THERAPEUTIC GOODS ADMINISTRATION

Submission to the Productivity Commission Review of Cost Recovery by Commonwealth Agencies

4 December 2000

Table of Contents

Executive Summary

The Therapeutic Goods Administration (TGA) administers the *Therapeutic Goods Act 1989* (the Act) with the object of ensuring quality, safety, efficacy and timely availability of therapeutic goods. In doing so, it aims to minimise the regulatory burden (including delay) to industry.

Benefits from Government to the Therapeutic Goods Industry

The therapeutic goods industry receives substantial benefit from Government, including five years additional protection under patent and data protection laws, remuneration under the Pharmaceutical Benefits Scheme (cost to Government over $3 billion per year), the Pharmaceutical Industry Investment Program ($300 million per annum under the new scheme and over $1 billion under the old Factor (f) scheme), and other government activities. These include purchases by State hospitals and the Department of Veterans Affairs, and promotion through programs such as immunisation and safe sex campaigns.

Costs borne by Government as a result of the use of therapeutic goods

As well as these benefits to the pharmaceutical industry, Commonwealth, State and Territory Governments bear many of the costs of use of therapeutic goods. While they bring benefits they are also responsible for a substantial morbidity and occasional mortality. Estimated costs of hospitalisation are estimated to be at least $300 million per annum and there are other substantial non-hospital costs and social costs associated with the community's use of medicines. These costs are incurred as a result of the use of all therapeutic goods, not just prescription medicines.

Improvements in TGA's efficiency that have minimised cost to industry

The TGA recovers its costs through four types of GST exempt fees: application and evaluation; annual charges for maintenance of listing or registration; manufacturing licences, and GMP inspections/audits.

In the transition to full cost recovery from 1 July 1998, the TGA was able to deliver a substantial financial return to industry. This was in the form of a significant discount on the increases (in excess of 60% in some cases) that would otherwise have been payable if the TGA had simply doubled the level of fees and charges payable at the 50% level on 1 July 1996. This was made possible through the implementation of substantial reforms benefiting each industry sector and through increased efficiencies across the TGA. In this context, it should be noted that despite the recent overall increases in fees and charges, the current overall level of cost recovery still falls short of that notional 100% target. TGA is closely monitoring this situation to determine whether it can continue to maintain fees at present levels.

Other TGA activities to minimise regulatory impact and maximise its benefits

In another effort to minimise the regulatory burden on industry, TGA has sought to harmonise the Australian regulatory requirements with international standards and practices. Bilateral and mutual recognition agreements ensure efficiency both within the TGA and industry in this regard.

The TGA's high standing internationally also provides Australian industry with a substantial benefit when marketing overseas. The fact that a therapeutic good is on the Australian Register of Therapeutic Goods (ARTG) is of great commercial benefit.

Close links are maintained world-wide and a constant stream of visitors from overseas regulatory agencies, particularly from Asia, come to TGA which enhances acceptance of Australian products in these markets. The costs for many of these visits are met by the visitors themselves or are subsidised by organisations such as AusAid and the World Health Organisation.

The fees cover the cost of all activities that fall within the scope of the Act. These include:

- pre-market evaluation and approval using a risk-based framework – the lower the risk the easier the process is;
- licensing of manufacturers with attendant inspection and auditing both for Australian and international purposes;
- post-market monitoring to ensure compliance and safety;
- management of the ARTG physical files and database, a resource central to TGA's operations; and
- approval of therapeutic goods for export.

These activities involve participation in international committees, establishment, management and participation in numerous Australian committees, and management of the TGA itself. The committees are both regulatory and consultative, with industry sectors and with States and Territories that have responsibilities for regulation other than for incorporated sponsors or those trading interstate.

The budgeted amount for running the TGA this year is $48 million. More than half of this amount is related to prescription medicines with the rest being fairly evenly spread over several other activities.

Performance of the TGA versus other regulatory agencies

The best international comparison for regulatory agencies is the time taken to evaluate New Chemical Entities (NCEs). A study published in 1998 showed that in the period 1990-1995 TGA's performance steadily improved and was essentially the same as most comparable countries. Evaluation times for NCEs remained constant over the second part of the 1990s but there was a considerable rise in throughput in the prescription medicines area for other activities (especially new indications for existing medicines) and this work competes with the NCEs for resources. There is a significant resource/time trade-off in this work to which the TGA has responded by greatly increasing efficiency while holding resources down. They are now at the same level as they were five years ago, when compared on a like-with-like basis.

Australia's system for listing or registering complementary medicines is unique in the world. Sponsors can list a product in days whereas virtually any other part of the Western world requires either full evaluation taking months, or the product has to be treated as a food and can make no therapeutic claim. Australia's unique system, we strongly contend, is world's best practice in term of both timeliness and public safety.

95% of devices are listable goods and most of those are routinely listed on the ARTG within 10 days or less for a fee of only $240. The registrable devices currently take an average of 60 days. The comparison with other countries is complex but the data demonstrate that TGA is **meeting or bettering** the performance of comparable countries across the board (see section 4.1.3).

The level of fee recovery overseas is another obvious comparison that can be made. The UK has had full cost recovery (including a 6% return on capital) since 1992, New Zealand meets 40% of Medsafe's costs from Crown revenue but the rest is from non-government sources, Canada recovers over 50% of the therapeutic products program in fees (higher for some areas, e.g. devices). Singapore and Indonesia have announced a move to full cost recovery and other European countries are also substantially cost recovering.

Australia has a unique process of sector agreements between TGA and the medicines industry and negotiations are under way with the medical devices industry. Each agreement sets out times frames that are always much less than the statutory time frames. They are effectively 'performance contracts' between TGA and industry. Industry can influence the content of these through a resources/performance trade off. The consultation process that resulted from cost recovery has led to increased transparency, openness and accountability.

In summary the TGA has been highly successful in implementing the 100% cost-recovery policy introduced by the Government in 1997-98. The cost recovery fees and charges at present are still under what they would have been if a simple doubling of the 50% level had been implemented. It has done this while greatly improving the time taken to list and register therapeutic goods, while handling increasing volumes of work, and while the TGA staff level remained fairly static.

Abbreviations

ADEC	Australian Drug Evaluation Committee
AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
AIHW	Australian Institute of Health and Welfare
ANAO	Australian National Audit Office
APMA	Australian Pharmaceutical Manufacturers of Australia
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
BSE	Bovine Spongiform Encephalopathy
CHC	Complementary/Complete Health Care Council
CMEC	Complementary Medicines Evaluation Committee
DVA	Department of Veterans Affairs
ELF	Electronic Lodgement Facility
EMEA	European Medicines Evaluation Agency
GMP	Good Manufacturing Practice
GST	Goods and Services Tax
MCA	Medicines Control Agency [UK]
MEC	Medicines Evaluation Committee
MIAA	Medical Industry Association Of Australia
MRA	Mutual Recognition Agreement
NCCTG	National Coordinating Committee for Therapeutic Goods
NCE	New Chemical Entity
NCP	National Competition Policy
NDPSC	National Drugs and Poisons Scheduling Committee
OTC	Over the Counter
PBS	Pharmaceutical Benefits Scheme
PER	Pharmaceutical Evaluation Reports
PIC	Pharmaceutical Inspection Convention
PIIP	Pharmaceutical Industry Incentive Program
PYLL	Person Years of Life Lost
RIS	Regulatory Impact Statement
SUSDP	Standard for Uniform Scheduling of Drugs and Poisons
TDEC	Therapeutic Devices Evaluation Committee
TGA	Therapeutic Goods Administration
TICC	TGA-Industry Consultative Committee
TPP	Therapeutic Products Program
WHO	World Health Organisation
WTO	World Trade Organisation

1 History of Cost-Recovery in TGA

1.1 Background

The Australian community expects therapeutic goods to be safe and of a high quality, to a standard equal to that of comparable countries. Legislative responsibility for the quality of therapeutic goods lay with States and Territories until a decade ago when the *Therapeutic Goods Act 1989* (the Act) came into force. This greatly simplified the requirements for industry, creating a single set of laws where there had previously been separate non-uniform State laws, and consolidating the law with the drug evaluation activity that the Commonwealth was already undertaking. At the time the Act was proclaimed in 1991, the Therapeutic Goods Administration (TGA) was established as a Division within the Commonwealth Department of Health and Aged Care. The TGA administers a national system of regulatory controls for the quality, safety, efficacy and timely availability of medicines and medical devices used in or exported from, Australia. Establishment of the TGA was a great advance in simplifying the regulation of medicines and medical devices in Australia, and brought the Australian system of regulation into line with world's best practice.

The principal client industries are the pharmaceutical, complementary medicines and medical devices industries. TGA aims to keep the regulatory impact on business to a minimum. This is achieved through a risk management approach which includes pre-market evaluation and approval of therapeutic products, licensing of manufacturers and post-market surveillance. In addition, the TGA aims to minimise potential public health risks posed by chemicals used in the community. This is achieved by providing advice to other regulatory authorities on toxicology, pre-market assessment and public health issues relating to agricultural, veterinary and industrial chemicals.

1.2 Legislation

The legislative basis for the national system of controls is the *Therapeutic Goods Act 1989* and the *Therapeutic Goods (Charges) Act 1989*. The Act prescribes the requirements for inclusion in the Australian Register of Therapeutic Goods (ARTG), and, together with its associated regulations, set out the steps, time frames, fees and charges.

Essentially, any product for which therapeutic claims are made must be either listed or registered in the ARTG before it can be supplied in Australia.

Listed products are considered to be of lower risk than registered ones. Listed products are assessed by the TGA for quality and safety but not efficacy. The sponsor is required to hold evidence of efficacy for listed goods.

Products assessed as having a higher level of risk must be registered (not listed). The degree of assessment and regulation they undergo is rigorous and detailed, with sponsors being required to provide comprehensive safety, quality and efficacy data. Those products which are for export only are listed (not registered) in the ARTG.

As the TGA's regulatory processes were developed from a series of State/Territory based regulatory environments that included fees, there was a move to include cost-recovery from the start in the TGA. This is reflected in the legislation setting up the TGA. The *Therapeutic Goods Act* 1989, the Therapeutic Goods (Charges) Act 1989, and their associated regulations dating from 1990, together form the principal legislative basis for TGA operations and charges. The cost-recovered revenue is accumulated in the TGA's Special Account.

1.3 Cost Recovery

In 1991, the Government introduced fees and charges from the therapeutic goods industry for applications, good manufacturing practice inspections and annual licensing. When introduced, the fees and charges were set out with the aim of achieving 50% cost recovery over the same set of services as is currently covered. In 1992/93 this generated some 28% of the total revenue requirement for the TGA. It was then agreed with industry to move, over the next three years, to reach the 50% target.

By July 1996, the 50% target for cost-recovery was achieved. In setting the 1996/97 budget the Government announced that the TGA would move to 75% cost recovery over three years. Then, in the 1997/98 Budget the Government determined that 100% cost recovery would be introduced from 1998/99.

2 The Rationale for the Recovery of TGA's Administrative Costs

Industry representatives sometimes argue that they should not pay for those TGA activities which they consider to be of a public health or public administration nature, on the basis that these do not provide a direct service to industry. This section examines why the TGA's activities should be seen in the broader context of Government relationships with industry and why, therefore, the cost recovery arrangements are justified.

2.1 Benefits to industry from the Australian regulatory framework

Commercial benefit

It is important to emphasise that TGA's decision gives sponsors marketing approval for their registered or listed products in Australia. This decision thus confers a large commercial benefit. Further, as TGA is one of the three or four most esteemed regulators in the world, TGA approval is also a powerful global marketing tool for those firms seeking to sell their products overseas. Additional marketing benefits are provided to industry through TGA's role in negotiating international treaties and agreements and through the positive profile it maintains with governments in Asia and across the globe.

Patent and data protection

The Act includes provision to protect submitted data from use by third parties, such as generic manufacturers using the originator's data to register generic copies of originator drugs. Registered products containing a new chemical entity will be protected for up to an additional five years. During this period, another company wishing to register a generic copy of the product will be required to seek agreement of the originator company to use its data, or otherwise develop its own data package. In a further commercial benefit to the therapeutics industry, the *Patents Act 1990* has extended patent terms for pharmaceuticals registered by the TGA for up to an additional five years. This measure puts Australian companies on a more equal footing with their competitors in the US, Japan and Europe.

2.2 Government programs that benefit industry

Programs that benefit industry either incidentally or as a deliberate strategy include:

The Pharmaceutical Benefits Scheme. This pays over $3 billion per year to pharmacists for medicines, with the patient co-payment adding a further $600 million. The pharmaceutical industry is the end recipient of much of this money. Under the structure of the Scheme, the supplier receives 90% of the Government agreed price to the pharmacist, the wholesaler gets 10% of that price and the pharmacist receives a mark-up of 10%, plus a dispensing fee.

Pharmaceutical Industry investment Program (PIIP). This is a direct subsidy to the pharmaceutical industry to ensure high levels of profitability are maintained for those undertaking research and development in Australia. This program replaced the Factor (f) scheme in 1999 and runs for five years with a review at four years. It entails expenditure of $300 million by the Commonwealth over that time to compensate the industry for its monopsony purchasing power under the PBS. It pays certain companies an additional amount for their products subject to meeting research and development targets.

The former Factor (f) Scheme operated for 11 years, and provided funding of $1.15 billion over that whole period for 17 companies, of which $958.2 million was paid as direct entitlements.

Other government purchase of pharmaceuticals. State hospitals are funded in part from Commonwealth funding and the medicines for veterans and their dependants is entirely Commonwealth government funding. These are also significant flows of other government funds to the pharmaceutical industry.

2.3 Managing the risk and consumer confidence post-marketing

Many of the registered therapeutic goods are complex and toxic chemical entities (such as prescription pharmaceuticals) or are highly advanced technological devices, with the inherent presence of risk in their use – potentially tragic or even fatal. In a market of this nature it is entirely appropriate that any additional costs from the public health component of activities such as surveillance, monitoring adverse drug reactions, recalling defective devices etc should be picked up by the industry itself as the industry would suffer loss of consumer confidence if adverse events get wide publicity (as they tend to) and because it is very difficult to separate the public and private components of such activities. The annual TGA fee to keep a product on the Register contributes towards meeting the cost of these post-market activities which in turn contribute to the quality and safety of therapeutic goods. But it must be emphasised that the cost to the health system of any further intervention or activity beyond the surveillance component is borne by the Commonwealth and State governments, not industry. The nature and extent of these additional, and unrecovered, costs are discussed below.

Industry is a substantial beneficiary from government health programs in a number of other ways which this section will outline. This needs to be borne in mind when considering the precise apportionment of costs that should be recovered.

2.4 Why both pre-market assessment and post-market surveillance?

One might assume that if the pre-market assessment has been completed diligently that post-market surveillance is not necessary. Both are essential, however, to ensure ongoing and adequate safety of medicines and devices on the market.

Compliance (post-market activities), including monitoring and enforcement of standards, contribute significantly to a level playing field for all sponsors of therapeutic products by ensuring that sub standard, non-compliant or counterfeit products are removed from the market. This, when combined with an effective system of product recalls, means consumers can be confident that the products they buy are safe for their intended use.

Risk is a function of intrinsic hazard and the level of exposure of people to that hazard. Initial evaluation of a medicine or device is based on relatively small numbers of both animals and humans. This will detect high frequency events well enough and if they are serious the likelihood is the medicine will not get on the market. Most medicines approved for marketing will have a significant level of low-impact adverse effects such as transient nausea, or rashes, etc.

Once on the market, however, a larger, older and sicker population will use the medicine. This may result in adverse effects which are rare and sometimes serious. These may not have been expected on the basis of the pre-market data. Reference to the Australian Adverse Drug Reaction Bulletin, published by the TGA will provide numerous examples.

Case Study – Cyclosporin and St John's Wort

ADRAC Bulletin, August 2000 (vol 19 no. 3)

CYP3A4 is the most abundant cytochrome P450 enzyme in the liver and gut wall. It has a number of important substrates (eg. nifedipine, cyclosporin, simvastatin) as well as specific inducers (eg. carbamazepine, rifampicin) and inhibitors (eg. erythromycin, verapamil, grapefruit juice). In a report to ADRAC, a 50 year old female with a renal transplant was taking cyclosporin [used to prevent transplant rejection]. Her blood concentrations of cyclosporin were stable for the weeks before she began to take a St John's wort preparation. Within a period of 22 days after starting to take this product, her blood cyclosporin concentration had fallen from around 180 ug/L to 42 ug/L and one week later it was 40 ug/L. The treating doctor could find no other cause for the change in cyclosporin concentration and asked the patient to stop taking St John's wort. About 6 days later, the concentration had risen to 89 ug/L and a further 8 days later it was 150 ug/L.

A recent study has shown a large reduction in the concentration of an HIV protease inhibitor, indinavir [i.e. used to treat HIV], by concomitant St John's wort.[1] Since CYP3A4 is the only major route of metabolism for indinavir, this study provides strong evidence that St John's wort induces CYP3A4. Two cases of heart transplant rejection due to reduction in cyclosporin blood concentrations have also been reported.[2] Apart from the rejection, these two cases are very similar to the ADRAC report. It seems likely that St John's wort induces CYP3A4 and this results in increased metabolism of, and consequent reduction in the blood concentration of, cyclosporin

References:

I. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J. Indinavir concentrations and St John's wort. *Lancet 2000*; 355: 547-8.

2. Ruschitzka F, Meier PJ, Turina M, Luscher IF, Noll G. Acute heart transplant rejection due to Saint John's wort. *Lancet 2000*; 355: 548-9.

2.5 Costs incurred by governments as a result of medicines use

As well as being a major purchaser of medicines, State, Territory and Commonwealth governments pay for the adverse effects that result from use of medicines. The costs of managing adverse outcomes of medicine use is very high.

Medicines have revolutionised living in the western world with, for example, modern antibiotics, anaesthetics and medicines to treat chronic disease having a marked impact on the quality and duration of human life. The use of medicines in Australia is, justifiably, very common and expectations are that the products on the market are of high quality, and are safe and efficacious. Safety is a balance of risk and benefit. Where the benefit is great, such as treating cancer, the level of acceptable risk may also be high. No medicine can be said to be completely safe. Balancing risk and benefit lies at the heart of the mission of the TGA.

The cost of adverse outcomes from medicines

In 1997 there were 195 million prescriptions dispensed in Australia, not including those from the public hospital system. This represents 10 prescriptions per person in that year. The 1995 National Health Survey revealed that in the two week survey period 60% of people had taken a medicine. Some 25% reported taking vitamins and minerals and 9% reported taking complementary medicines. Of those aged 65 years or more, 86% took a medicine in the preceding two weeks and 59% took three or more medicines. (Roughhead et al[1], submission to the Review of Drugs, Poisons and Controlled Substances).

Unfortunately, however, drug-related medical misadventure is a major source of morbidity and sometimes mortality. The total health system cost of medical and surgical misadventure, including adverse drug reactions, has been estimated as $401 million (Mathers and Penm [AIHW][2]). The harms associated with use of medicines in the community include unintentional poisoning, intentional poisoning, medicinal misadventure, abuse and diversion for abuse. The cost of the first three of these harms were described by Mathers and Penm. Listed below are some of their data.

Table 1

External causes of injury health system costs($millions) and PYLL–75 by sex 1994

	Total cost $m	Males			Females		
		Total costs	Deaths	PYLL–75	Total costs	Deaths	PYLL–75
Poisoning	26	13	211	8,506	13	115	3,746
Medical & Surgical Misadventure*	401	194	28	417	207	23	256
Suicide and self inflicted injury*	72	35	1891	63,844	38	454	13,994

*These are obviously not only drug related but a significant proportion are.
PYLL – person years life lost.
Source: Mathers and Penm (1999)

A higher figure for **total** direct cost of unintentional injury ($156 million) and a total direct and indirect cost figure of $600 million has been estimated (see Moller (1999) at www.nisu.flinders.edu.au). based on data from Victoria (Watson and Ozanne-Smith[3]).

Roughead[4] estimates that at least 80,000 hospitalisations annually are medication related. She estimates the cost of these at $350 million in hospital costs alone (although this seems high if the AIHW figure is accurate). Based on her analysis, she concludes that half of these are potentially preventable.

Over-the-counter medicines have also become more potent as 'switching' of medicines from the prescription only category has developed world wide. Anti-inflammatory medicines, for example, have been more widely used and this inevitably means greater incidence of the serious gastro-intestinal side effects.

Acute unintentional poisoning, particularly in small children, is a source of harm that particularly arises from over-the-counter products. Routley et al [5] estimated that 74% of 4,600 cases of poisoning in Victorian children under 5 from 1987-1994 were medication-related. Paracetamol was the most common, with others such as asthma medications and cough and cold remedies also commonly involved.

Complementary medicines are also capable of causing harm. The Review of the TGA [6] cited a number of cases where 'natural' medicines had been or could be responsible for illness and even death and the case study above provides one example. Another example occurred last year in Western Australia where a young girl died as a result of taking a guarana-containing product that she did not realise contained caffeine. All therapeutic goods in Australia containing guarana are now required to be labelled with their caffeine content.

And in June this year regulatory interest worldwide focussed on the problem in certain Chinese medicines of substitution or confusion of a range of relatively safe herbs with *Aristolochia* species. *Aristolochia* has been known to cause kidney damage, and an article published in the New England Journal of Medicine in June put forward strong evidence suggesting the herb also caused cancer of the urinary tract. All potentially affected products on the ARTG were tested by the TGA with the result that eight of them were subject to recall action, on safety grounds. The TGA is now working with the States and Territories and the Australian Customs Service to ensure the risk of entry of any further *Aristolochia* is minimised.

In summary, while the data are sometimes non-specific, it is clear that there is a substantial sum of public money spent on drug-related illness, particularly from prescription medicines but also from OTC and complementary medicines. While the benefits clearly outweigh the risks, the risks are significant and costly to manage.

Adverse effects from devices, while neither as well documented nor as costly, do occur and the costs are borne, in part, by governments through hospitalisation.

A recent report to the Australian Health Ministers Advisory Council by the Australian Council for Safety and Quality in Health Care[7] has identified as one its three priority areas: "Better using data to identify, and learn from and prevent error and system failure". In relation to the regulation of devices, the Council has set a goal of achieving a national 'code of practice' for promoting effective feedback from national data sets and registers, such as device tracking.

2.6 Improvement in efficiency in the operation of TGA

The TGA has steadily increased the number of applications it processes each year, as can be seen in the table below. Since 1995-96, there has been proportionally greater growth in some types than others, e.g. applications for registrable therapeutic devices have doubled, and those for listable medicines and listable therapeutic devices by almost 40%.

Table 2

TGA applications by type

Type of application	1995-96	1996-97	1997-98	1998-99	%change 1995-96 to 1998-99
Prescription medicines	806	993	1,006	1,133	40.5
Non-prescription medicines	420	420	556	540	28.6
Low risk non-prescription medicines (listable medicines)	2,173	2,176	3,052	3,564	64.0
Export only medicines	518	506	451	517	0.0
Therapeutic devices subject to evaluation (registrable devices)	72	140	187	144	100.0
Therapeutic devices not subject to evaluation (listable devices)	1,830	2,143	2,525	2,334	27.54
Certificate of Pharmaceutical Product	2,263	3,027	2,643	3,748	55.62

Source: Department of Health and Aged Care Annual Report 1998-99

Over the same period, while the TGA staffing level has remained fairly static, it is clear that TGA's productivity has improved dramatically. On 30 June 1992 the staff number was 369 and in 1996 was 365, one person less than it is today, against growth rates in applications processed in excess of 30% over 1995-96.

Following the introduction of the Electronic Processing Facility (ELF) in mid-1996, processing times for entry of low-risk medicinal products in the ARTG have come down from approximately five months in 1994/95 to ten days or less for around 90% of applications.

Similar reductions in processing time have been seen with devices. Over the last two years average approval time for registered devices went from 86 to 56 days and listed devices went from 27 to less than 8 days. A devices electronic application lodgement system (DEAL) is soon to be commissioned and this will greatly improve ease and speed of listing and registration of most devices. DEAL will be unique in the world.

2.7 International treaties and agreements

TGA participates in international harmonisation initiatives which enable Australia's therapeutic goods industry to be exposed to current trends and new technologies, and to further the harmonisation of Australian regulation of therapeutic goods with comparable countries. For example, Australia has representatives on the Global Harmonisation Task Force and associated Study Groups, which include the European Union, United States, Canada, and Japan, dealing with the development of standards for international medical device harmonisation.

An example of regional cooperation is the Regulators' Forum, which comprises the regulators of therapeutic goods from 14 countries in the Asia Pacific region. At a recent meeting in Sydney they issued a "Sydney 2000 Declaration" supporting shared information and experiences about the self-medication industry. This Declaration can be seen as a first step towards harmonisation in the region.

Bilateral agreements covering the exchange of evaluation reports and information on medicines under evaluation exist between Australia, Canada, and New Zealand. Australia and New Zealand are members of the Pharmaceutical Evaluation Reports (PER) Scheme for the supply of evaluation reports on pharmaceuticals. PER was established by the European Free Trade Association countries in 1980, but it did not work as originally anticipated. Over time it has become less useful to Australia with the advent of the European Medicines Evaluation Agency (EMEA) and regulatory constraints that prevent it making reports available in a timely manner.

The TGA's capability to assess medical devices to European standards has been specified in the Mutual Recognition Agreement (MRA) with the European Union in relation to medical devices, which took effect from the beginning of 1999.

2.8 What do these issues, taken together, mean for TGA fees?

The TGA is of the view that the cost recovery of its regulatory processes is only part of the total cost to Government of medicines and devices. These costs include the considerable sums provided to the pharmaceutical industry as a purchaser of medicines through the PBS and the PIIP arrangements, by DVA and by State and Territory health services, as well as the cost of treating adverse effects of medicines and devices. The work related to being an integral part of Government is cost-recovered on the basis that **all** regulatory effort by the TGA is undertaken solely because the industry exists, and consumers have a right to be sure that all therapeutic substances and appliances are safe to be used in accordance with the "licences" and "approvals" granted by the TGA.

Any cost incurred as a result of the fact that the TGA is a government agency are small compared to the revenue flowing from governments to the pharmaceutical industry, and the costs to governments of treating the adverse effects of use of the industry's products.

3 Approaches used by TGA to administer the *Therapeutic Goods Act* 1989

The Act and its associated regulations cover not only medicines but also medical devices and complementary medicines. This includes specialised medicinal products such as blood and blood products.

3.1 The work of the TGA itself

The TGA exerts control over the supply of therapeutic goods through five main processes:

1. Pre-market evaluation and approval of products intended for supply in Australia:
    - "high risk" products are subject to the most rigorous evaluation through the Australian Drug Evaluation Committee (mainly prescription medicines), the Medicines Evaluation Committee (over-the-counter medicines), and the Therapeutic Devices Evaluation Committee (registrable devices), with sponsors being required to provide comprehensive data on quality, safety and efficacy;
    - "low risk" products (most complementary medicines) are subject to a less rigorous review (listing), focussing on quality and safety only, not efficacy; they have lesser data requirements than the "high risk" category. The listing system requires self-assessment of efficacy; and
    - once approved by TGA, the products are registered or "listed", and entered on the ARTG.
2. Licensing of manufacturers:
    - a licence to manufacture specifies the specific products, the manufacturer and the premises where manufacture takes place. More than one licence is issued if there are different sites of manufacture;
    - applications for licensing are issued through an inspection, or audit of premises, including overseas; the audit uses the appropriate code of Good Manufacturing Practice;
    - once issued, a licence remains in force until it is suspended cancelled or revoked; and
    - follow-up audits are conducted every 15 to 24 months.
3. Setting of standards for therapeutic goods
    - standards are set and revised to comply with international approaches and standards. This process has resulted in an effective decrease in the overall

number of standards and greater harmonisation with international practices for those that remain;

- all Standards are constantly under review with the aim of minimising impact and reducing the requirements that are unique to Australia. At any time there may be ten new Standards under development and a similar number under active consideration for deletion or revision;

- a large number of new Standards for devices will be required in order to harmonise with EU but these are essentially the same as European requirements and need not be complied with if equivalence can be demonstrated; and

- standards development involves industry at every step and includes undertaking a Regulatory Impact Statement where appropriate, and ensuring World Trade Organisation requirements are not breached.

4. Post-market monitoring, through sampling and testing, adverse event reporting, surveillance activities, product recalls and response to public inquiries:

    - this process is to ensure that standards are maintained and any substandard or counterfeit products are detected and, if necessary, are removed from the market.

5. Assessment of medicines for export:

    - export-only medicines are required to be "listed" on the ARTG, and do not have to be evaluated.

6. Maintain a Register of all products approved for supply in Australia or for export:

    - the ARTG consists of a large number of documents on files and a large computer data base that contains information about therapeutic goods for human use which are imported, supplied in, or exported from, Australia; and

    - the Register contains a great deal of information on any given product; some of it is commercially sensitive or considered private for a variety of reasons; much is publicly available.

7. Manage the process for scheduling of medicines to:

    - -identify the level of professional intervention necessary to redress the information asymmetry between consumer and industry and to enable the medicines to be used safely and effectively;

    - facilitate a nationally uniform approach to controls on access to medicines.

3.2 The approval of prescription medicines

Prescription medicines are registered, not listed. The number of applications have fallen in recent times but change in evaluation time will not be reflected in processing times for 12 months or more. The data for all prescription medicine applications for two comparable six month periods in late 1996 and 1999 are given in Table 3. Productivity has steadily improved as workload in other categories has increased (see Figure 1) and only greater resources (which equates with higher fees) could bring the evaluation times down very much further.

Table 3

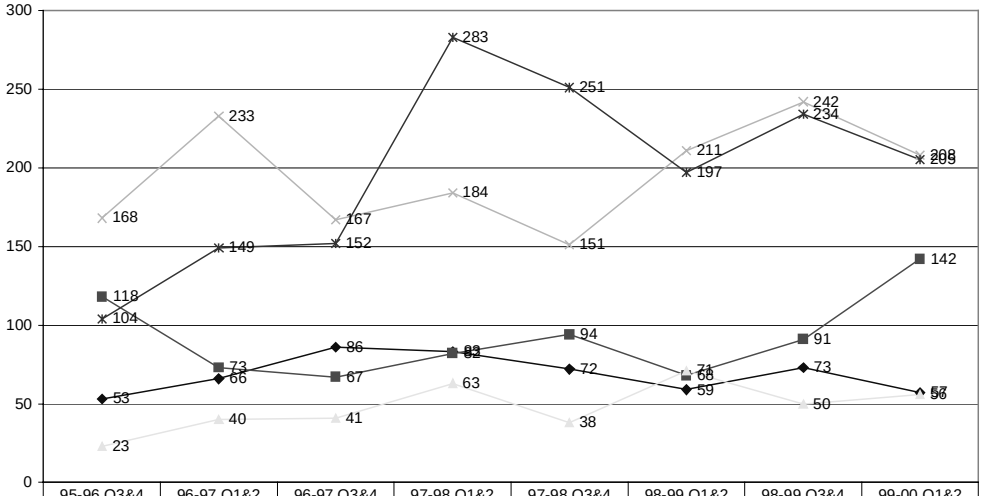
Comparison of Category 1 evaluation workload July-December 1996 and 1999

Application Type	96-97 Q1&2	99-00 Q1&2	% change 99/96
NCE	66	57	-13.64
New Indication	73	142	94.5
New generic	40	56	40.0
Prod Info Change	233	208	-10.7
Other	149	205	37.6
Total Category 1 Products/ Applic's	561	668	19.0

Source TGA Quarterly Reports

Figure 1

Changes in number of applications over four years 1996-2000



	95-96 Q3&4	96-97 Q1&2	96-97 Q3&4	97-98 Q1&2	97-98 Q3&4	98-99 Q1&2	98-99 Q3&4	99-00 Q1&2
NCE	53	66	86	83	72	59	73	57
New Indic'n	118	73	67	82	94	68	91	142
New generic	23	40	41	63	38	71	50	56
Prod Info Change	168	233	167	184	151	211	242	208
Other	104	149	152	283	251	197	234	205

3.3 The approval of devices

Some 95% of devices are listable and incur a low level of fees and charges. These are subject to a relatively simple and low cost evaluation process. The number of devices listed or registered and the time taken in each case are summarised in the Figures below.

Figure 2

Number and time taken to approve listable devices 1998-2000

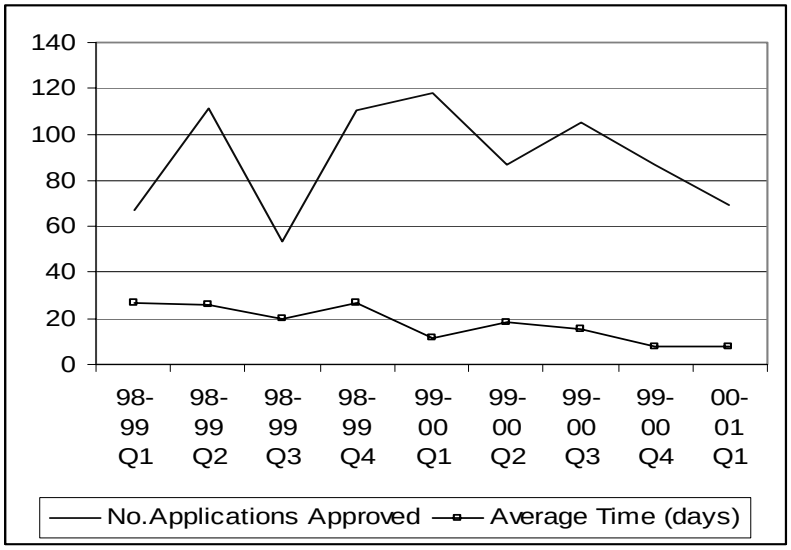
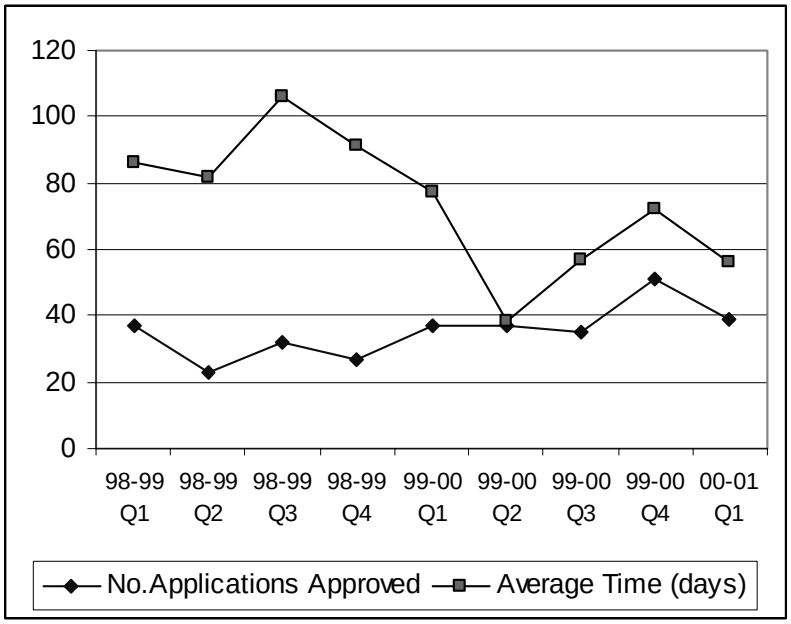


Figure 3

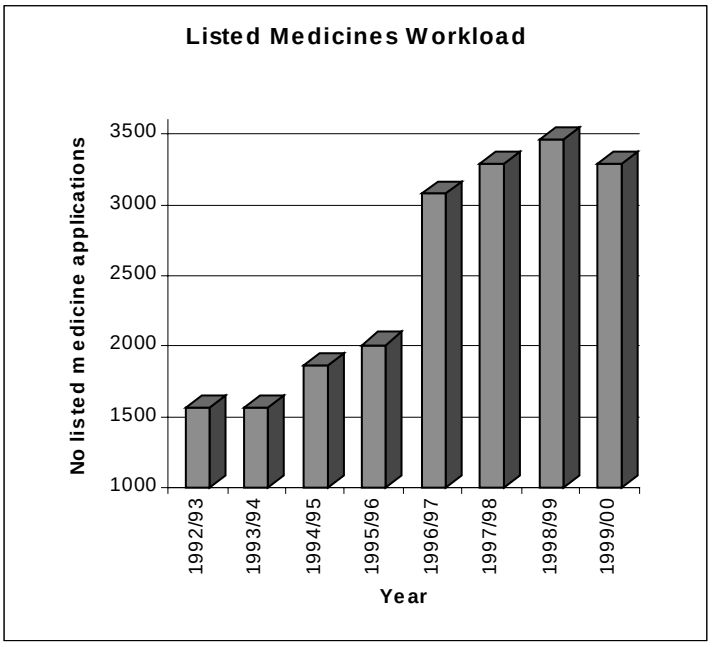
Number and time taken to approve registrable devices 1998-2000

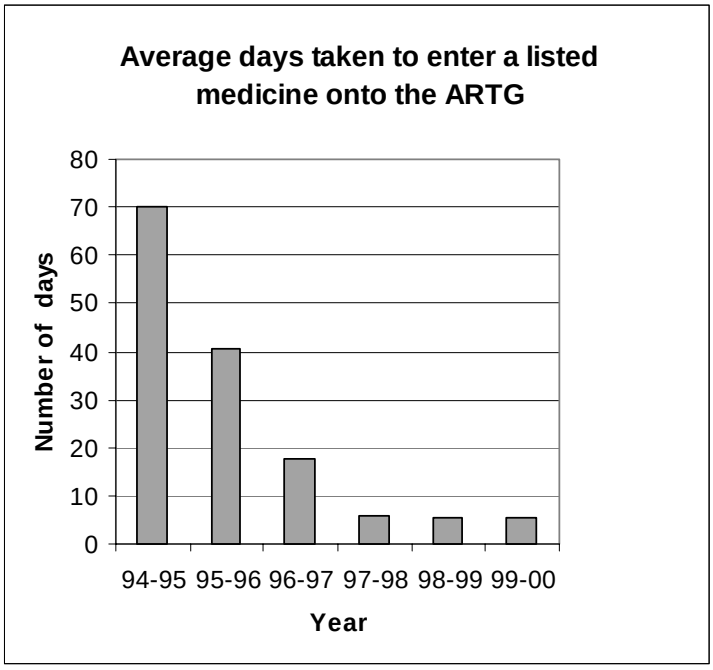


3.4 The approval of listed medicines

Listed medicines, which consist mainly of complementary medicines, have shown substantial growth over time while time required to grant approval fell dramatically to the present level of just a few days.

Figure 4 and Figure 5





3.5 International activities

A number of international activities are undertaken by TGA that benefit industry. These include negotiating agreements and promoting harmonisation, facilitation of exports and standards setting. These activities provide support for the industry generally:

- through a Mutual Recognition Agreement with the European Union, the TGA may assess devices made in either Australia or New Zealand for the European market;
- participation in WHO Certification Scheme for medicines moving in International Commerce;
- by undertaking GMP inspections under the international agreements, particularly the Pharmaceutical Inspection Convention.

3.6 Other activities undertaken by TGA

In addition to the above activities, the fees and charges collected from the therapeutic goods industry cover all the other activities undertaken by the TGA, including:

- Regulation of blood and blood products
    - Blood products have long been regulated by the TGA. This includes regulation of the sole fractionator of blood (plasma) in Australia;
    - recently TGA has also been given regulatory responsibility for fresh blood. This is an area of increasing concern in relation to human diseases such as Hepatitis C and BSE (Mad Cow Disease).
- Expert advisory and consultative committees. The TGA utilises a range of expert and consultative committees which all contribute to its regulatory functions. The main advisory and expert committees are:
    - **Australian Drug Evaluation Committee (ADEC**)provides advice and reviews summary reports of the evaluations undertaken for registration of new prescription medicines; it may review, as required, applications for registration of generic prescription medicines;
        - **Adverse Drugs Reactions Advisory Committee** reports to ADEC on all matters relating to adverse drug reactions, publishes regular bulletins and contributes to the WHO data bank on adverse drug reaction reports;
        - **Pharmaceutical Sub-committee** provides advice to ADEC on the quality control of all prescription medicines and injectables;
    - **Medicines Evaluation Committee (MEC)** provides advice and reviews applications for registration of over-the-counter medicines, as required;

- **Complementary Medicines Evaluation Committee (CMEC)** as required, provides and reviews applications for registration of complementary medicines; as required, may provide advice on applications for listing of new complementary medicines;
- **Therapeutic Device Evaluation Committee (TDEC)** provides advice and reviews applications for registration of therapeutic devices, as required;
- **National Drugs and Poisons Evaluation Committee** considers submissions for additions or alterations to the Standard for the Uniform Scheduling of Drugs and Poisons (the "Schedule"); undertakes tasks associated with the public health implications of drugs and scheduling;
- **Therapeutic Goods Committee** advises on the adoption of therapeutic standards, requirements for labeling/packaging, and manufacturing principles;

TGA has established the following consultative committees:

- **TGA – Industry Consultative Committee** (TICC) facilitates consultation between TGA and the industry regarding input to the TGA budget and accounting against the TGA Corporate Plan; also provides direct feedback from industry to TGA on broad policy, resource allocation and performance issues;
- **Complementary Healthcare Consultative Forum** promotes and fosters constructive relations between the government and the complementary healthcare sector and examines policy and issues including regulation, research, education, and industry, consumer and practitioner issues;
- **The National Coordinating Committee for Therapeutic Goods** is a Commonwealth-State and Territory committee which enables a national approach to the regulation of therapeutic goods to be established. Coverage of therapeutic goods under Commonwealth law is limited to corporations and interstate traders, and the States and Territories have responsibility for all other activities (authorising prescribers, licensing or otherwise authorising retailers (including pharmacies and other sole traders, distributors, carriers, etc). Coordination of these activities is an essential component of the national approach.

The full cost of these committees is not borne by the TGA. Members from other governments provide their expertise **at no cost to the TGA** including, in some cases, substantial volumes of work undertaken by the States and Territories. The travel and other costs may also be met by the jurisdictions.

These committees, both statutory and non-statutory, provide the TGA with an immensely valuable source of expert advice and consultation at very modest cost. They act as a check on the regulator through the quality of the advice, the need for consensus in some situations, such as working with the other jurisdictions on some matters, and the linkages and networks the committee system provides to the TGA in its day-to-day operations.

3.7 Concern about industry capture as a result of 100% cost recovery

Despite the strength of the legislation, the fact that the Secretary has arm's length decision making powers from the Minister for technical matters, the fact that all decisions are reviewable, and the fact that there are elaborate consultative mechanisms (outlined above) which include consumers, concerns have been expressed by consumer bodies to the Productivity Commission Review that cost recovery leads to industry capture.

This is categorically *not* the case. There are many checks and balances that prevent this from occurring:

- The TGA's activities are conducted within the frameworks of the *Therapeutic Goods Act 1989* and of Government policy.
- The committee system outlined above means that the most important regulatory decisions are based on a broad base of expertise and advice drawn from outside the TGA, indeed from some of the best and brightest health experts in the nation;
- Consumers are represented on TICC, the principal TGA-industry consultative body, and so the processes are quite transparent to both;
- The States and Territories through the NCCTG, Australian Health Ministers Advisory Committee and finally the Australian Health Ministers Council also oversee the work of the TGA;
- The TGA is part of a Department of State, and is accountable to the Parliamentary Secretary and Minister through the Secretary of the Department, not to a representative Board or Management Committee;
- The TGA's standing nationally and internationally is the best proof of our successful efforts to ensure quality, safety, efficacy and timely availability of therapeutic goods, without undue regulation and cost, as required by the Government and Parliament through the legislation.

3.8 How Cost-Recovery Operates

TGA's regulatory system is essentially one of product-by-product approval. TGA publishes a detailed list of its fees and charges and has produced a comprehensive information kit on its regulatory processes for medicines. A similar document will be produced covering medical devices, to coincide with the introduction of the new EU harmonised regulatory system in 2001.

Currently, there are four main types of fees and charges:

- application and evaluation fees;
- annual charges to maintain the registration or listing of a product;
- manufacturing licence; and
- good Manufacturing Practice (GMP) inspections and auditing.

These fees and charges are set to recover the costs of all activities in Section 3.

The TGA collects its revenue primarily through annual charges, evaluation fees and licence fees. These are set up so as to fully recover the operating costs associated with regulating the particular product group and also reflect the TGA's risk-based approach to regulation. It is important to recognise that revenue collected through fees and charges covers the cost of not only pre-market assessment but also post-market monitoring and compliance activities. Where appropriate, the evaluation fee schedule is modular with separate fees being charged for each section of the required submission. These 'modular' fees/charges are based on the number of pages and the type of information contained in each part of the submission (eg a 2,000 page submission of 'clinical data' as part of an overall submission on a prescription medicine attracts a fee of $39,400. The other parts attract equivalent fees).

The TGA applies annual charges to maintain entries for products included on the ARTG. These range from $350 for a listed medicine to $950 for a prescription medicine. The TGA also charges fees ranging between $3,500 and $6,800 for "Good Manufacturing Practice" licence audits. These audits are carried out on a regular basis or 'as required'.

There are provisions in the Act and Regulations that allow for fee reductions or waivers in certain instances. These provisions are designed to assist sponsors, particularly where products have a low annual turnover.

The TGA undertakes its own surveillance and investigation of breaches to the point of preparing a brief for the Director of Public Prosecutions. These activities are not subject to specific fees or charges, except where the costs are recoverable through the courts when an investigation leads to prosecution, but are absorbed across the overall revenue base of the TGA.

Each year the TGA meets with representatives from the major industry groups and consumers to discuss and agree on the TGA's schedule of fees and charges for the coming year.

TGA's estimate of revenue for 2000/01 is as follows:

Prescription medicines	$27.40m
Non-prescription medicines	$3.65m
Complementary medicines	$4.78m
Medical devices	$6.98m
GMP licences and inspections	$3.02m
Other (interest etc)	$2.65m
Total	**$48.48m**

4 Comparison with Overseas Practice

4.1 Evaluation times

4.1.1 Prescription medicines

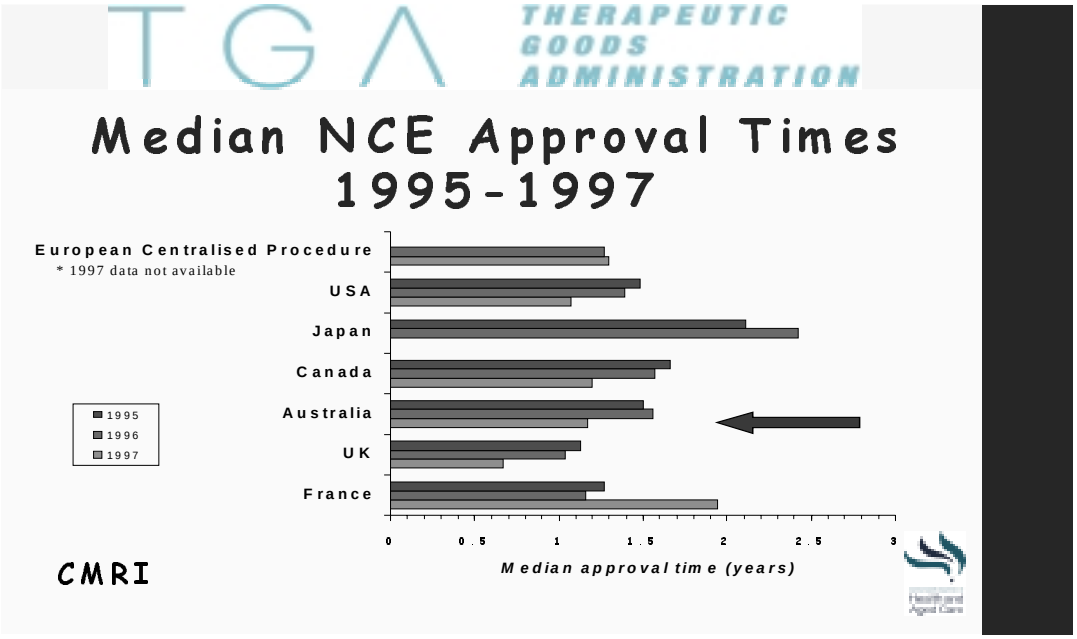
Industry world-wide is concerned when, after nearly a decade of development (in the case of a new chemical entity or NCE) it has to submit the data package to the regulatory agency for evaluation and, hopefully, approval. This is the first time the fate of the NCE has been outside the company's hands, it has cost a great deal of money to get to this point and companies are justifiably anxious to get approval quickly and without even more expense. Industry is, therefore, very focussed on the performance of the regulatory agencies themselves and wants to see efficiency and practicality in the evaluation process.

TGA strives to achieve this and its performance is comparable with similar countries although making the comparison must take account of the regulatory framework that each country has in place, how the time is counted, the quality of the submission itself, and the company response time in responding to questions.

In 1998 a study was published[8] comparing nine major pharmaceutical markets (Australia, Canada, France, Germany, Italy, Japan, Spain, the UK and the US). This showed the evaluation times falling in most countries from 1990 to 1995 (including Australia). The data are summarised in Figure 6 which is taken from that study.

Figure 6

Median approval times in nine countries (1990–1995) by year of approval



The authors comment that *"Focussing on approval times in 1995, median review times were lowest in the United Kingdom at 1.1 years, while Germany, Australia, the United States and Spain all had very similar median review times of between 1.43 and 1.65 years"*.

Since then, the evaluation time for NCEs in Australia has remained relatively constant but the overall prescription medicine evaluation workload has substantially increased due mainly to a doubling of the number of applications for new indications.

4.1.2 Complementary medicines

As outlined in Appendix 1, most comparable countries have systems where complementary medicines undergo either full evaluation, like an orthodox medicine, or are treated as foods and can make no therapeutic claims.

Australia, however, through the ELF system can provide sponsors of complementary medicines, making therapeutic claims, with market approval in days, compared with many months or longer for a full evaluation in other countries. The Australian system is unique in the world in its approach and provides speed, very moderate cost and minimal bureaucratic intervention through the ELF self-assessment and certification system.

4.1.3 Devices – TGA and international performance

In Australia, some 95% of devices are listed. Evaluation times for these are currently below eight days. Performance for both registered and listed devices over recent years is summarised in the Figures below.

TGA's processing of the registration of medical devices (i.e. the 5% of the market) is becoming progressively shorter over time. TGA's target for completion of evaluations is 90 working days. The average time taken over the last four quarters of 1998/1999 have been 82 days, 106 days, 91 days and 77 days.

While it is difficult to obtain published data to compare TGA's performance with that of USA, Canadian, Japanese and European regulatory agencies, and the methodology for reporting timeframes varies from agency to agency, the following comparisons show that TGA's performance can be benchmarked favourably with these countries:

- The US Food and Drug Administration's (FDA) annual report for the 1998 fiscal year states the average FDA review time for high risk devices (pre-market approval applications) was 154 calendar days/107 working days but the method of counting seems to be quite different from that of Australia. The clock does not start as early in the process. TGA time for the same period was 91 days. The FDA approved 46 devices whereas the TGA approved 119 devices. In 1997 the FDA published a report which indicated device approval took 16 months.[9]
- For lower risk devices, the FDA average review time (pre-market Notifications) for 1998/1999 was 89 calendar days/75 working days for approximately 3000 approvals. The TGA's average processing time for 2148 listable device approvals was 30 days.

- The Canadian TPP reports that between July and September 1999, the average review time for new Class II devices (equivalent to Australia's 'listable' devices) increased to 34 calendar days (24 working days). TGA processing times for listable devices has dropped from a high of 47 working days in 1998 to an average of just 14 working days in 1999. Class III and IV products in Canada (equivalent to Australia's 'registrable' devices), were given a 75 calendar day timeframe and now average 113 and 116 calendar days (79 and 81 working days). It is also useful to note that (unlike in Australia), each time a request for information is made in Canada, the timeframe starts all over again.
- Anecdotal data from the Japanese Ministry of Health and Welfare provides timeframes of 12 – 18 months for high risk devices.
- It is misleading to compare current TGA timeframes with those of European Notified Bodies as the requirements and systems are different. Under Australia's new regulatory system it will be the sponsor's responsibility to install and maintain the appropriate quality assurance system, declare the intended purpose of the device and select which route to conformity assessment they wish to use. However, figures provided by two Notified Bodies at a conference attended by a TGA officer, quoted average timeframes of 90 to 120 days for high risk devices, which does not compare favourably with the TGA's turnaround time at present.

4.2 Funding arrangements

4.2.1 United Kingdom

The UK Medicines Control Agency (MCA) is an Executive Agency of the Department of Health and operates as a Government Trading Fund, i.e. a separate business unit. Its activities are fully funded by fees paid by the industry in connection with the manufacture and sale of medicines including post market vigilance[10]. It is also required to earn a 6% return on capital employed.

MCA has been entirely industry funded since 1992. Between 1992 and 1999 it reduced fees but recently it has had to increase fees, due in part to a declining number of new medicine applications and as reserves have declined due to the long period of falling fees.

The UK system, like New Zealand, has not regulated dietary supplements which have been treated as foods and products on the market are not allowed to make therapeutic claims unless fully evaluated as medicines. There is no equivalent to the Australian 'listing' process. Homoeopathic medicines are registered for a fee comparable to the Australian listing fee (£170).

In the last five years the European Medicines Control Agency (EMEA) has undertaken some of the evaluation activity on behalf of all countries in the European Community. It is not clear what, if any, impact on the costs and time required for evaluation has been.

In the UK and the European Union generally, separate agencies, which are commercial organisations called 'Notified Bodies' undertake conformity assessment of medical devices on behalf of government. Advice from Australian manufacturers suggest that these Notified Body fees for assessment, testing, audit and ongoing surveillance of manufacturers can be considerably higher than the TGA's fees. On top of these charges, the government regulatory bodies charge specific fees for some of their activities. For example, the UK regulatory authority has estimated the cost of compliance of manufacturers of *in vitro* diagnostic products alone to be in excess of 1% of annual turnover. By way of comparison, the TGA fees and charges total some 0.5% of the Australian medical devices industry's annual turnover.

4.2.2 New Zealand

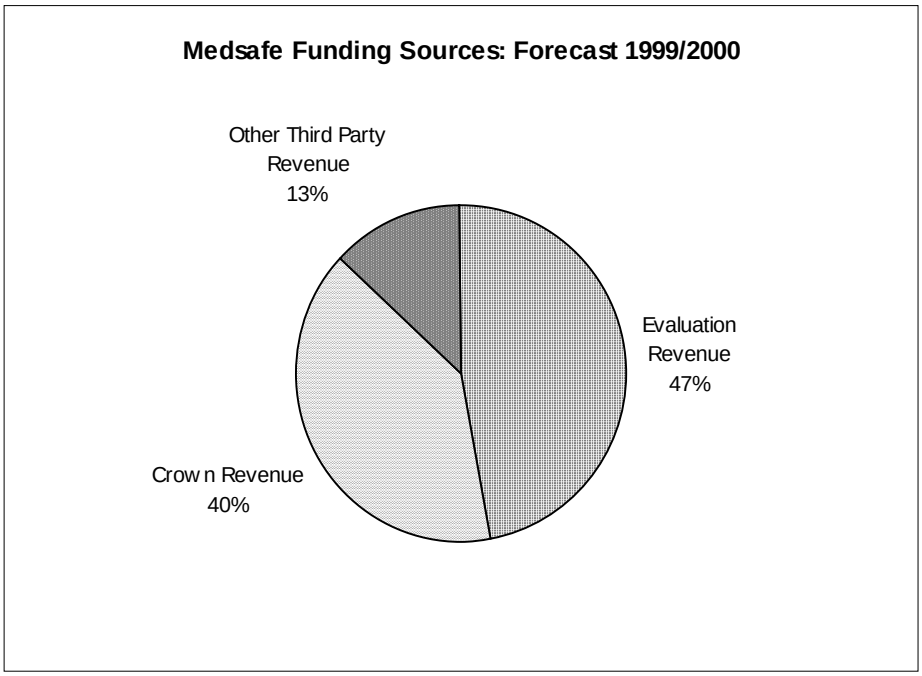
Medsafe is funded from a mix of Crown revenue and third party revenue as shown in the charts below[11]. The major portion of third party revenue is derived from fees paid by pharmaceutical companies for the evaluation of new and changed medicines and related products mainly prescription and over-the-counter (OTC) 'patent' medicines. Other sources of third party revenue include fees paid by industry for licences and special audits, and payment for audits of hospital and retail pharmacies conducted on behalf of the Pharmaceutical Society and the Health Funding Authority.

Medsafe undertakes a similar range of activities as the TGA in undertaking both pre-market assessment and post-market monitoring of prescription and OTC medicines. It is, however, unable to resource these activities to the same extent as Australia due to the very small domestic market. New Zealand is, therefore, examining the option of a joint regulatory agency with Australia as a means of enhancing capacity and retaining a viable safety assessment system.

There is no category equivalent to the complementary medicines category in Australia, with the result that these are treated as dietary supplements and are substantially unregulated unless a safety concern arises. Dietary supplements cannot, however, make any therapeutic claim and in that respect the Australian system is envied. New Zealand has signalled that it intends to regulate dietary supplements as medicines under a fully cost-recovered scheme.

Medsafe does not regulate devices and thus this cost is not included in the data.

Figure 7



4.2.3 Canada

The Canadian Treasury Board required cost recovery in Canada from 1994-95. It has been phased in by a three stage process with a fourth evaluation phase just completed. The Canadian approach is not to attempt to fully cost recover but takes into account the extent to which the good is a private or public good. This results in a mix of funding from cost recovery and from taxation. Presently about two thirds of costs are recovered from fees and one third from government revenue. Fee revenue in 1999-2000 was anticipated to be $34.7 million (Canadian) which is approximately 56% of total Therapeutic Products Program (TPP) expenditure[12]. Fees come from the following main areas: Authority to sell a drug in Canada (an annual fee), drug evaluation fees, establishment licensing; and a similar set of medical devices fees. It is understood that the medical devices fees collect 75% of the costs of their regulation by the TPP.

The TPP undertakes a similar suite of activities as the TGA in Australia including the regulation of medical devices and the equivalent of complementary medicines. Both pre-market assessment and post market monitoring activities are undertaken.

Table 4

Indicators of levels of activity by each agency

	Australia (TGA)	**Canada (TPP)**	**New Zealand**	**UK (MCA only)**
Budget (local currency)	$48.5 million	~$62million	~$6.5 million	~£30 million
% funded from fees	100%	56%	47%	100%
No. of Staff	375	~700	50-60	500
Population	19 million	30 million	<4 million	60 million

Note: MCA does not include device regulation and receives some services from EMEA which affects the direct comparability of the data. Source: TGA, TPP, Medsafe, MCA.

It is clear from this Table that a country such as New Zealand will struggle to remain viable given the amount of fixed cost in drug evaluation, irrespective of market size. Inevitably, the level of intensity of regulatory activity is reduced.

4.2.4 Other Countries

It is understood that Singapore will be implementing full cost recovery with 12 months and Indonesia and Taiwan are also moving to full cost recovery within the same time frame.

4.3 The regulation of complementary medicines

The approach to the regulation of complementary medicines differs from country to country. Historically most comparable countries (New Zealand, UK, US, Canada) have no such category and so they are either evaluated via a mechanism like prescription medicines or not at all. This creates a dilemma as to how to make these products available to the public. This has most often been responded to by calling them foods, with the result that a category of dietary supplements has arisen, but these **have not been allowed to make therapeutic claims.** A brief outline of recent Canadian and US approaches is given in Appendix 1. This indicates how vexed the issue in these countries.

New Zealand has also been wrestling with its system and is considering alternatives for reform. Issues unrelated to complementary medicines such as control of parallel importing still require resolution before that will occur.

In Australia, a more constructive approach was taken from even before the Act was written. Certain **therapeutic claims were allowed** (i.e. those which were not specifically prohibited by the Advertising Code as it was then) but the product was treated as a therapeutic good, and had to be listed on the ARTG. A product could either be regarded as a food and make NO therapeutic claim, or as a medicine and certain therapeutic claims

were then allowed. Sponsors almost always chose to make a therapeutic claim and so the products fell under the ambit of the Act. Recently the Advertising Review allowed further claims to be made, which was a significant gain for industry, and set up processes for still further substantiated claims to be allowed.

It is logical that the regulatory cost for a medicinal product with pre-market assessment[i] is more expensive than treating these goods as foods, with no pre-market assessment but no therapeutic claims. Industry could just as well position most of these goods as foods and pay no fees in Australia, but industry chooses the therapeutic route most of the time because making a therapeutic claim confers such as strong market benefit. There must be, however, some checks and balances with regard to issues such as quality, for example to ensure the dosage form is bio-equivalent from batch to batch, given that the product contains pharmacologically active principles.

It is worth noting that in the UK, where homoeopathic products are licensed (but not other complementary medicines) the annual fee is £170 initially then £80 per year which is in line with the Australian cost of listing. Homoeopathics are products with a very low level of public health risk.

In summary, the TGA has regulated complementary medicines with a very light hand, has been diligent in keeping costs as low as possible and the market benefit conferred by the regulatory framework in Australia (not to mention overseas) is considerable. The current fees are more than fair and reasonable and there is no comparison in overseas countries that provides the same market access and value for money.

One submission to the Review has provided two case studies with relate to the activities of the TGA and related bodies (NDPSC) in regulating selenium and skullcap. These submissions are addressed specifically in Appendix 2 and Appendix 3.

[i] Albeit a very limited one carried out in the main by the sponsor and the ELF software with limited auditing of the input by TGA after listing

5 Other key issues relating to therapeutic goods regulation in Australia

5.1 The regulation of medical devices

Submissions from the medical devices industry provide data which purports to show that the cost of regulation Australia is of a significantly higher order than in overseas countries. Some of these data are both misleading and some of it is considerably outdated. For example, fees quoted for Europe (TUV, a German commercial agency which is contracted to undertake conformity assessment on behalf of government) are rates from around 1993, while the TGA fees are current. The European fees would now be substantially more than the TGA charges in 2000. Further, the European governments' regulatory authorities charge the devices industry additional specific fees for their activities, and these have not been included in the table.

It is important to note that 95% of devices only attract a TGA listing fee of $240, and an annual charge of $450, which covers the product group. Only 5% of all devices are registrable. Of these, low level registrable devices (e.g. HIV/HCV tests; hospital instrument disinfectants; saline breast implants) attract evaluation fees in the range of $10,000 to $12,000. High level devices (eg active implantable devices such as cardiac pacemakers) have fees in the range of $17,600 to $73,600, with the most common fee around $37,600. All registrable devices are subject to an annual charge of $900 that contributes towards maintenance of the ARTG and post-market surveillance.

TGA carries out formal inspections of manufacturing premises and processes on behalf of other countries. The TGA fee for an inspection is $6,800, and the licence issued is valid for Australia, and usually also for other countries such as Japan, and Europe (TUV) under international agreements. While the licence is also recognised by the FDA in the US since an MOU with the FDA was signed two years ago, the FDA may still undertake its own inspection.

One submission to the Productivity Commission argues the Australian fees are much higher than those applied overseas which is unfair given the market size. This is further discussed in **Error! Reference source not found.** to this document which is submitted on a "Commercial-in-Confidence" basis.

TGA's devices evaluation throughput and time taken

TGA's performance in the evaluation of medical devices has steadily improved in recent years. This is seen in Figures 2 and 3 above.

5.2 General benefits to industry as a result of therapeutic goods regulation

There are a number of aspects of therapeutic goods regulation which apply to all sectors of industry and which provide substantial benefit to the industry as well as protecting public health. These include:

Maintenance of a level playing field. Industry must have the ability to compete with other companies on an equal footing, apart from the advantages they gain from their own ingenuity. If companies can break laws with impunity, the conscientious sponsor cannot hope to compete with the unscrupulous operator, resulting in substantial market disadvantage.

Maintenance of standards and identifying and removing substandard products – Public confidence in the industry is important to a robust market, and substandard goods affect that confidence as well as waste the purchaser's money and perhaps threaten their safety. Development and application of standards, and identification and removal of substandard products is critical to industry competitiveness, public safety and public confidence.

Effective recall systems. Again, if public confidence in the market is to be maintained it is critical to effectively and efficiently recall products without undue public alarm. TGA works with industry to provide a co-regulatory recall system that represents world's best practice.

5.3 Benefits to the therapeutic goods industry from recent reforms

There have been significant benefits arising from the implementation of reforms identified from the 1997 Review of the TGA, and in work initiated since then.

The **pharmaceutical industry** secured improvements including:

- Pre-submission meetings whereby companies wishing to submit an application for evaluation can present the application to the TGA evaluators and explain any issues or concerns;
- Submission of supplementary data, during the course of the evaluation and at the pre-ADEC phase;
- Greater flexibility in using appropriate United States Pharmacopeia standards as an alternative to European Pharmacopeia standards;
- A review of export arrangements;
- A new Orphan Drugs program;
- Re-location of OTC medicines evaluation from Victoria to the TGA itself;
- Changes to brand advertising of Schedule 3 products;

- Introduction of co-regulatory arrangements underpinned in the Regulations enabling the ASMI with the CHC to jointly administer advertising of complementary medicines.

The **complementary medicines** industry has secured improvements through :

- Establishment of CMEC and the inclusion of an industry representative on the Committee;
- Establishment of the Office of Complementary Medicines within the TGA;
- Review of allowable/prohibited advertising claims permitted under the Therapeutic Goods Advertising Code;
- A joint industry/TGA review of the Electronic Lodgement Facility (ELF) for listed products;
- Review and redefinition of the food-therapeutic goods interface with consequent clarity of that interface;
- More flexible arrangements to address complementary medicines through legislation which now defines complementary medicines so that substances do not have to be progressed through the processes required to examine evidence for prescription medicines; ongoing work to clarify the food/medicine interface;
- establishment of a herbal task force with industry to agree on names/identities of herbs and examine monographs, scientific and other reference material to agree therapeutic action, claimed efficiency, and safety.

The **medical devices** industry secured improvements including:

- a reduction in medical device listing application fees from $300 to $240. Listable medical devices comprise 95% of the devices market;
- the impending development of a Memorandum of Understanding with the Medical Industry Association of Australia linked to the TGA medical device fees and charges;
- the soon-to-be-introduced revised regulatory scheme that harmonises with that used throughout Europe.

5.4 Managing risk

The basis of regulation of products and substances by TGA is that the higher the risk, the more exhaustive the evaluation; the lower the risk, the lower the level of assessment. The evaluation of a high-risk product thus takes much longer and is more expensive than for a lower-risk product. Where some elements of the industry are seeking to have faster reviews, TGA believes that any move to "fast-tracking" evaluation would be substantially more expensive than the existing arrangements. Additional staff resources would be required, in order to ensure that there is the capacity to offer the fast track as well as meet agreed workloads and performance targets for the other industry sectors. This would mean creation of excess capacity which may be idle some of the time. It also presumes that the workforce is available to be recruited. In fact, skilled evaluation staff are very scarce and TGA struggles to retain its current capacity and building it up has a lead time of years. There is not a pool of potential private sector providers who are easily recruited. Some capacity exists in universities with more in industry but the latter are generally unaffordable for the TGA.

A 1996 report by the then Industry Commission[13] recommended that the private sector be involved in the conformity assessment of medical devices, along the lines of the EU model of "Notified Bodies" (described in ch. 5 above), and that the remainder of the TGA become a statutory authority. The Government did not accept these recommendations.

The EU model of contracting out pre-market assessment of devices has not been evaluated and its effects remain largely unknown. A review by Monash University[14] indicated that caution is warranted in importing solutions from overseas tailored to the cultures and institutional systems of other jurisdictions. The Monash review team also reported that there would need to be savings in excess of $3 million per year if there was an expectation of one additional death per year as a result of a reduced role for government in the regulation of medical devices in Australia. This is a relatively conservative estimate by some domestic and international standards. By way of contrast, they estimated that potential cost-savings from the introduction of any private sector conformity assessment services would almost certainly be less than $100,000 per year.

There are regular industry consultative processes to ensure that all stakeholders are aware of developments in both the regulatory and manufacturing environments. These meetings are with the four main industry peak bodies (APMA, ASMI, CHC and MIAA) and are focused on strategic issues, not just fees and charges.

5.5 Size of the therapeutics industry

The prescription medicines industry is dominated by a significant number of multi-national companies, typically headquartered in Europe or the USA. However, in other sectors of the industry there is a large number of smaller domestically headquartered companies.

Overall, there are approximately 1,700 companies with which TGA has dealings. The total industry turnover in 1998/99 was approximately $9 billion[15]. Thus the annual cost of regulation is only 0.5% of turnover.

Table 5

The pharmaceutical products industry in Australia ($b 1998-99)

Sector	Annual Sales	Local Production	Exports	Imports	Household Expenditure	Activity
Pharmaceutical	$6.44	$4.69	$1.26	$3.01	$1.930	120 companies
Complementary	$1.0	n.a.	n.a.	n.a.	$0.937	n.a.
Devices	$1.5	$0.882	$0.691	$1.309	$0.130	n.a.

NB: Due caution is needed with these data as they are not fully consistent nor thoroughly attested in all cases.
Source: NZIER report[16]

5.5.1 Complementary medicines

Unlike the much more concentrated, subsidised and tightly regulated pharmaceutical industry, there is not available a comprehensive and consistent set of data for this industry. However the industry body, the Complementary Healthcare Council (personal communication, August 2000) estimates wholesale turnover at $600 million and retail turnover at $1 billion p.a. currently[17].

5.5.2 Pharmaceuticals

The latest ABS manufacturing industry figures (June 1998) show that the Australian pharmaceutical industry had a annual turnover of $4.95billion.[18]

In 1998-99 the total cost of government payments for pharmaceutical benefits was $3.07 billion. Patient contributions were $601 million or 19% of the cost of these medicines.[19]

Overall, the pharmaceutical industry body APMA estimates total 1998-99 turnover as $6.44 billion for human-use pharmaceuticals.

5.5.3 Medical devices

The 1996 Industries Commission report into the medical and scientific equipment industry estimated that in 1995, total turnover was $1.1 billion, with imports of $225 million and exports of $525 million[20]. Local production was $670 million.

Assuming a 35% industry growth since then, the Medical Industry Association of Australia has calculated an estimated $1.5 billion turnover for 1998/99.

6 Conclusions

There have been numerous reviews of the TGA itself, its functions, and of legislation related to, or administered by, TGA. These include:

- the Baume Review (1991)[21]
- Industry Commission (1996)[22]
- ANAO (1996)[23]
- Poisons scheduling reviews (1992, 1994, 1996)[24]
- Review of the TGA by KPMG (1997)[25]
- Review of the approval mechanisms for unregistered drugs (1998)[26]
- Review of the Therapeutic Goods Advertising Code. (1999)[27]
- NCP Review of Pharmacy (2000)[28]
- NCP Review of Drugs and Poisons (2000)[29]
- ANAO Follow-up Review (2000)[30]
- Monash Review of therapeutic devices (2000)[31].
- Review of Orphan Drugs (in progress)[32]

While TGA has accepted and implemented most of these reviews' recommendations concerning improvements to the administration and management of its operations, the Government has not accepted any recommendations which significantly changed (or diluted) the TGA's regulatory functions.

The TGA is of the view that full cost recovery is appropriate and fully justified: given the benefit to industry, because of both the TGA's high standing as a regulator, and because of the considerable sums provided to the pharmaceutical industry as a purchaser of medicines through the PBS and the PIIP arrangements, by DVA and by State and Territory health services, as well as the cost to government of treating adverse effects of medicines and devices

- TGA's decisions confer significant commercial benefits to sponsors, both domestically and internationally, because of TGA's high standing as a regulator;
- All regulatory effort, including government administrative work, is undertaken solely because the industry exists, and the community has a right to be sure that all therapeutic goods are safe to be used in accordance with the approvals granted by the TGA;
- any costs incurred as a result of the fact that TGA is a government agency are small compared to the revenue flowing from governments to the pharmaceutical industry, and the costs to governments of treating the adverse effects of the industry's products.

The main therapeutics industry sectors are closely involved in TGA's operations, through representation on many of TGA's expert/advisory committees and consultative committees. They are directly involved in negotiations concerning cost-recovery arrangements and fee structures, through the TGA – Industry Consultative Committee, which also provides a forum for industry input to TGA on broad policy, resource allocation and performance issues. In addition, the Complementary Healthcare Consultative Forum promotes and fosters constructive relations between the government and the complementary healthcare sector.

The TGA has a graduated fee structure which is related to the risk inherent in a product seeking approval, with the highest fees set for prescription pharmaceuticals. The low fees for low risk products are of direct benefit to small businesses, which predominate in the devices and complementary health care sectors.

As the overall cost of TGA to industry is only about 0.5% of annual turnover, this represents excellent value for money.

The TGA consults with industry continuously, partly because of the 100% cost recovery, but also in negotiating time frames including turn-around times on both sides, and other performance issues. These are always negotiated transparently - in a setting where quality, safety and efficacy are not matters for compromise.

In summary, TGA has progressively demonstrated considerable productivity improvements, has significantly increased its ability to meet performance targets, and has greatly exceeded its statutory targets. TGA recognises that the shift to full cost recovery brings greater accountability and involvement by industry and consumers.

Appendix 1

Complementary medicines/dietary supplements/natural health products
A brief summary of the position in the US and Canada

United States

(From Kurtzweil, Paula. An FDA Guide to Dietary Supplements, FDA Consumer, 1998 (Sept-Oct). Revised edition up to January 1999 at http://www.fda.gov)
Key points:
DHSEA defines dietary supplements as a product intended for ingestion as a supplement to the diet.

Information required on the labels of dietary supplements includes:

- The words 'Dietary Supplement'
- A structure-function claim **and** the words 'This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease'
- Directions for use
- Other data similar to that required in Australia for all therapeutic goods
- From March 1999, a 'Supplement Facts' panel is also be required.

The FDA differentiates dietary supplements from medicines, ie articles which among other things are intended to diagnose, cure, mitigate treat or prevent disease. These have to undergo (DSEB style) evaluation before marketing. Thus a dietary supplement cannot bear a health maintenance claim and a therapeutic claim.

A new process has been allowed for **health claims** for foods to be made on the basis of an 'Authoritative Statement' from a Scientific Body (defined) but at present this process does **not** apply to dietary supplements.

To complicate matters, the same process is allowed for **nutrient claims** and it applies to **both** dietary supplements and foods (Office of Food Labelling, 1998 (June 11). Notification of a health claims or nutrient content claim based on an authoritative statement of a scientific body'. Available at http://www.fda.gov).

There are three potential types of claims relating to dietary supplements:

- Nutrient content claims - eg if >200mg Ca per serve may have a claim 'High in calcium'. There are 10 health claims allowed for foods[ii], not including dietary supplements (Kurtzweil, P Staking a claim to good health'. FDA Consumer November-December, 1998, available at www.fda.gov)
- Disease claims – as allowed through formal product evaluation
- Nutrition support claims, which includes structure-function claims.

Dietary supplements may be marketed without FDA approval. Data is sent to the FDA at least 75 days prior to marketing, and these data are released to the public 90 days after the FDA receives it. The FDA has to show the product is unsafe before it can take action to restrict the sale of the product.

Another alternative for manufacturers is to petition the FDA to establish conditions under which a dietary ingredient would be expected to be safe, but no such petitions have been received.

The sponsor is required to notify the FDA within 30 days of marketing a products bearing a structure-function claim. The manufacturer has to be able to substantiate the claim but does not have to provide this substantiation to the FDA. **Structure function claims may not be preventive claims'[iii].**

Dietary supplements are not required to comply with GMP but this is under review. It is notable that some of the problems cited in the FDA articles would have been prevented by adequate quality assurance mechanisms.

Canada

A brief review of the recent history of regulatory reform of 'natural health products' is instructive in indicating how difficult the issue is to advance in a constructive way. It also suggests that Australia is fortunate in having had a logical and effective system of allowing these products to make limited therapeutic claims from the outset, rather than remaining in a fixed position of requiring full evaluation before any claim of a therapeutic nature can be made, which has proved untenable.

ii Health claims for foods, NOT including dietary supplements, differ from structure-function claims in that structure function claims do **not** deal with **disease risk reduction**. Dietary supplements may say, for example 'calcium builds strong bones' but not 'prevents osteoporosis' at this point. The ten health claims for foods relate to: Calcium and osteoporosis; Sodium and Hypertension; Dietary fat and Cancer; Dietary saturated fat and cholesterol and Risk of CHD; Fibre-containing grains, fruit and vegetables and cancer; Fruits vegetables and grain products that contain fibre, particularly soluble fibre, and risk of CHD; Fruits and vegetables and cancer; Folate and NTDs; Dietary sugar alcohol and dental caries; Dietary soluble fibre such as that in whole oats and psyllium seed husk and CHD. As can be seen, few of these would relate to dietary supplements per se. Implied claims eg in the brand name, are allowed.

iii Kurtzweil, P Staking a claim to good health'. FDA Consumer November-December, 1998, available at www.fda.gov)

Natural Health Products in Canada - A Recent History

(from Health Canada website, posted May 2000)

In Canada, natural health products, also referred to as complementary medicines or traditional remedies, are subject to the Food and Drug Act and Regulations.

Internationally, the regulation of these types of products varies. Generally they are regulated as drugs in the European Union countries. Australia has recently classified many of these products as "complementary medicines" and has made legislative and regulatory changes to regulate these products as a subclass of "therapeutic goods." In the United States many natural health products are regulated as "dietary supplements", a category that does not require pre-market review or proof of safety by the manufacturer before marketing, and is not permitted to make treatment-cure claims.

Interest in natural health products continues to grow. In the last few years, as the use of natural health products has become more widespread, it became apparent that a review of the current regulatory framework was necessary. Currently, studies indicate that over 50% of Canadians use some form of natural health products.

May 1997

Many Canadians began expressing concerns about the regulation and accessibility of herbal remedies. Health Canada responded by establishing the Advisory Panel on Natural Health Products. The Panel provided the Department with direction and advice.

October 1997

The Minister of Health announced a full public review by the Parliamentary Standing Committee on Health (SCH) of the legal regime governing natural health products. The objective of the review was to ensure a balance between Canadians' freedom of choice with respect to natural health products and the assurance of consumer safety. The review was also to address the issue of an appropriate regulatory framework for natural health products in Canada.

October 1997- April 1998

The Parliamentary Standing Committee on Health (SCH) consulted a wide range of interested parties both at home and abroad. It heard from over 150 individuals, associations and coalitions representing many Canadians, including: health care providers, industry, consumer groups, herbalists, and the Advisory Panel on Natural Health Products. The SCH prepared recommendations on a regulatory framework for natural health products. Contained in the scope of the products to be considered in this framework included: traditional herbal medicines; traditional Chinese Medicine, Ayurvedic (East Indian) and Native North American medicine; homeopathic preparations; and vitamin and mineral supplements.

May 1998

The Final Report of Health Canada's Advisory Panel on Natural Health Products entitled Regulatory Framework for Natural Health Products was presented to the Parliamentary Standing Committee on Health.

November 4, 1998

The Standing Committee on Health tabled its Report "Natural Health Products: A New Vision" in the House of Commons. At that time, the Minister announced he would move quickly to address their recommendations.

March 26, 1999

The Minister tabled the Government Response to the Standing Committee on Health's Report, "Natural Health Products: A New Vision" in the House of Commons. The Government accepted all 53 of the Standing Committee's recommendations and indicated that these would form the basis of the broad policy framework to be established for natural health products. The Minister also announced the creation of the Office of Natural Health Products, which would provide Canadian consumers with the assurance of safe products while continuing to ensure access to a full range of health products, one of the Committee's key recommendations.

May 1999

On May 19, 1999 the Minister of Health announced the appointment of a 17 member Transition Team to help establish the new Office of Natural Health Products and its regulatory framework. The establishment of the Transition Team was recommended by the Standing Committee on Health in its report Natural Health Products: A New Vision, in order that a new regulatory framework be established quickly. The Team included 14 members from the natural health private sector, as well as representatives from Health Canada.

June - March 1999

The Transition Team worked diligently throughout the 10 months to determine ways for the Office to implement the 53 recommendations made by the SCH. The team produced six reports that highlight the team's progress during this period.

November 1999

Health Canada, in co-operation with Dalhousie University, held a Natural Health Products Research Priority-Setting Conference in Halifax, Nova Scotia, from November 6-8, 1999. Over 60 representatives from the scientific, governmental, academic, industry and community sectors took part in this unique opportunity to determine a direction for research activities in the area of natural health products.

January 2000

Dr. Losos, Assistant Deputy Minister, Health Protection Branch announced the appointment of Philip Waddington, Doctor of Naturopathy, as the new Executive Director of the Office of Natural Health Products.

April - May 2000

The Transition Team submitted to the Minister its final report entitled Final Report: A Fresh Start. The report, a summary of the discussions and recommendations of the Transition Team meetings, outlines broad policy directions toward a regulatory regime for natural health products. An Expert Advisory Committee was also formed to advise the Executive Director of the Office on issues related to the safety, use and regulation of natural health products.

Discussion

The final report of the Advisory Panel on Natural Health Products that was published in May 1998 aimed to describe a fair and effective regulatory framework for Natural Health Products (NHPs) which met '*consumer demand for free access and personal choice in health care, in a way that protects from misinformation, unsafe products or fraud*.' The Panel concluded that, provided recognised clinical, traditional or culturally based evidence supported them, NHPs should be able to make structure/function, risk-reduction and therapeutic claims.

They also reached an on-balance conclusion that products without claims should be allowed to be marketed **with a warning that efficacy had not been evaluated by Health Canada. The industry in Australia remains implacably opposed to such a step.**

In November, 1998 the Therapeutic Products Program and Food Directorate of Health Canada published a policy paper entitled 'Neutraceutical/Functional Foods and Health Claims on Foods'. This paper identifies three types of health claims, ie claims relating to alleviation treatment or cure of a condition, claims which reduce the risk of developing an illness, or structure function claims.

The final policy decision enunciated in the paper is to allow structure function and risk reduction claims for FOODS to be permitted, with other claims to be regulated as drugs, ie individually evaluated.

The requirements for supporting evidence and other controls on foods with claims would vary, depending upon the risk-benefit profile of the product submitted for review (ie an *a priori* process).

Lessons from and generic approaches which may be of use in Australia

While the operation of the US law at the detailed level is difficult to grasp, and the Canadian position is not law yet (just policy papers) there are some principles which can be drawn out, which may be of appreciating the strengths of the model that Australia currently has in place.

There are **three types of claims** which may be made in the US and proposed Canadian schemes:

- Nutrient claims
- Disease claims
- Health/structure function claims. These are NOT allowed to be preventive claims (in the US).

The US requires a **warning on all dietary supplements**. Canada will probably require a warning if NO claim is made. The allowing of products to make no claims has been controversial (and of course is not quite there yet, so may be reversed). They also have to be labelled *Dietary Supplement* to distinguish them from other goods.

Both the US and Canada require **full evaluation of disease claims**. There is no equivalent to the quasi-positive list in ELF and the NCCTG Guidelines (ie the things that are given as examples which are not prohibited).

At least in the US, a distinction between preventive claims and structure-function claims is maintained, and **preventive claims are not allowed** without evaluation.

The product is notified 75 days before sale and a health maintenance claim 30 days before marketing. The FDA can object if it can show the product is unsafe.

The arrangements for substantiation are similar to those followed in Australia for listed goods- ie the sponsor is advised to have data that can demonstrate the claim is not false or misleading but is not required to provide those data to the FDA. The FTC (like the ACCC) is the regulating body in this regard.

All of the regulatory alternatives used in the US and canvassed in the Canadian reviews were considered in the context of the Therapeutic Goods Advertising Review, a review chaired by a representative of the complementary medicines industry.

Appendix 2

The course of events relating to the relaxation of controls on selenium for human therapeutic use

Background

Following its eighth meeting in September 1998, the Complementary Medicines Evaluation Committee (CMEC) made a submission to the National Drugs and Poisons Scheduling Committee (NDPSC) proposing an amendment to the scheduling of therapeutic goods for human use.

NDPSC is a committee that considers the controls that will be applied to the sale and supply of drugs and poisons (medicinal substances, household and commercial chemicals, etc). These controls are applied through the laws of States and Territories and, therefore, the States and Territories are members of the committee, as well as experts in pharmacology and toxicology, industry, consumers and the Commonwealth. The recommendations of the NDPSC are published in the Standard for Uniform Scheduling of Drugs and Poisons (SUSDP) once confirmed by AHMAC. Jurisdictions are strongly encouraged to invariably adopt the entries of the SUSDP into their laws by reference and most do, but all have the capacity to vary any recommendation if the State/Territory wishes to do so.

The NDPSC is now established under the *Therapeutic Goods Act 1989* (but was not in 1998) but there is no power to enforce jurisdictions to conform with SUSDP recommendations.

The amendment proposed by CMEC was:

> *Therapeutic goods containing selenium in the form of sodium selenite, selenomethionine and selenocysteine at or less than 100 micrograms per daily dose be removed from the SUSDP.*

In support of its proposed amendment, CMEC forwarded a substantial report on the safety and efficacy of selenium.

The NDPSC considered this proposal at its November 1998 meeting but did not accept CMEC's recommendation. They did, however, propose an alternative amendment to the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP), summarised as follows:

- *Products containing 26 micrograms or less of selenium per daily dose - unscheduled*
- *Products containing more than 26 micrograms Se to 100 micrograms Se per daily dose - Schedule 3*
- *Products containing more than 100 micrograms Se per daily dose - Schedule 4*

The basis of the NDPSC decision on this matter

The decisions of the NDPSC in regard to selenium were based on its potential toxicity when used as a therapeutic good.

The decisions of the Committee took account of public health issues taking account of factors as detailed in the AHMAC Guidelines for Classification of Drugs and Poisons. These include:

- The need for access to a substance (Schedule) in the context of its toxicity compared to other substance(s) available for a similar purpose.
- The purpose for which it is to be used.
- The way the substance is to be used.
- The dosage form/formulation type.
- The extent and pattern of use and proposed use in the community.
- The misuse of the substance.
- The combined effects if used with other substances.
- Package type and size which reduce the possibility of childhood poisoning.
- Bioaccumulation.

The combined effect of decisions of the NDPSC November 1998 and February 1999 meetings was to relax the scheduling on therapeutic goods containing 100 micrograms or less of selenium per daily dose, allowing those products to be available without prescription.

In reaching this decision the NDPSC took account of the facts that:

- The normal Australian diet was adequate in selenium intake.
- The WHO recommendation for maximum safe intake is 400 microgram/day- (considered by the NDPSC to relate to total daily selenium intake)
- 5% of Australian adults are estimated to receive 200 micrograms per day of selenium and it was estimated that 1% of the population consume 300 micrograms of selenium in their normal diet.
- signs of chronic selenium toxicity develop at 1000 micrograms per day.
- The potential benefit to be gained by selenium supplementation, when dietary intakes are already adequate, were unclear. This lack of clear benefit was balanced against the known toxicity of this substance at intakes that could be achieved through the overuse of supplements.
- The Food Standards Code permits selenium at up to 26 micrograms per daily intake for organic forms and 52 micrograms per daily intake for inorganic forms and these levels were seen as appropriate for exemption for therapeutic goods containing Se at or below this level

The entries in the Standard for Scheduling of Drugs and Poisons now are:

Schedule 4 *[*prescription only*]*

Selenium for therapeutic use except:

*(a) when included in Schedules 3, 6 or 7; [*6 and 7 are not therapeutic schedules*]*

*(b-e) [*controls on use in animals*]*

(f) in preparations for oral human use with a recommended daily dose of:

(i) 26 micrograms of selenium in organic form; or

(ii) 52 micrograms or less of selenium in inorganic form; or

(g) in preparations for topical use….

Schedule 3 [Sale by a pharmacist]

Selenium in preparations for oral human use with a recommended daily dose of 100 micrograms or less of selenium except in preparations for oral human use with a recommended daily dose of:

(a) 26 micrograms of selenium in organic form; or

(b) 52 micrograms or less of selenium in inorganic form.

The net effect is that selenium for human therapeutic use is exempt from scheduling at 26 micrograms or less of selenium in organic form, and 52 micrograms or less in inorganic form. Products above these levels but below 100 micrograms of selenium can be purchased from pharmacists.

The Therapeutic Goods Regulations were subsequently amended to reflect these changes including making listable products that are exempt from scheduling.

Additional comments

The chronological details included in the Complementary HealthCare Council submission are substantially correct. The reference to the March 1999 meeting should read 'February 1999' meeting. Because decisions were made at two meetings there were two effective dates for the decisions (18 June 1999 and 19 September 1999).

The NDPSC has a wide and open public consultation process to which the Complementary Healthcare Council contributes on a regular basis. The issues canvassed are different to those considered by the CMEC. The delays that CHC refers to is to give industry (including CHC) and others time to respond to proposed changes to the SUSDP and for industry to prepare for amendments becoming law. The latter time could, perhaps, be shorter but industry consistently seeks adequate time to get ready for regulatory change.

Selenium is a highly toxic element and not one in which the Australian diet is deficient. Quite the contrary. Allowing certain levels in sports drinks is a quite different decision to inclusion in medicines that are likely to be consumed by a different population over a different time period. Hence the separate deliberations.

Appendix 3

Action taken by the TGA in relation to Skullcap

Concerns over the possible substitution of Skullcap (*Scutellaria laterifolia*) with other herbs were raised with TGA by the Traditional Medicines Evaluation Committee (TMEC) in mid 1996. A TMEC member was concerned that a *Teucrium* species was being used in products labelled to contain skullcap. *Teucrium spp*. require registration, not listing, because of concerns about toxicity. Substitution of *Teucrium* in Skullcap products had been reported in the literature.

The TGA Laboratories were asked to investigate possible substitution of Skullcap in Australian products. These results, conducted from late 1996 confirmed widespread quality problems with skullcap products, including substitution. The findings can be summarised as follows:

- Products using Australian grown Skullcap were found to be correctly labelled;
- Products containing US-sourced skullcap were found to contain *S. incana*;
- Products containing European-sourced skullcap were found to contain either *S .incana* or a *Teucrium* species, probably *T chamaedrys*;
- Other samples were found to contain little, if any, herbal material.

The most common finding was substitution of genuine skullcap, *S lateriflora*, with *S incana.*

The Laboratory's findings demonstrated a low level of basic quality control of ingredients by some manufacturers, including some Australian ones. This was confirmed through GMP inspections and document reviews. Contrary to the claims made by the Complementary Healthcare Council in its submission to the Commission, it is quite straightforward to distinguish the two *Scutellaria* species, both botanically and chemically. Extracts of the two species are also easily distinguished using basic laboratory equipment.

The two species of *Scutellaria* contain a very different range of chemicals. *S. lateriflora* contains the flavonoid, baicalin, as the principle ingredient whereas *S. incana* contains scutellarin. According to the literature scutellarin does not have the sedative properties that *S. lateriflora* is described as having.

TGA's findings were widely discussed with industry during 1997 as results came to hand and samples and methods were made freely available to allow manufacturers to clarify the contents of their products.

Recalls were considered on the grounds that:

- some products were mis-labelled (ie. *S. incana* not *S. lateriflora* as declared on the label and on the ARTG),
- some products had an ingredient present that was neither *S. incana* nor *S. lateriflora* and of which the manufacturer did not know the identity; and

- where *Teucrium,* was thought to be present. This is a substance whose products require registration because of toxicity concerns.

In total, 10 products were recalled between April 1997 and April 1998 mainly for the reason that they contained a species of *Scutellaria* other than *Scutellaria lateriflora* which they claimed to contain on the label.

Fortunately in this case the substitution issue is one of product identity and truthfulness of labelling rather that one of substantial risk to pubic health and safety. It is disconcerting that the peak industry body regard anything less than a direct threat to public health as warranting intervention to remove goods that are not what they purport to be from the market. It is particularly disconcerting that the industry can still claim that '*it was labelled in accordance with worlds best practice'*.

Had the TGA failed to take action, it would not only have failed those NOT engaging in substitution, but would have failed to administer its own legislation. The *Trade Practice Act* also provides powers in regard to false or misleading labelling and action may have been taken under that legislation also.

At the time the action was taken there was a high level of sales of Skullcap preparations with around 200 products on the market. Consumers would not expect the TGA, when aware of such widespread substitution, to fail to take appropriate action.

It is worthy of note that the scientists of the TGA received the US Vice President Al Gore's Hammer Award for their work in detection of counterfeit medicines, including this work.

References

1 Roughead EE 2000, Submission to the National Review of Drugs, Poisons and Controlled Substances, unpublished monograph.

2 Mathers c and Penm R 1999, *Health system costs of injury, poisoning and muscoskeletal disorders in Australia 1993-94,* Australian Institute of Health and Welfare, Canberra.

3 Watson WL and Ozanne-Smith J December 1997, *The Cost of Injury to Victoria*, Monash University Accident Research Centre, Report No 124.

4 Roughead EE 1999, "The nature and extent of drug-related hospitalizations in Australia", *Journal of Quality in Clinical Practice* 19: 19-22.

5 Routley V, Ozanne-Smith J and Ashby K June 1996 , "Poisonings in early childhood", *Hazard* 27, pp1-13, Monash University Accident Research Centre.

6 KPMG 1997, *Review of the Therapeutic Goods Administration*.

7 Australian Council for Safety and Quality in Health Care May 2000, *Safety First*, Report to the Australian Health Ministers Advisory Council.

8 Thomas K, McAuslane N, Parkinson C, Walker S, Luscombe D. 1998. A study of trends in pharmaceutical regulatory approval times for nine major markets in the 1990s. *Drug Information Journal*, 32:787-801.

9 FDA. 1997. New directions in medical devices regulation – an FDA progress report. Cited in *the RIS to the Canadian Medical Devices Schedule of amendments*, 26 August, 1998.

10 UK Medicines Control Agency 2000, *MCA's Activities*, and *MCA Fees for 2000/2001*, www.open.gov.uk/mca/

11 Medsafe. 2000. "Back to the Future" *Business Report*, at www.medsafe.govt.nz

12 KPMG March 2000, *Cost Recovery in the Therapeutics Program*, a review of the Canadian Therapeutics Products Programme.

13 Industry Commission 1996, *Medical and scientific equipment industries*, Industry Commission Report #56.

14 Peacock S, Mortimer D, Harris A, Carter R and Richardson J May 2000, *An Economic Analysis of Proposed Changes to the Conformity Assessment of Medical Devices*, Centre for Health Program Evaluation, Health Economics Unit, Monash University.

15 New Zealand Institute of Economic Research (NZIER) 2000, *Regulatory Impact Analysis*, unpublished report to TGA and Medsafe.

16 NZIER 2000, *op cit.*

17 *Ibid.*

18 *ibid.*

19 *ibid.*

20 Industry Commission 1996, *op cit*.

21 Baume 1991, *A Question of Balance – A report into the Future of Drug Evaluation in Australia.*

22 Industry Commission 1996, Report on the Pharmaceutical Industry

23 Australian National Audit Office 1996, *Drug Evaluation by the Therapeutic Goods Administration, Department of Health and Family Services,* Audit Report No 8 of 1996-97, AGPS, Canberra.

24 Wall B. *Review of the poisons scheduling process in Australia*; also KPMG 1994 and John Bissett and Associates 1992.

25 KPMG 1997, *op cit.*

26 Wall B. 1998. *Review of the approval of unregistered drugs.* Report to the TGA.

27 Therapeutic Goods Advertising Code Council. 1999. *Review of the Therapeutic Goods Advertising Code. Report to the Parliamentary Secretary.*

28 Council of Australian Governments 2000, *National Competition Policy Review of Pharmacy*.

29 Council of Australian Governments 2000, *National Competition Policy Review of Drugs, Poisons and Controlled Substances Legislation*.

30 Australian National Audit Office 2000, *Drug Evaluation by the Therapeutic Goods Administration – Follow-up Report,* Audit Report No 2 of 2000-01.

31 Peacock S, Mortimer D, Harris A, Carter R and Richardson J May 2000, *op cit.*

32 Hayes T. 2000. Review of the orphan drugs program (in progress).