attract different fees and require a range of times for completion of the NICNAS assessment.

6.2.1 Data Elements

In general the data requirements for assessment of environmental (where applicable) and human risk, for industrial chemicals are minimal in comparison with that required for a human or veterinary drug, food additives or pesticides. The difference reflects the, generally, higher potential risk from unconscious oral exposure to residues in food or the higher systemic exposures to bioactive chemicals as human drugs, and the higher potential for environmental exposures from pesticides sprayed over large areas. The differences also reflect the greater opportunity to control human and environmental exposure to industrial chemicals through engineering controls or use of personal protective equipment within an occupational setting. Across the range of NICNAS permit and assessment categories, data requirements are stratified to match exposure potential based on use volumes and pattern, or potential for hazard as identified from structural alerts.

6.2.2 Exemptions

New industrial chemicals are categorized for regulatory purposes primarily on the basis of either the exposure or hazard components of risk. The lowest level of regulatory activity is accorded to chemicals which are exempt from notification, but will generally require annual reporting, because they meet one of the following, primarily exposure based, criteria:

1. The chemical is for use only in research and development,
    a. and does not exceed 100 kg per year
2. The chemical is in transit and under customs control at a port for less than 30 days,
3. The chemical is for use in cosmetics and
    a. Does not exceed 100 kg per year or
    b. Is non Hazardous AND is present at less than 1% in final products
    c. Non-hazardous is defined as
        i. not being classified as a mutagen, carcinogen or reproductive toxin under the GHS and not suspected of having such hazards
        ii. Not bio-accumulative or persistent
        iii. Does not contain specified high risk functional groups
        iv. Is not, and is not expected to be, highly eco-toxic

The combination of annual reporting requirements, volume/concentration based cut offs and specified criteria to segregate highly hazardous materials from the exempt categories, provides a risk based regulatory exemption that retains visibility of imported chemicals, the volumes imported and the general areas of use. The visibility of exempted categories through the annual reporting mechanism provides NICNAS with scope to respond to emerging concerns whilst imposing a low regulatory burden for these chemicals. Importers of exempt chemicals are however required to consider the human and environmental risks associated with that chemical which places a minimal expectation of competence and responsibility on the importer.

6.2.3 Notifications and Permits

For new industrial chemicals that are not exempt, the degree of regulatory activity is stratified primarily on the basis of hazard potential. Two broad categories exist for assessing a new chemical, permits and assessment certificates. Which is applicable, depends on the type of chemical, the amount being introduced, proposed use of the chemical, the period of use and the company's business needs and commitments. The characteristics of permits and assessment certificates are:

- Assessment Certificates;
    - More substantial data requirements as specified for each chemical category,
    - Eventually listed on the AICS,
    - An assessment report including recommendations is published on the NICNAS web site,
    - Statutory time line for assessment of 29-90 days,
    - More substantial assessment cost as specified for each chemical category,

- Permits;
    - Permits are issued with conditions including their duration and volume of chemical use,
    - The data requirements, and the need to generate data, are generally reduced substantially,
    - The chemical is **not** included on the AICS as a result of the permit process,
    - The permit is published in the chemical gazette with some summary details,
    - Statutory or indicative timelines for NICNAS consideration are shorter at 14-28 days,
    - Fees are lower.

Table 8 NICNAS Permit Categories

Type of Permit	Quantity restrictions	Duration Restrictions	Assessment timeframe	Fees $ 2014-15
Commercial Evaluation Chemical (CEC)	≤ 4 tonnes	≤ 2 years	14 days	4200
Low Volume Chemical (LVC)	≤ 100 kg/yr	3 years	20 days	4200
Low Volume Chemical (LVC)	> 100 kg but ≤ 1000 kg/yr	3 years	20 days	4200
Controlled Use Permit (CUP)	Unlimited	3 years	28 days	4200
Controlled Use – Export Only (EOP)	Unlimited	3 years	20 days	4200
Early Introduction Permit (EIP)*	As per applicable notification category	Until certificate issued	28 days	2500
Permit renewal	As per original permit	3 years	20 days	2200

* This permit category accompanies a notification for a Polymer of Low Concern, a Standard or a limited notification.

Table 9 NICNAS Notification and assessment categories

Type of Notification	Quantity Restrictions	Duration	Assessment time frame	Fees 2014-15
Polymer of Low Concern (PLC)	unlimited	5 years	90 days	6000
Limited (LTD)	≤ 1 tonne/yr ≤ 10 tonnes/yr for site limited chemicals	5 years	90 dyas	12800
Standard (STD)	> 1 tonne/yr	5 years	90 days	18000
Self-Assessment	As per STD, LTD, PLC	5 years	28 days	11200
Extension (EX)	As per STD, LTD, PLC	5 years from granting of original certificate	45 days	5500

6.2.4 Common Permit Requirements

Permit conditions common to all permit types

Permit holders must submit an annual report to NICNAS, stating the name of the chemical for which the permit or certificate is issued, the volume of the chemical introduced during the year, and any adverse effect of the chemical on occupational health and safety, public health or the environment of which they may have become aware during the year.

In addition to specific clauses applicable to the permit type, all permits stipulate that the permit holder needs to;

- use the chemical in accordance with all relevant state or territory occupational health and safety, public health, environmental and poisons legislation,
- prevent or, where this is not practicable minimise, the risks to human health where a suitable and sufficient workplace risk assessment indicates that control measures are necessary and that control of exposure to workers is adequate,
- inform workers who will be exposed to the chemical and products containing it that it is being introduced into Australia under a permit,
- make the (M)SDS for the chemical available at all sites where the chemical is used,
- dispose of waste in accordance with Australian Government, state and territory government and local government regulations.

Table 10 Permit Types and Required Human and Environmental Risk Related Data

Permit Type	Purpose	Data requirement
Commercial Evaluation Permit (CEP)	permits the introduction of less than 4 tonnes of a chemical solely for a specified performance or product trial.	Notifiers need to provide a summary of the chemical's occupational health and safety, public health and environmental effects in addition to common data elements such as use chemistry, use patterns etc.
Controlled Use Export Only (EOP)	where the entire quantity of a new chemical manufactured or imported into Australia will be exported as such or used in formulating products that will be exported and the chemical can be demonstrated to be low risk. Under the highly controlled criteria, the notifier must have sufficient control measures in place to prevent exposure to workers and the public and release to the environment. Chemicals prohibited or severely restricted under Australia's international obligations are not eligible for an EOP (eg persistent organic pollutants).	For introduction volumes exceeding 10 tonnes per year, notifiers are required to provide all available toxicological and eco-toxicological data with their application but for lower volumes summaries of risks to human and environmental health and precautions taken to prevent public, worker and environmental exposure are required. NICNAS retains the discretion to ask for additional toxicological and eco-toxicological information to satisfy itself that there is 'no unreasonable risk'.

Permit Type	Purpose	Data requirement
Controlled Use Permit (CUP)	Chemicals that do not have any of a list of specified human or environmental hazards, have negligible or highly controlled and limited occupational, public and environmental exposures, may be eligible for a CUP for supply to a specified list of downstream users.	Specific data generated on the chemical may not be required where validated QSAR analysis has been performed, data is available on a close analogue or literature data can be provided
Early Introduction Permit (EIP)	Can be sought at the time a new chemical notification is submitted to NICNAS and allows introduction of a chemical into Australia before the assessment certificate is issued provided the chemical meets hazard or use criteria or where it can be shown their immediate introduction is in the public interest. The permit lapses when the assessment certificate is issued, the application is withdrawn, or the full assessment is stopped due to additional data requirements.	Eligible chemicals must be low risk and its introduction must be consistent with the reasonable protection of OH&S, public health and the environment. Data requirements are determined by the nature of the full notification and assessment certificate.
Low Volume Chemical <100 kg/yr & 100 to 1000 kg/yr	Allows a chemical to be introduced at a maximum quantity of 100 kg per year, or 1000 kg where certain criteria are met, for a maximum of three years. The higher volume is dependent on meeting the low-hazardous criteria	Summary of human health hazards. Full data reports only where a structural alert exists for the relevant endpoint. Evidence to demonstrate that each environmental hazard criterion has been satisfied.

6.2.4.1 Assessment Certificates

There are three types of chemical notifications, leading to a published assessment report and ultimately addition to the AICS, with a subset of these having the option for importers or manufacturers to conduct a self-assessment, ie prepare the assessment report themselves, and submit to NICNAS for review.

For all notification types a consideration of occupational, public and environmental exposure is required. Specific data requirements for toxicology and eco-toxicology consideration ranges from negligible to none for Polymers of Low Concern (PLC), through a summary of available data for Limited Notifications (LTD) to full reports for Standard Notifications (STD).

Polymers of Low Concern are polymers with chemical characteristics consistent with low to negligible potential human health and eco-toxicity hazards. PLC have a high molecular weight, lack specific functional groups identified as potentially hazardous, are stable under in use conditions, photo-stable, heat-stable etc, and have physicochemical properties that are consistent with low eco-toxicity. PLC notifications do not generally require toxicology or ecotoxicology studies, although summaries of any available studies would be expected to be provided.

Limited Notifications (LTD) are for chemicals, biopolymers and low MW polymers that;

- will be used in small volumes (<1 tonne pa), OR
- site-limited - that is, restricted to their manufacturing site and manufactured at a rate of not more than 10 tonnes/12-month period, OR
- synthetic polymers with Number Average Molecular Weight (NAMW) >1000 Da that do not meet the PLC criteria.

LTD notifications do not require toxicology or ecotoxicology studies to be submitted but summaries of published or other available data and Quantitative Structure Activity Relationship (QSAR) modelling is required.

Standard Notifications (STD)

STDs are for chemicals, biopolymers and low MW synthetic polymers (NAMW<1000 Da) that are imported or manufactured at greater than 1 tonne/year that do not fulfill the requirements of any other category.

STDs generally require the submission of the full study reports for a limited (relative to FSANZ, TGA and APVMA) battery of toxicity and eco-toxicity studies including;

- **Mammalian toxicity**
  - Acute toxicity data
    - Acute oral toxicity (TG[1] 401 or equivalent)
    - Acute dermal toxicity (TG 402 or equivalent)
    - Acute inhalation toxicity (TG 403 or equivalent)
  - Irritation and corrosion
    - Skin irritation (TG 404 or equivalent)
    - Eye irritation (TG 405 or equivalent)
  - Sensitisation
    - Skin sensitisation (TG 406 or 429 or equivalent)
    - Respiratory sensitisation
      - No standard OECD guidelines available non-standard studies, if they are available, and any human evidence regarding this effect to be submitted.
  - Repeated dose toxicity (TG 407, TG 410, TG 412 or equivalent)
  - Genetic toxicology
    - point mutations in established microbial systems (TG 471 or equivalent)

[1] TG = OECD Guideline for the testing of chemicals

        - Genotoxic damage *in vivo* (TG 474 or equivalent)
        - Chromosome damage (TG 473, TG 474, TG 479 or equivalent)
- **Eco-toxicity data** (QSAR estimates may be acceptable in some circumstances)
    - Fish, acute toxicity test (TG 203 or equivalent)
    - Daphnia, acute immobilisation test and reproduction test (TG 202 or equivalent)
    - Algal Growth Inhibition Test (TG 201 or equivalent)
    - Biodegradation TG 301A-F or equivalent
    - Bioaccumulation

6.2.5 Self-assessment Options

Self-assessment certificate categories allow industry to self-assess low regulatory concern chemicals (Polymers that meet the criteria for PLCs, or other non-hazardous chemicals or polymers) against specified criteria and provide an assessment report which is screened and amended by NICNAS in consultation with the notifier, if necessary, before publication. The assessment time frame is shorter at 28 days as opposed to 90 days, and the fees are lower. Nanomaterials, biopersistent or bioaccumulative chemicals and other polymers are not eligible for self-assessment. To ensure the robustness and integrity of the self-assessment process, the holder of a self-assessed assessment certificate may be subject to NICNAS audits. The self-assessor must keep records to support statements made in, or in connection with, the certificate application, for five years from the date the certificate is issued and must report annually as for permits.

7 Risk Based Approach to Imported Food and Plant Biosecurity & Safety

The Department of Agriculture helps protect Australia's food producers by managing the risk of exotic pests and diseases entering the country and also inspects imported food to check it meets Australian requirements for public health and safety and compliance with the Australian food standards Code. As this is a risk based and risk graduated scheme, with elements in common with other food and human health related regulatory frameworks considered above, it is briefly reviewed here.

7.1 Basic Principles

The Department of Agriculture has implemented a risk-based inspection allocation system to manage the biosecurity risk of historically low-risk imported plant product pathways. The system is known as CSP-3, and is a member of the CSP, or Continuous Sampling Plan, family (Arthur et al., 2013; Robinson et al. 2013). CSP-3 has been implemented for dried apricots, hulled sesame seeds, and other imported plant products in which the historical contamination rate is very low.

CSP is applied to a pathway, that is, to a sequence of consignments from the same importer to the same supplier that are identified by the same tariff code. The simplest CSP is CSP-1. CSP-1 captures all the important concepts and will serve as an example of the operation of the process. CSP-1 was introduced to solve problems of quality control for manufacturing by Dodge (1943), and CSP-3 by Dodge and Torrey (1951).

At the commencement of the process two values that underpin its operation need to be selected. These values are the **clearance number (cn)** and the **monitoring fraction (mf)**. These are explained more fully later in this discussion via an example, but for the moment we will choose 10 for the clearance number and 20% for the monitoring fraction. This instance of CSP-1 would then be implemented as follows;

1) Start the pathway in **census** mode, in which every consignment is inspected.
2) If all the first 10 (cn) consignments are clear, then the pathway switches to **monitoring** mode, whereas if any are contaminated/non-compliant then the pathway stays in census mode.
3) The pathway stays in census mode until 10 (cn) consecutive clean consignments have been inspected and cleared, whereupon the pathway shifts to monitoring mode.
4) Whilst in monitoring mode, a fixed percentage of consignments are randomly selected for inspection– in this example at a rate of 20% (mf). If any of these sampled consignments are contaminated/ non-compliant, the pathway shifts directly back to census mode.

The performance (success) of the system depends on the underlying contamination rate/non-compliance of the pathway, and the two chosen values.

The CSP family of algorithms is only suitable for pathways in which some leakage (compliance failure) can be tolerated. If no leakage can be tolerated then full inspection is essential. CSP is useful for detecting and responding to changes in the level of contamination/non-compliance. CSP is not particularly effective for pathways that suffer occasional spikes of contamination/non-compliance. Thus the approach is better suited for monitoring compliance with labelling requirements or the presence of soil derived contaminants that for adventitious presence of human pathogens such as the recent hepatitis A viral contamination of fresh frozen berries.

The Department has implemented CSP-3 within its Agricultural Information and Monitoring Service (AIMS) system, which allows CSP-3 to be used for any tariff code (commodity group). Previously, versions of CSP-1 have been implemented for other pathways, including the pratique-based (a license given to a ship to enter port on assurance from the captain to convince the authorities that she is free from contagious disease) inspection of first-port arrivals of international marine vessels, for auditing in the Broker Accreditation Scheme, and for the inspection of risk food and surveillance food by the Imported Food Inspection Scheme (IFIS).

7.2 Imported Food Inspection Scheme (IFIS)

The primary responsibility for ensuring that all food imported into Australia complies with the Food Standards Code (the Code) rests with the importer but the Dept of Agriculture maintains an inspection scheme to monitor imported food. This inspection scheme has 2 principle components targeting what are termed “Risk Foods” and “Surveillance foods”.

The IFIS process is essentially a mechanism to establish trust in individual importers with a low level, ongoing, monitoring component to maintain confidence and trust of that importer once that has initially been established.

7.2.1 Risk Food

FSANZ has responsibility for identifying foods that potentially pose a medium to high risk to public health and advising the Dept of Agriculture accordingly. The Department classifies these foods as “Risk Foods”. Risk food is initially inspected and tested at a rate of 100 per cent against an identified list of potential hazards which includes micro-organisms and contaminants. After five consecutive consignments (cn=5) have passed inspection, the rate of inspection is reduced to 25 % (mf) and after a further 20 consecutive inspections pass, the rate is reduced to 5 per cent where it remains. If a consignment fails inspection the rate of inspection for future consignments from that importer returns to 100% and the process essentially restarts at the beginning.

Risk foods are held, ie is not released for sale, until they have passed inspection and testing. Consignments that fail inspection and testing (do not meet Australian standards) cannot be

imported. If these foods cannot be treated or altered to bring them into compliance with the Code the food must either be re-exported or destroyed. Failures related to labelling may, for example, in many cases be remedied through over-labelling with the required information as specified in the Code.

7.2.2 Surveillance Food

All food not designated as a Risk Food are considered to pose a low risk to human health and safety and are classified as 'surveillance food'. Consignment of surveillance food is randomly selected for inspection at a rate of 5% (mf) of consignments. The random selection of surveillance food consignments is done using electronic profiles in the Customs Integrated Cargo System. Information such as the importer, producer or the country of origin of the goods does not affect the random selection and referral of a surveillance food. Testing of surveillance food may include analysis for pesticides and antibiotics above accepted levels, microbiological contaminants, natural toxicants, metal contaminants and food additives.

Because surveillance food is considered to be low risk, they are released for distribution for sale before test results have been received. If the food fails testing, State & Territory food regulatory authorities are advised so they may consider if a recall or other action is required. Any action, such as a recall or withdrawal taken on goods released by an importer is at the importer's expense.

The inspection rate for surveillance food that fails inspection is also increased to 100 per cent until a history of compliance is established for the producer or importer of the food. The process for increasing inspection of surveillance food is referred to as applying a 'holding order'. A holding order remains in place until favorable test results are received. Following five consecutive passes, the rate of referral returns to five per cent of consignments.

7.2.3 Food Import Compliance Agreements (FICA)

Although somewhat outside the scope of this review, compliance agreements between food importers and the Department of Agriculture provide food importers with an alternative arrangement to the inspection and testing of their products under the Imported Food Inspection Scheme (IFIS). In brief where an importer can demonstrate that they have a robust, effective, documented assurance and audit arrangement to provide assurance of the safety and compliance of food they import, they have the option of entering into a FICA with the Department. The advantage for importers is that they gain faster and more convenient clearance of their products into Australia with a reduced rate of regulatory intervention by the Department. The food safety and compliance system criteria are based on Australian Standard ISO 22000:2005 (Food safety management systems-requirements for any organisation in the food chain). In order to enter a FICA importers must have a documented

food management system that verifies that imports comply with the Code. The food management system includes components such as :

- approved supplier programs
- product specifications
- verification that food received complies
- corrective action procedures to address non-compliance when found
- traceability and stock control processes
- manufacturer assurance
- food safety and compliance assessments
- process control (on arrival clearance)
- traceability
- verification

This section of this review provides examples of some risk proportionate regulatory measures in the registration schemes for agricultural and veterinary medicines in the EU, Canada and the USA. Australia is somewhat unique in having veterinary and agricultural chemicals regulated through the same regulatory agency. In each of the three international regulatory jurisdictions considered here, veterinary medicines are regulated through the medicines regulator with agricultural chemicals regulated through a separate agency. In Canada veterinary medicines are regulated in a directorate of the Health Products and Food Branch of Health Canada, and agricultural chemicals are Regulated through the Pest Management Regulatory Agency, a separate Branch of Health Canada. In the USA veterinary medicines are regulated through the Food and Drug Administration (FDA) and Agricultural Chemicals through the Environmental Protection Agency (EPA). In Europe agricultural chemicals are regulated through the European Chemicals Agency and veterinary medicines are regulated through the European Medicines Agency (EMA). As a consequence there are six agencies responsible across the three regions of interest covering agricultural and veterinary chemicals regulation. A comprehensive review of all six agencies' regulatory regimes is beyond the scope of this review. Consequently this section focuses on a number of identified regulatory concessions that have been made for low risk products with the objective of providing a discussion of examples of mechanisms available within the existing regulatory systems in Canada, USA and the European Union for agricultural and veterinary chemicals to conduct or prioritise assessments in a risk based manner. The initial draft of this section was prepared by John Frangos and his team from Golder and Associates (Golders), an international consultancy with officers in each of the regulatory jurisdictions being reviewed. Golders developed their report through the following tasks:

- Review of USA, Canadian and EU Schemes to identify risk based instruments.
- Consultation with agencies or regulatory officers to check understanding of the context and reasoning for the instruments applied.
- Investigation of a range of regulatory parameters that are risk based in the above mentioned regulatory schemes. These included (but were not limited to); data requirements, timelines, fees, exemptions, or streamlined assessments.
- For each instrument identified a description of the arrangements and a comment on the context of the arrangement (scientific or risk management rationale) was provided.

Where veterinary drugs are regulated through a division of the human drugs regulatory Agency, the full range of risk proportionate measures applicable to human drugs are also potentially available to the regulation of veterinary medicines. The approach taken in Australia by the TGA for human medicines is broadly consistent with that applied internationally. The detailed discussion of risk proportionate regulation by the TGA serves to illustrate the general principles applied internationally. The review of the EU, USA and Canadian regulatory environments therefore focuses predominantly on the agricultural chemicals aspects. A discussion of the FDAs approach to environmental risk assessment of veterinary drugs is also included as this has both parallels with, and differences from, that of the TGA and APVMA.

Table 11 Food Drug and Agricultural Chemical Regulatory Arrangements in Selected Jurisdictions

Jurisdiction	Human Medicines	Veterinary Medicines	Agricultural Chemicals	Food Chemicals
Australia	TGA	APVMA	APVMA	FSANZ
EC	EMA	EMA	EFSA	EFSA
USA	FDA	FDA	EPA	FDA
Canada	Health Products & Foods Branch	Health Products & Foods Branch	PMRA	Health Products & Foods Branch

8 Canada - Pest Management Regulatory Agency (PMRA)

8.1 Introduction

PMRA has five submission categories (PMRA 2013):

- Category A (new active ingredient (AI), major new use, import maximum residue limit (MRL) for unregistered AIs)
- Category B (new pest control product (PCP)/registered AI, PCP amendment, emergency registration, conditional registration amendment, import MRL for registered AI)
- Category C (includes changes to AI, product chemistry, new or changed labels, similar products, administrative changes or re-instatements)
- Category D (submissions through particular programs. [e.g., User Requested Minor Use Label Expansion; URMULE])
- Category E (research authorization/notifications)

Within each category there are subcategories with specific timeframes for review as well as data requirements. Review times range from 69 to 655 days plus completeness check (usually 37 days) and public consultation (45 days if needed). The exception is submission to Category D which follows the timelines of specific programs. For a group of multiple related submissions, the longer review timeline will usually apply collectively to all of the submissions in the group (PMRA 2013). Data requirements are dependent upon the site of application and whether the registration is for an end product (EP), AI, or MRL. There are 3 general categories of sites: agricultural and forestry, industry, and society. There are subcategories within each for a total of 33 "use-site categories".

Figure 4 Canadian Chemical Review Timelines

Category Subdivision	Completeness Check in Days	Review Time in Days (Months)*	Public Consultation in Days
Conventional chemical	37	655 (22)	45
Reduced-risk**, other biopesticides, NSCLP***	37	555 (18.5)	45
Microbials	37	470 (15.5)	45
Pheromones – SCLP****	37	285 (9.5)	45
Joint reviews	37	negotiated	45
URMUR	37	470 (15.5)	45
URMUR – SCLP****	37	285 (9.5)	45
Program 914	37	negotiated (<470 days)	45
Import MRL*****	37	655 (22)	n/a

* Review Time = the time after the end of the completeness check to the final regulatory decision. The review time excludes:
- a 45-day public consultation period if applicable
- time when a submission is "on-hold" pending the applicant

** Reduced-risk refers to the expedited review timelines as outlined in Regulatory Directive DIR2002-02, *The PMRA Initiative for Reduced-Risk Pesticides*.

*** Non Straight Chain Lepidopteran Pheromone

**** Straight Chain Lepidopteran Pheromone

***** Maximum Residue Limit

8.2 Exemptions

Pesticides used in research may be exempt from research permits or qualify for a notification in lieu of a research permit. Research permits are not required for conventional chemical pesticides used for small scale research that meet the following conditions (PMRA 1998):

- A new AI applied on a maximum of 5 ha of land that is owned or operated by the research establishment.
- A new AI applied on a maximum of 1 ha or 5% of total crop under research on land that is owned or operated by a co-operator (whichever is less).
- A registered AI applied on a maximum of up to 10 ha or 20% of total crop under research on land that is owned or operated by the research establishment or a co-operator (whichever is less).

A notification in lieu of a permit is applicable to small and medium scale research for (PMRA 1998):

- A new AI applied on a maximum of 5 to 50 ha of land that is owned or operated by the research establishment.
- A new AI applied to a maximum of 1 to 5 ha of total crop under research on land that is owned or operated by a co-operator (whichever is less).
- A registered AI applied to 10 to 50 ha of land that is owned or operated by the research establishment or a co-operator.

No exception is allowed, however, if the treated crop is intended for food or feed use without an existing MRL. Furthermore, the product cannot be applied to any water body or where runoff water may remove residues from the treatment area. The exemption and notification options do not apply to antimicrobial products, products for research in greenhouses, specific land use areas (e.g. domestic/residential areas, industrial premises, food handling areas, etc.) or structural pest control or fumigation products.

Additional details on exemptions from research permits of notifications in lieu of research permits for conventional chemical pesticides can be found in PMRA Regulatory Directive Dir98-05 (PMRA 1998)

8.3 Recognition of International Assessments – "Simplified Procedures"

Expedited reviews of reduced risk pesticides are possible through the PMRA Regulatory Directive 2002-02 (PMRA 2002). This directive applies to all Category A, Category B and URMULE submissions. The intent of the reduced risk program is "to encourage pesticide manufacturers to apply for Canadian registration of reduced-risk products that are currently available in the United States (US)" (PMRA 2002).

Reduced risk does not imply reduced data requirements. The program was designed to be an extension of the existing joint review program with the US and, as such, uses the same factors and format as the reduced-risk rationale provided by the applicant to the US Environmental Protection Agency (US EPA). Furthermore, upon receipt of the rationale and review done by the US EPA, PMRA will approve the same designation as the US EPA as long as the AI, EP and uses specified in the US EPA reduced-risk authorization are identical to those being submitted to Canada (PMRA 2002).

The expedited timelines for a reduced-risk pesticide submission are 18.5 and 12 months for review of a Category A and Category B submission respectively, and 217 days total for a URMULE reduced risk pesticide submission (PMRA 2013).

8.4 Non-Conventional Pesticides[2]

PMRA recognizes that the registration framework for conventional pesticides may not be appropriate for non-conventional pesticides. As such, registration of these substances should follow Regulatory Directive DIR2012-02 "*Guidelines for the Registration of Non-Conventional Pest Control Products*". This guideline encourages applicants to engage in a pre-registration consultation such that the eligibility of products under this directive can be determined as well as the type of information required in the application. The timeline of review will be similar to that of reduced-risk pesticides (PMRA 2012). Furthermore, non-conventional pesticides may qualify for exempted or reduced fees (PMRA 2012).

[2] In previous directives, the terminology "low risk biochemical and non-conventional pesticides" was used. As of 2012, they are now just referred to as "non-conventional pesticides".

9 United States - Environmental Protection Agency (US EPA)

9.1 Introduction

Pesticides can be submitted for registration with the US EPA under four categories – conventional pesticides, antimicrobial pesticides, biopesticides, and inert ingredients. Each category has different criteria for pre-submission meetings, registration requirements, timelines and fees. Timelines for review range from 3 to 24 months (US EPA 2013). There are also three types of applications - new active, new use and identical/substantially similar product.

9.2 Exemptions

Minimum risk pesticides are exempt from federal registration under section 25(b) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). To qualify as a minimum risk pesticide, all five of the following criteria must be met (US EPA 2014a):

- The product must contain **only** exempted active ingredients (listed here: http://www.USEPA.gov/pesticides/biopesticides/regtools/25b_list.htm#activeingredients)
- The product must contain **only** "Inert Ingredients of Minimal Concern" (listed here: http://www.US EPA.gov/opprd001/inerts/section25b_inerts.pdf).
- All active and inert ingredients must be listed on the label.
- The label cannot claim that minimum risk pesticides protect human or public health nor include any false or misleading statements.
- The label cannot include public health claims.

Pest control organisms (such as insect predators, nematodes, and macroscopic parasites) are also exempt from registration under FIFRA according to 40 CFR 152.20(a) wherein it has been determined that this class of pesticides has been adequately regulated by other Federal agencies (CFR 2011).

Exemptions also exist for emergency registration of pesticides wherein "a serious pest problem jeopardizes production of agricultural goods or public health but no pesticides are currently registered for that situation" (US EPA no date). If the situation meets the statutory definition of an emergency situation and safety standards for the pesticide use are met, temporary unregistered use of a pesticide is granted. Decisions on emergency exemption requests are typically conducted within 50 days.

9.3 Simplified Procedures

Simplified procedures are in place for amending registered pesticide products. For amendments that involve minor changes without the need for a review of scientific data, notifications can be made to a registration (US EPA 2014b). Examples of label modifications permitted through notifications include changes to a brand name, addition/deletion of pests

on the label, additional of indoor non-food sites for antimicrobial products, risk reduction statements, etc. Examples of product chemistry notifications include a change in the source of active or inert ingredients, changes to the source of starting materials for integrated systems products, and changes in the formulation process for non-integrated systems. For all notifications, the US EPA must be notified before the change is made and before the product is distributed or sold.

Non-notifications are changes that can be made without notifying US EPA. Examples of non-notification actions include the correction of label typographical errors, changes to non-pesticidal characteristics, changes to packaging size, etc. (US EPA 2014b).

Minor formulation changes (i.e. the addition, deletion, or substitution of one or more fragrances, colorants, or other inert ingredients in a formulation) can be made through an application for amended registration (US EPA 2014b). Minor formulation amendments may be eligible for an accelerated review if it meets the criteria outlined in Pesticide Registration Notice (PR) 98-10 (US EPA 1998).

Products that are either a) identical in use and formulation; or b) substantially similar in use and formulation; or c) "differ only in ways that would not significantly increase the risk of unreasonable adverse effects on the environment" can be registered as an identical/substantially similar (Formerly "Me-Too") product (US EPA 2014c). Registration applications for the identical/substantially similar product may cite the applicable data of the already registered product rather than submitting product-specific data for the new product. Under Section 3(c)(3)(B)(ii) of FIFRA, US EPA is required to expeditiously review applications for identical/substantially similar products (US EPA 2014c).

9.4 Self-Assessment

A program for the self-certification of product chemistry data is in place whereby registrants may choose to summarize in one page the products physical/chemical properties without submitting the study upon which the summary is based (Johnson 1998). The self-certification process applies to registration of a new combination of active ingredients that have already been registered. The registrant must generate or own the physical/chemical studies (conducted in accordance with US EPA guidelines) for the proposed formulation and make such studies available to the US EPA upon request. The use of the self-assessment program is optional. This program applies to manufacturing-use and end use products of conventional, biochemical and microbial pesticides for registration or reregistration.

10 United States – Food and Drug Administration (FDA)

Veterinary pharmaceuticals in the USA are regulated through the FDA which also has responsibility for human pharmaceuticals, cosmetics and food for regulation. In the context

of the current review the principle difference between the FDAs regulatory environment and that of the TGA is that the FDA is required to consider Environmental Risk Assessment, and the FDAs approach to this aspect of its work is discussed below.

10.1 Environmental risk assessment

The FDA although theoretically bound by a requirement to conduct environmental risk assessments on pharmaceuticals, through the National Environmental Protection Act (NEPA), has "categorically excluded" most pharmaceuticals for individual human or terrestrial animal use and food additives from the requirement to do so (US FDA, 2014). Specific exclusions from the relevant regulation (21CFR25) for animal pharmaceuticals are provided below;

- New animal drug applications that do not increase the use of the drug
- New animal drug applications for substances that occur naturally in the environment when the action does not alter significantly the concentration or distribution of the substance, its metabolites, or degradation products in the environment,
- New animal Drug Application for:
    - Drugs intended for use in non-food animals
    - Anesthetics, both local and general, that are individually administered
    - Nonsystemic topical and ophthalmic animal drugs
    - Drugs for minor species, including wildlife and endangered species, when the drug has been previously approved for use in another or the same species where similar animal management practices are used; and
    - Drugs intended for use under prescription or veterinarian's order for therapeutic use in terrestrial species

11 European Union (EU)

11.1 Introduction

In the EU, the active ingredients (AIs) must be registered at the EU level and products containing the AIs are registered at the Member State (MS) level. Registration of pesticides follows the regulations as set forth in Regulation (EC) No 1107/2009 and takes 2.5 to 3.5 years.

11.2 Simplified Procedures

11.2.1 Mutual Recognition

Since pesticide products must be registered in each member state for which they are used, sold or imported, the principle of mutual recognition was introduced to avoid duplication of work for both industry and Member States (EP 2009). The principle of mutual recognition states that "authorizations granted by one Member State should be accepted by other Member States where agricultural, plant health and environmental (including climatic) conditions are comparable" (EP 2009).

Product approval through mutual recognition (MR) can be conducted in parallel or in sequence but the exact procedures for MR applications may differ by Member States (UK CRD no date (a)). Parallel mutual recognition occurs when the MR application is submitted to multiple Member States with one Member State (i.e. the Reference Member State) being responsible for evaluating the application and providing the proposed conditions of authorization for the product to the other Member States (i.e. the Concerned Member States). The product is then authorized by the Reference Member State and concerned Member States at the same time (UK CRD no date (a)). Mutual recognition in sequence occurs with the product is first authorized in a reference member state, after which, an application for mutual recognition is sent to the other concerned member states. However, according to UK CRD (no date (b)) for both mutual recognition in parallel and mutual recognition in sequence, Concerned Member State may "propose to refuse to grant an authorization or to adjust the terms and conditions of the authorization to be granted if they can justify that such measures can be justified on grounds of:

- the protection of the environment;
- public policy or public security;
- the protection of health and life of humans, particularly of vulnerable groups, or of animals or plants;
- the protection of national treasures possessing artistic, historic or archaeological value; or

- the target organisms not being present in harmful quantities".

11.2.2 Simplified Authorization

The simplified authorization procedure allows for the registration of a biocidal product in multiple member states without the need for mutual recognition should it meet all of the following criteria (ECHA no date):

- "all active substances contained in the product appear in Annex I of the Biocidal Products Regulation and comply with the specified restrictions
- the biocidal product does not contain any substance of concern
- the biocidal product does not contain any nanomaterials
- the biocidal product is sufficiently effective
- the handling of the biocidal product and its intended use do not require personal protective equipment"

Although an application for mutual recognition is not required when a simplified authorization is granted, each concerned member state must be notified 30 days prior to placing the product in its territory.

11.2.3 Risk envelope

The aim of the risk envelope approach is to achieve an acceptable workload for Member States with respect to the authorization of PPPs and, in theory, can be applied to all sections of the dossier (EC HCPDG 2011). The risk envelope approach refers to the grouping of plant protection products (PPP) according to specific criteria (e.g. crop, application rate, number of applications, timing, etc.) such that an assessment of the group rather than each individual use can be conducted. Using this approach, it may further be possible to determine a "worst case group" or "worst-case use". The assessment of the worst-case group/use can then be applied to other groups where the Good Agricultural Practice (GAP) are the same or less critical. Under the risk envelope approach, a Member State may approve a product and its uses without requesting the evaluation from the Reference Member State should it pose less risk than an identified worst-case group (EC HCPDG 2011).

11.2.4 Substitution principle and Comparative Assessment

The aim of the substitution principle is to identify "active substances of greater risk to human, animal or environmental health, and put them forward as candidates for substitution" (EC 2009). These candidates for substitution are identified at the EU level with comparative assessments between the products containing the candidates for substitution and the alternatives presenting less risk being carried out at Member State level (EC 2009).

A substance is a candidate for substitution if any of the following criteria are met (Faust et al. 2014):

- "its ADI, ARfD or AOEL is significantly lower than those of the majority of the approved active substances within groups of substances/use categories,

- it meets two of the criteria to be considered as a persistent, bioaccumulative, and toxic (PBT) substance
- there are reasons for concern linked to the nature of the critical effects (such as developmental neurotoxic or immunotoxic effects) which, in combination with the use/exposure patterns, amount to situations of use that could still cause concern, for example, high potential of risk to groundwater; even with very restrictive risk management measures (such as extensive personal protective equipment or very large buffer zones),
- it contains a significant proportion of non-active isomers,
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, if the substance has not been excluded in accordance with the criteria laid down in point 3.6.3,
- it is or is to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as toxic for reproduction category 1A or 1B if the substance has not been excluded in accordance with the criteria laid down in point 3.6.4,
- if, on the basis of the assessment of Community or internationally agreed test guidelines or other available data and information, reviewed by the Authority, it is considered to have endocrine disrupting properties that may cause adverse effects in humans if the substance has not been excluded in accordance with the criteria laid down in point 3.6.5."

Comparative assessment is used to determine if ***all*** of the following criteria are met (indicating that substitution is mandatory) (EP 2009, Article 50):

- Alternatives have similar effect on target organism
- Chemical diversity sufficient to minimize resistance
- Alternatives significantly safer for humans and environment
- Sufficient product experience has been achieved
- Substitution would not present practical and economic disadvantages
- Impact on minor uses taken into account

Products registered under the comparative assessment are approved for 7 years instead of 10 years and cannot be authorized under the mutual recognition program.

12 New Zealand

Although New Zealand was not included in the initial scope for Jurisdictions to review the group approval procedure provides an example of an alternative approach to review of existing chemicals that may warrant consideration under some circumstances and is therefore included here.

12.1 Simplified Procedure - Group Approval and Downstream Regulatory Efficiency

Using the broad definition of a chemical within the GHS[3], a Group Standard is an approval for a group of hazardous substances under Part 6A of the *Hazardous Substances and New Organisms Act* 1996 (HSNO Act). In New Zealand Group Standards allow approval under the HSNO Act for a group of substances with similar hazardous properties and patterns of use.

The product groupings called 'Group Standards' is a simplified procedure based on GHS principles. The Group Standards are used as a simplified procedure to demonstrate compliance with Part 6A of the HSNO Act and to allow importers and manufactures to understand regulatory requirements for classification, hazard information, transport, storage and occupational handling.

The key part of a group standard is its 'scope'. The scope sets the allowed use and hazard parameters of the group standard, and may also set other limitations (e.g. allowable hazard classifications, specific use restrictions etc.). For a product to be approved under a group standard, it must fit within the scope of the group standard.

There are three group standards in New Zealand for Veterinary Chemicals:

- Veterinary Medicine (Limited pack size, Finished dose) Group Standard 2012
- Veterinary Medicines (Non-dispersive Closed System Application) Group Standard 2012
- Veterinary Medicines (Non-dispersive Open System Application) Group Standard 2012
- The group approval procedures of the HSNO Act also act to simplify the assessment and re-approval of groups of existing products as demonstrated by the following examples:

Organophosphate and carbamate (OPC) insecticides, an example. The reassessment program for OPCs started with reassessing four compounds; acephate, diazinon, dichlorvos and methamidophos. However, the NZ EPA decided that it was more *appropriate, efficient and cost effective* for all concerned to reassess the substances as a whole to ensure not only safe management of such substances but also to ensure that the suite of tools available for plant protection and biosecurity was not seriously undermined (NZ EPA 2013a).

- The reassessment included review of 60 approvals for paint formulations manufactured in New Zealand or imported. The following active substances were

[3] The GHS is an acronym for Globally Harmonized System of Classification and Labelling of Chemicals. It is a system for standardising and harmonizing the classification and labelling of chemicals. The approach is published by the United Nations (UNECE 2011) and has been implemented for classification of chemicals (including pesticides) in various parts of the world including Australia.

included in the review; 3(2H)-Isothiazolone, 4,5-dichloro-2-octyl- (DCOIT), Chlorothalonil, Copper (I) oxide, Copper pyrithione, Copper thiocyanate, Dichlofluanid, Diuron, Irgarol 1051, Mancozeb, Octhilinone, Thiram, Tolyfluanid, Zinc pyrithione, Zineb, Ziram. The following rationale for grouping the re-approval of these compounds is provided by the EPA (NZ EPA 2013b):

- Technical efficiency and effectiveness in reassessing as a larger group of antifouling paints than individually.
- Efficient use of industry and EPA resources by reducing the number of reassessments being undertaken
- Dealing with substances which have similar effects in a single group reassessment will ensure that any risks that may arise from the substitution of one antifouling paint substance for another are properly understood and managed.
- To ensure consistent and effective controls to manage risks are put in place across the group of substances.

13 Discussion

There are substantial conceptual, and legislative, differences between the structure and scope of the various Australian regulatory regimes for chemicals in Australia as illustrated in Table 12. None of the other regulatory systems reviewed here is directly equivalent to that of the APVMA but all have elements, or cover products/ingredients, that are similar to a greater or lesser degree to that of the APVMA.

Table 12 Principle Regulatory Approaches of the TGA, FSANZ and NICNAS

Agency	Regulatory Category	Regulated commodities	Safety Assessment Paradigms			Assessment Basis
			Hazard Based	Risk Based	Risk Benefit Based	
TGA	Therapeutic goods	Pharmaceuticals			+	Product Product Monograph (OTC)
		Complimentary/ listed medicines		+		Substance Self-Assessment
		Medical Devices		+	+	Product
FSANZ	Food and food constituents	Food Additives & processing aids		+		Substance
		Added nutrients		+	±	Substance
		Food Products		+	+	Substance Product Monograph
		Food from biotechnology	+	±		Modified crop
NICNAS	Industrial Chemicals	Industrial chemicals	+	±		Substance
		Cosmetics	+	±		Substance

+ Principle or predominant safety assessment approach, ± Secondary, limited, or ancillary safety assessment approach. The distinctions are a matter of degree rather than dichotomous.

NICNAS, and some aspects of the FSANZ and TGA, regulation is primarily substance based rather than product based. Most goods regulated by the TGA are regulated on a product by product basis, although a substantial proportion of those products are in essence regulated through substance specific approvals to reduce the regulatory burden on lower risk products. While FSANZ does not formally assess individual food products, some food standards provide specific regulatory requirements for classes of products such as infant formula and special medical foods and there are specific pre market requirements for novel foods and food produced from crops developed using biotechnology. The schemes also vary

in terms of the human health safety assessment paradigm applied, ranging from principally hazard based to a full risk benefit assessment. Although these approaches are outlined in Table 13, as discrete paradigms in reality they form an overlapping spectrum such that although the NICNAS approach is primarily a substance by substance hazard assessment there is scope to introduce elements of the broader risk assessment paradigms through the setting of limits for levels of a substance in finished products for example . The NICNAS scheme is philosophically different to the primarily risk based regulatory paradigm applying to food, some therapeutic goods and agricultural and veterinary chemicals, and particularly to the risk-benefit paradigm applying to prescription medicines and some medical devices. To a large extent this is necessitated by the substance based NICNAS regulatory regime, as opposed to the more commodity or product based foundations of the other regulators considered here.

Table 13 regulatory Human Safety Assessment paradigms for chemicals and chemical products

Concept	Description	Example
Substance based assessment	Assessments are conducted for Individual substances without, or with limited, regard to the formulation, presentation or use pattern of products that will contain that substance when marketed.	New industrial chemicals (NICNAS), new ingredients for listable medicines (TGA), new food additives and processing aids (FSANZ)
Product based assessment	Each new regulated product is assessed individually, having regard to the nature and concentration of every ingredient in the product, the presentation of the product and the purpose for, and manner in, which the product is to be used.	All human and veterinary prescription pharmaceuticals, Agricultural chemical products
Product Monograph assessment	Specifications are developed which set permissible ranges for allowable ingredients in a product for a specific purpose. Products complying with those specifications do not require, or require limited, further assessment.	Foods for special medical purposes (FSANZ) Pholcodine linctus (TGA)
Hazard Based Assessment	An assessment based on the range of adverse effects that a substance or product is capable of causing and the doses at which they occur.	
Risk	The likelihood that a substance with known hazards will produce adverse effects in exposed individuals at specific levels and routes of exposure when used in a defined manner for a defined purpose. Risk is a function of hazard and exposure.	Botulinum toxin is the most toxic, hazardous, substance known to man yet is used by injection for cosmetic purposes to reduce wrinkles. The risk from food contaminated with this toxin is extreme but that from the appropriate use of the injection is low. The difference lies in exposure levels, use pattern, product formulation etc.
Risk Assessment	The integration of hazard and route and extent of exposure to estimate risk to humans or the environment for a product or substance used for a specified purpose in a specified manner by a specific type of user.	

Risk Benefit Assessment	The direct weighing of identified risks of a product or substance against the likely benefits – usually but not necessarily for the same individual.	Anti-cancer drugs have severe side effects that would not be acceptable for most therapeutic purposes but the benefit of curing or arresting the progression of cancer outweighs the risk presented by those side effects

13.1.1 Applicant Risk

Although beyond the scope of this review, an important consideration is that in addition to differences in the regulatory structures in place for the various regulators there are differences in the capabilities and expertise available to the commercial entities regulated, both across and within regulatory regimes. To some extent any risk stratification of regulatory focus needs to factor in these differences in capability and include mechanisms to ensure commercial entities permitted to take advantage of any reduced regulatory burden are capable of adequately self-assessing or self-regulating their products. In this respect the confidence building aspects of the Imported Food inspection Scheme (IFIS) of the Department of Agriculture may be pertinent. The IFIS utilises a risk based process that recognises and facilitates the establishment of trust and confidence in individual importers to enable regulatory intervention to be decreased, or increased, based on the outcomes of inspections and testing.

13.1.2 Risk Proportional Regulation in Australian Agencies

Across all of the major chemical regulatory regimes a stratified risk based regulatory approach is applied, in theory and, with some exceptions, mostly also in practice. Each regulator has established a range of regulatory pathways that allow for most or all of;

1. Exclusion of substances/products or classes of substances/products from regulation by that regulator,
2. Exemptions from some or all otherwise applicable regulations or regulatory requirements for assessment and approval, but the product is retained within the scope of that regulators oversight,
3. Self-assessment of products or ingredients by the applicant/sponsor/notifier or supplier/manufacturer/importer
    a. With scope for random or targeted compliance audits,
4. Desk audit, without technical assessment, of the compliance with specific regulatory requirements,
5. Graduated risk based regulatory requirements and technical assessment for higher risk products/ingredients,
6. A fee and assessment time proportionate to the level of regulatory oversight and risk applicable to classes of products/ingredients,

7. Some level of recognition of international assessments of a subset of products/ingredients covered by the regulator.

Across the regulatory agencies considered here, both within Australia and Internationally, the norm is for human health risk assessment activities to be an integral aspect of the agency, as opposed to outsourced to another agency. The APVMA appears to be unique in drawing both its human health and environmental risk assessments from external agencies. The only exception to this general principle amongst the agencies reviewed here is the provision of environmental risk assessment to NICNAS by the Department of the Environment.

13.1.3 Environmental Risk Assessments

Neither FSANZ nor the TGA perform environmental risk assessments. The TGA has explicitly not adopted the European Medicines Agency (EMA) guideline on the environmental risk assessment of Pharmaceuticals for human use, in recognition of the limited range of environmental risk management options available and the unlikelihood of rejecting an otherwise valuable human pharmaceutical on environmental grounds. The Australian position is similar to that of the FDA which, although theoretically bound by a requirement to conduct environmental risk assessments on pharmaceuticals, has "categorically excluded" most pharmaceuticals for individual human or terrestrial animal use from the requirement to do so.

Environmental risk assessment requirements for NICNAS is stratified against risk in a parallel manner to human health risk assessment, based on the potential hazards of classes of substances or the quantity in use, which defines the upper bound for the potential exposure.

14 Options & Opportunities

A number of opportunities and options that may be suitable for consideration by the APVMA can be identified from the regulatory approaches of other Australian chemicals regulators and international Agricultural and Veterinary chemicals regulatory bodies. The options canvassed below are those that are potentially compatible with existing legislation or may require minor adjustment without a substantial shift in Policy settings. While there are potential strategies such as mutual recognition, as applies to medical devices between Australia and the EU, these approaches require formal binational treaties and have very substantial ramifications for both regulatory agencies and industry stakeholders. Equally the cost benefit equation for such approaches are complex and require careful analysis.

14.1 Listing & Self-Assessment By Applicants

The APVMA has considerable experience with, and data on, a wide range of active and non-active ingredients commonly used in agricultural and veterinary products. These ingredients have been assessed for efficacy on the target species and for safety to humans, crops or animals, and the environment, on multiple occasions in multiple use scenarios, and the nature and magnitude of the various risks have been extensively characterised. There is therefore scope to identify classes of products that are either inherently low risk or have extensively characterised and well defined risks, and are therefore potentially suitable for self-assessment and electronic listing by applicants, provided they consist only of a pre-approved list of ingredients within defined concentration ranges for a defined range of uses. This approach has the potential to reduce both the regulatory burden on manufacturers/suppliers and resource requirements within the APVMA, and therefore the overall cost of regulation, while maintaining at least the same level of protection for consumers, agricultural workers, the environment and crops and animals. Indeed, the necessary review of active and non-active ingredients prior to their inclusion in an electronic database supporting a listing process, combined with increased consistency in labelling arising from an algorithm based computer listing facility, inclusive of a suitable compliance audit program, has at least the potential to improve overall regulatory outcomes.

Products suitable for this approach may include;

1. Veterinary products for companion and other non-food producing animals;
    a. containing only pre-approved, unscheduled (& potentially some non-schedule 4) ingredients, and
    b. for use to manage veterinary conditions that are self-assessable by pet owners, and
    c. labelled according to defined requirements appropriate to the active ingredient and the condition being treated.
2. Home garden products;
    a. containing only pre-approved, unscheduled and schedule 5 ingredients, and
    b. labelled according to defined requirements appropriate to the intended purpose.
3. Agricultural products for non-food production use;
    a. containing only pre-approved, unscheduled and schedule 5 & 6 ingredients, and
    b. labelled according to defined requirements.
4. Agricultural products for food production use;
    a. containing only pre-approved, unscheduled and schedule 5 & 6 ingredients, and
    b. with existing MRLs, and
    c. labelled according to defined requirements.

5. Insect Repellents;
    a. containing only pre-approved, unscheduled and schedule 5 ingredients, and
    b. labelled according to defined requirements.

14.2 Product Monograph Based Approvals

A wide range of products for agricultural and veterinary applications in food production are based on existing approved active ingredients with common non active constituents. In many cases a large number of products with similar or identical actives and approvals for use are available. Where such products are not suitable for listing due to the poisons scheduling, or to other risk based considerations, an alternative approach (currently under trial by the TGA for registered OTC medicines) might be developed, where a monograph is prepared that specifies the range and concentration of actives and non-actives that may be used, the approved uses and the labelling requirements. Approval for such products would then be based on a non-technical desk audit to ensure the product complies with the applicable monograph. Many veterinary products, including those with a previously approved S4 active ingredient, may be suitable for this approach. Similarly many agricultural products, where there are, or are likely to be, a number of similar products on the market, may be amenable to this approach regardless of the poisons schedule applicable to the active, provided the active(s) and ingredients have all previously undergone the necessary technical assessments to characterise potential risks. This approach involves some resource investment in each product type for which a monograph is to be developed. Consequently, the approach is likely to be principally suited to product types that are likely to attract a substantial number of registrants.

14.3 Use of existing approvals in other regulatory schemes

Many agricultural or veterinary products have previously been approved in other regulatory jurisdictions either internationally or in Australia. Many veterinary drugs, for example, have previously been approved and used for human medicine and a considerable amount of experience in human therapeutics will have been gained prior to introduction as a veterinary medicine. The principle risks to humans associated with their use in non-food producing animals is essentially the same as that accruing to non-patients that may be exposed to the medicine when the medicine is prescribed for humans. These risks accrue either to carers handling, administering or applying the medicine to a patient or to an animal, or to a child that might inadvertently consume or be exposed to the medicine. There is scope to consider the range of data required to be assessed in these circumstances, particularly if a non-clinical (toxicology) assessment on the active ingredient is available from the TGA prescription medicines area and the non-actives have previously been assessed by the APVMA.

Similarly many non-active ingredients and biocides have been assessed for their environmental and/or human risks through the regulatory arrangements administered by NICNAS, the TGA or FSANZ and there is scope for these assessments to fulfil some or all of the assessment and data requirements for applicable Agricultural products.

14.4 Value Of Information (VOI) and Cost Benefit Considerations.

Data requirements should be matched to the available risk management options for veterinary drugs, applying a Value of Information (VOI) paradigm. In essence the VOI approach is to determine the scope of options available for risk management of, in this case, a product, and to ask what data has the potential to inform or change the RM decisions. Data that is unable to alter the RM outcomes is considered unnecessary. In practice there is a need for the APVMA and supporting agencies to be able to defend the registration/approval of products on the market and to be able to interpret and respond to adverse incident reports, so there will frequently be a need for more data than a strict VOI approach would dictate to ensure the range of potential hazards is fully characterised. There is however the potential to tailor the level, detail and resource requirements of the risk assessments using the VOI approach. In this regard, other than rejection of an application, the Risk Management (RM) options available for a schedule 4 veterinary tablet for companion animals for example, are largely confined to child resistant closures, and warnings to keep out of reach of children and to seek medical advice if swallowed. More extensive label statements are an option, but in most cases are unlikely to have any greater effect on the actual risks of the product in use. On this basis an intensive and extensive assessment of the original data would be unlikely to meet a VOI consideration where an existing evaluation was available – a preclinical toxicology assessment from the TGA for example or a reasonably detailed assessment from the FDA or the EMA. A similar conclusion would be drawn from a cost benefit consideration of the most appropriate level of regulatory scrutiny for products of this type. Similar conclusions would apply to environmental risk assessment where risk management is largely limited to label statements around disposal of unused tablets for example. For veterinary products intended for food producing animals, particularly in high concentration animal husbandry environments such as feed lotting, quite different considerations may apply as is also true where more extensive human or environmental exposure may result – eg spot on formulations, washes, drenches or similar products.

For lower risk agricultural and veterinary active ingredients extensively assessed internationally, and where a comprehensive monograph or report of that assessment is available such as those from the WHO JMPR, consideration might be given to using such assessment as the basis for the Australian assessment to reduce both time and cost to the regulator and the applicant. Where two or more major regulatory jurisdictions (eg Canada, USA, EU, WHO) have published assessments, the data requirements might be considered for

further refinement, to a comprehensive summary &/or pre-identification of pivotal studies. In each case, a requirement for the underlying data to be submitted to allow cross referencing of the report(s) to the original data and to allow any interpretive point of contention to be resolved may be advisable. This approach has, at least in theory, been applied by the TGA for prescription medicines and is applied to some extent by FSANZ for food contaminant issues, and more extensively to food flavouring chemicals.

14.5 Conclusions

Risk proportionate regulatory Frameworks are the norm for Australian Chemical Regulatory agencies, providing reductions in regulatory burden and agency resource utilization for low commodities or commodities that have previously had their risks extensively characterized and for which risk management or risk mitigating strategies have been established. These frameworks also employ various strategies to manage the risks arising from the capabilities and behaviors of applicants and consumers of the commodity regulated, and the risks associated with the commodity itself. This report has provided an overview of the various strategies employed by a range of key regulatory agencies in Australia and New Zealand and identified a number of options through which the APVMA might seek to improve the risk proportionality of its regulatory framework.

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