A History of Therapeutic Goods Regulation in Australia

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ACRONYMS

AAN	Australian Approved Names
ACCC	Australian Competition and Consumer Commission
ADEC	Australian Drug Evaluation Committee
ADR	Adverse Drug Reactions
ADRAC	Adverse Drug Reactions Advisory Committee
ADSL	Australian Dental Standards Laboratory
ANAO	Australian National Audit Office
ANZTPA	Australia New Zealand Therapeutic Products Authority
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self-Medication Industry
BP	British Pharmacopoeia
BPC	British Pharmaceutical Codex
CASC	Congenital Abnormalities Sub-Committee
CMEC	Complementary Medicines Evaluation Committee
CSIRO	Commonwealth Scientific and Industrial Research Organisation
C.S.L.	Commonwealth Serum Laboratories
CTN	Clinical Trials Notification
CTX	Clinical Trial Exemption
DSEB	Drug Safety Evaluation Branch
ELF	Electronic Lodgement Facility
ELISA	Enzyme Linked Immunosorbent Assay
FDA	See US FDA
GHTF	Global Harmonization task Force
GMP	Good Manufacturing Practice
GTN	Global Training Network
HPLC	High Pressure Liquid Chromatography
IAC	Industries Assistance Commission
IPU	Individual Patient Use
IVD	In Vitro Diagnostic
JCPAA	Joint Committee on Public Accounts and Audit
JETACAR	Joint Expert Advisory Committee on Antibiotic Resistance
MJA	Medical Journal of Australia
MOU	Memorandum of Understanding
NADFC	Indonesian National Agency for Food and Drug Control
NBSL	National Biological Standards Laboratory
NCCTG	National Coordinating Committee on Therapeutic Goods
NDF	New Drug Form
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NMP	National Medicines Policy

NRTG	National Register of Therapeutic Goods
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
NTGC	National Therapeutic Goods Committee
ODBT	Office of Devices, Blood and Tissues
OGTR	Office of the Gene Technology Regulator
OPAL	OTC Medicines Electronic Lodgement System
PBS	Pharmaceutical Benefits Scheme
PER Scheme	Scheme for the Exchange of Pharmaceutical Evaluation Reports
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PMAC	Victorian Proprietary Medicines Advisory Committee
SAC	Standing Arbitration Committee
SEND	Subcommittee for Emerging and Niche Drugs
SPF	Specific Pathogen Free
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TAFE	Technical and Further Education
TDEC	Therapeutic Devices Advisory Committee
TGA	Therapeutic Goods Administration
TGAC	Therapeutic Goods Advisory Committee
TGAL	TGA Laboratories
TMEC	Traditional Medicines Evaluation Committee
TPIMC	Therapeutic Products Interim Ministerial Council
UMC	WHO Uppsala Monitoring Centre
UNICEF	United Nations Children's Fund.
US FDA (FDA)	United States Food and Drug Administration
USP	United States Pharmacopoeia
WHO	World Health Organization
WPA	Working Party on Antibiotics
WSMI	World Self-Medication Industry

INTRODUCTION

The Therapeutic Goods Administration (TGA) is an internationally respected industry regulator of therapeutic goods.

The TGA represents the product of a long history of evolution moulded by a variety of political, public health, community and industry influences.

This history of the regulation of therapeutic goods aims to capture these influences, not only as an interesting example of the development and role of a regulator but also to record the lessons learnt as the TGA's path continues forward.

Perhaps a primary question is 'what is the role of a regulator?'

Regulation is a mechanism to control an industry sector when the market forces within that sector, or the nature of the sector's products, may significantly disadvantage its customers. This may occur when an industry player has a monopoly, where there is asymmetry of information for the customers or where there are community risks associated with the product.

While there are a variety of mechanisms to counter these aspects such as increased competition or improved information, establishing rules of conduct through imposed regulation may also be necessary.

Good regulation is where the correct balance is reached between adequate protection of consumers without undue restriction on the industry. Good regulation in fact can greatly assist industry by enhancing customer confidence and encouraging innovation and trade.

The regulator is established, usually by government, to implement legislated regulatory requirements on the industry. However, there can also be a shared or co-regulatory approach with the industry or self regulation by an industry itself.

Therapeutic goods offer a relatively clear cut example of the need for regulation. Medicines are novel consumer goods in that they involve consumers intentionally introducing chemicals into their bodies. While providing great benefits, the industry's products can be potent and indeed toxic and often a great deal of specialist skill and knowledge is required to use them correctly.

Medicines have always been part of human evolution. The earliest medicines were made from natural materials. Over time, the type and methods of preparation for medicines became increasingly sophisticated evolving from simple solutions or powders, to extracts, to extracted chemicals, to synthesised chemicals in a variety of presentations such as tablets, injections or transdermal patches.

As medicines, and other therapeutic goods such as medical devices, have evolved so has their regulation around three primary pillars of:

- their quality
- their safety
- their effectiveness.

The evolution of therapeutic goods regulation in Australia can be broadly segmented into:

the period until 1938	During this period there was an increasing number of proprietary medicines appearing on an unregulated market, with many products regarded as 'quack' medicines with amazing therapeutic claims. Increasingly some State governments moved to control claims for these products. At the same time, the Commonwealth strengthened controls on imported biological products.
1939-1961	The NHMRC was active in developing a more uniform national approach to labelling and standards and emphasised the need for independent laboratory testing. The federal government moved to enact legislation to regulate the standards for medicines, particularly to require that Pharmaceutical Benefits were of good quality. The Industry was rapidly evolving both in the sophistication and variety of products and in the multinational nature of many companies. The National Biological Standards Laboratory was established to independently test medicines on the Australian market and regulate their manufacture.
1962-1988	The pre-market assessment of quality, safety and efficacy evolved and finally was integrated into a national system of therapeutic goods regulation and the establishment of the TGA.
1989-2007	The national system continued to mature into an internationally harmonised regulatory system

reflecting the increasing globalisation of markets.

The regulation of therapeutic goods became a major component of Australia's National Medicines Policy. Risk managed regulation was refined with the level of regulation of each of the classes of therapeutic goods being commensurate with the risk they represent.

The focus on international harmonisation and cooperation in therapeutic goods regulation is continuing.

It is interesting to note how the same issues have repeated themselves over the years and how certain seminal events have been catalysts for the major advances that result in the regulatory framework which we have today. One constant factor has been the dedication and expertise of the people who have devoted themselves to this role of public health and safety.

Dr David Graham
National Manager
Therapeutic Goods Administration

September 2007

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1. THE EARLY YEARS (1900 – 1936)

Therapeutic Goods includes medicinal products and medical devices. Medicinal products have generally been considered in terms of medicines (covering materials of plant origin as well as chemically synthesised active substances, for which the term drug has often been used interchangeably) and biologicals (which, until the recent evolution of products such as monoclonal antibodies and hormones produced by fermentation using genetically manipulated organisms, were principally vaccines, sera, insulin, antibiotics and antitoxins).

Prior to the federation of Australia on January 1, 1900, the colonies (which became the States of the Commonwealth) had legislation controlling poisons and the practice of pharmacy.[1,2] There were also some powers in Health Acts to control claims related to treating certain diseases but taken together these powers of the colonies had very limited impact in controlling the sale of medicines.[3] The Constitution gave only limited powers to the Commonwealth that might be effective in the control of medicines and most relevant powers remained with the States.

The first action about medicines by the Commonwealth of Australia was probably when it established a Royal Commission on Secret Drugs and Cures, which reported on 3 August 1907. This Royal Commission was subsequent to a Royal Commission in New South Wales in 1903 into the Decline of the Birth-rate and the Mortality amongst Children, which had included within its terms of reference to examine into the trade in secret nostrums, in proprietary child-foods, and in secret preparations for the prevention of conception, and for the destruction of the human embryo. The Commissioner was Octavius Charles Beale, a Sydney piano manufacturer who is said to have personally funded the enquiry. Beale had been a member of the NSW Commission who had as part of his work reported on those secret nostrums. The Commonwealth Commission expanded on the earlier work.

The Commission was appointed to inquire into:

> "The manufacture, importation, announcements, offering for sale, sale, and use of preparations commonly known as patent or proprietary medicines, and of drugs, alleged curative agents, medicinal preparations, toilet articles, foods, and drinks, the composition of which is not disclosed, and which are alleged to have medicinal or remedial properties ;
>
> The effects or consequences of the use of any such articles; and
>
> The legislation and administration in Australia or elsewhere relating to the aforesaid matters;
>
> and all matters relevant or material thereto."

Commissioner Beale concluded his report with "Section XII. Commonwealth Health Office and Laboratories."

"As it is of national importance to prevent the introduction into Australia of epidemic diseases of men and animals, so it is of higher importance to prevent the introduction of deleterious, demoralising, and homicidal drugs, when the nature and composition are not fully known. The same in some cases even when the formula is attached, or when the drugs are inert, unsound, not to a stated Governmental standard, or when adulterated or misnamed. The same when qualities or virtues are claimed by packers which the articles do not possess, as in the case of many alleged cures, digestives, and so-called pre-digested foods. Prohibition is needed against the introduction of instruments, appliances, and applications, in any form, for which extravagant and false claims are made in other countries, with the object of obtaining money from the sick or afflicted, there and here, by false pretences."

and also

"For the purpose, then, of effective control, to be conducted upon uniform lines in the various parts of the Commonwealth, it is of urgent necessity to provide a Bureau of chemistry, which would be of inestimable service in the preservation of health and life from frauds and mistakes, as also in the furtherance of agricultural and other industry within the Commonwealth. There is a field of ceaseless activity for our social, industrial, and commercial welfare before the officers of such an institution. As already remarked, they will receive and can interchange valuable information at all times from and with similar departments of foreign governments."

Beale concluded his report by saying:

"..... and upon the architraves of the Commonwealth Health Offices should be engraved the ancient maxim, in any language that will be most effective "ΜΕΜΝΗΣΟ ΑΙΠΙΣΤΕΙΝ" – REMEMBER TO DISTRUST".

The Commonwealth's Parliamentary Papers for the Session 1914-15-16-17,Volume V" page 753 include the Report of the Select Committee of the (United Kingdom) House of Commons, April 1915, titled Patent Medicines. It its report, the Select Committee states that:

"2. Of these (42) witnesses nine represented Government Departments, either of this country ***or of Australia,*** *....."*

and

"3. In evidence given before your Committee, the following public authorities or associations have been represented:-The Customs and Excise,..., ***the Commonwealth of Australia,*** *...."*

"The Committee heard much valuable evidence regarding the law and its administration in Australia, from Dr W Perrin Norris, who until recently was director of Quarantine under the Commonwealth Government, and is now Chief Medical Officer for the Commonwealth in London, and from Mr H.E. Neal of the High Commissioner's Office.

Under this (i.e. Commonwealth) administration, strict supervision is exercised upon all printed matter, labels, &c., accompanying medicines imported into the Commonwealth; extravagant or otherwise objectionable statements are required to be modified or excised; and if necessary the goods are not allowed to be imported until such modifications have been made. In a few cases medicines or medical appliances have been refused admission absolutely. Your Committee was informed that this is carried out without any considerable difficulty, and they have in the course of their inquiry noticed numerous cases in which there are substantial differences between the labels, &c., accompanying goods sold in this country and the same goods as sold in Australia. It is to be noted, however, that the action of the Commonwealth authorities is confined to dealing with the goods at the port of entry, and the control of the conditions of retail sale, or internal manufacture, is in the hands of the respective State Governments; but it would appear that the State laws tend to approximate to those of the Commonwealth, and in some cases even go beyond them."

The report goes on to give examples of different requirements in Western Australia, New South Wales and Tasmania. In a later part (paragraph 52), some examples of Commonwealth actions are given to do with the labels or circulars of products including 'Steedman's Soothing Powders', 'Beecham's Pills' and 'Woodward's Gripe Water'.

The Committee's recommendations were reported in Australia[4] and were intended for consideration throughout the British Empire.[3] In response to the reports of the Royal Commission and the UK Committee, the States introduced laws to restrict the claims that could be made on labels or in advertisements for patent or proprietary medicines for human use.[3] Controls by individual States over veterinary ("stock") medicines came later, generally in the 1930s. Progress towards further uniform national control of therapeutic substances was, however, very drawn out.

The earliest Commonwealth legislative action for the regulation of therapeutic goods appears to be the amendment of section 87 of the Quarantine Act 1908 on 14 November 1915, (Amendment No. 42, 1915). This amendment gave power to the Governor – General under s87 (r) to make regulations *"for prescribing the conditions under which any prophylactic or curative vaccine or serum may be prepared and offered for sale."* Section 87 (r) remains in the Quarantine Act 1908 to the current time (September 2006). As best can be established, however, no regulations were ever put in place using this power.

A.H.Brogan, in his history of the Commonwealth Serum Laboratories, puts this action in the context of a decision of the Federal Government in 1915 to *"establish a Government institute for the preparation of vaccines, serums and anti-toxins."*, which led to the creation of the Commonwealth Serum Laboratories.[5] He states that *"Legislation to give effect to the Government's*

decision was the next step, but whether valid legislation to establish C.S.L. was passed is arguable. It has often been suggested that the whole procedure was quite unconstitutional." "The parliamentary debate reveals the Government's intention clearly enough –whilst at the same time revealing the ignorance of some of the parliamentarians – but the amendment seems to fall short of authorising the establishment of C.S.L."

Draft Quarantine (Human Biological Products) Regulations 1922 were prepared by the Attorney– General's Department at the request of the Commonwealth Department of Health which had been established in 1921.[6] Of importance with respect to the Commonwealth's Constitutional powers, this draft included provisions to regulate individuals. For example, paragraph 3 stated *"No person, other than a registered medical practitioner or a person acting under the immediate direction and continuous supervision of a registered medical practitioner, shall prepare for sale any human biological product."* The advice to the Department of Health that *"There appears to be no legal objection to the draft Regulations in their present form"* was signed on behalf of Sir Robert Garran, the first Secretary of the Attorney-General's Department and an acknowledged expert on the Constitution.[7] For reasons that are unknown, it appears that the Regulations were not promulgated at that time.

In 1928, the Commonwealth established a Royal Commission to investigate what had become known as the Bundaberg Disaster. The City Council of Bundaberg, Queensland, had in late 1927 endorsed a recommendation that a diphtheria immunisation campaign be conducted, following a severe outbreak of the disease in the previous year. Multi-dose containers of a diphtheria toxin – antitoxin mixture were sent to Bundaberg and stored in an unrefrigerated instrument cupboard in a doctor's surgery. Following use in other people over several days, twenty-one children were given doses on 27 January 1928. Eighteen of the children became ill and twelve died. The findings and recommendations of the Commission focused on the Bundaberg events and, whilst making some recommendations about the packaging and labelling of biological products, did not mention any need for legislation.

A paper provided at a meeting of the Public Health Committee of the National Health and Medical Research Council, October 13, 1952, titled Standards for Foods and Drugs in Australia – Historical Survey, has an extensive catalogue of the occasions between Federation and 1942 when discussions and conferences between the Commonwealth and the States were held on the subject of uniform standards applied to the wider field of foods and drugs.[8]

The catalogue includes:

- Premiers' Conference 1908;

- First Interstate Conference on Uniform Standards for Foods and Drugs, June 1910;
- Report of Royal Commission on Uniform Standards for Food and Drugs, 1913;
- Second Conference of Commonwealth and States on Uniform Standards for Food and Drugs, 1913;
- Third Commonwealth and States Conference on Uniform Standards for Food and Drugs, 1922;
- Royal Commission on Health, 1925 – a recommendation made by the Commissioner was *"That the Parliaments of the several States should refer to the Parliament of the Commonwealth the matter of the control of imported foods and drugs, and of such foods and drugs of Australian origin as are or may be the subject of interstate trade, and that the Parliament of the Commonwealth should thereupon make laws for the control and regulation of such foods and drugs."*
- First Conference of Commonwealth and State Analysts connected with Food and Drug Legislation, February 1926;
- Conference of Ministers of Health, July 1926;
- First Meeting of the Federal Health Council, January 1927;
- Fourth Conference of Uniform Standards for Foods and Drugs, May 1927;
- Second Meeting of the Federal Health Council, 1928.

The Historical Survey notes that at later meetings of the Federal Health Council and its successor, the National Health and Medical Research Council (NHMRC), interest in the matter continued but only when specific problems were submitted. These appear to have related mainly to foods and included matters about specific food products such as the content of flour and milk and the use of sulphites in sausages.

In 1941 the National Health and Medical Research Council recommended against the holding of a further Federal and Interstate Conference to bring about uniformity in the regulations relating to food and drugs, noting that *"the history of previous conferences is that while uniformity may be formally achieved as a matter of Conference agreement, practical uniformity is not ultimately achieved because of differences in legislation and local factors."*[9]

The following year the Council drew on the wartime circumstances and, in the words of the Historical Survey, "*closed the door for the time being on any further action."*[10]

Concerning Biological Products specifically, the files of the Federal Health Council in the National Archives include a paper titled *"Therapeutic Substances Bill. Notes on the International Movement to Establish Standards for Biological Products."*[11] This document is annotated *"+Resolution 7 of F.H.C (9th session) 1936"* and may have been prepared for that meeting. It includes the following useful précis:

"This question of control (of biological products) in Australia has been under attention intermittently since the Commonwealth and States Food and Drugs Conference of 1922 when certain labelling requirements were recommended. Later, consideration of standardisation and control was given by the Food and Drugs Conference of 1927, by the Royal Commission on Health (1925) and by more recent sessions of the Federal Health Council.

The question of control of biological preparations for veterinary use has been under notice since the Australasian Association for the Advancement of Science in 1921 passed a resolution advocating control of the manufacture and sale of tuberculin. The Australian Veterinary Association in 1923 and subsequently, and the Commonwealth and States Conferences of Veterinary Officers in 1933 also dealt with the whole question which had, meanwhile, already been the subject of legislation in some States.

At the seventh session of the Federal Health Council (1934), Dr F. G. Morgan, Director of the Commonwealth Serum Laboratories, who had examined the question in Europe and America, presented a review of the position which indicated certain important administrative difficulties were being experienced. This (i.e. 1934) session of the Federal Health Council, after discussion, passed the following resolution:-

"It is considered that immediate steps should be taken towards greater control of the standards for certain 'drugs' including biological remedies and endocrine gland preparations; that such control should be vested in the Federal Health Council; and that the Chairman proceed to the formulation of a plan for this purposes (sic) and to the circulation of this plan to the members of the Council."

At the eighth session of the Federal Health Council in March, 1935, a comprehensive report was presented by the Commonwealth Director-General of Health (Dr J.H.L. Cumpston). Following discussion, the matter was deferred for further study of certain administrative aspects involved. As an indication of varying practice in Australia it might be noted that the standard for diphtheria and tetanus antitoxic sera in Victoria are "the number of immunizing units contained in any stated volume expressed in terms of the units prescribed by the English Therapeutic Substance Regulations under the Therapeutic Substances Act 1925, or adopted by the Hygienic laboratory of Washington, United States of America." Queensland, Western Australia and Tasmania retain the 'Washington unit' recommended by the Food and Drugs Conference of 1927, whilst New South Wales and South Australia have not adopted any standard by legislation.

Australia has generally been well served with the quality of biological preparations marketed and supplied for medical and veterinary use. None the less, it is agreed that the development of the use of therapeutic remedies which come within this category definitely calls for new legislation to ensure adequate and uniform control along the lines already defined and the procedure recommended by the League of Nations and adopted by advanced countries overseas."

The document does not disclose the unexpected difficulties Dr Cumpston had encountered prior to his reporting to the Federal Health Council in 1935.

Doubtless reinforced by the clearance by the Attorney-General's Department of the draft Quarantine (Human Biological Products) Regulations in 1922, Cumpston had in August 1934 sent to the Attorney-General's Department *"a memorandum dealing with the legal and administrative control of the preparation and sale of biological products and an outline of an Act to bring the proposals into practical form."* [12] The proposed Act drew on the Commonwealth's quarantine powers and those relating to trade and commerce with other countries and among the States. It included provision for the licensing of manufacturers and created offences for persons who, amongst other things, *"imports, prepares, exports or sells any therapeutic substance in contravention of this Act" or "sells or has in his possession for sale any therapeutic substance knowing it to have been imported or prepared in contravention of this Act."*

The Attorney-General's Department on 10 September 1934 responded by acknowledging Commonwealth powers over interstate and foreign trade but advising that the quarantine powers did not extend generally to control or regulation of the manufacture or sale of biological products, thus taking away Cumpston's assumed mechanism of control over intra-state activities.[13] In his opening paragraph in response, Cumpston wrote *"The principles laid down in this memorandum (i.e. Attorney –General's of 10 September) are such as to cause myself, as Head of this Department, grave concern as they are so completely at variance with the attitude adopted without question for many years and with the decisions, tacit or expressed, of your Department."*[14]

The Federal Health Council documents also serve to highlight the central role played by the Commonwealth Serum Laboratories at that time. In about 1932, the Commonwealth Serum Laboratories were appointed as a distributing centre for Australia, to hold and distribute biological standards on behalf of the League of Nations. Supplies of the vitamin and oestrus-producing hormone standards were received and maintained at the Laboratories. In 1935, Dr F. T. Wheatland of the Commonwealth Serum Laboratories represented Australia at an Inter-Governmental Conference on Biological Standardisation in Geneva. [14]

These activities set the stage for the introduction of Commonwealth legislation to regulate biological substances.

CHAPTER 1 REFERENCES

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3. Newgreen D. PMAC to MEC – the Story of Registration of Medicines in Victoria. Pharmacy History Australia 2 (23) 2004: 4
4. Select Committee on Proprietary Medicines. Publication of the Report. Australasian Journal of Pharmacy 1914; 29: 359-361.
5. Brogan AH. Committed to Saving Lives. A History of the Commonwealth Serum Laboratories. Hyland House. Melbourne. 1990:3
6. National Archives of Australia. Series A432. Item 1951/1068. A copy of the draft is an attachment to the letter of Dr JHL Cumpston (Reference 14)
7. National Archives of Australia. See letter of Dr JHL Cumpston. (Reference 14).
8. National Archives of Australia. Series SP1063/1. Item 508.
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10. National Health and Medical Research Council. Session 14. November 1942.
11. National Archives of Australia. Series A1928. Item 362/30 Section 5.
12. National Archives of Australia. Series A432 Item 1951/1068. Letter of Dr JHL Cumpston, 1 August 1934.
13. *op. cit.* Letter of G S Knowles, 10 September 1934.
14. *op. cit.* Letter of Dr JHL Cumpston. 13 September 1934.
15. National Archives of Australia. Series A1928. Item 362/30 Section 5.

2. THE FIRST THERAPEUTIC GOODS LEGISLATION (1937 – 1938)

The Therapeutic Substances Act 1937 and the Therapeutic Substances Act 1938 were never proclaimed, due to the disruption of the war years.[1] They are worth considering, however, as the ways in which many issues were dealt with remain until the present time.

On 18 June 1937, the Therapeutic Substances Bill 1937 was introduced to the Senate by Senator Brennan (Senator without portfolio assisting the Minister for Commerce and the Minister for Industry).

"This bill is designed to give control over the importation and exportation of that group of medical remedies which are known under various names but which can be brought together under one general description as substances of biological origin. Perhaps the two most familiar of these substances are diphtheria anti-toxin, as an example of a substance prepared by bacterial action, and insulin, as an example of a substance prepared from animal glands.

These two will serve to indicate the type of remedies, the control of which is contemplated by the bill.

It is obviously necessary that these substances shall comply with the following basic requirements:-

(a) they shall be true to a determined standard, that standard having an official and legal status;

(b) they shall be free from contaminations, more especially from bacterial contamination;

(c) they must be properly and safely packed;

(d) they must be accurately labelled as to dosage."

The Senator drew a distinction about the sale of these remedies "*which are not like ordinary chemicals, prepared in the mass according to well-recognized processes, but, being prepared from living tissue or from the action of bacteria, are more sensitive and require more delicate methods of analysis."* He explained that a great deal of international laboratory investigation has resulted in the formulation of international standards laid down by a committee especially appointed for this purpose by the League of Nations. *"It has not been possible to take action earlier as these standards have only recently been formulated. They are now being rapidly adopted by the principal countries and the bill is designed to enable the Commonwealth to fall into line with other countries in adopting these standards for therapeutic substances and prescribing the necessary precautions in respect of their manufacture, transport, and sale."*

"The ambit of the bill is limited to imports and exports and follows closely on the lines of English legislation dealing with the same subject." (The United Kingdom Parliament had passed the Therapeutic Substances Act in 1925 with the aim of regulating the manufacture of biological substances through controls on standards and labelling.)

"There will be complete reciprocity between countries, so that the substances prepared under official supervision in, for example, England and America, will be recognized on arrival in Australia, and, similarly, preparations exported from Australia will be recognized in importing countries."

"The bill provides simple machinery giving the Minister power to license importers so as to give an official supervision over the channels of importation and to supervise the preparation of these substances for export."

"Provision is also made in respect of the necessary analyses to determine whether the dosage as prescribed on the label adequately represents the strength of the preparation so labelled."

"There is complete accord on this matter between the Commonwealth and the States, the State representatives on the Federal Health Council having recognised that such action should be taken; and it is anticipated that this lead given by the Commonwealth will be followed by State regulations, so that the system will be uniform and include imports and exports and preparations manufactured within Australia, in respect of which the same standards will be recognized by all authorities."

The Senate debate was quite short. Senator Collings (Queensland) reminded the Assistant Minister about the Bundaberg incident, "*due to carelessness in the preparation or handling of the vaccine.*" Senator Leckie (Victoria) asked whether the bill would protect the Australian public from therapeutic substances manufactured and sold in Australia and was referred to the need for complementary State legislation.

In the House of Representatives, the bill was read for a first time on 29 June 1937. The second reading on 15 September 1937 was moved by the Minister for Health (Mr Hughes – North Sydney). He was more succinct in describing the purposes of the bill:

"*.....they shall comply with the following basic requirements: -*

(a) They shall be true to a determined standard, that standard having an official and legal status;

(b) They shall be free from contamination, more especially from bacterial contamination;

(c) They must be properly and safely packed; and

(d) They must be accurately labelled as to dosage."

"The standard adopted is fixed by the League of Nations. It is international in its acceptation, and is recognized everywhere the League of Nations is recognized."

"The bill applies only to importations and exportations; it does not apply to serum anti-toxin and vaccines manufactured at the Commonwealth Serum Laboratories, which are covered by laws and regulations designed to ensure their absolute purity, and compliance with standard requirements."

The only other second reading speaker was Mr Forde (Capricornia). *"This bill deals with a subject with which lay members cannot hope to make themselves familiar in the short time at our disposal. The Minister for Health (Mr Hughes) was good enough to explain to me before the House met what the bill is intended to do. He was supported by the advice of the medical officers of his department, men in whom we have the greatest confidence. Therefore, the Opposition can safely support it."*

The bill passed the House of Representatives and was returned to the Senate without amendment on that day. Assent to the bill was reported to the Senate on 30 November 1937.

Material at the National Archives includes a first hand-written draft of the Bill, which was initially to be titled the Therapeutic Substances Bill 1936. The author of this draft and the author's location are not recorded.[2] A typed draft of the Bill was sent to the Government Printer on 3 September 1936 and there are several versions following various amendments.

The National Archives material shows also that quite soon following the passage of the 1937 Act, amendments were being proposed.[3] The initial typed and printed drafts for a bill to amend the Therapeutic Substances Act 1937 are dated 1/12/1937. These drafts focus on Section 7 of the 1937 Act.

Section 7 provided that:

"*1. The Minister may, by notice in the Gazette, declare any substance used in the prevention or treatment of disease in man or animals which is wholly or in part derived from microscopic organisms or from living cellular tissue to be a therapeutic substance for the purposes of this Act.*

2. The Minister may, by notice in the Gazette, revoke or vary any declaration made in pursuance of the last preceding sub-section."

By the time the bill reached the Parliament, the proposed amendment of Section 7 was:

"(1.) The Minister may, by notice in the Gazette, declare any substance which –

(a) is wholly or in part derived from microscopic or ultra-microscopic organisms or from living cellular tissue;

(b) is prepared from tissues removed from recently slaughtered animals; or

(c) is the result of the activities of microscopic or ultra-microscopic organism,

and which is used or intended for use in the prevention, diagnosis or treatment of disease in man or animals, to be a therapeutic substance for the purposes of this Act."

A subsidiary matter in these drafts was to correct an error in Section 9 of the Act by replacing "except" with the intended "exempt". The National Archives include also a handwritten note. It is undated but is annotated "*Recd from Dr Richards 22/2/38*" and initialled.[4] It is presumed that this refers to Dr R E Richards who was a Departmental Officer – Dr R E Richards appears as the Medical Recorder of the NHMRC Council meetings in the 1940's.

The note relates to adding a provision to Section 11 to permit an officer authorized in writing by the Minister to take samples of all therapeutic substances which are imported or sought to be exported and to require any therapeutic substances specified by the officer to be delivered for examination or analysis, or both, to a laboratory appointed by the Minister for the purpose and, second, to add to Section 15 a provision for the making of regulations about sampling and examination of samples.

The note also includes in the same handwriting:

"Regulations – look up American methods of sampling from local manufacturers.

-then draw up regulations

Importers shall present invoices

CQO's (Chief Quarantine Officers?) shall check and examine samples for labelling and whether from approved overseas manufacturers."

A subsequent typed draft incorporating the Section 11 amendment also has a draft Section 14A to be inserted after Section 14 (offence provision).[5] The draft Section 14A provided for forfeiture to the Commonwealth of any therapeutic substances which are imported or exported in contravention of any of the provisions of the Act.

On 28 April 1938, Mr Archie Cameron was given leave to bring in a bill for an Act to amend the Therapeutic Substances Act 1937. The Therapeutic Substances Bill 1938 was introduced and read a first time. The second reading on 20 June 1938 was moved by Mr Cameron Barker – (Acting Minister for Health).

"This bill is not intended to alter, in any way, the spirit of the principal act. It is a simple measure designed, first, to remove any uncertainty as to the scientific meaning of certain terms used in the principal act, and as to what substances are actually included within the term "therapeutic substance", and secondly, to simplify and facilitate the working of the Act."

The Minister explained that Clause 2 of the amending bill was to remove uncertainty as to what substances come within the meaning of the term "therapeutic substance" in Section 7 of the principal act, Clause 3 was to correct the typographical error and Clause 4 provided for forfeiture of non-complying imported substances. The Minister then stated that by inadvertence in the preparation of the introduced bill, two clauses had been omitted. They had been printed and circulated as amendments which the Minister proposed to introduce at the committee stage. This resulted in some renumbering of the sections of the bill. One clause was to provide that the 1938 Act would operate from the date of commencement of the original act, which had not yet been brought into force.

"The second replaces Section 11 of the principal act – under which it is compulsory for the owner of any consignment of therapeutic substances either entering or leaving Australia to send samples to an approved laboratory for examination and analysis. This has proved cumbersome and unnecessary. Clause 5 of the bill provides that samples will be taken and examined or analysed at a laboratory only when that is thought necessary by the officer authorized by the Minister."

The Acting Minister concluded his second reading speech by saying: *"In order that this legislation shall work efficiently, it is proposed to circulate the draft regulations amongst the principal importers and others concerned before they are brought into effect."*

The second reading resumed on 13 October, 1938. Mr Forde (Capricornia) was the only other speaker. He took the opportunity to have a grumble about the need for amendment of the 1937 Act, the bill providing *"further evidence that Ministers, towards the close of a session, bring down measures without proper consideration of their provisions."* He went on, however, to support the bill on behalf of the Opposition, concluding by remarking that *"I understand that the passage of this measure is also required to enable precautions to be taken to obviate the possibility of the introduction of foot and mouth disease into this country. Realizing what a serious scourge that would be in the dairying districts*

and in the cattle industry generally, the Opposition is pleased to lend support to the measure."

The bill, including its accidentally omitted clauses, was adopted and read a third time. It was introduced into the Senate on the next day and read a first time. The second reading was moved by Senator Allan MacDonald (Western Australia-Assistant Minister) on 19 October 1938. It was supported by the Opposition (Senator Collings – Queensland) and adopted. It was read a third time and returned to the House of Representatives on the following day. Assent to the bill was reported to the Senate on 26 October 1938 and to the House of Representatives on 8 November 1938. The Acts were not, however, brought into effect.

CHAPTER 2 REFERENCES

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2. National Archives of Australia. Series A2863 Item 1937/2
3. National Archives of Australia. Series A2863 Item 1938/41
4. *op. cit*.
5. *op. cit*.

3. TOWARDS NEW COMMONWEALTH LEGISLATION (1939–1952)

The wartime and immediate post-war priorities did not include active control of therapeutic substances. Throughout this period, however, the National Health and Medical Research Council dealt with a number of issues to do with access to and quality of various therapeutic substances.

At its 12th Session (November 1941) *"The matter of the control of extravagant advertising in the several States was again brought forward…"* Council requested the Commonwealth Department of Health to prepare a statement for the next meeting.[1] At the following meeting (13th Session, May 1942), Dr R E Richards presented a statement on the subject and also informed Council that a bill on Broadcasting then before Parliament included a provision for the Director-General of Health, or his delegate, to approve the text of proposed advertising matter before it is broadcast. The Director-General indicated to Council that he proposed to arrange with his State colleagues to act as his delegates. He also set out certain principles, not recorded in Council's report, in relation to this censorship.[2] Council was advised that a bill was shortly to be presented to the Victorian Parliament. The bill's provisions included requirements that the label on patent medicines shall include the ingredients and their proportions. Council was also advised that in South Australia legislation *"similar to that in Queensland"* was being prepared for presentation to Parliament.

The State of Victoria took additional actions to control the quality, compliance with Pharmacopoeial standards and the claims made about patent medicines for human use with the passage of the Health (Patent Medicines) Act 1942, which came into operation in 1948, and its 1953 amendments.[3] Many years later, there was a stepwise transition of the activities of the Victorian Patent Medicines Advisory Committee and its support staff into the Therapeutic Goods Administration's Medicines Advisory Committee and the Non-Prescription Medicines Branch.

By the time of this same Session 13, there were urgent activities in Australia to produce medicines locally including from native plants. Council resolved (Resolution 8) that *"In response to a request from the Chairman, Medical Equipment Control Committee, the Council agreed that the National Security Act might be used to override the provisions of the British Pharmacopoeia in cases in which scarcity of imported drugs required modifications or in other cases rendered necessary by the national situation."*[4]

At the November 1942 Session (Session 14), [5] Council appointed a Drug Production Committee to report to Council on the following:

(a) The steps that are being taken to produce drugs for clinical use from Australian plants or introduced plants grown in Australia

(b) Details of staff being employed under NHMRC grants and "other authority for expenditure."

(c) The advances that have been made with full details of processes and results (this may be supplied either by reference to publications or by report to Council direct).

(d) The steps that have been taken to supply full information as to processes and results to any person interested or to any persons making inquiries.

The Committee held its first meeting on December 15, 1942 and reported to the Council at the next Session.[6] This Committee's work, along with that of a number of other wartime committees, was terminated in November 1945.[7] Also at Session 14, Council considered statements concerning Uniformity in Labelling of all Drugs and Medicines having an Official or Approved Name and Uniformity of Dangerous Drugs Legislation.

Concerning labelling, Council resolved (Resolution 7) *"That Commonwealth and State Governments be requested to take legal action to require that proprietary packs of certain specified drugs shall bear in a conspicuous place on the label the official or approved name in letters no less conspicuous than those in which the proprietary name is printed."*

At Session 21 (May 1946) Dr Simmons (the nominee of the Australian Branch of the British Medical Association) stated that the question of the nomenclature of drugs had been before the Branch's Federal Council for some years and that a great amount of confusion had resulted from the multiplicity of names under which the various drugs appeared.[8] The Association's Council referred this matter to the Council (of NHMRC) with a view to the appointment of a Committee of Reference to deal with the question of nomenclature of drugs.

The Acting Chairman of Council intimated that the question of nomenclature of British Pharmacopoeia (BP) and other drugs was very much alive in both England and America at the present time. He thought that the special committee appointed by the British Pharmacopoeia Committee to deal with this matter *"would be a most authoritative body and we could rely on their judgement."*

Council returned to the matter of Uniformity of Labelling in November 1947 (Session 24), to ascertain whether action in line with Resolution No 7 of the 19th Session had been taken by the States to implement the resolution. [9]

The following information was given by the various State representatives of the Council:

- South Australia – Regulations have been drafted but not yet put into effect pending advice from other States.
- Western Australia – No action taken other than to ask for a list of specified drugs.
- Other States – No action yet taken.

The difficulties of putting this resolution into effect were outlined to Council which, after discussion, decided to defer the matter until the next meeting. That next meeting bleakly recorded *"No alteration in relation to this item since the last meeting."*

Progress on Uniformity of Dangerous Drugs Legislation following Session 19 was also slow. At the following (20th) Session, this matter and that of Uniform Standards for Foods and Drugs were both discussed.[10] *"It was left in the hands of the Chairman to explore the possibilities of arranging for a joint meeting of the members of the Council with departments and commercial interests concerned, to consider the matter of uniformity in dangerous drugs legislation and uniform standards for foods and drugs."* Insights into the Council's involvement over the following years are sparse. At Session 26 (November 1948), a letter from the Pharmaceutical Society of South Australia was read and received, [11] and at Session 29 (May 1950) Council decided to take no action in the matter.[12]

Council's more direct involvement in the control and standardisation of medicines dates from Session 27 (May 1949).[13] At this Session, Dr F H Shaw, Department of Physiology, University of Melbourne (and later that University's first Professor of Pharmacology) addressed Council and elaborated on a report he had submitted concerning his visit in 1948 to Canada, USA and Great Britain. His visit had been sponsored in part by the NHMRC. The report includes interesting observations on contrasting attitudes to control of advertising of Patent and Proprietary Medicines.

"One receives the impression (concerning Great Britain) that as long as "we get by" and the manufacturer does not overstep the bounds the policy is "we shall let be." That is in marked contrast to the positive policy in Canada and in the (United) States that no stone must be left unturned to protect the public."

Shaw's report concludes *"…my visit overseas has convinced me more than ever that we in Australia have insufficient control over our own manufactures and over imported products, especially those from the Continent about whose origin and testing we know nothing whatever. It has been my pleasure to help some of our local firms with advice and testing facilities, however these facilities are inadequate and of course we have only tested that which has been supplied voluntarily. The pharmaceutical industry is only struggling in this country, it*

would be greatly assisted by the establishment of a central laboratory with testing cum research facilities. Industry requires it, public health demands it."

In thanking Professor Shaw, the Chairman of Council suggested that information concerning the facilities available at universities and elsewhere for testing drugs and biologicals should be collected in time for consideration at the next meeting. Shaw volunteered to assist in this matter.[14]

The agenda papers for the next Session include a report from Shaw.[15] He reports that he had circularised eight laboratories, asking if and to what extent they would be prepared to undertake biological assay, a) for private concerns, b) for government departments. Six replies were received. Only two laboratories (University Pharmacology Departments of Sydney and Melbourne) were willing and/or able to carry out all the assays required for both private concerns and governments. A list of eleven substances and classes of substances which could be assayed was given. It was noted that these two Departments could also undertake toxicity tests, especially those of recently introduced compounds, and pyrogen tests.

"The Physiology Departments at Adelaide and Brisbane also offered to help in some small measure and the Commonwealth Serum Laboratories may undertake some official work."

Shaw did not miss an opportunity. The second part of his report puts forward to Council *"a tentative proposal"* that the nucleus (Shaw's underlining) of two testing laboratories be set up at the Universities of Sydney and Melbourne, with funding to be provided by a Commonwealth grant (suggested initial capital outlay of £5000 and yearly maintenance £2000 for each establishment).

Curiously, Council decided that the consideration of Professor Shaw's report on the existing laboratory facilities for testing therapeutic substances be deferred and that a letter received from Professor Thorp (first Professor of Pharmacology, University of Sydney) on this subject should be circulated to members.[15] Thorp's letter is not in the Department of Health and Ageing Library's collected NHMRC reports and agendas.

Eighteen months later (Session 31, May 1951), Council returned to the subject of *"Biological Testing and Standardization Laboratory"*. The Council's Report states that the matter was introduced by Dr G E Cole (the representative of Victoria) and *"had previously been before the Council."* The agenda papers include a paper from Dr Cole noting that no further action appears to have been taken since the deferral to allow for the circulation of Thorp's letter. Cole's paper includes a memorandum by Professor Shaw *"prepared at my request."* Shaw's memorandum refers to a number of instances overseas of problem products, reiterates that the Commonwealth should set up a laboratory, and

concludes with a proposal that the Commonwealth Department of Health make available £1500 per annum towards the expenses of such a laboratory. *"The Physiology Department of the University of Melbourne is willing to train a worker in this field and provide accommodation and apparatus until such a time as staff and services require the erection of a central laboratory."*

After considerable discussion the Council decided that the need for setting up a National Therapeutics Standardization Laboratory and the introduction of an up-to-date Therapeutic Substances Act should be investigated. Council passed Resolution No 2:[16]

"The Council wishes to investigate the possibility of setting up a National Therapeutic Standards Laboratory and the introduction of a Therapeutic Substances Act, brought up-to-date, and to this end appoints a sub-committee consisting of Dr G E Cole (Chairman), Dr F G Morgan and Professor F H Shaw, with power to co-opt, to report to the Council upon (sic) the implementation of such a project." Dr F G Morgan was the Director of Commonwealth Serum Laboratories.

At Session 32 (November 1951),[17] the sub-committee appointed to draft suggestions in this matter reported to Council *"that the 1937 Act should be proclaimed and the 1938 Act repealed and a new Amending Act proclaimed at the same time as the original Act, which had never been brought into force."* It was pointed out that the Commonwealth could only have power over importation and exportation of any therapeutic substance. (It is not known why a reference to interstate trade was not made also). The legal foundation of the Act would be necessary before testing laboratories were established. Local production was a State matter, but States could agree to act in aid of each other. After discussion, the Council recommended that the Minister be requested to refer it to the next Ministers of Health Conference after obtaining the necessary legal advice from the Attorney-General's Department.

The Minister was undoubtedly receptive to the idea of improved control of therapeutic substances. During wartime and the immediate post-war years, the Commonwealth passed legislation to provide pharmaceutical benefits to all residents of Australia. The activities in this period are described in detail in *A History of the Pharmaceutical Benefits Scheme 1947 – 1992*. The Australian Constitution was amended at a referendum in 1946, giving the Commonwealth powers to legislate for the provision of pharmaceutical, sickness and hospital benefits, as well as medical and dental services, with the proviso that this did not involve civil conscription.[18] Following these amendments, and a change of government in 1949, the incoming government introduced a scheme to provide a list of 139 *"life-saving and disease-preventing drugs"* free of charge to the whole community. This scheme came into force on September 4, 1950 and was

advertised in the daily press over the Minister's signature.[19] In June 1951, legislation authorising the supply of a more extensive range of medicines free of charge to pensioners came into effect. These initiatives were later brought together in the National Health Act 1953.

A Department of Health file at the National Archives is titled Conference Local – Therapeutic Substances Act. It includes, amongst other things, a letter from the Minister for Health to the Prime Minister enclosing a draft letter for his signature, in which the Minister points out that *"the Commonwealth is now committed in the purchase of drugs and medicines to the extent of 5 million pounds or more per annum. This means that the Commonwealth is now the largest purchaser of drugs in the Commonwealth and, in some instances, is probably the sole purchaser. This gives the Commonwealth the right to insist that the products it is paying for are of the highest standard."* [20]

Also on file are a copy of the letter signed by the Prime Minister (21 December 1951), the responses from State Premiers and later nominations for attendance at the Therapeutic Substances Conference. The Prime Minister's letter acknowledged the limitations of Commonwealth powers to the importation and exportation of therapeutic substance and then said *" However, the National Health and Medical Research Council was of the opinion that if the Commonwealth could draft model legislation which could be accepted by the States, it would be a big advance in combating this problem."*

All States with the exception of Queensland responded by agreeing to attend the Conference. The response from Premier Vince Gair of Queensland on 3 June 1952 indicated that Queensland would be represented but continued that *"You will understand that any recommendations made by the conference will not necessarily be accepted by my Government. Under no circumstances will this State agree to the acceptance of uniform standards which are not considered to be adequate in the public interest"* [21]

and

"I mention that there is power under the existing Health law of this state to prescribe standards for therapeutic substances, and insofar as Queensland is concerned fresh legislation would not be required."[22]

As a further step in the preparation for the Conference, the Commonwealth Director-General of Health distributed copies of the British Act of 1937, the Australian Act of 1937 and what was described as *"Consolidated Australian Act shown with the amendments recommended by the National Health and Medical Research Council Sub-Committee."*[23]

This provoked an extraordinarily blunt response from the Under Secretary of the Queensland Department of Health and Home Affairs, including that "... *I*

desire to inform you if the purpose of the conference is to discuss the proposed Consolidated Australian Act it does not appear that any useful purpose will be served by attendance of representatives of this State at the conference." [24] In the event, Queensland was represented.

Also in preparation for the Conference, the States were asked to advise of the extent of testing of therapeutic substances in their jurisdictions. All of the States indicated that some testing was being undertaken by their own departmental laboratories or State Government analysts though the extent ranged from *"very little"* to a list of 114 products ranging from Ammonia and Senega Mixture to various barbiturates and sulphonamides examined by the Chemical Laboratory in New South Wales in 1951.

The Conference took place on 17 November 1952. A later Cabinet briefing by the Minister for Health, dated 26 November 1952, includes that *"Recent tests carried out by Officers of my Department have indicated that there are some inferior drugs being imported and marketed in Australia, many of which are of little therapeutic value. This constitutes not only a fraud on the community, but a menace to the health of people using them."* The briefing also refers to the Commonwealth's large annual expenditure following recent successful developments in the provision of Pharmaceutical Benefits. The briefing states that *"For the purpose of discussing the many problems involved, the Prime Minister recently invited a Conference of Commonwealth and State representatives to confer on this matter in Canberra."* [25]

The Minister for Health was unable to be in Canberra for the opening of the Conference. He asked the Director-General to welcome guests on his behalf and to read to them his letter. The letter includes the words *"I have been very disturbed to learn, as a result of tests which have been carried out since the Pharmaceutical Benefits Act developed, that some of the drugs prescribed when actually supplied are of such inferior quality that they may have no therapeutic value. The fact that this exists indicates a dangerous state of affairs and should not be allowed to continue."*[26]

The Contents page of the agenda for the Conference has been preserved and included as an item *"Analysis of Products under the Pharmaceutical Benefits Act."* [27] Unfortunately the full set of agenda papers have apparently not been preserved. (The Department of Physiology, University of Melbourne and the Department of Pharmacology, University of Sydney have been contacted in the hope that records of testing undertaken in 1952 or earlier on behalf of the Commonwealth might be available. Unfortunately, it seems that any such records no longer exist). Some other limited references to the Conference have been found. The Annual Report of the Director-General of Health and Medical Services, Queensland 1952-53. (Dr Abraham Fryberg) includes the following:

"At the present time lack of uniformity in the Food and Drug regulations of the different States results in difficulties and misunderstandings in industry. To overcome this the Public Health Committee of the National Health and Medical Research Council, which consists of the Chief Medical Officers of each State, has held two meetings in an endeavour to find standards acceptable to all concerned. Queensland has been rightly proud of the purity of food and drugs available to the people of this State, and while we are prepared to co-operate to achieve uniformity, we are not prepared to do so at the cost of lowering the present standards." (This may in fact not refer directly to the Therapeutic Substances Conference).

The 1952 Annual Report of the Department of Public Health and the Central Board of Health for the Year ended 31 December, 1952 (South Australia), (Section 6. Food and drugs. Page 10) records "*Therapeutic substances–A conference on therapeutic substances was held in Canberra and attended by Officers from the Commonwealth and State Health Departments. The conference recommended that the Commonwealth should introduce legislation within its constitutional powers and that States should do likewise within their powers for the effective control of the import, manufacture, and sale of therapeutic substances in Australia."*

The 34th Session of NHMRC was held on the two days immediately following the Therapeutic Substances Conference (November 18-19, 1952). The Chairman read the report of the Conference and informed the Council that the recommendations of the Conference would be submitted to the Minister. The Council of NHMRC thereupon passed Resolution 1-Therapeutic Substances. *"This Council, having heard the resolutions brought forward by the Chairman from the Therapeutic Substances Conference registers its firm approval of the principles laid down and recommends that any necessary action be taken as a matter of urgency."*[28]

Serving to emphasise the importance the Commonwealth placed on this matter, the Acting Prime Minister wrote to the State Premiers conveying the resolutions passed at the Conference [29]:

(1) The Conference invites attention to the urgent need for the establishment of a Commonwealth Standards Laboratory for testing therapeutic substances with the object of ensuring that only drugs and medicines that conform to prescribed authoritative standards of quality are permitted to enter into and be used in Australia.

(2) The Conference recommends that the State Governments to develop legislation of a uniform pattern to provide for the licensing of the manufacture of drugs and medicines in each State. The Commonwealth

should undertake to submit draft model legislation for this purpose for the consideration of the States.

(3) The Conference recommends that there should be an Expert Committee set up to advise the Commonwealth and the States on suitable standards for drugs not yet in the British or other recognized Pharmacopoeia and on such related matters which are incidental thereto.

(4) The conference recommends that the Commonwealth Government should enact legislation to the limit of its constitutional powers relating to the standard of purity of drugs used as therapeutic substances.

(5) The Conference recommends that the Commonwealth and the States should jointly, within the limits of the respective constitutional powers, take the necessary legislative and administrative action with respect to the marketing and labelling of therapeutic substances as is, from time to time, deemed necessary to give general and particular effect to the policy inherent in Resolutions 1 to 4.

(6) The Conference recommends that the definition of therapeutic substance, as set out by the National Health and Medical Research Council Sub-committee, plus an addendum relating to physiological processes, reading as follows:-

> *"……..any substance or mixture or compound of substances or biological product which is intended to be administered or applied whether internally or externally, to persons for the purpose of preventing, diagnosing, curing or alleviating any disease, ailment, defect or injury or for the purpose of testing susceptibility to any disease or ailment in man or animals, or for the purpose of altering physiological processes, to be a therapeutic substance for the purpose of this Act….*
>
> *be adopted for the purposes of the Commonwealth Act, that the States extend their existing definitions of "drug" to include such substances as covered by the Commonwealth definition, and that the States introduce a definition of therapeutic substance which shall be defined by the Governor in Council, the manufacture of which shall be licensed in accordance with our previous resolution, and that such list will include the list proclaimed by the Commonwealth under its Therapeutic Substances Act."*

It seems clear that for one or more reasons there was a sudden increase in concern and a consequent increased pace of action in the second part of 1952. It may have been due to the recent detection of substandard products entering Australia or worries about fraud and poor value for Commonwealth money

through the Pharmaceutical Benefits Scheme. The Senate, on 25 November 1953, was informed that recently, an examination of drugs supplied under the medical benefits (presumably pharmaceutical benefits) scheme had been made. Of ten drugs examined, involving 100 separate tests, seven contained sub-standard products. Of the 110 individual products tested, 45, or approximately 41 per cent, failed to meet official requirements. *"It is not contended that the high percentage of failure reflects the overall picture, because some of the products tested were known to be unstable and were tested because of that knowledge." "The main reason for their failure was because their strength did not come within the permissible limit of variation which has been laid down, a point which is very important in medical practice."* It is possible that it was these results that were presented at the Therapeutic Substances Conference.

Certainly no time was wasted following the Conference. The Minister for Health (Sir Earle Page) signed a submission to Cabinet on 26 November 1952, which included Resolutions 1 to 4 of the Conference.[30] The Minister noted that some countries including the USA, Great Britain and Canada had a Therapeutic Substances Act, but are not very interested in the quality of the drugs exported. *"There is no legal obstacle, therefore, to drugs which have been rejected for use within these countries being "dumped" into Australia." "The Customs Department have (sic) no means whatsoever of determining whether any particular product is of the quality that it purports to be. It is therefore essential that there should be developed within Australia adequate machinery to advise the Commonwealth whether or not products are suitable for therapeutic use."*

The Minister referred to some interim steps taken by the Commonwealth to provide facilities for the testing of imported therapeutic substances in the *"Pharmacological Departments"* of the Universities of Melbourne and Sydney *"but with many therapeutic substances being developed, these facilities are proving inadequate to meet the situation."* Commonwealth Serum Laboratories was said to be carrying out testing for its own products.[31]

The Minister stated that the Commonwealth had no constitutional authority to licence manufacturers. The Minister attached to the submission advice given by Professor Bailey, the Solicitor-General, on the constitutional aspects of the issue. It is of interest that Bailey's advice had been sought by the Director-General of Health on 22 October 1952 and that his response was dated 17 November, 1952 – the same day as the Therapeutic Substances Conference, reinforcing the sense that some real concerns were driving the action.[32] Bailey's advice includes a series of short answers to the Director-General's questions.

His views were that:

- *the Commonwealth could not legislate to establish standards generally for all drugs, but could establish standards for those available as Commonwealth benefits;*
- *the Commonwealth has legislative competence with respect to the import of narcotics but not with regard to distribution and consumption of narcotics, unless in implementation of an international convention to which Australia is a party* (Bailey was referring to the use of the "external affairs" power (section 51(xxix) of the Constitution)*;*
- *the Commonwealth had no power to regulate intra-state trade in drugs but had full power (not limited to imported drugs) with regard to inter-state trade;*
- *the Commonwealth had the power to take samples of drugs included in the prescribed list of pharmaceutical benefits from pharmacists but not from manufacturers, and the power to establish and conduct standards laboratories to test drugs according to existing standards and to conduct activities relative to the maintenance and establishment of standards for therapeutic substances;*
- *the Commonwealth had no direct constitutional authority to legislate for the control, supervision and licensing of manufacturers of drugs, but may be able to achieve some measure of control by other means.*

Bailey was referring to where a manufacturer supplies drugs under a contract with the Commonwealth as, for example, for the use of the Defence Forces. Bailey was clear, however, that any attempt to generally exclude from the list of Commonwealth pharmaceutical benefits products not manufactured under Commonwealth supervision would not be upheld by the Courts.

The Minister's submission foreshadowed that at a later date he would seek the approval of Cabinet to establish a National Standards Laboratory. At this time, the Minister sought the endorsement of Cabinet for *"The preparation of an Act, to the limit of the constitutional powers of the Commonwealth, to be submitted at the next Session of Parliament, which will provide that only drugs of specified quality be allowed entry and use in Australia, such drugs to conform to standards as laid down in the British Pharmacopoeia or other recognised authoritative standards."*

The submission (GA/53) was considered by the General Administrative Committee of Cabinet on 2 December 1952.

The Minutes record that in discussion the following points were made:

(a) there should be an Act which made it clear to everyone that the Commonwealth would admit to the country only drugs of high standard;

(b) the need to carry out testing of drugs might involve increased costs and improved laboratory facilities and it was necessary, therefore, to consider administrative cost possibilities for the future;

(c) the Department of Trade and Customs maintained that it possessed the necessary facilities to undertake any examination of drugs, but it was felt that this department should confer with the Department of Health on the matter.

The Cabinet Committee authorised the preparation of the legislation, agreed that the Bill be introduced in the next session of Parliament and invited the Minister for Health and the Minister for Trade and Customs to submit to Cabinet administrative proposals and cost estimates for giving effect to this legislation.

The Federal Council of the British Medical Association (Australia Branch) had also had concerns. The Federal Council Report published in the Medical Journal of Australia on 19 December, 1953 records that at a previous meeting of Federal Council, it had been resolved that it should recommend to the Minister for Health that he should introduce a Therapeutic Substances Act for the purpose of ensuring that pharmaceutical products should conform to an approved standard.[33] The General Secretary advised Council that in addition to conveying its resolution, he had also asked the Minister that consideration might be given to requesting manufacturers of pharmaceutical substances to produce proof to the Department of Health of their claim in respect of substance by means of a certificate from an approved laboratory that the product fulfilled the claim made for it, or that it conformed to the prescribed standard. The Council of the Association was advised at its meeting in October 1953 that the Minister had replied, outlining the outcomes of the Conference of Officers and indicating that a Commonwealth bill was being prepared. [34]

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4. THE THERAPEUTIC SUBSTANCES ACT 1953 AND ITS CONSEQUENCES (1953 – 1955)

A Cabinet list of bills for the sitting of Parliament commencing February 17, 1953 includes "*National Health Bill (Consolidate benefit provisions)"* in the Important and Urgent section and *"Therapeutic Substances Bill (Quality of imported drugs)"* in the Not Important section.[1] An accompanying Minute by the Assistant Secretary of the Cabinet Legislation Committee indicates that the Important and Urgent group had been determined on the advice of Ministers as being "*musts*" for the sitting.

A printed draft Therapeutic Substances Bill was available in August 1953. The National Archives include this draft, a Memorandum from the Parliamentary Draftsman to the Legislation Committee of Cabinet dated 17/8/1953 and an extensive Explanatory Memorandum, undated but presumably an attachment to the Parliamentary Draftsman's Memorandum.[2]

The Parliamentary Draftsman explained that the Bill provided that therapeutic substances in the four categories advised by the Solicitor-General shall conform to standards. Those categories were:

(a) imported into the Commonwealth;

(b) supplied to the Commonwealth under contract;

(c) the subject of inter-state trade;

(d) supplied as pharmaceutical benefits.

The Bill was solely about compliance with standards except for provision for the repeal of the 1937 and 1938 Acts and for a single other clause (Clause 18). Clause 18 was similar to section 13 in the 1937 Act, providing for the proclamation of a therapeutic substance where it or its use *"is likely to cause the serious outbreak of disease in persons or animals or is likely to endanger the life or health of persons or animals in Australia". "The significance of this clause is that as some biological products or bacteriological vaccines, etc. consist of live organisms, any danger which might arise accidentally from such substances can be dealt with under the Quarantine law of the Commonwealth."*

The Bill included definitions, amongst others, of *"therapeutic substance"*, *"therapeutic use"* and *"controlled therapeutic substance."*

Therapeutic substance was defined as *"a substance which has a therapeutic use and includes a surgical ligature, suture or dressing, but does not include a vaccine prepared from microscopic organisms from the body of a person or animal for use in the treatment of that person or animal."* The Explanatory Memorandum includes that *"It is doubtful whether surgical ligatures, sutures*

or dressings would normally be regarded as having the character of a substance, but as standards for these articles are in the British Pharmacopoeia and as it is very necessary that they conform to required standards they have been expressly included within the definition."

"Therapeutic use", in brief, followed closely the NHMRC definition, referring to diagnosing, curing or alleviating a disease, modifying physiological function and testing for susceptibility of a disease. For each of the three activities (diagnosing, etc; modifying; testing), the sub-clauses included the words *"in persons or animals."*

"Controlled therapeutic substance" was defined as a therapeutic substance

(a) which is the subject of a monograph in the British Pharmacopoeia or in the British Pharmaceutical Codex and is not specified in the regulations as a therapeutic substance that is not a controlled substance; or

(b) which is specified in the regulations as a controlled therapeutic substance.

The Parliamentary Draftsman clearly encountered some of the complexities of regulating medicines. The Bill included a provision (Clause 19 (a)) for making regulations describing by reference to the composition, strength, potency, stability, sterility, quantity, quality, or method of preparation therapeutic substances which are by force of the regulations to be declared to be controlled therapeutic substances. *"It is necessary to word this sub-clause in this way because the desirable standards with respect to therapeutic substances often can only be established or connected by requirements or descriptions related to the various characteristics of certain substances such as the composition, strength, potency, etc. of the substance."*

The Bill provided for the prohibition of importation into Australia and trade or commerce between the States of therapeutic goods unless they bore an accepted scientific or technical name or description and the name and address of the manufacturer. It provided, in addition, that for controlled therapeutic substances, they must bear the official name of that substance, conform to the standard for that substance and bear the particulars of quantity, by volume or weight, and any other prescribed particulars.

The Bill provided that where a pharmaceutical benefit was a controlled therapeutic substance, it should not be supplied unless it conformed to the standard. The Explanatory Memorandum indicated that *"it is the intention to have all pharmaceutical benefits declared controlled therapeutic substances in order that the provisions about standards would apply." "This will involve, in some cases, the establishment of standards by the Commonwealth itself, as not all drugs, particularly the more recently developed anti-biotics (sic), are found*

in standard authorities such as the British Pharmacopoeia, in which there is anything up to a two years lag before monographs are published."

The Bill also included a provision to prohibit the supply to the Commonwealth or authority of the Commonwealth or a Territory of the Commonwealth of controlled therapeutic substances which did not conform to the relevant standard.

There were provisions that the BP and British Pharmaceutical Codex (BPC) monographs might be modified by regulation, that the Minister might exempt from the importation provision goods for the purposes of scientific research or in the public interest or where they were not intended for a therapeutic use and for the Ministerial delegation of all or any of his powers *"to a person."* There were also provisions for regulations to be made for *"the examination, testing and analysing"* of goods that consist of a therapeutic substance in any of the four categories (a) to (d) described earlier. Interestingly, this provision was to apply also to goods that consist of a therapeutic substance *"which are proposed to be exported from Australia."* The Explanatory Memorandum is silent about why goods for export were included, it incorrectly refers to the Bill applying to classes of therapeutic substances *"which have been previously dealt with under the preceding clauses of the Bill"*. Goods for export had not been mentioned previously.

Lastly, the Bill provided for regulations to authorise the establishment of committees to advise the Minister on matters relating to therapeutic substances, the functions and powers of those committees and the payment of remuneration and allowances to members of committees.

The Bill for a Therapeutic Substances Act was introduced into the House of Representatives on 12 November 1953 by the Minister for Health (Sir Earle Page). The Minister explained to the House that the British Pharmacopoeia was not keeping up-to-date with new medicines and that this created difficulties for controlling the standards of drugs. He expressed particular concern about the need for proper standards in relation to the control of the expenditure by the Commonwealth on pharmaceutical benefits. *"I regret to state that at present there is evidence that drugs are being supplied that do not conform to the requisite standards and, so, are incapable of carrying out the job which the medical profession believes that they will carry out. It would be criminal to allow such a state of affairs to exist and continue merely through lack of appropriate action."*

He indicated that the Commonwealth intended to proceed with the preparation of model complementary legislation for implementation by the States and acknowledged that the testing for purity of modern therapeutic substances had become more difficult and exacting. After acknowledging the recent assistance

of the staff of several Australian Universities in the testing of drugs, he stated that *"It is the responsibility of the Commonwealth to extend both numerically and qualitatively the tests of purity of medicines used by the sick people of this country, and arrangements will be speedily completed after this bill is passed to give full effect to this responsibility."* Just what the Minister had in mind was not shared with the House.

The Minister indicated that the Commonwealth had accepted the recommendation of the Therapeutic Substances Conference that an expert committee should be set up. He concluded his introductory speech with the hope that the passage of the bill and that of complementary legislation by the States would result in uniformity of packaging and labelling of therapeutic substances throughout Australia. *"One of the causes of the present high prices of drugs is that each State prescribes a different basis for the packaging of drugs with the result that a manufacturer in Victoria, for example, must pack drugs according to the relevant law of the State to which they are to be despatched."*

The first speaker in the second reading debate was Dr Evatt (Leader of the Opposition). In a succinct speech, he was generally supportive of the bill. *"I think that everybody agrees that it would be criminal to allow such a state of affairs to continue through lack of appropriate action."* Dr Evatt drew attention to what he described as the changing situation in connection with life-saving drugs, illustrated by Chloromycetin. (Chloromycetin was the original brand name for the antibiotic chloramphenicol). Introduced into Australia in 1951 as an important addition to therapeutic agents, by June 1952 the results of a nation-wide survey in the United States of America by the Food and Drug Administration (FDA) were known and in the Australian press. The FDA had identified 200 new cases of a blood disorder known as aplastic anaemia (referred to by Evatt as plastic anaemia) in patients treated with Chloromycetin. Some deaths had occurred. *"This shows how changes can occur. A great discovery is made. A new drug is used, apparently successfully. But then disaster and death are caused by over-use of the drug or its use in unsuitable cases. Nothing could illustrate more strikingly the necessity to have standards for drugs than the varying reports in connexion with antibiotics."* Almost a decade before the events with thalidomide, it was seemingly not well understood that medicines complying with standards could none the less be responsible for adverse reactions.

The other major part of Evatt's contribution was a discussion of the powers of the Commonwealth. He acknowledged the undoubted powers of the Commonwealth over imports and in respect of pharmaceutical benefits being provided by the Commonwealth. He went on to express concern that while the Commonwealth had powers over interstate trade, there would be enormous

difficulty in applying that concept of interstate trade to a subject *"that cries out for uniform regulation."*

"At present the Australian Parliament has a power over imports and over pharmaceutical benefits within our territories. We have a power over interstate trade and commerce for the purpose that I have mentioned (conformity to certain standards). A person is bound to conform to a standard. But it is very difficult to apply a rule that is laid down. It is almost impossible to distinguish between goods for interstate trade and goods for trade within a State. Our object should be to establish a standard that is safe whether the goods be for local use or for interstate trade." "Therefore what is required – and the Minister's second-reading speech indicates that he appreciates the position-is action not merely by the Australian Parliament but also by the State parliaments, assuming of course, that there is a reference of power to the Commonwealth to deal with the subject on a uniform basis. The Commonwealth should be empowered by State statute, until there is a constitutional change, to deal with drugs and therapeutic substances." Evatt then went on to indicate that the Opposition supported the bill.

Mr Haworth (Member for Isaacs) was less enthusiastic. Who knows what he would make of today's Therapeutic Goods Administration as twice in his speech he sought to *"remind the Minister that there are still six State health departments in this country and, as far as I know, six pharmacy boards, all policing their own standards and administering their own regulations in regard to the sale of drugs. I hope the Minister will assure the House that another big branch will not be set up in within the Health Department in order to administer this bill."* Mr Haworth also made a plea for the membership of the proposed expert committees to be composed *"not only of medical practitioners but pharmaceutical chemists, manufacturers and possibly the wholesalers of drugs (who) all have their own distinct province to represent."*

Several other members spoke. The Opposition speakers raised concerns about the continued existence of quackery (with references to Beale's Royal Commission of 1907) and the misuse of antibiotics and took the opportunity to criticise the Minister for alleged delays *("After fourteen long, weary years, the Minister has now introduced a measure….)".* But all clearly supported the need for the legislation and it was passed by the House of Representatives on 18 November 1953.

The matters raised in the Senate followed a similar pattern. Senator Cooper (Minister for Repatriation, representing the Minister for Health) responded to an Opposition question about facilities for the testing drugs. *"At the present time the testing facilities of the Department of Trade and Customs and the Commonwealth Serum Laboratories are used. For the present, it is not*

proposed to set up a new organization. The Department of Health is confident that it can operate efficiently by using the existing facilities, such as those of the Department of Trade and Customs for testing spirits and drugs imported into this country. The biological side will be handled by the Commonwealth Serum Laboratories."

The government obtained agreement to an amendment to clarify the offence provisions and there was brief questioning about to whom the Minister would be able to delegate his powers. The bill passed the Senate on 25 November 1953 and, in its amended form, by the House of Representatives two days later.

Commonwealth regulatory action seems to have almost hibernated in the following two years, as the Regulations were not brought into effect until 1956. However, events that may have influenced the later decision to set up the National Biological Standards Laboratory occurred as a consequence of the Cutter incident in April and May of 1955. A US company (Cutter Laboratories) distributed more than 300,000 doses of its Salk poliomyelitis vaccine, mainly in California and Idaho. Some 204 cases of poliomyelitis and eleven deaths occurred in vaccinated people and the contacts of the vaccinated, attributed to residual live virus in the vaccine. When considered by the Australian NHMRC in November 1955, the Director of C.S.L. suggested that C.S.L.'s poliomyelitis vaccine should be submitted to a final check by an authority independent of C.S.L. Similar testing independent of the manufacturer had already been introduced in the USA. The research laboratory at the Fairfield (Melbourne) Infectious Diseases Hospital tested the vaccine for residual viral infectivity and the Pathology Department at Melbourne University submitted a further independent report on each batch of vaccine as well as undertaking histopathological studies on each monkey used for testing. It emerged that the Director-General of Health had approached Fairfield Hospital before the matter had been discussed at NHMRC. [3]

During the 1953 debates, references were made to the apparent testing of medicines by the Department of Trade and Customs. It is difficult to establish the extent to which this occurred. The Analytical Services Branch of the newly established Department of Science published its first Annual Report in 1973.[4] Prior to its incorporation into the Department of Science, it had been known as the Australian Government Analytical Laboratories and formed part of the Department of Customs and Excise.

The 1973 Report stated that, on behalf of the Department of Health, the Analytical Services Branch examines imported drugs and medicines to ensure that they comply with the requirements of the Therapeutic Goods Act (1966) and the Quarantine Act and also tests prescriptions made up by pharmacists as Pharmaceutical Benefits under the National Health Act. This 1973 Report

indicates that references to its earlier work appeared in earlier Annual Reports of Department of Customs and Excise. Such reports have not been located but a *"Report of Activities 1954-1955 presented to Conference of Collectors of Customs, September 1955"* [5] includes that *"Preparations have been made to commence the analyses of drugs and medicines for the Departments of Health and Navy and the submission of these samples has commenced."* That seems contrary to the impression on reading the Parliamentary debates that such testing had been occurring prior to 1953. It is consistent, however, with the implementation of import sampling of controlled therapeutic substances which started on a trial basis in June 1957 and of biological and antibiotic products which started in May 1958. In most of the Director-General of Health's Annual Reports until 1973-74, the numbers of samples examined annually by the Department of Customs and Excise Laboratories (later referred to as the Analytical Laboratories of the Department of Science) were reported. The Reports in following years do not comment on the omission of this information, but the 1975-76 Report, commenting on the implementation of the amended Customs (Prohibited Imports) Regulations effective on 12 May 1976, states that the new regulation rationalises the administration procedures relating to the import of those goods for which application previously had to be made to the Bureau of Customs.

The Director-General of Health's Annual Report for 1969-1970 provides information about the ongoing involvement of the Department of Customs and Excise. *"On importation into Australia some controlled therapeutic substances are subjected to examination in respect of packaging, labelling and conformity to standards. To avoid undue delays to importers, many analyses are conducted in Department of Customs and Excise Laboratories in the States."* A table is provided showing the number of samples tested in each of the States. In total, 213 samples were tested and, of these, eleven failed.

CHAPTER 4 REFERENCES

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2. National Archives of Australia. Series A4933/XM1. Volume 18. LEG/4A.
3. Brogan AH. Committed to Saving Lives. A History of the Commonwealth Serum Laboratories. Hyland House. Melbourne. 1990: 118.
4. National Library of Australia. Department of Science. Analytical Services Branch. Annual Report 1972-73.
5. National Library of Australia. Department of Trade and Customs. Report of Activities 1954-55 presented to Conference of Collectors of Customs. September 1955: 64

5. IMPLEMENTING REGULATION (1956 - 1961)

The Therapeutic Substances Regulations were proclaimed by the Governor-General on January 18, 1956 (Statutory Rules 1956 No 4) and notified in the Commonwealth Gazette on January 26, 1956. Given the apparent urgency for the Act in 1952-53, it is unclear why the making of the Regulations took more than two years.

The Regulations had four parts:

> **Part I** – Preliminary;
>
> **Part II** – Controlled Therapeutic Substances which are imported into Australia or which become the subject of Interstate Trade;
>
> **Part III** – Examination, Testing and Analysing of Goods.
>
> It is of note that the laboratories which were appointed were those controlled by the Department of Pharmacology at the University of Sydney, controlled by the Department of Pharmacology at the University of Melbourne, The Commonwealth Laboratory, Department of Customs and Excise, Melbourne and The Commonwealth Serum Laboratories, Melbourne.
>
> **Part IV** – Committees.

The regulations made provision for three committees. The Therapeutic Substances Advisory Committee was to inquire into and advise the Minister on any matter relating to the Act or Regulations referred to the Committee by the Minister. As well as the Director-General of Health, an officer of the Department of Health appointed by the Minister and the Commonwealth Analyst, the membership was to include appointees chosen by the Minister from nominations by the Drug and Allied Trades Council of Australia, Association of Ethical Pharmaceutical Manufacturers, Federal Council of the British Medical Association in Australia, Pharmaceutical Association of Australia and the Federated Pharmaceutical Services Guild of Australia.

The Biological Standards Committee was to consist of the Director-General, an officer of the Department of Health and four other members, all appointed by the Minister. Its role was to inquire into and advise the Minister on the standards, and matters relating to the standards, of antibiotics, antigens, antitoxins, blood derivatives, insulin products, sera, toxoids, vaccines and other biological products.

Third was the Therapeutic Substances Standards Committee. As well as the Director-General and an officer of the Department of Health, the membership was to comprise the Commonwealth Analyst, two Professors of Pharmacology

appointed by the Minister, a legally qualified medical practitioner and a person approved as a pharmaceutical chemist under the National Health Act 1953-1955, also appointed by the Minister. This Committee's role was to inquire into and advise the Minister on the standards, and matters relating to the standards, of therapeutic substances other than those that were the responsibility of the Biological Standards Committee.

A Schedule to the Regulations listed those controlled therapeutic substances which were required under regulation 6(c) to bear an expiry date. There were twenty-six substances in the Schedule –principally antibiotics and vaccines but including Tablets of Glyceryl Trinitrate, the Tuberculins and Schick Test Toxin.

According to the Director– General of Health's Report for July 1, 1954 to 30 June, 1956, Parts I, III and IV took effect from February 1, 1956 and Part II from August 1, 1956. From this point in time, control of imported biologicals was exercised in conjunction with the Department of Customs. Manufacturers and importers were required to produce to the Collector of Customs a certificate issued by the Director-General of Health to indicate that there were no health or quarantine objections. Applications for import certificates were handled by the National Biological Standards Laboratory (NBSL) which was established in 1958 despite the original intent to use existing laboratories. At the same time, the Laboratory undertook examination of products supplied, or to be supplied, as Pharmaceutical Benefits or to other Commonwealth Departments. Minor amendments to the Regulations were proclaimed in December 1956 (amending the font size for the official name of the substance in labelling) and October 1957 (requiring controlled therapeutic substances subject to a monograph in the British Pharmacopoeia to be also labelled "*For Therapeutic Use*"; increasing the remuneration and allowances for committee members).

Two more substantial matters arose early in the life of the Therapeutic Substances Regulations 1956.

First, in June 1956, the Association of Ethical Pharmaceutical Manufacturers of Australia provided the Department of Health with an opinion on the scope and validity of the Therapeutic Substances Act, which it had sought from Gordon Wallace, Q. C. [1]

The Director – General of Health sought the prompt opinion of the Attorney-General's Department *"as these matters are due for discussion at the meeting of the Therapeutic Substances Advisory Committee, to be held in Sydney on the 13th July, 1956."* [2]

Wallace's opinion devotes considerable discussion to the breadth of substances and mixtures and compounds of substances that were captured by the terms "*therapeutic substance*" and "*controlled therapeutic substance*." The

manufacturers' concern appears to have arisen from problems with compliance with the packaging and labelling provisions for therapeutic substances and controlled therapeutic substances, particularly for products with multiple ingredients including excipients covered by BP or BPC monographs. Wallace stated *"Further, I am advised that many compounds, perhaps in tablet form, contain many substances each of therapeutic use and they are marketed in very small containers or boxes which would make compliance with the statutory provisions difficult if not impossible."*

In his conclusion, Wallace stated *"It seems to me that this Act is of extraordinary width particularly in relation to the definition of "therapeutic use" and the way in which mixtures and compounds are dealt with, and it must have a very onerous impact on the manufacturer."*

Then Wallace added further opinion which doubtless caused the Director-General great concern. *"Furthermore, the powers of the Minister are extremely wide. In this connection and having regard to the reference to interstate trade in the title to Part II of the Regulations I think that a serious question of validity of the Act and regulations arises having regard to the provisions of section 92 of the constitution (cf. Hartley v. Walsh 57 C.L.R. 372; and Duncan v. Queensland 22 C.L.R. 556)."*

The Acting Secretary of Attorney-General's replied on 4 December 1956.[3] He was unequivocal that the width of definitions did not invalidate Sections 7, 9 or 11 of the Act. Concerning Section 9, which put controls on therapeutic substances and controlled therapeutic substances that are *"the subject of trade or commerce among the states"*, he was of the view that the width of the definitions was not a problem but that this Section also warranted consideration of section 92 of the Constitution.

He advised, in part, that:

"Section 92 of the Constitution provides that trade, commerce and intercourse among the States shall be absolutely free. The Courts have held that regulation of interstate trade is consistent with its absolute freedom, and direct restriction, or prohibition, of interstate trade is not."

Concerning the cases cited by Wallace, the Acting Secretary commented that both cases dealt with legislation which was in fact upheld as not contravening section 92, *"but it is possible that they would be decided differently today."* These latter words reflect that the application of Section 92 was before the High Court in the nineteen-fifties. *"In any event, however, the legislation is different from the Therapeutic Substances Act in that it operated to prevent the owner of property from disposing of his property in interstate trade." "However, I have little doubt that, in regard to what, for lack of a more precise term, I will call*

undoubted therapeutic substances, the High Court would uphold, as reasonable regulations of interstate trade, the provisions of Section 9 – that is, regulations which are reasonable having regard to the nature of the interstate trade, the interests to be protected, and the comparatively small burden on the traders."

The Acting-Secretary did in addition recommend that the Act be amended to exclude from its operation goods which are intended for use other than for a therapeutic purpose. He suggested that the words in paragraph (b) of therapeutic use ("influencing, inhibiting or modifying of a physiological process in persons or animals") be omitted. *"In my opinion, the generality of those words contributes in no small measure to the doubts that have arisen in connexion with the Act."*

Second, an important deficiency in the practical administration of the Act and Regulations seems to have emerged quite quickly. On August 15, 1956 the Director-General wrote to the Attorney-General's Department seeking advice about the extent of the powers conferred by section 13 of the Act, which related to the making of regulations for the sampling and testing of therapeutic goods.[4] At question was whether pharmacists approved under the National Health Act to provide pharmaceutical benefits and persons who are party to a subsisting contract to supply therapeutic substances could be required only to submit therapeutic substances in their possession for analysis and would be immune from prosecution by the Commonwealth if such substances were found to be below standard? (This situation is different to that where the goods had actually been supplied, which was also covered in section 13). The Director-General went on to request advice as to whether it may be practical to create an offence for an approved pharmaceutical chemist to have sub-standard substances in stock and, in addition, create an offence for a manufacturer or wholesaler to supply sub-standard substances to an approved pharmaceutical chemist.

The response of the Acting Secretary of Attorney-General's Department was unequivocal that as they existed at the time neither the Therapeutic Substances Act nor the National Health Act created an offence for possession of a sub-standard therapeutic substance.[5] Concerning the request for advice about creating offences for pharmacists, manufacturers and wholesalers to be in possession of sub-standard therapeutic substances, the Acting Secretary replied in the tradition of a lawyer addressing a doctor: *"These matters raise grave and difficult questions of constitutional law. In this connexion, I refer you generally to the Secretary's memorandum dated 17 November, 1952 and my memorandum dated 4 December, 1956, where some of the constitutional issues are discussed. If the position is that the Minister wishes to submit to Cabinet proposals for the amendments mentioned referred to in your memorandum, I shall, on your advice to that effect, be glad to give my views on the*

constitutional questions involved. If that is not the position, however, I would not feel justified in embarking on a detailed consideration of those questions."

As the Department of Health assumed greater control of therapeutic substances following the coming into force of the Therapeutic Substances Regulations, it requested amendment to the Customs (Prohibited Imports) Regulations. The object of the proposed regulation was to permit effective control by the Department over the standards for all new therapeutic substances which were antibiotic or biological products imported into Australia. The Minister for Customs was advised that *"The Director-General of Health before granting permission to import the substance will require the intending importer to submit details as to ingredients, use, tests for potency, purity, safety, etc."* [6]

The then Third Schedule of the Customs (Prohibited Imports) Regulations was amended by inserting Item 28A:-*"Therapeutic substances, being*

(a) sera, toxoids, toxins, antitoxins, vaccines, antigens or glandular extracts; or

(b) antibiotic substances. – The importer shall produce to the Collector (of Customs) the permission in writing of the Director-General of Health to import the goods."

The amendment was gazetted on 16 January 1958 and came into effect on 1 May, 1958.

Although, as noted below, a small number of other substances may have been covered by the Customs (Prohibited Imports) Regulations, control on imports was largely limited to biological products and antibiotics and did not include most pharmaceuticals.

As reflected in the Senate speech of Senator Cooper (Minister for Repatriation) in late 1953, the Department of Health did not intend initially to establish a separate testing facility, relying instead on existing laboratory capabilities such as those of the Department of Trade and Customs for testing imported spirits and drugs and the Commonwealth Serum Laboratories (C.S.L.) for testing biologicals, as well as those of the two nominated University departments.

By mid-1958, however, action had been initiated towards the establishment of the National Biological Standards Laboratory. In his Report for July 1, 1956 to June 30, 1958, the Director-General of Health commented that the Laboratory was originally planned as a section of the Commonwealth Serum Laboratories, Melbourne. *"However the Australian National University, Canberra offered to make available their Physiology Block for the use of this Department and this offer was accepted to enable the establishment of the National Biological Standards Laboratory as an independent unit. Action was taken at the close of*

the two year period under review (i.e. mid-1958), to appoint Dr L.F. Dodson to the position of Director, National Biological Standards Laboratory. Steps were also taken towards amending the Therapeutic Substances Regulations to authorise the establishment of the Laboratory during the year 1958-59."

Whether it was demand for services or other factors which led to a change in attitude towards the need for a separate Commonwealth facility is not clear. In his history of C.S.L, Brogan refers to C.S.L's submission to a Cabinet review on 11 April 1957.[7] The submission, in a section headed *"Biological Standards Laboratory"*, stated *"The only body with any experience in this field (examination, testing and analysis of therapeutic substances including biological products) in the Commonwealth is the C.S.L. and it is proposed that certain of C.S.L.'s staff and facilities be used for the purpose so that a commencement can be made to carry out essential tests on imported products to ensure that only products of the standards laid down are made available in Australia. The staff so employed will be responsible direct to the Director-General of Health and not to the Director of C.S.L."* As Brogan notes, *"Ultimately, this role was not given to C.S.L, and the National Biological Standards Laboratories (sic) were established"*. The reasons for this are not known, as the testing laboratory role was not the subject of a specific recommendation put forward in the submission and is not mentioned in the Cabinet minute.[8] There was also an episode in 1958-perhaps after the decision to establish NBSL in Canberra-in which the Director-General (Dr Metcalfe) refused the release of a batch of Salk poliomyelitis vaccine despite it having been certified as fit for use by the Director of C.S.L. (Dr Bazeley). Brogan notes that *"He (Bazeley) was further irritated by Metcalfe's refusal either to give a reason for his decision, or to reimburse C.S.L for the value of the vaccine."* [9]

In 1959 Cabinet considered the National Health Bill 1959 which included a series of amendments to the principal National Health Act, which included reference to the British Pharmacopoeia in Part VII dealing with Pharmaceutical Benefits. These amendments included giving the Minister for Health the power to fix, by notice in the Gazette, the date on which a new edition, or amendments, of the British Pharmacopoeia would take effect. Under the existing definition in the Act, a new edition or amendments took effect on the date on which they took effect for general purposes in the United Kingdom. The justification given to Cabinet for the proposed change was quite vague – *"There may well be cases where it will be necessary to delay the application (in Australia).....until necessary administrative amendments have been made."*

At the same time, a much shorter Bill making the same amendments concerning the British Pharmacopoeia to the Therapeutic Substances Act 1953 was approved by Cabinet.

The National Archives has considerable indexed historical material lodged by the Attorney-General's Department. Documents about a series of small matters are worthy of mention because they illustrate the evolutionary matter in which the practical limits of the Commonwealth's powers to regulate therapeutic substances were tested.

The Regulations of 1956 had been amended in October 1957 by the addition of regulation 5A, which provided that controlled therapeutic substances subject to a monograph in the British Pharmacopoeia must additionally be labelled *"For Therapeutic Use"* in letters not less than six point type. The Department of Health had devised this requirement to facilitate the identification of goods which required inspection at the point of importation. The pharmaceutical industry, through the Drug and Allied Trades Council and the Australian Association of Ethical Pharmaceutical Industry, initially requested Departmental agreement that only outer containers of *"finished pharmaceutical products"* (those not requiring further compounding and thus obviously intended for therapeutic use) and not each and every individual container be required to carry this labelling. The Department of Health *"agreed to administer the regulation in this liberal fashion"* and issued instructions accordingly. By 1959, the industry bodies were seeking further liberalisation, making representations to the Department and later to the Attorney-General, apparently without avail. [10]

In May 1960, the Department advised the Attorney-General's Department that a procedure had been devised to obtain samples of therapeutic substances *"so that the provisions of the Therapeutic Substances Act apply*." In brief, the sampling officer was to present the manufacturer or supplier with an *"Order for supply."* It was argued that the goods, having been sampled, had been supplied. If the goods conformed to the prescribed standards, payment was to be made in due course. Unfortunately for the would-be regulator, advice in return was that if a prosecution were launched against a person who had supplied a sub-standard therapeutic substance to the Commonwealth and he was able to show that the substance was not required by the Commonwealth for any one of the purposes of the Commonwealth under the Constitution and was, perhaps, supplied merely for the purpose of sampling, the prosecution would be likely to fail.[11]

A year later (April 1961), what may well be the first endeavour to regulate medical devices was raised with Attorney-General's. The Director General of Health wrote *that "A number of appliances used in day to day medical practice, such as transfusion sets, syringes, plastic tubes, needles, etc., are now on the market in what is claimed to be a "sterile" condition, i.e. ready to use without further sterilisation. Your advice would be appreciated as to whether such items could be included under the definition of "therapeutic substances" in the*

Therapeutic Substances Act 1953-1959." [12] It did not take long for Attorney – General's to reply, concluding with *"Accordingly the appliances referred to by you would not, in my opinion, come within this definition. I see no reason, however, why, if this should be desired, these appliances should not be included in the definition by a suitable amendment."* [13]

In May 1961, advice was again being sought. This time it was as to whether the Director-General of Health or the National Biological Standards Laboratory had the legal right to disclose the results of the analysis of a therapeutic substance to outside purchasing authorities such as State Departments or Hospital Commissions.[14] The concern of the Attorney-General's Department was whether the Commonwealth could be made liable to pay damages in an action for defamation brought by the manufacturer. The advice to the Department of Health, as a consequence, was about lessening the risks of such an action-results should be supplied on request rather than volunteered; every effort should be made to ensure the results supplied were accurate in every particular; the drug and batch should be identified sufficiently well as to avoid any possibility of misunderstanding; the results should be supplied without comment – eg *"Drug X was tested by this Department on…. and the following were the results [set out analysis]."* Whether this could extend to commenting that the drug passed or failed a prescribed requirement was not discussed.

The Attorney-General's Department, however, did not convey to the Department of Health the comment of the Principal Legal Officer, Advisings recorded in an internal memorandum: *"Not for the first time, we see here that Health wishes to extend their function beyond the limits of the Therapeutic Substances Act, an Act which already goes as far as can possibly be gone under the Constitution. This proposed procedure therefore requires, I think, careful scrutiny."* [15]

A brief file note dated 22 June 1961 records an appointment at Attorney-General's for Dr Leigh Dodson (Director NBSL) and another person ("Daniels") to discuss the examination of therapeutic substances for export.[16] Section 13 (3)(b) of the 1953 Act provided for the making of regulations for examination, testing and analysing of therapeutic substances proposed for export. The file note records *"we have advised on S13(3)(e)"*. This presumably refers to earlier advice about therapeutic substances supplied to the Commonwealth.

CHAPTER 5 REFERENCES

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3. *loc.cit.*

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7. Brogan AH. Committed to Saving Lives. A History of the Commonwealth Serum Laboratories. Hyland House. Melbourne. 1990: 132
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13. *loc.cit.*
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16. *loc.cit*.

6. REGULATION BECOMES MORE THAN QUALITY CONTROL (1962 – 1966)

It was in December 1961 that the landscape for the regulation of therapeutic substances was to change dramatically. On December 1961, The Lancet published a brief but succinct letter from Dr William McBride, Hurstville, NSW.[1] Its first paragraph stated *"Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distival') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%."* An editorial footnote drew attention to the publication in The Lancet, two weeks earlier, of the decision of Distillers Company (Biochemicals) Ltd to withdraw from the market all its preparations containing thalidomide pending investigation of reports from two overseas sources associating thalidomide with harmful effects on the fetus in early pregnancy.

It might have been expected, given the strong Australian association with the identification of the terrible harm caused by thalidomide, that this would have been a prominent topic for the Department of Health and in the Australian medical journals. Surprisingly, thalidomide is not mentioned in the Director-General of Health's introduction to the Annual Report for 1 July 1961 to 30 June 1962 and is mentioned quite uncommonly in the Medical Journal of Australia (MJA) in the two years following the publication of McBride's letter.

In July, 1962 the MJA reported that the Minister for Health, Senator Wade had announced that the World Health Organization (WHO) was to investigate the possibility of establishing a system whereby information concerning the evaluation of new drugs, particularly with regard to serious side effects, could be transmitted to governments on a world-wide basis as expeditiously as possible.[2] In August 1962, a letter from Richard Lovell, Professor of Medicine at the University of Melbourne, titled *Congenital Abnormalities and Thalidomide* was published in the MJA.[3] Lovell's point was that a number of other new drugs were being found to have serious unwanted effects and that *"it should not be supposed that the withdrawal, because of its harmfulness, of a widely advertised drug is a unique event."* Lovell proposed that individual doctors should satisfy themselves, before prescribing a new drug, that the drug had been critically evaluated and shown to be substantially superior in effect and safety to an existing remedy *"whose limitations and dangers the doctor already knows"*.

By mid-1962, the renal toxicity of phenacetin had also come into the spotlight. Some references to thalidomide and, more generally, the safety of medicines are

to be found in the MJA's detailed reporting of *"Medical Matters in Parliament."* On August 8, 1962, the Minister for Health (Senator Wade) responded to a question in Parliament about Distival (thalidomide): *"I want to say that whilst the manufacturers have withdrawn the drug from world markets, we in this country are not prepared to see it rear its ugly head in any form again, and I shall be very happy to confer with my colleague, the Minister for Customs and Excise, to make quite sure that it is kept out of this country."* Questions in this area continued to be asked in Parliament over the following months.

The issue was discussed with the Minister for Health by the Federal Council of the Australian Medical Association at its session in March 1963.[4] *"Federal Council gave broad approval to his plans. These will need to be worked out with great care. The Minister has not pleased certain sections of the community by taking as long as he has to reach the present stage of planning, but this is a decidedly difficult problem, the solution of which is by no means obvious. It will take time to work out further details, and we hope nothing will be done precipitately."*

In time, a Government response was formulated. An Editorial in the MJA (April 20, 1963) [5] included the following:

> *"The Australian Government has, despite somewhat emotional public pressure, declined to act precipitately. After a meeting of the Federal Council of the Australian Medical Association early in March of this year, when support was given in general terms to the Commonwealth Health Department's approach to the problem of the safety of drugs, the Minister for Health, Senator Wade, issued a statement in which he said that the Commonwealth had for some time been greatly disturbed at recent unfortunate incidents as the result of the side-effects of some drugs and had sought the cooperation and advice of the Australian Medical Association to solve this problem. The Commonwealth proposals included the establishment of a small section in the Commonwealth Health Department to coordinate all the activities necessary for an effective system of drug supervision. This would become an information centre on all aspects of drug toxicity. It would work in cooperation with overseas drug administrations, the State health departments, the medical profession, the World Health Organization and the drug manufacturers. It would also supervise the import of new drugs after carefully examining evidence from research and clinical developments within Australia and overseas. In addition it was proposed to set up a committee of independent experts as an advisory body to report on the safety of drugs generally. Senator Wade said that the proposals in no way absolved the drug manufacturers from the responsibility of continuing to conduct adequate laboratory and clinical tests and trials to ensure the safety of drugs before they were offered to the public."*

Similar information was provided by the Minister in an answer given in the House of Representatives on May 23, 1963 and in the Director-General of Health's Annual Report for 1962-63. This latter document states that prior to the establishment of the expert committee, there was consultation with the Australian Medical Association and the Royal Australasian College of Physicians. The expert committee, known as the Australian Drug Evaluation Committee, was appointed on 3 June 1963.

The Minutes of several of the first sixteen meetings of ADEC, to April 1966, reflect a growing impatience with inadequate controls over the importation of new drugs. After hearing an explanation of the situation from a senior officer of the Policy and Legislation Branch of the Department of Health at the sixteenth meeting, the Committee recorded in its conventional upper case style that:

"THE MINISTER OF HEALTH BE INFORMED AGAIN OF THE COMMITTEE'S GRAVE CONCERN AT THE CONTINUING LACK OF ADEQUATE STATUTORY CONTROL OVER THE IMPORTATION OF NEW THERAPEUTIC SUBSTANCES".[6]

Whether known to ADEC or not, the Minister for Health had sought the approval of Cabinet in May 1965 of *"the introduction as soon as practicable of amendments to the Therapeutic Substances Act."* In an extensive memorandum, the Minister catalogued a number of amendments to the Act needed to enable its full and efficient administration.[7]

In his summing up of the submission, the Minister itemised the proposed amendments:

- *to permit the fixing of standards by Ministerial determination instead of by regulation, with the determinations to be subject to disallowance by the Parliament;*
- *to enable standards constituted by a monograph of the BP or British Pharmaceutical Codex to be replaced by a standard determined by the Minister where the BP or BPC monograph was unsatisfactory for Australian purposes;*
- *to permit the determination of general notices and general standards for classes of products (i.e. tablets, capsules, injections, etc), the relevant statements in which to apply to all therapeutic substances, including those covered by individual monographs;*
- *to enable recognition to be given where necessary to the monographs of the British Veterinary Pharmacopoeia as standards for veterinary therapeutic substances;*

- *to permit the prescribing of general requirements for labelling, containers, packaging, etc to apply to all therapeutic substances (and not only to "controlled therapeutic substances");*
- *to widen the scope to include excipients, equipment used in the administration of therapeutic substances, etc;*
- *to include provision for prohibiting the importation of hazardous substances, such that a determination by the Minister for Health would invoke the relevant provisions of the Customs Act.* (The hazardous substance in mind at the time was thalidomide, which had been controlled under the Customs (Prohibited Imports) Regulations and the aim of the amendment was to facilitate the administrative procedures which to that time had required the co-operation of the Minister for Customs).

The Minister advised Cabinet that the amendments were not of a kind to provoke opposition from the drug industry. He did, however, propose that with Cabinet's concurrence he would consult representatives of the industry before the bill was introduced. Concerning the Cabinet Submission, the Attorney–General was advised by his Departmental Secretary that the proposals did not raise any questions of substantive law but difficulties in formulation may arise in the course of drafting. The Secretary continued by highlighting a proposal that instead of standards for controlled therapeutic substances being constituted by descriptions of the substances in the Therapeutic Substances Regulations, the Minister should be authorised by the Act to make determinations fixing standards. The determinations should be tabled in each House of the Parliament and be subject to disallowance in the same way as regulations. *"This proposal, if adopted, might prove a useful precedent for relegating to ministerial instruments matters that, in the past, have been the subject of regulations."*

Cabinet, too, noted that the proposal for Ministerial determinations included *"with the Parliamentary processes being met by requiring the determinations to be laid before Parliament and giving Parliament a right of disallowance of them."* Cabinet noted that this would involve a new procedure in relation to Parliament and concluded that such a procedure might raise a number of practical difficulties. Cabinet decided therefore that it would not approve the proposal (for tabling in Parliament). The Minute goes on to state: *"If the matter became an issue when the amendments to the Act were before Parliament, the Cabinet decided that the Government could argue on the grounds of technical complexity and the eminence of specialist advice under the procedures for arriving at the standards."* [9] As put to Parliament and subsequently enacted, the making of an Order was required to be notified in the Gazette, but not tabled in the Parliament or subject to disallowance.

The Therapeutic Goods Bill was introduced into the House of Representatives by the Minister for Health (Dr Jim Forbes) on 28 April 1966. The Opposition speakers indicated general support for the intentions of the bill but argued that wider powers were needed. They cited their (Labor) party's policy which advocated a referendum to give the Commonwealth Parliament the power to make laws with respect to health or reference by the States to the Commonwealth of such powers. The party's platform advocated that the Commonwealth approach the States to achieve national drug and food laws. They also raised concerns about the extent of the presence of overseas-owned companies in the Australian pharmaceutical market.

It was again Mr Howarth, a member of the Government who had spoken to the 1953 bill, who voiced the strongest criticisms in the Lower House. He was concerned with the proposal for Ministerial declaration, wanting to know the reasons for the withdrawal of important safeguards such as regulations approved by the Governor-General-in-Council. He also wanted to know why in 1960, without any reference whatsoever to industry, most of the committees established by regulation under the 1953 Act to recommend standards had had industry representatives removed from their membership. The only committee on which industry representatives remained was the Therapeutic Substances Advisory Committee which, Mr Haworth informed the House, had never met, despite requests and protests from industry! He had also been particularly pleased to hear that general control of family remedies would remain a State interest. *"State Governments have their own health departments, pharmacy boards, poison laws and pure food acts relating to drugs and it would be duplication, bureaucracy gone mad, to inflict any further legislative action on the manufacturers when the State Governments are already doing a good job in this direction. They are efficient watchdogs for drug safety."* This contribution was reported in a newspaper article on the files of the National Archives. In a section headed *"Capital Talk from E. H. Cox"* is a headline *"A Minister sidesteps Parliament"*. The article describes the Minister as having *"set out again this week to keep the parliamentary nose out of public affairs"* and that this had brought him into sharp conflict with Mr Haworth in a series of Parliamentary clashes.

During the debate, a number of instances of problems with individual medicines and vaccines were discussed. In closing the debate, the Minister, concerning the removal of industry representatives from committees, explained *that "I understand that this was done a number of years ago because it just did not work; it was found to be impracticable."* He gave as reasons that nobody could represent the whole industry in this expert process and that information placed before the expert committees about processing and the constituents of drugs might become known to competitors. He also said that it was the intention of

the Government, under the regulations, to set up an industry advisory committee to bring before the Government matters which come within the ambit of the Act and to advise the Government on anything referred to it by the Minister. The Bill was passed unamended by the House of Representatives on 5 May 1966.

In the Senate, it was the proposal for Ministerial Orders that drew much of the attention of members on both sides. Senator Wright (Liberal-Tasmania) rose to speak *"because of the obnoxious structure of the Bill from the point of view of an assault on Parliament.*" Senator Murphy (Labor-New South Wales) supported the view put by Senator Wright that Parliament should make legislation or, for subordinate legislation made under the authority of an act of Parliament, it should be under the supervision of Parliament. He opposed the departure from this principle. Senator Cormack (Liberal, Victoria) resorted to an historical analogy, likening the proposal for Ministerial Orders to *"seizure of power for ministerial orders"* by King Henry VIII. Notwithstanding these criticisms, the Bill also passed the Senate without amendment. The Therapeutic Goods Act 1966 received Royal Assent on 24 May 1966, but it was not until November 1970 that it was proclaimed.

CHAPTER 6 REFERENCES

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6. Minutes of Australian Drug Evaluation Committee. 16th Meeting. 22 April 1966. (accessed in subject index, ADEC Secretariat, Therapeutic Goods Administration).
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7. EVOLUTION OF THE NATIONAL FRAMEWORK (1967 - 1991)

The organisational structure, legislative base and the physical environment of today's Therapeutic Goods Administration are very different to those of the National Biological Standards Laboratory and the Therapeutic Goods Branch (a part of the National Health Division) in 1967. Although the pace of change quickened towards the late nineteen-eighties, there is no single date which demarcates a point of great change. Rather, structure, legislation and physical environment each evolved at a different pace and with different dates as landmarks for key changes.

In 1974, a restructure of the Department of Health created a Therapeutics Division consisting of the Pharmaceutical Benefits Branch, the Therapeutic Goods Branch (with a Drug Evaluation Section headed by a Senior Adviser in Clinical Pharmacology) and a Drugs of Dependence Section (which became a Branch in 1982). The NBSL remained as a separate Division of the Department.

A more far-reaching reorganisation of the Department took place in June 1985 with ten Divisions being rearranged and compressed into five Divisions and two smaller Branches. A new Therapeutics Division resulted from the amalgamation of the former Therapeutics Division (excluding the Drugs of Dependence Branch) and the National Biological Standards Laboratory, which lost its separate identity. The Division was subdivided into seven Branches- Pharmaceutical Benefits, Pharmaceutical Operations, Therapeutic Goods Compliance, Drug Evaluation (no longer a section), Medical Devices and Dental Products, Pharmaceuticals and Biologicals – the last two having previously made up NBSL.

As at June 1988, the two Pharmaceutical Benefits Branches had been moved from the Therapeutics Division, the Therapeutic Goods Compliance Branch had become the Drug Evaluation Support Branch and the two former NBSL Branches had been renamed as the Pharmaceutical Laboratories and Biological Laboratories Branches. In addition, a position of Principal Medical Adviser for the Division was created. Further rearrangement occurred in August 1989 when the Therapeutics Division was restructured and designated as the Therapeutic Goods Administration. The Drug Evaluation Branch remained, the Medical Devices and Dental Products Branch became the Therapeutic Devices Branch and the two laboratory branches were fused into a branch titled TGA Laboratories (TGAL).The Drug Evaluation Support Branch was abolished and the General Administration Branch and the Compliance Branch were created. It was this organisational structure that carried forward the commencement of the new Therapeutic Goods legislation on February 1, 1991.

Concerning legislation that followed passage of the Therapeutic Goods Act 1966, the same senior officer who had briefed ADEC in 1966 (see Chapter 6) made a further presentation to the Committee in November 1967, the text of which is preserved in the ADEC minutes.[1]

He summarised the existing Commonwealth controls over therapeutic goods. The Therapeutic Goods Act 1966 "*basically is legislation to establish standards for therapeutic goods."* In addition, he itemised the then existing cover of therapeutic substances in the Third Schedule to the Customs (Prohibited Imports) Regulations:-

Item 3-chloramphenicol, penicillin, streptomycin, etc.

Item 22-poliomyelitis vaccine.

Item 28A-sera, toxoids, anti-toxins, vaccines, antigens, glandular extracts and antibiotic substances.

The briefing indicated that proposed regulations under the new 1966 Act would cover:

- the items currently in the Third Schedule (which would be removed from it and included in the new regulations),
- "new" therapeutic substances (to be defined as those not imported during the previous two years) imported by licensed importers,
- and all therapeutic substances imported by other than licensed importers.

The Committee was informed that, originally, fairly simple legislation was planned. Following discussions with Attorney-General's Department, it was decided to introduce regulations under Section 50 of the Customs Act, relying particularly on the provisions that empower the prohibition of importation unless a licence or permission to import has been granted and provide for such licence or permission to be conditional.

The proclamation of amendments to the Customs (Prohibited Imports) Regulations in May 1958 and the coming into effect of the Therapeutic Goods Act 1966 and the Therapeutic Goods Regulations in October 1970 were contributors to greatly expanded activity in Commonwealth therapeutic goods regulation. Further amendments to the Customs (Prohibited Imports) Regulations included the addition of a separate Regulation 5A concerning the importation of antibiotic substances in 1970 [2] and the addition of Regulation 5H and the Eighth Schedule in May 1976.[3] This Schedule was a consolidation of a broad variety of substances for which Regulation 5H provided that importation was prohibited except with the permission of the Director-General of Health.

Also important were the establishment in March 1971 of the National Therapeutic Goods Committee (NTGC) with membership from the States,

Territories and Commonwealth and subsequent involvements in recall procedures and the control of advertising.[4] Aspects of these activities are discussed in separate chapters.

The issue of uniform national controls was not solved by the 1966 legislation. The Australian Health Ministers agreed at their conference in 1970 that the NTGC should investigate the feasibility of introducing a uniform registration scheme for pharmaceutical products marketed in Australia. A Sub-Committee of the NTGC on registration prepared two reports outlining the broad details of a scheme and possible methods for its implementation. Lack of resources within the Department led to a postponement of further detailed consideration of the scheme. The 1974-1975 Director-General's Annual Report includes that:

"During the past year, the Committee (NTGC) agreed it would be worthwhile and practicable to proceed now with a national product register of therapeutic goods, in order to provide a national data bank and as a first step towards a national registration scheme. Information would be stored on such aspects of pharmaceutical preparations as their composition, therapeutic claims, dosage, and status of use in man, in the first instance, and eventually all other therapeutic goods. Establishment of the register would also allow control of any therapeutic goods sold in Australia should an acute need become apparent. It is hoped to present the Health Ministers with a viable modified scheme in the near future."

The Australian Health Ministers endorsed a proposal for a modified scheme at their 1976 Conference. NTGC planned to implement the scheme in progressive stages with each further stage being undertaken only when adequate resources became available. A pilot study was said to have provided useful information on such matters as likely staff requirements and automatic data processing of information on products to be registered.[5] Consultation with the pharmaceutical industry and the professions was undertaken through the Therapeutic Goods Advisory Committee.

In 1978 the Committee recommended that the Commonwealth and States proceed immediately to bring down legislation enabling the gathering of information that was to be held on the register. The NTGC established a working party to guide the formation of the register [6] but progress was not rapid.

In 1981, the Senate Standing Committee on Social Welfare, in its report titled *"Another side to the drug debate…a medicated society?"* recommended that the national registration scheme be instituted as soon as practicable.

The omnibus Health Acts Amendment Bill 1981 included a number of amendments to the Therapeutic Goods Act 1966. The amendments as described in the explanatory memorandum were to:

(a) *broaden the scope of the Act to include a wider range of medical devices-if declared by the regulations to be goods for therapeutic use, goods used in testing for pregnancy, contraception, prosthetics ("such as the provision of dentures or artificial organs and limbs") and orthotics ("such as the provision of contact lenses, hearing aids and heart pace-makers") would be subject to the Act;*

(b) *update the references to British publications which are sources of standards and authorize the Minister for Health to set standards by reference to other published sources;*

(c) *establish a scheme to monitor the manufacture and testing of biological products and to regulate the release of biological products (this involved the insertion of a new Part IIIA into the Act);*

(d) *establish the National Register of Therapeutic Goods and provide the power to acquire information from manufacturers and suppliers of therapeutic goods for inclusion in the Register.* (this involved the insertion of a new Part IIIB into the Act – a new section 23H provided that veterinary products were not to be included in the National Register of Therapeutic Goods).

(e) *increased penalties for breaches of the Act.*

Although not highlighted in the Outline in the explanatory memorandum, the Bill also included the insertion into the Act of a new s29A, headed Applications for Review. This gave the right to persons affected by a *"relevant decision*" to make application to the Administrative Appeals Tribunal for review of the decision. Relevant decisions were those of the Director-General which would prevent the production or supply of a biological product in Australia.

The Director-General of Health was empowered to require, by notice, information about therapeutic goods (s23M(1)) but that information was limited to goods declared by the regulations to be goods to which s23M applied and the information related to matters prescribed in the regulations. Further, these requirements *"have effect only so far as they are within the constitutional power of the Commonwealth"* (s 23J).

Amendments to the Regulations consequent to the 1981 changes to the Act were made on 29 March 1984 (Statutory Rules 1984 No 53). These declared pregnancy testing products and contraceptives to be therapeutic goods. They also declared therapeutic goods that consist of a substance, being goods other than:

- homeopathic goods;
- diagnostic goods for *in vitro* use other than for diagnosing pregnancy;

- ingredients or components for preparation or manufacture of a substance or article;
- and goods "in the process of being prepared or manufactured for therapeutic use".

to be goods to which the requirements for supply of information to the National Register applied. The amendments also prescribed the nine matters about which information was required.

The first notices requiring information to be supplied for entry on to the National Register were served on about sixty companies in 1984.[7] Subsequent compliance with the requirement to provide information was variable between companies, probably because entry on the National Register was not central to the lawful supply of therapeutic goods, unlike the later situation with the later Australian Register of Therapeutic Goods. In February 1991, those companies which had supplied information were advantaged, however, as they were supplied with computerised printouts about their products, in the form of an application for entry onto the new Australian Register of Therapeutic Goods, for checking and return to the TGA.

In 1986-1987, meetings of the Australian Health Ministers' Conference, Australian Health Ministers' Advisory Council and the NTGC discussed proposals for a uniform national registration scheme for therapeutic goods for human use, as well as a system for licensing of manufacturers. Further consultations with State Health Authorities, industry groups and consumer groups were foreshadowed before any legislation was to be presented to Parliament. Stress was put on the potential to deal with some local manufacturers who escaped scrutiny under existing legislation. [8]

The Public Service Board Review of Drug Evaluation Procedures [9] reported in June 1987 and included amongst its sixty-eight recommendations a recommendation for uniform national registration:

"Legislation providing for the establishment of a uniform national registration scheme for therapeutic goods should be drafted urgently, with a view to consultation with the States and industry before its passage in the Autumn 1988 Session of Parliament. The target date for the introduction of the scheme should be 1 January 1989. The draft legislation should include provision for:

- *registration of pharmaceuticals and therapeutic devices*
- *licensing and inspection of manufacturers and wholesalers*
- *uniform application of standards to imported and locally produced goods*

- *application of uniform testing procedures*
- *an adequate appeal mechanism"*

The Review also recommended a re-direction of effort by the Department, to promote informed professional and *public* (the Review's emphasis) discussion of rational drug use, and to ensure the provision of better information to consumers. Within a relatively short period, Departmental support for rational drug use activities was transferred to the Pharmaceutical Benefits Branch.

The Public Service Board Review was closely followed by *A Review of Therapeutic Goods Evaluation and Testing Program* by the Parliament of Australia's Joint Committee of Public Accounts.[10] The Joint Committee had previously inquired into the National Biological Standards Laboratory in May 1985 and May 1987 in connection with the Report of the Auditor-General, March 1984. The Joint Committee acknowledged the Public Service Board review, which it noted had concentrated on drug evaluation and related aspects, with reference to NBSL only where necessary. The Joint Committee recorded that its inquiry had a wider purview and included all aspects of *"the therapeutic goods function"*. The Joint Committee took into account the Public Service Board Review's recommendations with which it largely agreed.

The Joint Committee's recommendations included important general policy recommendations in two areas. First, it recommended that the Department should ensure full consultation with all interested parties including the States and industry and consumer groups and that urgent efforts be made to ensure introduction of the bill for uniform national legislation to control therapeutic goods into the Parliament in the Autumn sittings 1989 with a commencement date no later than 1 January 1990.

Second, it recommended that the Department actively pursue the development of a national drug policy.

In the Budget brought down in August 1988, it was announced that the Therapeutic Goods Program should raise fees and charges against industry to meet the costs of therapeutic goods regulation. In October 1988 a proposal for the legislation was released for discussion.

The proposal for regulation was examined by the Business Regulation Review Unit which had been established some years earlier to service the Industry Committee of Cabinet in the area of business regulation.[11] Its *"Information Paper No 13 Therapeutic Goods Regulation*" considered that there were many areas where therapeutic goods regulation generated unnecessarily high costs and that the proposed *"intensifications of controls were not, in the main, warranted and that the charging proposals both for these intensifications and for the on-going program were excessive."*

Notwithstanding this negative report to Government, the Therapeutic Goods Bill 1989 and the Therapeutic Goods (Charges) Bill 1989 were introduced into the House of Representatives in October 5, 1989 and debated concurrently. The Government had indicated its intention that, if passed, the Therapeutic Goods legislation would have effect from 1 March 1990, with fees and charges to be collected from 1 July 1990.

The proposed Therapeutic Goods Act was in seven parts.

Part 1 (Introduction) included many definitions, including of "*therapeutic goods*" and "*therapeutic use*", the latter relating to use in persons or animals. In effect, the definitions encompassed all medicines (including non-prescription medicines), medical devices and any goods declared to be therapeutic goods. It also in section 4 set out the Object of the legislation – "*To provide, so far as the Constitution permits, for the establishment and maintenance of a national system of controls relating to the quality, safety, efficacy and timely availability of therapeutic goods that are:*

(a) used in Australia, whether the goods are produced in Australia or elsewhere;

or

(b) *exported from Australia.*

Part 2 (Standards) included empowering the Minister to make an Order to specify a standard and where there was no Order applicable to the goods for the British Pharmacopoeia to apply to goods for human use and the British Pharmacopoeia (Veterinary) to apply to goods for use in animals. Provisions for exemption from standards in certain circumstances were proposed.

Part 3 (Australian Register of Therapeutic Goods) provided for the establishment of the Register with two forms of entry – Registered Goods and Listed Goods. Entry on the Register was to be required for the lawful supply by a sponsor or wholesaler of a therapeutic good in Australia. Provisions were included for exemption from the requirement for registration and also for the approval of the supply of unregistered goods in certain circumstances, such as use in individual nominated patients and in clinical trials. Provisions were also proposed to specify the information to be included in applications for entry on the Register, the power to cancel an entry and the power to demand information from a product sponsor.

Part 4 (Manufacturers) proposed that Australian manufacturers of therapeutic goods must be licensed. To be licensed required observation of written principles determined by the Minister (Code of Good Manufacturing Practice). Overseas manufacturers were to provide an acceptable form of evidence from a relevant overseas regulatory authority to establish that the

manufacture of the goods was of an acceptable standard or to have a GMP inspection by the Australian regulator.

Part 5 (Payment of Charges) proposed Annual Registration, Listing and Licensing fees.

Part 6 (Miscellaneous) covered a wide range of topics including Search and Entry Powers and Offences. Some notable provisions in this Part included:

- empowering the Secretary of the Department of Health to issue Export Certificates (Certificate of a Pharmaceutical Product) and specifically prohibiting States and Territories from issuing them;
- a provision for many types of decisions of the regulator (in legal wording the Secretary of the Department) to be subject to reconsideration by the Minister and subsequent review by the Administrative Appeals Tribunal;
- detailed specifications about the release of information including internationally unique provisions to allow certain information to be provided to the Director-General of WHO or to foreign national regulatory authorities, and less restrictive provision to foreign national regulatory authorities with whom the Commonwealth has co-operative arrangements relating to the assessment or regulation of therapeutic goods.

Part 7 (Transition) related to the commencement of the proposed legislation. Provision was included to repeal the Therapeutic Goods Act 1966. Therapeutic goods supplied in Australia in the period immediately before the date of commencement of the legislation were, if an application was lodged, to be entitled to entry onto the Register without further evaluation – a process colloquially known as grandfathering. Provision was also proposed to enable the later evaluation of such goods in certain circumstances.

The Therapeutic Goods (Charges) legislation was to enable the implementation of the Government's announced policy to recover 50% of the costs of the Therapeutic Goods Program through annual fees and charges to be paid by the industry.

During the Second Reading debate in the House of Representatives, the Shadow Minister (Mr Shack, Tangney, WA) indicated that both the Opposition and the therapeutic goods industry supported the broad objectives of the Bill. The Opposition opposed the Bill, however, for a number of reasons including doubts as to whether a national system of controls is achievable *"in this way"*; whether the Government's proposals contain adequate checks, balances and avenues of

appeal; whether the codes of good manufacturing practice were excessive and unreasonable on a benefit to risk basis; the damage that may be done to the manufacturing and export industry by the proposed fees and charges; and the fact that *"the whole structure is to be underpinned by regulations which have not yet been finalised let alone made available to the Parliament."* Rather than try to amend the Bill, it was foreshadowed that in the Senate the Opposition would seek to refer the legislation to the Senate Standing Committee on Industry, Science and Technology, believing it to be the most appropriate committee *"to examine these proposals from an industry point of view"* and to permit further consultation with industry and the States. The debate was conducted along party lines with the Opposition further canvassing the points made by the Shadow Minister and, in addition, drawing on the report of the Business Regulation Review Unit. Despite this, the two Bills were passed in the House of Representatives on 26 October 1989.

The Bills were then introduced into the Senate on 1 November 1989. Senator Coulter (Democrats, SA) indicated the general support of his party for the Bill but expressed concern about four aspects:

1. that the labelling of export items could be of a lesser standard than applicable to goods supplied in Australia;
2. that the National Health and Medical Research Council was not an appropriate body to determine the Drugs and Poisons Schedules. Concerns included the part time nature of its committees, a lack of transparency and the absence of an appeals process. (The role of NHMRC in the Drugs and Poisons Schedules was not a subject of the proposed legislation);
3. that existing Victorian state legislation for the registration of medicines would not be repealed at the time of the commencement of the Commonwealth Act; and
4. that manufacturers of a large range of small volume products (principally herbal medicines) and start up companies making medical instruments would be discouraged or killed off by fees of the magnitude proposed. Provision for the waiving of fees in some instances was proposed.

As foreshadowed in the House of Representatives, the Opposition sought to have the Bills referred to the Senate Standing Committee on Industry, Science and Technology for inquiry and report, by the first sitting day in March 1990, on twelve separate matters. These included such things as the impact on industry (especially export and product innovation), levels of service to be provided under the Therapeutic Goods Program, evaluation procedures, whether

the proposed intensification of controls was warranted, the role of the NHMRC with respect to Poisons Schedules and the need or otherwise for complementary State and Territory legislation before the commencement of the Commonwealth Acts. When put as an amendment, the proposal for referral was defeated with Democrat Senators voting with the Government.

In addition, the Opposition raised complaints by certain sections of the industry claiming that they had not been provided with details of the proposed regulations. Also raised was a concern similar to that raised in the Senate debate on the 1966 legislation. That concern was that Ministerial Orders, including that for the Code of Good Manufacturing Practice, should not be permitted as proposed, but should be required to be incorporated into regulations, and thus be tabled in and be disallowable by the Parliament. In the Committee stage, the Opposition moved to amend the date of commencement of the legislation. It was described as a procedural device to provide that the Act would not come into effect until the date on which both Houses of Parliament had approved the regulations to be made under the Act. This amendment was carried, with the Democrat Senators voting with the Opposition.

Other amendments that were agreed to were:

- concerning export, that except in exceptional circumstances and with the consent in writing of the Secretary, persons must not export therapeutic goods that do not conform with an applicable Australian standard, except to do with labelling;
- that the Secretary must (rather than "may" as initially proposed) publish a list of the therapeutic goods included in the Register not less than once every twelve months;
- that no licence fees or inspection fees are to apply to non-profit hospital supply units;
- Government amendments to sections 50 and 51, relating to the validity of search and seizure warrants.

The Therapeutic Goods (Charges) Bill was amended to include that the regulations shall provide that annual charges in respect of the registration or listing of therapeutic goods are not payable by persons whose turnover of those goods is of low volume and low value.

The two Bills were then read a third time, thus being passed by the Senate. The Bills were again considered in the House of Representatives on 21 December 1989, when all the Senate amendments were agreed to. The Bills were returned to the Senate on the same day and received assent on 17 January 1990.

As a consequence of the Senate amendments, the two Acts and the regulations under them could not come into effect until the regulations had been approved by both Houses of Parliament. On 9 May 1990, a Notice of Motion to approve the Therapeutic Goods Regulations was given in the Senate. Two separate actions to disallow the Regulations then arose. First, on 14 May 1990, Senator Colston (Chairman, Senate Standing Committee on Regulations and Ordinances) indicated that the Committee had eight separate concerns about aspects of the proposed regulations. Subsequently, on 17 May, Senator Colston tabled in the Senate copies of correspondence between the Committee and the Minister, and indicated that he would withdraw his notice of intention to seek disallowance as the Minister had met the Committee's concerns. Second, however, on 15 May Senator Coulter (Democrats, South Australia) gave notice that he too would move disallowance of the regulations, on the grounds that further consultation was needed.

On 16 May 1990, the Senate was informed that the Minister for Aged, Family and Health Services had advised that he intended to withdraw the regulations to allow those consultations to continue. Revised Regulations were tabled in the Senate on 11 December 1990 in Statutory Rules 1990 No 394, and debated on 20 December 1990. In introducing the motion to approve the Regulations, the Minister for Justice and Consumer Affairs (Senator Tate, TAS) referred to *"much public debate and extensive consultations with interested parties"* in the intervening period.

Senator Tate indicated that amendments to the earlier proposed Regulations had been made to meet concerns, particularly of the herbal medicines and other alternative medicines industries. They included that an exemption of advertising controls to health professionals would be extended to include members of identified homeopathic and natural therapy associations, homeopathic products provided to practitioners for their dispensing would be treated as listable products together with complete exemption from product certification and licensing requirements for many more dilute homeopathic products, additional nutritional substances would be accepted for listing rather than registration, manufacturers of alternative medicines would be represented on the Therapeutic Goods Committee and adjustments would be made to the scale of fees and charges so as to reduce or in some circumstances waive those costs for herbal and homeopathic products. Further, a separate committee, the Traditional Medicines Evaluation Committee (TMEC) was to be established to evaluate traditional medicines for registration and would include representatives of the manufacturers and practitioners. Following debate, the Regulations were approved by the Senate, the Democrats voting with the Government. Later on the same day, the House of Representatives, after further debate, also approved the regulations.[12]

This enabled the Therapeutic Goods Act 1989 and the Therapeutic Good Regulations 1990 to come into effect on 15 February 1991. TMEC met for the first time on 22 February 1991.

Important progress was also made in dealing with the very unsatisfactory situation of the accommodation of the Therapeutic Goods Administration Laboratories, the history of which is described in the chapter about the National Biological Standards Laboratory.

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8. NATIONAL BIOLOGICAL STANDARDS LABORATORY (NBSL) – LATER THE THERAPEUTIC GOODS ADMINISTRATION LABORATORIES.

Dr Leigh Frederick Dodson graduated in Medicine at the University of Sydney in 1943. After holding house posts and then the Deputy Directorship of Pathology at St Vincent's Hospital, Sydney and obtaining a D Phil degree at Oxford University, he was Senior Research Fellow in Pathology at the Australian National University from 1954 to 1958.[1] Following his appointment as Director of the National Biological Standards Laboratory in June, 1958 Dr Dodson was granted a World Health Organization Travelling Fellowship and visited biological standards laboratories in the USA, Canada, the UK and Europe during the latter part of 1958.[2] On his return, temporary quarters were provided at the Institute of Anatomy, Canberra, and staff recruitment commenced. During the first half of 1959, the organization of the Laboratory was defined and the techniques for the assay of antibiotic products were set up. The Australian National University made available to the Laboratory for a five-year period one of the temporary buildings previously occupied by the Physiology Department of the John Curtin School of Medical Research. The building was re-modelled by the Department of Works and handed over to the Laboratory in June 1959.[2]

Initially the Laboratory was organised into two Branches. The Biological Products Branch comprised separate laboratories for the Bacterial Products, Viral Products and Antibiotic Products Sections. In time an Animal Breeding Section and an Inspection Unit were added. The Pharmaceutical Products Branch consisted of laboratories for Analytical Chemistry, Endocrine Products and Pharmacology Sections. Several of the laboratories commenced to function during 1959-1960. (The Director–General of Health's Report for 1958-1960 and Report for 1960-61 describe the Laboratory as being organized in two Divisions. Several long-serving members of the staff of NBSL have uniformly indicated that they do not recall the use of the term Divisions-the terms Branches and Sections were used. At least from 1984, the Annual Reports and organisation charts describe the Laboratory as a Division of the Department of Health, with a Biological Branch and a Pharmaceutical Branch. This nomenclature, describing two Branches, each with several Sections is consistent with the general structure of the Australian Public Service and has been used in this history).

The Director-General of Health's report for the two years to June 1960 recorded that positions had been created for officers to supervise each of the six laboratories with the exception of the Pharmacology Section which for the time being was to be supervised by the Director. At mid-1960 the Laboratory staff

consisted of four professional officers and ten technicians. Dr Dodson is remembered by early NBSL staff for the emphasis he put on recruiting staff who had prior scientific research experience and preferably a Ph D. This was at a time when the Ph D degree was not common in Australia as they were first awarded by many Australian universities in the late 1940's and early 1950's.

Despite difficulty being met in recruiting officers to direct several of the laboratories, two key initial appointments were made. Dr F. E. Peters was appointed Officer-in-charge of the Analytical Chemistry laboratory in January 1960, while resident in the USA.[2] A graduate of Sydney University, he held a research post with the NHMRC at Sydney University and was later Biochemist-in-charge of a Nutrition Laboratory for the South Pacific Commission. He obtained his doctorate at Purdue University, Indiana and was an Analyst with the Indiana State Chemist before taking up his post at NBSL in March 1960.

Mr (later Dr) David Howes was appointed in April 1960 as Officer-in-charge of the Viral Products laboratory.[2] He graduated from the University of Adelaide and prior to his appointment held research posts at the Institute of Medical and Veterinary Science in Adelaide, Yale University and the Australian National University.

The early testing of products by the Laboratory soon highlighted the need for adequate standards against which to judge products. Perhaps this had been foreseen because "Standards" was included in the Laboratory's name.

Dr Dodson saw the setting of standards as a key activity of the NBSL, and as a means of reconciling the interests of government and the pharmaceutical industry. In a November, 1966 address,[3] he spelt out his thinking:

"The most successful pharmaceutical firms are well aware that an essential condition of success is the quality of their goods. To attain quality, it must be measured; and to maintain quality a standard for rejection must be established. By quality in this context is meant the safety, purity, potency and efficacy of drugs. In the government-industrial symbiosis the means by which this quality is maintained in the pharmaceutical field is good design, process control, effective quality control departments and, in the government's province, it is the provision of institutions like the National Biological Standards Laboratory."

"It is necessary for governments to provide legal standards-that is specifications which are minimum requirements for therapeutic goods for the government's own purposes. Standards are used for the surveillance of goods to indicate whether proper manufacturing procedures are being practised. Moreover they are essential when large purchases are made by government authorities if the quality of the goods to be supplied is to be checked.

In the past pharmacopoeial standards were satisfactory for these purposes. Unfortunately the British Pharmacopoeia and the British Pharmaceutical Codex are no longer adequate. The first deficiency is their limited scope. A pharmacopoeia is an official compendium of standards for therapeutically important drugs. It is not intended to be comprehensive. There are about 1,000 monographs in the British Pharmacopoeia and of the order of 15,000 pharmaceutical preparations on the Australian market. There are standards for about half a dozen anti-histamines available but some 50-odd preparations are sold in Australia.

It is also fair to say that a number of standards in the pharmacopoeia are inadequate for a variety of reasons. Sometimes they are not detailed enough, for example the standards for Salk vaccine and Sabin vaccine. Frequently standards are not consistent amongst themselves for a class of substances, such as antibiotics. They are, moreover, not explicit in a legal sense.

This is not to condemn the British Pharmacopoeia but it must be recognised that the B.P. is not used in the same manner in the United Kingdom as it is being applied in Australia, both by the Commonwealth and the States. Another problem with the Pharmacopoeia and the Pharmaceutical Codex is that these books take too long to be changed, even with amendments coming forward at two-yearly intervals. There is a need for ways to deal with emergency problems that arise from time to time.

The overall result of the use of the Pharmacopoeia is that there are reasonably tight standards for some products, fair standards for others and none at all for a large number of closely allied and analogous products. It is believed that there is a need for a large number of comprehensive standards to cover all products of importance available in Australia."

It is of interest that Dr Dodson did not put forward *"extreme climatic conditions in Australia"* as a reason for specific Australian standards, as this appears to have become a common assumption within the Department and the pharmaceutical industry. It had been mentioned in an earlier (1960) presentation by Dr Peters, who cited that sugar-coated tablets of dried ferrous sulphate are not stable in the humid conditions of North Queensland as a reason to modify the British Pharmacopoeia monograph to permit the use of enteric-coated tablets.[4]

From the earliest reports of NBSL activities, a co-operative approach to industry, with a policy to discuss product problems, was espoused. *"If a product at some time is not safe, pure or potent, and we can advise the manufacturer where or why his product does not meet these standards, and he is able to correct the fault and market a good product, we feel we are achieving our purpose."* [4]

The promulgation of the Therapeutic Goods Act 1966 in November 1970 put into effect the powers needed for the creation of Australian standards and this became a major part of the work of NBSL for about thirty years. A Therapeutic Goods Standards Committee was appointed in 1971 to advise the Minister for Health on standards and matters relating to them.

The Director-General's Annual Report for 1973-74 described the process for generating standards. A procedure for achieving consensus about standards was developed, intended to give all interests – public, professional and industrial-an opportunity to scrutinise proposed standards and suggest improvements. Initially, a program of priorities was drawn up by NBSL and approved by the Therapeutic Goods Standards Committee and the National Therapeutic Goods Committee. Early development of a standard was undertaken by NBSL, assisted by external individual experts if available. The draft standard and supporting documentation were then considered and if necessary modified by the Therapeutic Goods Standards Committee – which frequently appointed sub-committees and working parties to examine the more complex problems. In time, the full Committee approved the draft standard for notification and circulation.

The availability of the draft standard was notified in the Australian Government Gazette and appropriate scientific journals. *"The essence"* of comments received by the nominated closing date was presented to the Therapeutic Goods Standards Committee. Next, the National Therapeutic Goods Committee (composed of State and Federal officers) examined the standard with a view to its incorporation into State legislation. The standard was then prepared in legal format for presentation to the Therapeutic Goods Advisory Committee (TGAC) – a body representing industrial and professional interests affected by standards, which had been established under the Therapeutic Goods Regulations and which first met in February 1974.

Following consideration by TGAC, a Draft Ministerial Order and recommendations were forwarded to the Minister for Health for approval. Orders made by the Minister for Health became effective on the date of notification in the Gazette or a subsequent specified date. Copies of Orders were distributed to members of the National Therapeutic Goods Committee and State Health or Agriculture Departments and concurring State Departments were formally requested to implement the Order.

The 1976-77 Annual Report refers to a review by the Therapeutic Goods Standards Committee of programs and policies relating to the development of Australian standards for pharmaceutical and immunological goods. The review considered *"whether the policies being followed continued to be relevant in the light of overseas developments affecting the primary sources of Australian*

standards, namely the British Pharmacopoeia, the European Pharmacopoeia and the British Veterinary Codex. The European Pharmacopoeia had become a significant source of standards for well-established drugs and was progressively moving into the field of vaccines and biological products generally. The British Pharmacopoeia had concentrated on rapidly developing standards for newly introduced drugs and had begun incorporating the British Veterinary Codex as a veterinary supplement." Why the review did not also refer to the British Pharmaceutical Codex, the British Veterinary Pharmacopoeia and to an increasing number of United States Pharmacopoeial and World Health Organization Biological standards is not known. The review acknowledged that, for practical and economics reasons, Australian standards could not diverge widely from those applying in a major segment of the western world. It was decided that in future the NBSL should place greater emphasis on review, the remedying of deficiencies and rationalisation of overseas standards, and less emphasis on other aspects of the development of standards.

The Public Service Board Review [6] reported in 1987 that there were currently 22 promulgated Australian standards with more at various stages of development. The Report noted that a consistent theme in submissions from industry was that Australia should not produce its own official standards except in cases of demonstrated medical need. It noted that similar recommendations had been made by the Pharmaceutical Manufacturing Industry Inquiry ("Ralph Report") in 1978,[7] the Senate Standing Committee on Social Welfare (1981) [8] and in the Report of the Industries Assistance Commission (IAC) Inquiry into the Pharmaceutical Products Industry (1986).[9]

The Public Service Board Review recommended that the routine development of Australian standards for therapeutic substances should cease, that new Australian standards should only be developed for uniquely Australian products or in response to a public health need, where the benefits of the Standard outweigh the costs involved and the issue cannot be or is not being addressed internationally. The Review did acknowledge that Australians can, and in some instances were, making a worthwhile contribution to the development of official standards and recommended that this be expanded through the participation of laboratory staff in international activities. The report by Baume in 1991 supported the IAC and Public Service Board recommendations but went further, recommending that any existing Australian standard in excess of British Pharmacopoeia requirements should be assessed by an appropriate committee, which should include industry representation, to determine if they are necessary in terms of the Public Service Board criteria.[10] If they were not necessary for any of these reasons, but still considered preferable to existing British Pharmacopoeia or European Pharmacopoeia standards by the TGA, adoption by

the European Commission should be negotiated. If this could not be achieved by 1 July 1993, the Australian Standard should be dropped.

From its establishment, NBSL quickly became involved in a variety of international collaborative and assistance activities and an important centre for expertise and the training of laboratory staff from regulatory agencies in the region. As early as 1968, the Director served as a short-term consultant for WHO in India, to report on measures to strengthen drug evaluation in that country and as Seminar Director for the WHO Western Pacific Regional Office Regional Seminar on Quality Control of Pharmaceutical Preparations in 1970. In time, a number of NBSL staff served as short term consultants. In 1984, with support from WHO and the Australian Development Assistance Bureau (now AusAID) fifteen overseas scientists, particularly from the South-East Asia region, received training at NBSL for periods ranging from one day to twelve weeks. This included a six-week training course for staff from the agencies in Thailand, Indonesia, Singapore, the Philippines and Malaysia in the preparation and maintenance of national and regional reference lots of antibiotic preparations. In the following year, three month training programs in pharmaceutical analysis were provided for a WHO Fellow from Malaysia and two chemists from the regulatory agency in China.[11]

Potency assays on samples of Sabin poliomyelitis vaccine used in Papua New Guinea were performed on behalf of WHO (from 1979) and on measles vaccine on behalf of the New Zealand Ministry of Health (1979) and pertussis reference vaccines were tested for the Peoples' Republic of China (1985). At the request of WHO, samples of vaccines supplied to South Pacific countries were tested (1985). Five of nineteen batches of polio vaccine and one of five batches of measles vaccine were found to be sub-potent. In 1990, forty batches of candidate measles vaccines for purchase by UNICEF were tested. A number were found to be of low potency and were subsequently rejected. The 1960-61 Annual Report of the Director-General records details of the analyses of pharmaceutical products on behalf of other government departments and especially the Department of Territories. *"The New Guinea area provided a particularly severe test of the quality and packaging of pharmaceutical products."*

The NBSL was designated a WHO Collaborating Centre for Serology and Production and Quality Control of Vaccines in February 1983. The terms of reference and title of the Centre have varied down the years to the present day WHO Collaborating Centre for Quality Assurance of Vaccines and Other Biologicals. In 1987, NBSL was designated as a WHO Collaborating Centre for Drug Quality Control (now Drug Quality Assurance), providing advice to developing countries in the South Asian and South Pacific regions.[11]

International collaborative assays, involving other regulatory agency laboratories and on occasions pharmaceutical companies, provide a means for testing proposed assay methods in a number of different hands and for arriving at potency values for new medicinal substances. NBSL, down the years, participated in a number of such collaborative endeavours. They included the assay of antibiotics (viomycin, 1965: chlortetracycline and rolitetracycline, 1967; kanamycin, 1984), biologicals (standards for posterior pituitary peptide hormones, 1977; low molecular weight heparins and follicle stimulating hormone, 1987; luteinising hormone, 1988) and comparison of tablet dissolution rate testing equipment (1982).[11]

From the early days, NBSL contributed information and comments to those developing international standards and pharmacopoeias, and particularly the British Pharmacopoeial Commission. The 1988 British Pharmacopoeia records the heads of the Antibiotics Section and Pharmaceutical Chemistry Section as corresponding members of the British Pharmacopoeial Commission committees which reviewed monographs.[12]

While the initial activities of the NBSL were product testing and the development of standards, in time the need to evaluate information submitted by pharmaceutical companies seeking approval to conduct clinical trials or to market new medicines became significant. Some staff undertook evaluations whilst also performing laboratory work while others were employed as full-time evaluators. These full-time staff were later transferred to the Drug Evaluation Section.

From its inception, the lack of adequate accommodation was a constant problem for NBSL. As a consequence, sections were moved from the Australian National University to other sites. Anecdotes are legion, including when the Director's Office and the Sterility Laboratory occupied what had previously been a restaurant in the Currong Flats, with sterility testing being carried out in the converted kitchen, to the annoyance of residents on the floors above.

Following consideration of possible sites in Belconnen and on Black Mountain, the principle of building a laboratory adjacent to the new Australian Mint in West Deakin was approved in 1964. By 1965, a site of 15 acres had been provisionally allocated and preliminary plans for a building that would allow the six Sections of the Laboratory to be brought together were developed.[13]

Following a feasibility study by the Department of Works and consultations with the National Capital Development Commission and the Department of Health, it was decided in 1968 that the West Deakin site did not allow sufficient area for possible development.[14] It has also been suggested that potential neighbours were not enthusiastic at the prospect of a very high, but necessary, chimney for the Laboratory's incinerator. A 50 acre site at Symonston in the

ACT was set aside, a feasibility study undertaken and preliminary plans prepared and costed.

By 1971, the need for a biologically secure building in which to test the potency of vaccines for the joint Commonwealth-State program to eradicate brucellosis and tuberculosis in cattle had been identified and it was decided to build this laboratory on part of the land at Symonston. A year later, planning for the Brucella building was at an advanced stage and Parliamentary approval had been given. As though a sub-plot in the story of the main building, things then went astray. The contractors for the Brucella building went out of business and cracks were discovered in concrete, designed to form an impervious barrier, in some parts of the building. It was not until the 1975-76 Annual Report that it could be recorded that the Brucella Building *"is now operating as intended during design"*.[15]

A revised design brief for the permanent main building was completed by 1974 and sketch plans and preliminary estimates prepared, only to be deferred in 1975 pending a Government decision on the possible inclusion of NBSL in a new science growth centre in Geelong, in association with the Australian National Animal Health Laboratory (now the Australian Animal Health Laboratory). [16] This concept did not proceed.

Four years later, planning stages for a building complex were again well under way and in November 1979 the Parliamentary Standing Committee on Public Works recommended the construction of a permanent building at Symonston, then at an estimated cost of $36 million, to accommodate NBSL, the Australian Dental Standards Laboratory and sections of the then Therapeutics Division. Preliminary site works, including general site formation works, were completed in 1981. A contract for *"the repair and completion of the site works"* was completed in January 1984, just one month before the tabling of the Ross Report into all Commonwealth Laboratories, a consequence of which was a ban on further building contracts. The Ross Report conceded the urgent need for new NBSL facilities but was critical of the cost and design of the laboratory animal facilities.[17] An independent review was undertaken, followed by a review of all the collated materials by Sir Gustav Nossal. Sir Gustav concluded, in part, that given the importance of NBSL's mission and the fact that staff had worked for many years in laboratories that varied from just adequate to disgraceful, any further delay would be irresponsible and unfair. [18]

In 1988 Government approval was given for *"a new home for the National Biological Standards Laboratory"* at Symonston, with work to commence in July 1989 and expected completion in late 1992. By that time, NBSL occupied some 18 often substandard sites or buildings in Canberra and Melbourne. A 1989 report of the Parliamentary Standing Committee on Public Works includes

a tabulation of the eleven sites and 18 buildings then occupied by NBSL.[19] The design process was recommenced from the beginning and the approved works commenced in July 1989. Despite the name changes from NBSL to the Pharmaceutical Laboratories Branch and Biological Laboratories Branch and then to Therapeutic Goods Administration Laboratory in the context of restructuring associated with the passage of the Therapeutic Goods Act 1989, the building project continued to be known as the *"NBSL building*" to avoid confusion in the construction industry. By June, 1990 the building program was ahead of target and within budget.

Another consequence of the Ross Report was the formation of an independent Advisory Committee for NBSL. Its purpose was to review and formalize the operational policies and activities of NBSL, so as to conform to new management principles being introduced into the Commonwealth Public Service.

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9. THE BIOLOGICAL PRODUCTS BRANCH OF THE NBSL

The Biological Products Branch initially comprised separate laboratories for Viral Products, Bacterial Products and Antibiotic Products. In time, it spawned a Unit for the inspection of manufacturers and an Animal Breeding section.

Viral Products Section [1]

The earliest laboratory work was performed while the Section was located in Canberra and involved a veterinary product, infectious laryngotracheitis vaccine for poultry. In 1960 eighteen batches of vaccine produced by two Australian manufacturers were assayed for infective potency. One sub-standard batch was identified and not distributed for use. This led to collaboration with the New South Wales Department of Agriculture in field trials and the development of an interim standard for the vaccine. This collaboration was to continue for many years after the Section was transferred to Melbourne, in the grounds of the Commonwealth Serum Laboratories (C.S.L.), Parkville.

As mentioned earlier, a consequence of the Cutter incident in the USA, in which supposedly inactivated vaccine had contained residual live virulent poliovirus, was a decision that each batch and its several poliovirus components should be tested by an independent laboratory before release. In Australia, where the sole manufacturer and supplier was C.S.L., the independent laboratory was initially at Fairfield Hospital for Infectious Diseases, Melbourne. Problems with the availability of Salk vaccine followed the failure of safety testing of two batches of the C.S.L. product in late 1960 and early 1961.[2] The Officer-in-Charge of Viral Products was sent to Melbourne to investigate and advise on the matter. This led to a subsequent decision to transfer the testing role to the newly formed NBSL and to temporarily move the Viral Products Section to Melbourne for this purpose. A planned transfer for two years was to stretch to twenty-six years.

Salk vaccine was derived from three separate strains (types 1, 2 and 3) of virulent poliovirus. These were grown in cultures of monkey kidney cells inoculated with seed viruses. Individual harvests were treated with formaldehyde under carefully controlled conditions and tested separately for residual live virus in further kidney cell cultures. The sensitivity of this test system required confirmation by challenge of control uninoculated cultures with very low standardised doses of live polioviruses. This required rigorous procedures to avoid cross-contamination leading to misleading results.

A newly-built building at C.S.L. was specially modified to a design of Dr David Howes. It contained distinct areas for media and cell culture preparation, virus assays and safety tests. Each area was fitted with airflow systems in which handling of materials was performed under "*sterile hoods*", each with strong

flows of sterile air. These pre-dated laminar flow cabinets later obtainable commercially.

Salk vaccine was also tested for the presence of live Simian Virus 40, a contaminant from the monkeys which were the source of the kidney cells needed for growing the viruses.[3] At the time SV40 was thought to be a potent pathogen in humans and the testing revealed that it was not always completely inactivated during vaccine production. These tests were performed independently of C.S.L., using methods developed at C.S.L. All released batches of Salk vaccine were satisfactory in these tests.

Safety testing of Salk vaccine continued until production at C.S.L. ceased in the 1960's and the vaccine was replaced by imported live Sabin poliomyelitis vaccine. Sabin vaccine contains a mixture of the three types of live attenuated (i.e. non-virulent) polioviruses and is given orally. Successful immunization depended on the vaccine simultaneously causing a mild gut infection by all of the three components. The absolute and relative virus doses of the three types were critically defined to avoid interference between the types after administration.

Virus content was measured in a "*plaque*" assay in which known dilutions of vaccine were spread over a monolayer of cultured monkey kidney cells. After incubation, individual virus particles multiply and cause visible local *"plaques of infection"* which can be counted. Sophisticated statistical methods were developed to avoid systematic bias which can occur if plaques are too crowded to be clearly differentiated. Methods using highly potent and specific antibodies were developed to selectively measure the content of each of the three types of virus in the vaccine. The sensitivity of these assays can vary substantially because of subtle differences in the cell culture system, so it was essential that each vaccine sample be assayed in parallel with a relevant Reference Virus Preparation of a known defined potency. These require large numbers of single-use containers stored at ultra-low temperatures for stability and must be standardised by repeated assays, in parallel with an International or manufacturer's Reference Preparation, which in turn has been calibrated during field clinical trials. To avoid operator subjectivity when counting plaques, all cultures were randomised and coded, then read and decoded during an assay.

Sabin vaccine was in general use in Australia by 1967 and over time several manufacturers entered the Australian market. Each manufacturer's product required full evaluation through the drug evaluation process before obtaining marketing approval. Individual batches, imported for distribution by C.S.L. , were sampled and assayed by the Viral Products Section and the manufacturer's detailed batch testing results were reviewed before release. Retained samples were frequently tested for stability under the recommended storage conditions.

All batches of Sabin vaccine that were released in Australia complied with the potency requirements.

In due course the experience gained with the regulatory control of poliomyelitis vaccines was applied to live attenuated measles, rubella and mumps vaccines, alone or in combinations and later to live attenuated yellow fever vaccine. These vaccines were produced using various other cell substrates and embryonated eggs.

While all batches of these live attenuated vaccines released for use complied with the potency requirements, some other causes of vaccine failure occurred. Soon after the release of a batch of rubella vaccine in 1980, the manufacturer detected an antioxidant substance in a new batch of rubber stoppers which had been used to seal vials of vaccine.[4] It was thought that this contaminant might inactivate the virus so the batch was withdrawn before distribution. Testing by the Section of retained samples of a batch of measles vaccine from the same manufacturer, which had been released, showed that about 25% of vials had low levels of potency. This was then confirmed by the manufacturer and a large-scale re-immunization campaign was conducted for recipients of this batch. The failure of a distributor to maintain an adequate cold chain was identified as the cause of a substantial loss of potency, demonstrated by the Section, of live attenuated measles-mumps vaccine being distributed in the Outback.[5]

The Section was continuously involved with human influenza vaccines, particularly after C.S.L., in 1968, introduced Sub-Unit Influenza Virus Vaccine, which was developed at C.S.L. in collaboration with the Australian National University.[6] The vaccine is prepared from suitable strains of virus grown in the allantoic cavity of embryonated chicken's eggs, inactivated by formalin, purified by zonal centrifugation and disrupted by a detergent substance, sodium deoxycholate. It contrasts with the earlier generation of whole virus vaccines which not infrequently caused adverse reactions.

Studies by the Section have included bacterial contamination of the embryonated eggs during production, factors affecting disruption of the influenza virus by detergents and formalin during manufacture and the interference of residual formaldehyde with the Single Radial Immunodiffusion assay method used for measuring virus antigen potency. Samples of vaccine, usually containing antigens of two or three strains of influenza viruses were regularly assayed to ensure the antigen content complied with limits agreed with the manufacturer.

Influenza vaccines frequently alter their antigenic nature, with new viral strains causing influenza in previously vaccinated populations. The Section developed the capacity to rapidly develop *"high yield"* recombinant strains with genetic components of older high yield virus and new antigen from recently emerging

strains. These have the potential for use in the new season's vaccines. The special facilities of the Brucella laboratory were used in 1976 by the Laboratory, in collaboration with Australian National University, to rapidly develop the *"high yield*" recombinant strains of influenza virus for use in production of the newly identified A/Victoria component. The World Health Organization has an effective surveillance system to isolate and characterize these new viruses with a view to their rapid inclusion in influenza vaccines. Because the recommendations made by the World Health Organization for the composition of the annual Northern Hemisphere influenza vaccine are not necessarily appropriate for the following Southern Hemisphere winter, there is a need to separately determine the annual composition of the Australian vaccine. As a consequence, the Section has been involved, initially informally, in the selection of the influenza strains for each season's vaccines.

From 1969, the composition of the vaccine was determined each year by an expert Committee appointed by the Federal Minister of Health.[7]

From 1986, the Committee was no longer appointed by the Minister but meets each year under the auspices of the Therapeutic Goods Administration. It consults with the WHO Influenza Reference Centre (Melbourne), regulatory agencies in New Zealand and South Africa and the Australian and overseas vaccine manufacturers supplying the Australian market.

The Laboratory's expertise was occasionally called upon in unexpected circumstances. These have included the advising on appropriate methods for making vaccines against bluetongue viruses in Australia.[8]

By the late nineteen-eighties, staff members were actively engaged in issues relating to the licensing and regulation of monoclonal antibody products and recombinant DNA products for human use, including the writing of guidelines.[9]

With the emergence of HIV and AIDS, concerns were raised that human serum in commercially available *in vitro* diagnostic products, widely used in pathology laboratories, might be a source of infection in laboratory workers. A standard was developed by the Section, specifying a test for antibodies to HIV as an indicator of possible presence of HIV in the serum. The Section testing detected three antibody positive batches, which were recalled from use. More extensive testing in research laboratories in the USA confirmed the results, but newly-developed highly sensitive tests did not detect the presence of live HIV.

The Section's work on veterinary virus vaccines continued after the transfer to Melbourne and expanded to include the testing of batches of canine distemper vaccine for potency. The Australian poultry industry rapidly expanded in the 1960's, carrying the risk that outbreaks of disease could result in substantial economic loss. Several types of avian vaccines made by several manufacturers

were in use. The work on veterinary vaccines led to concern that starting materials (including eggs) used in vaccine production could be a source of harmful avian viruses and bacteria capable of transmission to vaccinated poultry. To test this possibility, a Specific Pathogen Free (SPF) poultry flock, which was not then available in Australia, was needed. In 1973, at the laboratory in Melbourne, facilities for establishing an SPF flock were developed. The breeding program involved hatching of embryonated eggs from specially tested birds, raising of the chickens and their later mating as mature birds, all within a suite of microbiologically-contained units. With SPF materials available, it was possible to set up a wide range of diagnostic test systems. Routine tests were performed for 18 types of possible microbial contaminant. The initial testing of commercial vaccines found that a high proportion of the seed lots and vaccines were contaminated.

Within about two years, approximately 350 SPF chickens and 12,000 SPF eggs were produced annually, and by 1984 the birds were in their twelfth generation and the 100,000th embryonated egg had been produced. The SPF facility was then progressively transferred to Canberra. Over a number of years, the Section worked closely with veterinary vaccine manufacturers, state departments of agriculture and the CSIRO to ensure that Australian-manufactured veterinary vaccines were free of viral contaminants.

The Section was proactive in ensuring that through advice and guidance manufacturers were testing their products correctly, and the Assistant Director (Biological Products) became a member of the research committee of the Glenfield (NSW) Veterinary Research Station. The Section produced reference sera to enable the manufacturer's SPF flocks, seed viruses and vaccines to be tested for absence of a range of viral and microbial agents. This work contributed substantially to local high quality poultry vaccine manufacture, which in turn has enabled the development of the Australian poultry industry as it is known today.

A review by the Therapeutic Goods Standards Committee of programs and policies of NBSL in 1977 included consideration of, and support for, its role with respect to veterinary products. The Annual Report of the Director-General of Health 1976-77 stated that *"In the past, the Laboratory has concentrated on preparing standards for veterinary biological products which generally have been less refined than those for human products. The review recommended that this policy should not change." "In this field, moreover, standards developed overseas are not so directly applicable largely because the strains of organisms causing the same diseases in Australia differ from those in Europe and Great Britain."* and further that *"In the field of biological standards, particularly those for veterinary products, it is not possible to adopt overseas standards in their entirety. Current policies were endorsed by the Standards Committee.*"

Thus, work on veterinary viral vaccines continued. Similar support was given by Nossal in 1985.

Antibiotics Section[10]

At the time of the establishment of the NBSL, antibiotics had been used in clinical medicine for less than twenty years, but already made up an important and expensive part of the medicines being subsidised under the Pharmaceutical Benefits Scheme. Available antibiotics were then principally the products of fermentation of bacteria and moulds and, as a consequence, often consisted of a mixture of related substances and varied in their exact composition from time to time. Their testing for potency required microbiological assays. From September 1959 to May 1960, 317 samples of antibiotics listed as Pharmaceutical Benefits were collected from manufacturers and from pharmacies throughout Australia and tested for potency and, where applicable, moisture content, tablet disintegration time, consistency, toxicity, pyrogenicity and alkalinity of the glass containers as well as their labelling. Overall, this involved about 1500 assays. The results were reassuring with only six items failing to meet the British Pharmacopoeial standards.

It was an early observation by the Section that *"a number of instances where differences between the standards of the British Pharmacopoeia and the United States Pharmacopoeia have led to the marketing of products in Australia which are not uniform in standard and sometimes even in potency."* [11] The Section also tested veterinary antibiotic products and there found much more considerable problems. The program of the Antibiotics Section expanded in the following years to include non-PBS listed antibiotics for humans, products containing more than one antibiotic and more veterinary antibiotics. In addition work was directed at developing Australian standards for certain antibiotic products such as tetracycline capsules as well as participation in international collaborative assays to establish internationally agreed standards and reference preparations.

In 1969, a small analytical chemistry unit was added to the Antibiotics Section to expedite testing by chemical as well as biological methods, to investigate impurities and to characterise reference preparations of antibiotics. In the following year, the Section started work on the nature of antibiotics in commercial antibiotic sensitivity discs used in clinical microbiology laboratories while the analytical laboratory commissioned infra-red and gas chromatography equipment.

The Antibiotics Section embraced emerging technology, installing a computer terminal linked to a Department of Health Central Office computer to increase efficiency with statistical analysis of antibiotic assays and data processing

(1978) and validated the use of an automated machine for reading the zones around antibiotic discs on bacterial cultures.

The quality of antibiotics for veterinary use remained a problem for many years. In 1984, for example, 44% of samples of products for veterinary use failed testing, with 24% failing for important reasons such as subpotency.

The National Health and Medical Research Council carried responsibility for national policy about antibiotics from the time they were introduced into Australian clinical medicine, for a time through its Antibiotic Standing Committee, which in 1988 was redesignated as the Expert Panel on Antibiotics, and later renamed as the Working Party on Antibiotics (WPA). With the encouragement of the Director of NBSL, the head of the Antibiotics Section became actively involved in the work of this committee, serving as a member of the Standing Committee and then Secretary to the Expert Panel and Working Party, as well as Secretary to several working parties on use of antibiotics as stockfeeds, in agronomy and horticulture and in veterinary medicine. Information about the importation of antibiotics was collated and published.[12]

Following a restructure by the NHMRC in 1997, the WPA continued to function under the auspices of the Therapeutic Goods Administration. The Report of the Joint Expert Advisory Committee on Antibiotic Resistance (JETACAR) in September 1999 made several recommendations including the need for a formally constituted body with secure funding, which "*could extend the functions of the WPA*". This led to the establishment, again under the NHMRC, of the Expert Advisory Group on Antimicrobial Resistance in 2001.

The bacteriological skills of its staff resulted in the Antibiotics Section, from its initiation, undertaking testing of products for sterility. This led also to the Section's involvement in the systematic examination of each import consignment of supposedly pre-sterilised, disposable hypodermic equipment from a particular country, which found shortcomings in the packaging and labelling of some brands, including one brand which did not appear to have been sterilised. This activity evolved by 1970 into a sterility testing unit examining sterilised disposable medical equipment imported into Australia and sterility testing of injectables and ophthalmic products. In 1975 responsibility for this work was transferred to the Bacterial Products Section.

Bacterial Products Section

Difficulty in recruiting a suitable section head delayed the commencement of operations until June 1964. It was announced that the NBSL was *"now in a position to test bacterial vaccines, anti-toxins, sera and diagnostic agents for human and veterinary use, and to draft standards for these products."* [13]

As with viral vaccines, the early work on bacterial veterinary vaccines revealed a very troubling picture. In 1968, of 31 veterinary vaccines against tetanus, 39% failed. Pulpy kidney (enterotoxaemia) vaccines gave somewhat better results with only 15% failing. The Director–General's Annual Report stated – overly optimistically as it turned out that *"the manufacturers offered various explanations for the failure of their products but did not contest the Laboratory's results, which revealed a real discrepancy in veterinary clostridial vaccines. The industry has been most co-operative in implementing suggested quality control procedures and it is evident that they are now exercising tighter quality control."*

Unfortunately, when the testing was expanded to also include vaccines against blackleg, black disease and malignant oedema, it was apparent that the earlier improvements had not been sustained. The testing program continued over many years with it reporting in 1983 that the failure rate for individual components was now about 6% of vaccines tested compared with about 30% when testing started. In later years, the work involved testing multiple component ("*5 in 1*") vaccines, in which there was suspected to be antigenic competition between components resulting in some vaccination failures. Testing of veterinary clostridial vaccines by NBSL continued until about 1991.

From 1970, the Section was involved in the planning for the construction of the Brucella Laboratory. This needed to be a high security building because brucella organisms are extremely contagious, and a primary concern was the safety of the staff and others. In many ways, the Brucella building was a precursor for the Australian National Animal Health Laboratory, subsequently built at Geelong. The problems with construction are mentioned elsewhere. Initially, the role of the Brucella Laboratory was the testing of each batch of vaccine being used in the National Brucellosis and Tuberculosis Eradication Program in cattle, to ensure potency. On occasions, as in 1980 for example, several batches were found to be unsatisfactory and distribution was stopped. The Brucella Laboratory also began testing each batch of Rose Bengal antigen used in the field diagnostic procedure and later the antigen used in the milk ring test, used for screening dairy herds.

In 1981 the Brucella Laboratory assumed from the Commonwealth Serum Laboratories the responsibility for the operation of the National Brucellosis Reference Centre, which typed strains of Brucella isolated at other laboratories. These national activities continued until July 1987, when they were transferred to the Australian National Animal Health Laboratory, as the eradication program moved to its completion.

After some years of research to develop alternative methods for testing the commonly used bacterial vaccines for humans, such as tetanus, pertussis

(whooping cough) and diphtheria, because the official methods were not satisfactory, routine testing of these vaccines commenced in the late 1970's.

The pertussis vaccine was the first product to be tested as it had a reputation for being difficult to both prepare and standardise. At first, samples were tested after they had entered use. In a neat piece of investigative research in collaboration with the Microbiology Department, Princess Margaret Hospital for Children, Perth a correlation was shown between the use of some batches of vaccine later shown to be of reduced potency and an increased incidence of pertussis in infants who were given those batches.[14] The pertussis assay in particular was technically demanding but by June 1980 all bulk batches of pertussis vaccine and all batches of the combined diphtheria, tetanus and pertussis vaccine used in Australia were tested prior to release.

By 1990, it could be foreseen that the "*whole cell*" pertussis vaccine, which caused common and annoying transient adverse effects in the infant recipients, would be replaced in time by "*acellular sub-unit*" vaccines, made by mixing several different antigens, each extracted from the pertussis organism. The Section undertook development of replacement assay methods applicable to these anticipated products, the first of which was approved for use in Australia in 1996.

In 1965, the Section had started a project to determine the efficacy of known preservatives against various bacteria and fungi, with particular reference to those used in eye preparations. At the same time, at the request of the Australian Atomic Energy Commission, a study was made of the efficacy of steam sterilisation of radioactive materials. As well as testing sterile products, the Section later (1973) examined samples of Australian non-sterile pharmaceutical preparations with a view to proposing limits on microbial contamination of such products. On assuming responsibility for the Sterility Testing Unit (1975), the Section undertook testing of many batches each year of both imported and locally manufactured products, and the development of an Appendix to the Code of Good Manufacturing Practice on Sterility Testing Procedures. The staff of the Section also became involved from about 1977 in several committees which considered standards for disinfectants, contact lens soaking solutions and the sterilisation and packaging of sterile disposable goods

Each year, the Section examined numbers of pharmaceutical products, which down the years came to include antiseptics, enemas, kidney dialysis units and sterilising filters that had been the subject of complaints of significant microbial contamination. In 1981, the Section tested 2500 tampons following cases in Australia of toxic shock syndrome. The causative Staphylococcus aureus was not found in any but Staphylococcus epidermidis was found on some tampon wrappers. A special concern arose in 1982, when testing revealed that many

imported wound dressings required to be sterile were not sterile and were contaminated with organisms capable of serious infections, including a number of Clostridia species. Similar organisms were found when the testing was extended to bandages and other non-sterile products and the Section's findings were confirmed by the United Kingdom authorities. Interim import controls were put in place on all wound dressings and bandages whilst a system of permanent controls was devised in collaboration with industry. A follow-up survey of these products in 1999 showed that their microbiological quality was by then acceptable. Continued vigilance has been justified.

In 1989, following concern expressed by TGA's inspectors about manufacturing standards, major microbial contamination was found in some herbal preparations and, in 1991, batches of catheters and similar products made by an overseas company were found to be contaminated and were withdrawn from sale.

The Section has made a major contribution to the current international standards for the testing of products for sterility.[15,16] In 1980 the then Chief Microbiologist presented the results of a review of the NBSL's experience with sterility testing in the preceding five years at a Conference in Washington, D.C. Two different methods for sterility testing were mentioned in the various official standards at the time including the British, United States, Japan and European Pharmacopoeias (Membrane filtration; Direct Inoculation). All essentially permitted a 7 day incubation for the Membrane Filtration sterility test while the requirements for the Direct Inoculation Sterility Test varied between the standards – some requiring 7, others 14 days of inoculation. The NBSL data clearly showed that if incubation was stopped at 7 days, 25% of contaminants would not be detected.

The NBSL observations led to a 14 day incubation period for both tests being incorporated into the Appendix C of the Australian Code of Good Manufacturing Practice (1981) and the Therapeutic Goods Order No 11 Standard for Sterile Therapeutic Goods (1984). A consequence that led to tension over more than a decade was that the results of many sterility tests undertaken overseas during product development, and submitted in Australian marketing approval applications, were not acceptable because they did not meet the Australian standard. In time, the Therapeutic Goods Administration Laboratories successfully defended the Australian standards from the Baume recommendation that uniquely Australian standards should no longer exist. In 1993, staff of the Section published the results of a review of a further ten years experience, again demonstrating the need for 14 day incubation periods.

The persistence of the NBSL and TGAL staff, coupled with the quality of the data, have in time influenced the world. A uniform requirement for a 14 day

incubation period for all sterility tests was adopted by the European and British Pharmacopoeias in 1998 and more recently the United States Pharmacopoeia has come into complete harmonisation on this standard.

As in other sections, the Bacterial Products Section progressively adopted emerging technologies. In particular, use from the early 1980's onwards of Enzyme Linked Immunosorbent Assay (ELISA) techniques to measure antibodies permitted large reductions in the numbers of animals used in product testing.

Animal Breeding Section

This Section was established in 1973 under the control of a veterinary surgeon to ensure that animals being bred by the Section were as healthy as possible. In addition, the Section eventually undertook the breeding of Specific Pathogen Free (SPF) guinea pigs and responsibility for the SPF poultry flock which was transferred from Melbourne. The Section worked in liaison with the then Bruce College of Technical and Further Education (TAFE) which instituted an Animal Technicians Certificate Course, graduating its first students in 1981.

By 1981, the Section was breeding 90,000 mice each year, many of which were needed for the testing of the pertussis vaccine. Two factors-the desire to use fewer animals in laboratory testing and the advances in laboratory technologies-influenced the needs of the Laboratories, especially during its first thirty years.

The British Pharmacopoeial biological assay for the potency of a batch of insulin, for example, required the injection of ninety-six mice. It was not only the rising "anti-vivisectionist" and "animal rights" groups but also those involved in performing testing themselves who desired alternatives to the use of animals. The switch to non-animal methods was facilitated by the advent of physico-chemical techniques such as chromatography and immunological techniques such as radio-immunoassay, as well as the emergence of powerful computing facilities. The breeding of animals reached its peak in about 1985 and thereafter the activity, which was transferred to the vacated Brucella Laboratory, was progressively down sized and external sourcing of animals needed for vaccine testing commenced.

Inspection Unit [17]

From its inception, a guiding principle of NBSL was that quality needed to be built into products. As part of the early close liaison with pharmaceutical companies over manufacturing problems, senior officers of NBSL occasionally visited the Australian manufacturing sites but there was no formal basis to such visits. The Australian industry at that time received considerable informal training through these visits. At that time, some States had systems for the

licensing of pharmaceutical manufacturers. The Director-General of Health's Annual Report for 1968-69 highlighted, as a "*significant achievement*", the preparation by a working party of Commonwealth and State Health department officers of a Code of Good Manufacturing Practice covering all aspects of pharmaceutical manufacture. The Code was proposed as a basis for the licensing and inspection of pharmaceutical manufacturing establishments and was fully discussed and modified with the assistance of representatives of the National Council of the Chemical and Pharmaceutical Industry. *"The power to license manufacturers is a State responsibility but it has been agreed that the Commonwealth Department of Health will help co-ordinate action amongst the States."* When the first edition of the Code was published in 1970 it was, at that time, only the third Good Manufacturing Practice (GMP) requirement in the world to be published – the first two were the GMP requirements of WHO and the US FDA.

In 1970, the NBSL established the nucleus of an inspection unit to undertake inspections and further specialised training of State and Commonwealth officers. Forty-eight inspections were carried out in that year. The inspections necessarily involved the presence of a State inspector as well as the Commonwealth inspectors, who had pharmaceutical manufacturing experience and were often also accompanied by an NBSL staff member with appropriate expertise, such as in the sterilisation of products. By the criteria of the Code, the practices of the Australian pharmaceutical industry at that time varied from very good to very poor. In the case of at least three companies, it was recommended that unless there was considerable reorganising and upgrading of facilities, licences should not be issued. The Unit stressed to industry the need to shift its focus from compliance with final product tests to compliance with the multiple requirements of the Code, including such things as assays of source materials, in-process tests and sterility tests, in order to build in quality. This philosophy was most readily accepted by the subsidiaries of American and European pharmaceutical companies, whilst many other companies found the requirements very demanding.

In the following year, the first Chief Commonwealth Manufacturing Inspector attended a four week training course sponsored by the US Food and Drug Administration, and also visited the Canadian and United Kingdom agencies. A two week training course was held in Canberra for Commonwealth and State inspectors.

In each following year until 1990, joint Commonwealth-State inspections were conducted, often numbering more than 200 inspections in a year. Especially in the early years, the Annual Report was somewhat cryptic, using phrases like *"Inspection reports show a continued general increased compliance with the Code, although there is still concern with inadequate quality control in certain*

areas." Even by 1988, there was continuing concern that about one third of manufacturers did not operate at an acceptable level of compliance with the Code. In the following two years, several companies were notified that delisting of their products from the Pharmaceutical Benefits Scheme could occur unless their compliance improved. Most did, but some products were removed from the Scheme. In addition to inspections, the Commonwealth inspectors frequently met with companies to discuss plans for new or modified buildings.

In 1972, a working party of Commonwealth and State officers continued to examine ways to ensure the quality of therapeutic goods for animal use. In 1975, following initiatives from the Society of Hospital Pharmacists of Australia, the Inspection Unit prepared an Appendix to the Code for minor manufacturing operations in hospital pharmacies and in following years inspections were made of pharmacy departments of hospitals as well as of pharmaceutical manufacturers. A revised Code was distributed in 1977.

In some years, special attention was paid to certain aspects of manufacture. In 1980, for example, a program directed against microbial contamination in therapeutic goods was pursued, with the inspectors paying close attention to sanitation and hygiene. In what was believed to be an innovation unique to Australia, the draft proposed Appendix C to the Code – *Guideline on Tests for Sterility* was circulated for comment.

Many therapeutic goods are imported into Australia, and in 1986 negotiations commenced to establish a bilateral inspection arrangement between the United Kingdom and Australia. In the following year, Australia made a formal application to join the Pharmaceutical Inspection Convention (PIC) whose membership comprised most countries of Western Europe and whose function was to facilitate the mutual recognition of the results of GMP inspections by member countries. In the same year, a series of joint inspections with UK inspectors was held in Australia. In 1990, a bilateral agreement was arranged with Sweden.

Also in 1990, in anticipation of the Commonwealth taking sole responsibility for licensing therapeutic goods manufacturers following the passage of the Therapeutic Goods Act 1989, the Code of Good Manufacturing Practice was revised again and reflected more closely agreed international requirements. This was the fifth edition of the Code and the last edition to be published as a unique Australian Code. It became know as the "blue book" because of its blue cover and was recognised in Australia and internationally as one of the most useful and instructive GMP requirement documents in the world at that time. A first edition of the Code of Good Manufacturing Practice for Blood and Blood Components, which focussed on the practices of blood collection centres taking blood for plasma fractionation, was published in July 1992.

The same working party of representatives of Commonwealth and State Departments of Health that developed the first Code of Good Manufacturing Practice also developed the initial uniform procedure for the recall of dangerous and substandard drugs. The basic mechanisms of that initial procedure, now known as the Uniform Recall Procedure for Therapeutic Goods, are still utilised today. The responsibility for the updating of the Procedure now rests with the National Coordinating Committee on Therapeutic Goods (NCCTG).

CHAPTER 9 REFERENCES

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10. THE PHARMACEUTICAL PRODUCTS BRANCH OF THE NBSL

Initially, the Branch consisted of the Analytical Chemistry Section (renamed Pharmaceutical Chemistry Section by 1963); Endocrine Section and Pharmacology Section. [1]

Pharmaceutical Chemistry Section

This Section started testing products in April 1960 and in the first three months, notwithstanding staff and equipment shortages, performed 300 assays on 80 samples, using the British Pharmacopoeial standards or, where they did not exist, "*a reasonable standard*". Failures to meet the British Pharmacopoeial standards emerged with amylobarbitone, amylobarbitone sodium and potassium chloride products. Following adverse publicity in the United Kingdom and questions from Australian general practitioners, an early clinically important piece of research, in conjunction with the Pharmacology Section, was the examination of dried thyroid gland extracts, a monograph for tablets of which was current in the BP.[2] The findings that there were difficulties with the assay and considerable and inconsistent variation in content of thyroxine and liothyronine led to the National Health and Medical Research Council recommending that preparations of thyroxine should replace the use of thyroid gland extracts in clinical practice. At about the same time, the Section commenced a collaborative study with industry about excess free salicylic acid (a breakdown product) in aspirin, possibly due to poor storage or packaging.[3]

The uptake of emerging analytical technology and information technology with time is well illustrated by the Pharmaceutical Chemistry Section. Examples of how the Section kept pace with the developments are the introduction of infra-red spectroscopy for checking samples of active ingredients (1965), automated spectrophotometric analysis of single tablets (1968), the coupling together of a number of commercially available ultra-violet spectrometers to create an automated facility, allowing for fifty samples to be fed for absorbance readings at up to three wavelengths per sample instead of only one, which was usual with most automated machines, and for the results to be printed out (1970), linking of equipment to computer-calculators (1971), high pressure liquid chromatography (HPLC) (1973), automated scanning of thin layer chromatographic plates (1984), improved HPLC and gas chromatography-mass spectrometer (1990). The work of the Section in developing an application for infra-red spectroscopy warrants recording. The use of this technology for the routine checking of bulk drugs and preparations containing more than about 25% of active material was developed in 1967 and, three years later, a project was started to compile a comprehensive index of chemical data on drugs, including a reference collection of infra-red spectra on all drugs used in

Australia. In 1977, the British Pharmacopoeia adopted what had been a long standing policy in Australia. Modern infra-red spectroscopy techniques were sufficiently accurate to allow the use of reference spectra for the confirmation of identity of ingredients at the time of manufacture. This avoided the need for running comparison spectra with an authentic specimen of the drug. In 1979, sixty infra-red reference spectra produced at NBSL using a specially-acquired photocopier were forwarded to the British Pharmacopoeia Commission.

In the early 1960's, it was common to observe particles floating in bottles of fluids for intravenous use, and these could be shown to block very small diameter blood vessels in experimental animals. After trials of many different methods, the Section succeeded in adapting an electronic device (Coulter Counter, usually employed in haematology laboratories for counting blood cells) to measure the number and size of the particles. Draft monographs for particulate matter in intravenous fluids were prepared and in March 1967 a symposium was held in Canberra to demonstrate the equipment and methods and to explain the rationale for the monograph. *"The symposium attracted representatives from leading hospitals and local and overseas manufacturers."* By 1970, a repeat survey of products reflected efforts by industry with over 80% of the samples examined able to meet the proposed standard.

The Section also worked from 1965 in liaison with manufacturers concerning the use of plastics for containers for injections, infusions, solutions and vaccines. Problems identified at that time included vapour transfer through the container walls, interactions between the contents and the plastic pack and the mechanical properties. Most plastics were not heat stable and could not be heated enough to ensure sterility.

Pharmaceutical products, especially those to be taken by mouth, should deliver their active ingredient to the body consistently. The content of active ingredient should not vary from tablet to tablet and, likewise, the release and absorption should not vary between doses. The concepts of uniformity of content and bioavailability were in their infancy when the Section started work.

Work in this area started in 1967 in collaboration with the University of Otago, New Zealand, in studies of tablet disintegration and the release of active materials in tablets. Soon, a project was begun on the development of automated spectrophotometric analysis of single tablets to determine whether active materials in small amounts were uniformly distributed.

In 1969, a sample of cortisone tablets which met the existing BP standards but were not clinically effective was investigated, and the study extended to a broad range of other tablets whose active ingredients were, like cortisone, poorly soluble. This led to, amongst other things, a systematic study of the dissolution rates of tablets of corticosteroids. It was found that the content of the worst

sample varied from 50% to 124% between individual tablets. Development work in this area continued over many years and was merged into the routine sampling each year of large numbers of products listed on the Pharmaceutical Benefits Scheme. This included substantial work, involving approximately 2500 assays, on content and dissolution of digoxin tablets. The best Australian products were comparable with the best available overseas, but some were inadequate in uniformity of content between tablets or had dissolution rates slow enough that only a fraction of digoxin would be readily available to the patient. [4]

In 1982, the Section organised an inter-laboratory study to compare performance of dissolution rate equipment. Twenty-five pharmaceutical company laboratories each determined the dissolution rates of prednisone and salicylic acid tablets provided by the United States Pharmacopoeial Convention and a number of sets of equipment unacceptable for testing against official requirements were identified.

In time, work extended to developing methods for analysing active ingredients in other dose forms such as ointments, creams and eye drops containing hydrocortisone and led to the development of standards incorporating the assay methods.

By the early 1970's, the inhalation of bronchodilators and other drugs to treat asthma had evolved to the use of metered aerosols. The Section commenced studies of foreign particulate matter including metal and rubber particles which could potentially be inhaled by the user and by 1972 a draft standard had been prepared.

The testing activities of the Section were extended in about 1967 to examination of surgical dressings. Much of this work was undertaken on behalf of the Departments of Repatriation and Army, but also with a view to developing new standards. It was reported in 1969 that *"Most imported products (cotton wool dressings and bandages) met British Pharmaceutical Codex (BPC) standards but a number of locally manufactured products were sub-standard. A draft standard for modern absorbent cotton wool has been prepared."* [5] The detection of contamination of imported wound dressings (see Bacterial Products Section) in 1982 highlighted the need for more comprehensive standards and the Surgical Dressings Unit carried out development and appraisal of test methods for inclusion in Department of Health and Standards Association of Australia draft Standards for various bandages, dressings and sutures.

The Pharmaceutical Chemistry Section also took the carriage of two important initiatives, relating to the labelling and packaging of therapeutic goods. In 1973, a start was made on compiling a comprehensive file of names of drugs used in Australia with cross-references to names used in the principal drug producing

countries. Over following years, the list was developed with the aim of providing a schedule of single official names to be used uniformly on the labels of medicines. By 1977, the list of Australian Approved Names (AAN) was prepared for printing using photo-typeset methods from computer tapes. It had been intended that the list would accompany the proposed Standard for the Labelling of Therapeutic Goods but the development of the Standard took a number of years – the draft General Requirements for Labels of Therapeutic Goods was not circulated for comment until 1983 and not proclaimed as a Ministerial Order until 1986.

The other initiative was the development of an Order requiring the use of child-resistant containers for drugs most commonly involved in the poisonings of children under five years of age. Ministerial Orders on Child Resistant Container were promulgated in 1980 (No 3) and 1981 (No 7) and the expectation was expressed that the State authorities would implement them uniformly. A new Ministerial Order (No 20) was promulgated in 1986 to consolidate and extend the requirements. This order added digitalis glycosides, quinine and chloroquine in solid dose forms and digitalis glycosides in liquid preparations to those products required to be supplied in child resistant containers. More substances were added to the Schedules in 1990 (No 33). A new Ministerial Order (No 65) will have effect from 1 July 2007.

Endocrine Section

Staff for the Endocrine Section were recruited in late 1960. Testing of insulin products commenced in the following year and steps were taken towards preparation of a National Insulin Reference Standard. The Section additionally developed a sensitive assay for heparin and started testing products. Later, corticotrophins and gonadotrophins were included in the testing program. By 1966, the Section had been invited to take part in an international collaborative assay of heparin, sponsored by WHO.[6] In 1966, also, the Section investigated a wasting syndrome in guinea pigs in animal facilities in Sydney, Canberra and Melbourne and established that the disease was due to excessively high levels of fluorine in their pelleted diet. The fluorine source was powdered rock phosphate from Christmas Island that was being used as a calcium and phosphorus supplement.[7]

The Section developed techniques for radio-immunoassay of hormones and undertook collaborative studies with the Garvan Institute, Sydney, on a radio-immunoassay for secretin (1968).[8] Assays of insulin, heparin, hyaluronidase and protamine sulphate preparations were continued in the following years.

The Section Head resigned in 1966 and the search for a replacement was not successful. The acting Officer-in-Charge was awarded a three month WHO

Fellowship (taken in 1968) to study radio-immunoassay techniques in endocrinology. When this officer was promoted to the drug evaluation sub-unit of the Pharmacology section in 1971, the routine duties were transferred to the Pharmacology Section and the Endocrine Section ceased to exist.

Pharmacology Section

The initial development of the Pharmacology Section was delayed by the necessity to use its staff in the Antibiotics Section. During June 1960, however, samples of several products were taken for analysis. *"Part of the work of this laboratory has been complementary to that carried on in the Analytical Chemistry laboratory since the more precise chemical methods frequently need checking by less precise but more specific biological assays."* [9]

The initial work of the Section largely involved the use of traditional pharmacological techniques for both routine testing of samples and for research. Samples of marketed injections and intravenous fluids were infused into rabbits, checking for the unwanted presence of temperature-elevating pyrogens. Isolated animal tissue preparations were used to test for trace amounts of contaminating substances in eye drops reported to have caused anomalous reactions. Early research included investigating the effects of the infusion of particulate matter in intravenous fluids, other aspects of which were being investigated at the same time by the Pharmaceutical Chemistry Section.

The advent of Australian Drug Evaluation Committee's (ADEC) information requirements for new drug applications soon placed a heavy workload on the Section, which carried responsibility for the review of the animal pharmacology and toxicology information submitted by applicant companies. By 1969, the Section reported a doubling of the number of pages of pre-clinical material for review, reaching 45,000 pages for the year. Added to this were a number of reviews undertaken by the Section at the request of ADEC of periodic and other submissions of information about prolonged dog and monkey studies of most of the systemic contraceptives used in Australia and of studies for potential adverse effects on the developing fetus of tricyclic antidepressants, phenothiazines, butyrophenones and sulphonamides. An additional activity in 1971 was the retrieval and review of additional information about imipramine, following claims by Dr McBride of Sydney that the drug caused birth defects. The continually growing workload led to a re-organisation in 1974 of the Section into two sub-units, one for pharmacological testing and the other for evaluation of submitted information about new drugs. The latter was subsequently to come under the control of the Drug Evaluation Section in the Therapeutics Division of the Department of Health. In 1974 and 1975, the writing of guidelines for the submission of pre-clinical information and

discussion of them with industry became a significant workload, eventuating as part of the NDF4 Guidelines (see Chapter 13).

By the end of the first decade of its existence, the Section had started a growing program of testing of samples of products on the Pharmaceutical Benefits Scheme, in addition to the routine safety testing. Early research projects had included the applicability of a toxicity test for injectable iron preparations which had been introduced into the British Pharmacopoeia, examination of samples (most frequently eye drops) following complaints by medical practitioners of unexpected side effects and work on behalf of the Australian Atomic Energy Commission to ensure that certain radio-active pharmaceutical products were pyrogen-free.

By 1973, the section had started new research to validate new methods of analysis proposed for inclusion in standards. Other research was into improving the official assay for Heparin BP, which had a subjective end-point, and development work on assays for enzymes and polypeptides, including calcitonin, corticotrophin, glucagon, asparaginase, pancreatin and streptokinase, some of which were new to medicine in Australia. Radio-immunoassay methods began to be incorporated into routine activities of the Section. Because of problems with the bioavailability of commercial digoxin preparations, a survey was undertaken of the radio-immunoassay kits for digoxin assay.[10]

The Section collaborated with the World Health Organization on a standard for posterior pituitary peptide hormones (1977) [11] and arginine vasopressin, lysine vasopressin and oxytocin (1978).[12] In 1978, also, evaluation was undertaken of a new *in vitro* test for pyrogens (Limulus Amoebocyte Lysate test), which was to largely replace the use of rabbits for pyrogen testing.[13] The Section was subsequently very active in encouraging manufacturers to use this test in place of the rabbit pyrogen test. The Section's development work had an emphasis on development of other isolated cell techniques which would permit reduced use of animal testing. These included isolated adrenal cell assays for corticotrophin and tetracosactrin, and use of cell cultures for toxicity testing of plastics. Testing was undertaken of pregnancy test kits and methods for standardising allergen extracts in response to user dissatisfaction over the reliability and quality of some products (1980-1981). On the basis of the test results, recommendations were made to restrict the availability of one brand of pregnancy test kit for home use.

Insulin was an important focus in 1980. It had become a requirement that the animal source of each insulin product should be printed on the label and the Section developed an HPLC method which could identify the source. In addition, the proposed replacement of 40 and 80 Unit/ml insulin products with

100 Unit/ml products in August 1980 involved the Section in the evaluation of nearly forty new presentations of the new strength.

Two new research activities were started in the early 1980's and continued for a number of years. The quality of albumin products was investigated, including for the presence of polymerised albumin which was believed to be a cause of allergic reactions. Cell culture techniques and *in vivo* implantation methods were used in the investigation of possible leaching from a variety of medical devices including syringes, rubber gaskets on syringe plungers, renal dialysis units, blood bags and latex urinary catheters. Concern about clinical reports of urethritis and strictures following use of latex urethral catheters led to a cell culture test being introduced as a safety test in a draft Australian Standard for Single Use Urinary Catheters.[14] The Section became increasingly involved in the biocompatibility and safety testing of medical devices and biomaterials.

The Annual Report of the Director-General of Health 1983-84 stated that currently, because of limited resources, the Section was responding only to specific requests for testing and went on to itemise the following activities:

- demonstrated that an inline filter in a blood giving set released a toxic chemical, caprolactam;
- found that some recycled dialysers, intended for once only use in haemodialysis, were unsafe after reprocessing for multiple use;
- contributed to an Australian standard for blood bag collection sets;
- drafted a standard for the Limulus Amoebocyte Lysate test for endotoxins for final product release of medical devices.

From 1985 onwards, there was steady progress towards use of alternatives to whole animal assays and tests and developing systems to establish biological safety and compatibility of tissues of medical devices. The analysis of insulins and somatotrophins using High Pressure Liquid Chromatography replaced animal tests. The Section also worked at developing expertise to meet anticipated problems from the increasing number of therapeutic molecules being manufactured by recombinant DNA technology and hybridoma culture. An early need was to assess the quality and potency of biosynthetic human insulins and biosynthetic human growth hormone. Methods were developed for the detection of very small amounts of contaminating DNA in monoclonal antibodies and similar products and were assessed in 1988 in a WHO collaborative study.

Also from 1985, the Section took part in collaborative studies organised by WHO to establish the potency of reference standards for low molecular weight heparin, follicle stimulating hormone and lutenising hormone. In later years,

participation included collaborative assays for calcitonin, tumour necrosis factor and granulocyte colony stimulating factor. The Section's expertise in these areas paid dividends in 1990. The testing of human gonadotrophins used in fertility programs revealed problems with the composition, potency and stability of marketed products. The Section introduced processes to monitor and check manufacturers' batch release results and imposed requirements for the approval of the release of individual batches on some products.

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11. TOWARDS MEDICAL DEVICE REGULATION – THE MEDICAL DEVICES AND DENTAL PRODUCTS BRANCH

At a time when the implementation of the initial Commonwealth Therapeutic Goods legislation was being held in abeyance, the National Health and Medical Research Council provided funding starting in 1939 for a Research Scholar (Howard Worner) to continue studies of dental amalgams at the University of Melbourne. This resulted in the establishment of the Dental Materials Research Laboratory, which although still located in Melbourne, became a part of the Commonwealth Department of Health under the title Commonwealth Bureau of Dental Standards in 1947. In 1974, the Bureau was restructured as the Australian Dental Standards Laboratory (ADSL). A history of the Laboratory 1938-1975, with an Epilogue 1976-1988 was published in 1988.[1] It was in 1979, in the period covered by the Epilogue, that the Laboratory was placed under the administrative control of the NBSL. As summarised in the Epilogue, the ADSL continued after 1975 its traditional roles in the areas of Dental Standards development (with increased adoption of international standards), testing to Standards, research, education and advice. Testing of dental materials by the ADSL and its successors continued until 1991.

The regulation of therapeutic devices in Australia took a considerable time to crystallise. As early as August 4, 1936, the Acting Premier of New South Wales wrote to the Prime Minister concerning not only Legal and Administrative Control of the Preparation and Sale of Biological Preparations but also about catgut.[2] *"It is pointed out risks may and do arise from the lack of control of the quality of catgut used not only in public hospitals, but by medical practitioners."* The files of the Attorney-General's Department at the National Archives reveal that this provoked much opinion seeking within the federal bureaucracy. The Director-General of Health thought that it seemed impossible for the Commonwealth to control the manufacture and sale of catgut within a State.

Between August 1936 and January 1937, the NSW Premier's Department wrote four more times seeking a response about catgut, and the Prime Minister's Department harried Attorney-General's for a response. In April 1937, the Premier was advised that *"the limitations which the Constitution imposes (in respect of legislation along the lines suggested by the Federal Health Council) are definite and apply principally to the importation and exportation of therapeutic substances, with application to a limited extent only in respect of their sale, distribution and use in Australia."* [3]

The Therapeutic Substances Act 1953 included *"a surgical ligature, suture or dressing"* within the definition of a therapeutic substance. In April 1961, the

Director-General wrote to Attorney-General's Department pointing out that a number of appliances used in day-to-day medical practice, such as transfusion sets, syringes, plastic tubes, needles, etc., were now on the market in what was claimed to be a "sterile" condition, ready for use without further sterilisation. [4] The advice in response was that these appliances did not come within the definition of therapeutic substances. In his submission to Cabinet in May 1965, when seeking approval to introduce what became the Therapeutic Goods Act 1966, the Minister for Health commented that "*there is little point in ensuring the purity of a therapeutic substance if there is no corresponding control on the vehicle or article used in its administration."* [5]

A list of articles proposed to be covered by the new Act included devices used in or on the body for contraceptive purposes such as sheaths (condoms) and diaphragms, surgical equipment of the nature of sutures such as vein staples, bone ties and plates, articles of the nature of bandages such as plastic burn kits, adhesive plasters, and articles claimed to be sterile and to have a therapeutic use. The Therapeutic Goods Act 1966 subsequently defined "*goods for therapeutic use"* rather than "*substances*" and, concerning therapeutic use, *"includes use in, or in connection with, testing for pregnancy, contraception, prosthetics or orthotics.*"

By 1979, the Australian Dental Standards Laboratory had for some years been involved in a small amount of medical device testing, particularly of syringes and needles. In that year, as mentioned earlier, ADSL was brought under the administrative control of the NBSL. At that time, it was stated that the ADSL would remain with its individual identity. In 1980 there were problems with the application of the Standards Association of Australia Standard for 100 Unit/ml insulin syringes, which had been adopted by the Department as a basis for approving imported syringes. It was found that imported 1 ml single use minimal dead-space syringes did not comply completely with the Standard in terms of ensuring sterility. To avoid problems with insufficient supply during the changeover to 100 Unit/ml insulins, the Department suspended the requirement for compliance with the leakage test of the Australian Standard, initially to 30 June 1981. During 1981, the ADSL undertook testing of all brands of single use insulin syringes made for use with 100 Unit/ml insulins.

The ADSL in that year also started, in conjunction with NBSL, developing a nation-wide notification scheme to inform users of potential hazards arising from faulty health care equipment. Extensive testing of tampons for bacterial contamination was undertaken following concern about possible association with toxic shock syndrome.

The Annual Report of the Director-General of Health 1981-82 included, under the description of NBSL activities, that problems with medical devices "*-that is,*

therapeutic goods which produce their effects by physical rather than chemical interactions with the body –" demanded for the first time a significant proportion of the resources of the NBSL.

In 1981-82, there were recalls from sale of indwelling urinary catheters alleged to have caused urethritis. A program of *in-vitro* and *in-vivo* testing was implemented, leading to the development of methods of routine safety testing. Imported wound dressings labelled "*sterile*" that were found not to be sterile were also recalled. In following years, the Pharmacology Section and the ADSL in particular became increasingly involved in the biocompatibilty and safety testing of medical devices and biomaterials.

In 1984, a Medical Engineering Section was established at the ADSL in Melbourne, consisting of biomedical engineers and technical support staff. In the same year, the therapeutic devices work of NBSL was combined with the dental and device work at ADSL to form the Medical Devices and Dental Products Branch.

The medical device testing by the Branch in the following years embraced a wide range of products including infusion sets, condoms, implantable infusion pumps and ports, heart valves, urinary catheters, blood bag systems, sphygmomanometers and hand-held resuscitators.

Ministerial Orders were signed on 10 April 1986 specifying that the standards for Rubber Condoms (No 27) and for Diaphragms (No 28) would be the standards published by Standards Australia. The Ministerial Order concerning condoms has been replaced by Ministerial Order 61A, but Order No 28 remains in place.

A comprehensive program designed to ensure the quality, safety and efficacy of medical devices was developed. On 2 February 1987, amendments to the Customs (Prohibited Imports) Regulations came into effect requiring prior approval for the importation of devices in five "*designated*" categories – prosthetic heart valves; cardiac pacemakers and accessories; intra-ocular lenses; intrauterine contraceptive devices; drug infusion systems.

Therapeutic Device Advisory Panels gave advice on the information to be supplied for the pre-marketing evaluation of these devices, and *"Guidelines for Preparing Applications for the General Marketing or Clinical Investigational Use of Designated Therapeutic Devices"* were issued. The establishment of an interim Therapeutic Devices Evaluation Committee (TDEC) was followed by its formal establishment after amendments to the Therapeutic Goods Regulations and the Committee held its first meeting at Parliament House on 10 December 1987.

As part of the development of a National Register of Therapeutic Goods, a computerised Register of Therapeutic Devices was established in 1986 using software provided by the Emergency Care Research Institute in the United States of America. The development of the safety reporting system was launched in May 1987 with the first issue of the Therapeutic Device Bulletin, which contained a report form. By the end of the first twelve months of operation, 150 problem reports had been received.

The year 1989 saw several recalls of condoms following tests in which they failed to meet the requirements of the Australian standard.

In practical terms, the capture of therapeutic devices by Commonwealth legislation continued to be stepwise. The 1989 Therapeutic Goods Act broadened the definition of therapeutic devices to mean "*therapeutic goods other than goods that are represented to achieve, or are likely to be taken to achieve, any of the principal purposes of their use as a result of chemical action within or upon the body of a person or animal, but does not include therapeutic goods declared by the Secretary, by order published in the Gazette, not to be therapeutic devices."*

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12. DRUG EVALUATION AND SAFETY SURVEILLANCE FROM 1963 – THE THERAPEUTIC SUBSTANCES BRANCH

The power to control imports of certain controlled therapeutic substances under the Therapeutic Goods Regulations came into effect in 1956 and the power to control importation of certain biological and antibiotic substances under the Customs (Prohibited Imports) Regulations came into effect on 1 May 1958. It is likely that following the establishment of the NBSL in 1958, the Director of NBSL was responsible for the administration of the controls under the Therapeutic Goods Regulations while the Bureau of Customs administered the Customs (Prohibited Imports) Regulations.

It was not until later that a branch, separate from the NBSL, was established. The establishment of the planned Therapeutic Substances Section as a branch appears to have happened after the first meeting of Australian Drug Evaluation Committee (ADEC) in July 1963, as the Committee suggested that, when established, the ADEC should meet in Canberra to allow Committee members to inspect the facilities including NBSL at first hand. The Branch was in operation by the close of the 1963-64 financial year, headed by Dr B W Royall as Assistant Director-General. Dr Royall also became the Secretary of ADEC.

The Branch was established within the National Health Division, which also had the Pharmaceutical Services, Public Health and Toxicology Branches and a Nursing Section. By 1974, the Department's growing involvement in therapeutic matters led to the creation of a Therapeutics Division. It had three main areas – the existing Pharmaceutical Benefits Branch, a restructured Therapeutic Goods Branch and an entirely new area, the Drug Evaluation Section. The restructure of the Therapeutic Goods Branch was intended to provide administrative cells which performed specialised functions.

The initial role of the Branch was described as the co-ordination of Commonwealth activities in the control of therapeutic substances under the provisions of the Therapeutic Goods Act and Regulations and, in respect of certain items, the Third Schedule to the Customs (Prohibited Imports) Regulations. The Branch also provided the Secretariat of the ADEC and, from 1964, maintained the Registry of Adverse Drug Reactions.

Until August 1970, when amendments to the Customs (Prohibited Imports) Regulations were implemented, importations of new therapeutic substances, except for biologicals, antibiotics and a small number of other designated therapeutic substances, were not covered by Commonwealth law. Until that date, a voluntary scheme was in operation under which pharmaceutical manufacturers and importers seeking to import new drugs for general marketing or clinical investigational use submitted data on the drugs to the ADEC. It was

acknowledged that this arrangement was not satisfactory and that some drugs were being marketed without the submission of relevant data for evaluation. In his 1970-71 report, the Director-General noted that *"Since the introduction of the legislation it has become apparent that a number of importers have not completely understood the detail required and many applications have had to be supplemented with additional data."*

In broad terms, the administrative processes operated from August 1970 much as had been foreshadowed to ADEC. Most commercial importers of therapeutic substances became licensed importers. They were issued with a licence (Form TS 10) which certified that they were licensed under the Customs (Prohibited Imports) Regulations for the purpose of importing therapeutic substances into Australia. The licence remained in force for a stated period unless revoked by the Director General of Health and was to be presented to the Collector of Customs at a nominated import point.

All other persons wishing to import therapeutic substances required a Permit to Import (Form TS 6), which granted a permission to import on a single or on multiple occasions the therapeutic substances that were stated on the Permit. The form provided for requirements or prohibitions to which the permission was subject to be recorded. As with the TS10 licence, the Permit was to be presented to a nominated Collector of Customs. [1]

The Branch's functions in import control extended to personal importation. Small quantities of medicines could be brought into Australia by passengers returning from overseas, but for importation by post the approval of the Director-General of the Department was required. This authority was exercised under delegation by Departmental pharmacists located in the State-based offices of the Department, who visited the mail exchanges and made decisions when the medicine was identifiable, while all other products and substances were referred to pharmacists in the Branch in Canberra for examination. The pharmacists' main functions were to ensure that the medicine was what the importer claimed it to be, and that it was intended for that person's personal use. Often, the Branch would require the importer to obtain a prescription from a registered medical practitioner in the importer's Australian jurisdiction to cover the provisions for possession of prescription-only medicines. On occasions, controversy which sometimes involved Ministers arose when permission to import was denied. The Public Service Board Review (1997) suggested that this activity should be examined in the context of the then proposed new registration scheme for therapeutic goods.

Because of its role in control of imports, the Branch was made responsible for departmental activities in relation to narcotics and other drugs of dependence and a Drugs of Dependence Section was created in the 1969-1970 year with the

task of developing an Australia-wide system to monitor licit transactions in these drugs.

For a number of years, countries importing therapeutic goods had frequently required the regulatory authority in the exporting country to attest that the product was on the market in the exporting country by issuing a Certificate of Free Sale. From 1976, Australia had been a signatory to the World Health Organization's Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. The objectives of the scheme were, principally, for the national regulatory agency to certify, by issuing a Certificate of a Pharmaceutical Product in the WHO format and not a Certificate of Free Sale, that a product was registered in the exporting country and that the premises were regularly inspected and conformed to Good Manufacturing Practice. In the course of a review by the Joint Committee on Public Accounts in 1989, it emerged that some States and the Branch were continuing to issue Certificates of Free Sale that did not conform to the WHO requirements, sometimes in circumstances where there was not compliance with the Code of Good Manufacturing Practice. The Committee recommended that the Department "*urgently and formally*" ask State authorities to cease the practice.[2]

The later Therapeutic Goods Act 1989 included a prohibition on a State or Territory issuing export certifications for goods for therapeutic use in humans (s 58(2)).

In addition to providing the secretariat services for the ADEC, the Branch provided the secretariats for two other committees – National Therapeutic Goods Committee (NTGC) and the Therapeutic Goods Advisory Committee (TGAC), and was the co-ordinating authority for the Uniform Drug Recall Procedure.

The NTGC was established by an order of the Federal Executive Council on 17 March 1971, with a membership consisting of representatives of the State and Commonwealth Health Departments. During 1971, it expressed concern at the lack of information in advertisements of therapeutic goods to the medical and allied professions and received recommendations from the National Health and Medical Research Council that there should be a review of the controls on advertising of analgesics, vitamins and substances included in the Uniform Poisons Schedules. As a consequence, NTGC established a Sub-Committee on Advertising to formulate draft requirements.

In April 1973, the Australian Health Ministers gave in principle support to controls over all forms of advertising of therapeutic goods proposed by the National Therapeutic Goods Committee and advertising controls became a responsibility of the Branch. Following the support of the Health Ministers, extensive consultation with the health professions, pharmaceutical industry and

media industry followed. The NTGC held a special meeting in April 1974 to discuss the advertising proposals and while concluding that there was some need to modify the proposals, reiterated its opinions and recommendations and directed its Sub-committee on Advertising to conclude negotiations by the end of July 1974.

In 1975, the Therapeutic Goods Branch assumed responsibility for examining revised promotional literature submitted for approval by pharmaceutical companies, which later expanded to promotional material for newly-approved drugs and product information. At the same time, the Branch became responsible for the prior censorship and approval of advertisements for medicines and other therapeutic goods on radio and television, under the Broadcasting and Television Act. "*This allows a closer liaison between the officer responsible for these functions and the medical officers of the Drug Evaluation Section, who consider the promotional literature for therapeutic substances in conjunction with their evaluation of data submitted in support of applications for approval…"* [3]

Advance notice was given to the media and pharmaceutical industries that NTGC's Requirements for Advertising of Therapeutic Goods would become the basis of censorship for radio and television from 1 September 1975 and that any existing prior approvals still in effect would be cancelled on 1 September 1976.

The so-called "*Voluntary Code for the Advertising of Goods for Therapeutic Use"*, which was the result of discussions between representatives of industry members and the Department, came into effect on 1 June 1977 as the guidelines for radio and television advertisements for therapeutic goods. The Australian Newspaper Council, in the public interest and with a view to establishing uniformity in advertising standards for therapeutic goods, started to apply the Code to publications covered by the Media Council of Australia. In time, the Code was updated and became known as the Therapeutic Goods Advertising Code.

The Branch's exit from close regulation of advertising happened in three stages. Review of product information became a responsibility of the clinical streams in the Drug Evaluation Branch. In December 1987 a two year trial of self regulation of advertising of prescription medicines to health professionals by the Australian Pharmaceutical Manufacturers Association commenced. Following review of the experience by the Trade Practices Commission, the scheme has been continued until the present time. The Therapeutic Goods Act 1989 and the associated Regulations 1990 together with amendments to the Broadcasting Act in 1991 permitted the delegation of the approvals of advertisements for non-prescription medicines to the Proprietary Medicines

Association of Australia (later know as the Australian Self-Medication Industry(ASMI)) for both print and electronic media.

The role of the Therapeutic Goods Advisory Committee, which first met on 5 February 1974, lay in the somewhat tortuous route for the development of standards, as described in the Chapter about the NBSL. The Committee was established under the Therapeutic Goods Regulations to advise the Minister on matters relating to the administration of the Therapeutic Goods Act (except section 29 which related to the importation of substances that might cause a serious outbreak of disease or endanger health), the standards applicable to any goods for therapeutic use, and the requirements for labelling and packaging applicable to any such goods, insofar as those standards or requirements relate to the manufacture, distribution or use of the goods. The Committee comprised representatives from the medical, veterinary and pharmaceutical professions, and from the pharmaceutical and veterinary manufacturing industries. In practice, the Committee's main function was to provide an opportunity for all parties and sectional interests affected in their professional and commercial activities by standards proposed to be proclaimed by Ministerial Order to put their views before the Minister regarding the implications for their group.

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13. DRUG EVALUATION AND SAFETY SURVEILLANCE FROM 1963 – THE AUSTRALIAN DRUG EVALUATION COMMITTEE (ADEC).

As described in Chapter 6, the Australian Drug Evaluation Committee (ADEC) was established by Minister, Senator the Hon Harrie M Wade on 3 June 1963.

The formal functions of the Committee were defined as:

- *to make medical and scientific evaluations of such therapeutic substances that the Minister referred to it for evaluation,*
- *to make medical and scientific evaluations of other therapeutic substances if, in the opinion of the Committee, it would be desirable to do so,*
- *and to furnish such advice to the Minister as the Committee considered necessary related to the importation into, and the distribution within, Australia of therapeutic substances that were the subject of evaluations made by it.*

Amendments to the Therapeutic Goods Regulations were gazetted some time later, on 20 May, 1965.[1] These inserted Regulation 21A, which set out the membership and functions of ADEC.

The Minutes from the earliest meetings onwards of the ADEC have been preserved in a filing system organised by subject at the ADEC Secretariat, Therapeutic Goods Administration. In addition, the ADEC published a report covering its activities from June 1963 to December 1966, a copy of which is held in the TGA Library.[2]

The first meeting was held in the Board Room, Royal Prince Alfred Hospital, Sydney on Thursday, 25 July 1963, under the chairmanship of Dr Edgar Thomson. The Committee was composed of seven members eminent in the fields of clinical medicine and pharmacology. Dr Leigh Dodson was the initial Secretary to the Committee. The Committee met three times in 1963.

The establishment of ADEC was thus contemporaneous with the establishment in the United Kingdom of the Committee on Safety of Drugs, known popularly as "*the Dunlop Committee*" after its first Chairman, Sir Derrick Dunlop. The Committee on Safety of Drugs was set up in June 1963. The first meeting of ADEC was addressed by the Director-General of Health who conveyed that the Minister for Health had asked him to tell the Committee that he greatly regretted his inability to attend the first meeting. A message from Senator Wade was read to the Committee, particularly emphasising the independence of the Committee and its freedom from political pressure.

The Director-General outlined the proposals for the further regulation of drugs, including a mechanism of drug control. It was proposed to create a category of "*approved drug importer*", being a person or company who agrees, as a condition of the approval, to provide the Director-General with certain information about new therapeutic substances proposed to be imported or distributed interstate. A further condition for approval is the agreement of the person or company not to distribute new drugs until the Director-General's permission has been granted. Thereafter, an approved drug importer will suffer no hindrance to his importation of therapeutic agents.

Any person not approved who wished to import therapeutic agents would be required to seek the Director-General's approval for each shipment of all such agents to be imported. The usual quarantine and Customs practice would still be followed and there would be no restriction on the Director-General's right to prohibit the importation of any particular substance were this deemed necessary. The Director-General also stated that the "*Therapeutic Substances Section*" (which was in fact established as a Branch) would function in cooperation with the National Biological Standards Laboratory but there would be individual Directors for the Therapeutic Substances Section and the National Biological Standards Laboratory.[3]

In the Annual Report of the Director-General of Health 1963-64, it is stated that the Committee *"will report on the safety of drugs generally, evaluate specific drugs referred to it by the Director-General and act as an independent arbiter in cases where an importer or manufacturer of drugs desires a review of a prohibition imposed by the Department."* It can be noted that the *"independent arbiter*" role is not exactly congruent with the formal designation of functions. It can also be noted that until the Therapeutic Goods Act 1989 came into effect there was essentially no avenue of appeal against a recommendation of ADEC. Until 1991, ADEC heard its own appeals.

The Committee in its first meeting advised the Department on the definition of a "new therapeutic substance" and considered the stages of drug development, including what information should be sought from manufacturers. It took into account the report of the Cohen Committee issued in March 1963 (Joint Subcommittee of the Standing Medical Advisory Committees for England and Wales and for Scotland, chaired by Lord Cohen of Birkenhead) and the United States' New Drug Regulations.

The Committee defined four stages in drug evaluation:

(I) Toxicity tests on animals.

(II) Limited clinical trials – to test efficacy, formulation, dosage, etc.

(III) Properly controlled clinical trials.

(IV) General distribution - still governed by new drug status.

At its first meeting, the Committee responded to the Director-General's request for a recommendation with regard to the best means of issuing warnings of drug toxicity. The Committee recommended that in very urgent cases a circular letter from the Director-General of Health direct to medical practitioners would be advisable and in certain cases, depending on the urgency, the press and radio may need to be utilised also. In the less urgent cases the Australian Medical Association's monthly Bulletin should be utilised. In both cases the information should subsequently be sent to the Medical Journal of Australia.

The matter of competing interests was also raised at the first meeting, because Therapeutic Committees were being established in the States by the Australian Medical Association. ADEC decided that it would be quite proper for a member of the Australian Drug Evaluation Committee to be a member of a State Therapeutic Committee of the Australian Medical Association.

The published report of ADEC spanning June 1963 to December 1966 is a very valuable and detailed record of ADEC's early activities. From 30 June 1964, when new drug submissions were first required, to December 1966, ninety-six submissions were received by the Director-General. In practice, the information was considered by the medical and scientific staff of the Department of Health, many of whom were staff of NBSL, and their assessments were circulated to Committee members for consideration. In many instances, however, the Department referred full details to the Committee for expert advice. One of the ninety-six submissions was withdrawn by the applicant before assessment. In sixty-two cases approval was recommended for the applicant's proposals for marketing or clinical trials. Of the remaining thirty-three submissions, developmental information was inadequate for marketing purposes but clinical trials were permissible in all except three instances.

At its second meeting in October 1963, the Committee recommended that a registry of Adverse Reactions to Drugs be established within the Commonwealth Department of Health and that medical practitioners in Australia should be asked to co-operate in a scheme to report any instances of serious adverse effects of drugs to the Committee. The implementation of the scheme is dealt with in Chapter 15. The Australian reporting often formed part of the information supporting drug safety warnings issued by the Director-General on the advice of the ADEC.

At the second meeting ADEC also made its first recommendation for the withdrawal of a product from the Australian market.[4] ADEC was advised that the medicine bunamiodyl sodium (Orabilix) used to visualise the gall bladder in X-rays had been withdrawn from the market in the USA because of an association with the development of renal tubular necrosis leading to death. The

ADEC Secretary explained to the Committee the mechanisms under Section 18 of the Therapeutic Goods Act and Item 18 of the Customs (Prohibited Imports) Regulations that could be utilised to prohibit importation into Australia. After discussing the matter, ADEC asked that a letter to the Minister recommending such prohibition be prepared. The text of the letter was read to the members of the Committee and subsequently signed by the Chairman. Not very long afterwards, in April 1964, the Chairman called a special meeting of the ADEC to consider a proposal of the US Food and Drug Administration to withdraw from the US market a laxative and tannic acid combination (Clysodrast) used as an enema to prepare the bowel for X-ray examinations and to label tannic acid preparations with a warning against use in enemas.[5] An association had been noted between tannic acid administered rectally and necrosis of the liver. In this instance, ADEC resolved that State Health Authorities, the Australian Medical Association and Medical Colleges should be advised that ADEC recommended the suspension of the use of tannic acid and any proprietary preparations containing it administered rectally pending further investigations and until such time as a safe dosage level had been established. Publicity in the Medical Journal of Australia and referral to the Poisons Schedule Subcommittee (of NHMRC) were also recommended. In this instance, the College of Radiologists of Australasia took issue with the recommendation and the matter was the subject of consideration at seven more meetings, the last being in February 1968. On the basis of a lack of adequate evidence to support safe use, ADEC stood by its recommendations.[6]

Twenty-two items from the Director-General on sixteen individual drug safety issues were published in the Medical Journal of Australia from 1964 to December 1966. They included warnings about the occurrence of Stevens-Johnson syndrome in association with long-acting sulphonamides (repeated in the period), Dimethyl Sulphoxide (DMSO) (repeated twice), sympathomimetic drugs and asthma, methyldopa and haemolytic anaemia, phenylbutazone and blood dyscrasias, nitrofurantoin and various reactions, methysergide and fibrosing conditions and small bowel lesions with enteric-coated potassium tablets. These warnings are reproduced in full in the ADEC 1963-1966 report.

Over following years, in addition to considering applications to market new drugs, the Committee continued to review marketed drugs about which efficacy, safety or appropriate use issues had been raised. For example, the Committee in 1979 recommended that only one strength of insulin (100 Units/ml) should be on the Australian market, instead of five strengths ranging from 20 Units/ml to 300 Units/ml.[7] The change was implemented on 1 August 1980, with a single exception – 300 Unit/ml products remained for the treatment of severe hyperglycaemic episodes. The change required the availability in Australia of

special syringes. This aspect was managed by the Australian Dental Standards Laboratory and was not without its problems.

In the early years of its existence ADEC operated in an international vacuum for policies and guidelines. Today, the TGA relies heavily on European guidelines on regulatory issues such as the necessary content of applications for registration of medicines for various uses and the requirements for post-market safety monitoring by pharmaceutical companies, but the Directive providing for the establishment in Europe of the Committee for Proprietary Medicinal Products (now the Committee for Human Medicinal Products), which has supervised the production of those guidelines, was not published until 1975. Thus, an important part of ADEC's role was the development of advice on policy and of guidelines.

During its early meetings, until mid–1964, the Committee and the Department refined the document setting out the information required from importers of New Therapeutic Substances. This document was issued as the New Drug Form 2 (NDF 2). Its contents reflected the Stages I to IV, described above, and it covered importation of new drugs for clinical trials as well as applications for marketing approval. A major revision (NDF 3) was distributed in about 1970. In late 1974, the third revision of the series (NDF 4) was distributed.[8]

In 1968, ADEC started to pay attention to the content of the product literature provided with marketed drugs [9] and in 1974 recorded its concern that few of the physician-oriented package inserts, where they existed, reached doctors but that some did reach patients who could react in "*unfortunate ways*".[10] This was the start of a consideration of the need for and content of patient-oriented package inserts.

By 1973, the Committee recognised the importance of the demonstration of efficacy as well as safety for medicines proposed for marketing. This in turn raised the question of whether demonstrations of relative efficacy, compared with an already marketed product, should be required in addition to absolute efficacy. The Committee discussed this matter with the Minister of Health who directed that, in view of the complexities involved, studies on comparative efficacy and safety should not necessarily be mandatory in all cases, and it would be left to the discretion of the Committee. Also, if an established product came under question, the Committee should examine each situation on its merits.[11] In so doing, the Minister made clear his expectations of the Committee in terms of taking responsibility.

In the same year, the Committee advised that it was generally not in favour of fixed combination products, but set some guidelines for possible approval. Concerning clinical trials, it recommended that the trial protocols should be submitted as part of applications for approval to conduct clinical trials,[12] and a

year later (1974) that each institution used for the conduct of clinical trials must have an Ethics Review Committee, which would also be required to consider and approve the protocol of a proposed trial.[13]

The Committee in its early days became involved in the evolving issue of bioavailability. In November 1968, the Committee considered a number of reports of adverse effects of the Dilantin brand of phenytoin sodium, consistent with the well-documented effects of phenytoin overdosage.[14] In both Brisbane and Dunedin, markedly elevated plasma concentrations of phenytoin had been documented, despite the fact that the correct content of phenytoin sodium in the capsules had been verified in both places. The cause of the overdosage was attributed to a change in the excipient of Dilantin 100mg capsules from calcium lactate to lactose. Importantly, the capsules, both before and after the change of excipient, had conformed to the relevant British Pharmacopoeial Standard. The matter was revisited in 1970. Noting the phenytoin experience and some other recently published material concerning the absorption of oxytetracycline, the Committee concluded that the tests then required by pharmacopoeias may not ensure that equivalent serum drug levels were attained following the administration of preparations of the same formulation produced by different manufacturers, although they may all have met the requirements of the relevant pharmacopoeial monograph. The Committee set out some circumstances in which applicant companies should be requested to provide *"the results of studies which establish a correlation between clinical efficacy, absorption data and suitable in vitro tests."* [15] In 1973, it noted reports of variable patient responses with different formulations of products and issued warnings about a need for alertness with digoxin and levodopa preparations.

In December 1974, ADEC considered a draft standard for digoxin tablets and a proposed set of guidelines which had been developed by a subcommittee of the Therapeutic Goods Standards Committee. The proposed guidelines dealt with *in vitro* release rates of formulations and the ADEC minutes convey the impression that it felt that the guidelines were based on a restrictive WHO definition of bioavailability and should go further, *"to cover the availability of the substance to perform its biological function"*.[16] Another year later, following considerable changes and consultations with industry, members of ADEC agreed that the *"Guidelines for Bio-availability Studies"* were satisfactory and should be included as an appendix to the NDF4.[17]

In 1979, the Committee noted that it had in the past two years considered a number of applications to market non-steroidal anti-inflammatory drugs (NSAIDs). The majority of these applications had been rejected at the first consideration because of efficacy and safety deficiencies, many of which were common to all applicants. A similar situation existed with applications for sustained release formulations and single daily dose regimens proposed for

already marketed drugs. The Committee adopted guidelines drawn up, at its request, by the Department of Health, setting out the type and extent of data required for both of these categories of products. It was recorded that "*Where similar problems become apparent with other groups of drugs, it is proposed to produce further sets of guidelines in an attempt to reduce the delays caused by inadequate data.*" [18]

Some requirements in these guidelines caused discomfort in the pharmaceutical industry. A requirement in the NSAID guideline for the study of faecal blood loss at one month, when some other regulatory agencies were approving these drugs on the basis of a seven day study, resulted ultimately in ADEC moving to a requirement for a fourteen day study. At that time, too, a study of the effect of food and increased gastrointestinal motility (achieved by giving a high fat meal) on the bioavailability of a sustained (or modified) release product was not a requirement in some other jurisdictions but is now a requirement in the major international jurisdictions. [19]

Through the advice it gives to the Department, ADEC wields considerable influence. Contrary to concerns held from time to time by some in the pharmaceutical industry, ADEC did recommend approval of the majority of applications it reviewed. The statistics for 1975-76 are probably typical of other years. [20] In that year, ADEC considered 69 applications for the marketing of new drugs. Forty-eight were recommended for approval, including 40 at the first consideration. Eleven applications were recommended for rejection, and ten deferred pending the submission of additional information. In the same year, seven applications to extend the indications of already marketed drugs were considered, of which four were recommended for approval.

On occasions, the ADEC process has clearly protected the Australian community from major harm caused by medicines. In early 1982, for example, the Committee considered an application to market a new anti-arthritis drug, benoxaprofen. The drug had been marketed in the United Kingdom for about two years and there was building pressure for it to be available in Australia. The Department of Health's evaluation had drawn attention to a high frequency of photosensitivity reactions (skin reactions caused by light) in clinical trials. The Department had then ascertained that a high incidence of these reactions had been recorded in the UK as well as a small number of reports of more serious and potentially fatal skin reactions. The expert advice of ADEC was that the UK experience was considered to render the drug unsuitable for use in Australian conditions. [21] ADEC subsequently received representations from medical specialists that marketing in Australia should be permitted, with instructions to patients to use sunscreen on exposed areas and have gradual exposure to the sun, as well as monitoring of such Australian use. ADEC held its ground because of the apparent extent of photosensitivity and some

emerging reports of liver toxicity in elderly patients taking the drug.[22] Benoxaprofen was never marketed in Australia. It was withdrawn from markets world-wide after its marketing was suspended in the United Kingdom on 3 August 1982.

A fully-reported study of the impacts of ADEC's expert advice has never been undertaken. A paper describing a review of restrictive actions recommended by the ADEC in the period March 1976 to June 1978, undertaken by Dr Graham Dukes, Consultant, and Ms Inga Lunde, Temporary Adviser, WHO Regional Office for Europe, Copenhagen, Denmark, was published in the Medical Journal of Australia in 1982. [23] The reviewers were given privileged access to ADEC decisions, which made impossible independent assessment and criticism of the review. Their findings, as set out in the paper's abstract, are nonetheless worthy of note:

"*An analysis of restrictive decisions taken by the Australian Drug Evaluation Committee (ADEC) over a period of 27 months (from March 1976, to June, 1978) was made by two non-Australian observers. During this period, the ADEC took 32 useful restrictive measures (a little more than one a month). The analysis was limited only to cases in which ADEC took substantial action; if less comprehensive measures were included, the number of valid actions to counter the occurrence of iatrogenic complications would be much greater. It is concluded that, although it is an undisputed fact that many pharmaceutical companies maintain the highest ethical standards, there is a need for the type of objective and dispassionate control exercised by the Australian Drug Evaluation Committee."*

Unfortunately, because of the privileged access, the paper did not report explicit individual examples of ADEC decisions.

A Committee of seven experts could not reasonably be expected to provide all the needed knowledge across the growing array of therapeutic substances. ADEC sensibly established a number of working parties and subcommittees to provide the needed expertise. Following the establishment of the Adverse Drug Reactions Advisory Committee (ADRAC) in 1970, the setting up of a Vaccine Subcommittee and an Endocrinology Subcommittee soon followed.

The setting-up of the fourth subcommittee occurred in somewhat unusual circumstances. As later described by the Chairman of ADEC, these were that *"In the Journal (Medical Journal of Australia) of March 4, 1972, Dr W.G. McBride stated that he had seen one child with amelia and had learned of two others with a similar deformity. He reported that in all three pregnancies the mothers had ingested imipramine, which he believed to be a cause of limb deformities. Further details were not provided."* Perhaps fortuitously, ADEC had some 18 months previously initiated an in-depth investigation of tricyclic

antidepressants, phenothiazines and butyrophenones as a result of isolated reports of a variety of congenital abnormalities. This had included obtaining information about unpublished teratogenicity studies in animals from manufacturers and contact with major obstetric hospitals in each State. The Committee held a special meeting in Sydney four days after the publication of Dr McBride's claims and discussed the details of the cases with Dr McBride. He corrected certain details of his original letter to the Journal. In the March 25, 1972 issue of the Medical Journal of Australia, the Committee, over the Chairman's signature, reiterated that, although the absolute safety of imipramine during pregnancy had not been established, current assessment proved no causal relationship with congenital abnormalities of the limbs.[24] Following this episode, the Congenital Abnormalities Sub-Committee (CASC) was established by ADEC to provide for "detailed and specialised consideration" of the safety of drugs in pregnancy.

CASC devoted much of its time in following years to staying abreast of the relevant literature, although from time to time new suggestions of drugs causing abnormalities surfaced, including stilboestrol and adenocarcinoma of the vagina (1972), the antiseptic hexachlorophene associated with both minor and major birth defects (1980), the proprietary anti-emetic product Debendox and limb deformities (1980 – being another association proposed by Dr McBride), sodium valproate and spina bifida (1983), isotretinoin and major defects (1986) and danazol and foetal masculinisation (1986).

By 1984, however, the principal focus of the work of CASC was the production of a system for the categorisation of the safety of drugs when used in pregnancy. CASC recommended the adoption with some minor alterations of a categorisation used in Sweden, which if implemented would be included in product information. This work came to fruition in 1989 with the publication of ADEC's booklet *"Medicines in Pregnancy – An Australian Categorisation of Risk"*, which was distributed free to medical practitioners and pharmacists. Subsequent editions were printed in 1992, 1996 and 1999 (renamed Prescribing Medicines in Pregnancy).

A Parenteral Nutrition Subcommittee was established in January 1975, to draw up guidelines for information to support registration and recommended procedures for use of parenteral nutrition products in hospitals. Parenteral Nutrition Guidelines were introduced in 1982 and the Subcommittee was dissolved in 1984.

In 1976, an ad-hoc subcommittee on anti-cancer drugs was established. This Anti-cancer Sub-committee successfully established links with the US National Cancer Institute and the then Bureau of Drugs of the US Food and Drug Administration to give clinical investigators in specialised Australian cancer

units easier access to investigational anti-cancer drugs developed in the USA. Such access avoided the laborious need for repeated Individual Patient Use applications as well as introducing more systematic collection of information about efficacy and safety. The links with the National Cancer Institute were strengthened by a Senior Medical Officer from the Drug Evaluation Section working at the Institute for a year. A Background and History of the Anti-cancer Sub-committee was published in the Medical Journal of Australia, February 4, 1984. A later paper in the same journal on August 18, 1984, detailing the use of the drugs, recorded that considerable progress had been made in the availability and monitored use of investigational anticancer agents in Australia. An encouraging pattern of use of these agents had evolved, from usage in uncontrolled conditions for individual patients to increased use of clinical trial protocols, with specific patient eligibility criteria and assessment of response and toxicity.

In the following year, having formed the view that it would be appropriate for it to supervise the major input into any nation-wide drug information service, ADEC initiated the formation of a National Drug Information Service Advisory Sub-committee.

Until January 1, 1978, radiopharmaceuticals were supplied without charge by the Australian Radiation Laboratory. At this date, such supply ceased and an open market for processing and supply began. A Radiopharmaceuticals Working Party was established to develop guidelines on information to support their use in humans. In 1981, the guidelines were finalised and issued by the Department of Health as an appendix to the NDF4.

In what was probably the peak year for its subcommittees, all eight subcommittees – ADRAC, CASC, Endocrinology, Vaccines (later to become Vaccines and Allergens), Parenteral Nutrition, Radiopharmaceuticals, Anti-Cancer and National Drug Information Service Advisory Subcommittee -were active during the 1980-81 year. [26]

In 1985, on the advice of the Anti-Cancer Subcommittee, ADEC recommended that an ad hoc subcommittee should be established to formulate guidelines to be applied to the clinical use of monoclonal antibodies. There was some delay because of administrative matters and the Subcommittee did not meet until August 1986. In 1987, ADEC agreed to change the name to the Biotechnology Products Subcommittee and to amend its terms of reference. Guidelines for the Preparation and Presentation of Applications for General Marketing of Monoclonal Antibodies Intended for Use in Humans were completed in 1988. The Subcommittee also prepared guidelines for Substances Produced by Genetic Manipulation, which were first distributed in 1990.

The Gestalt Affair and the Review of Drug Evaluation by the Public Service Board, described in the next chapter, were amongst events that raised the need for ADEC to have an expert Pharmaceutical Subcommittee, which it was envisaged would provide in-depth review of pharmaceutical chemistry evaluations and provide advice on relevant policy issues, content of regulatory guidelines and standards. This Subcommittee met for the first time as the Pharmaceutical Working Party on 18 August 1988 and became a formally established Subcommittee in December 1989. This period also resulted in the recognition that pharmacopoeial standards for chemistry and quality control were not necessarily sufficient and that it was appropriate for additional requirements such as measurement of dissolution rate and on occasions bioavailability studies to be required.

Nineteen eighty-nine also saw the establishment of a Working Party to consider regulatory aspects of metered dose aerosol products. Conventional bioequivalence data were not useful in assessing the comparative efficacy of different metered dose aerosol products. The Working Party met in June 1989 and after subsequent carriage by the Pharmaceutical Subcommittee and consultations with industry, the guidelines concerning metered dose aerosols (pressurised and non-pressurised) were adopted by ADEC in August 1991.[27] Despite some concern of the Therapeutic Goods Administration that the adoption of *"uniquely Australian guidelines"* at a time of considerable reforms in the wake of the Baume Report would be inappropriate, the guidelines were issued.

Following the promulgation of the Therapeutic Goods Regulations 1990, which had taken effect in February 1991, ADEC reconstituted its existing subcommittees, with some minor membership changes, until 31 December 1991, pending the outcome of the Baume Review.

Perhaps of all the products to which ADEC, from its inception, gave continuing attention because of safety concerns, it was the oral contraceptives. The minutes of ADEC's second meeting record that it was seeking a copy of a report on which an FDA warning about the combination product Enovid (norethynodrel and mestranol), presumably about thrombo-embolism, was based. The early oral contraceptive products contained what are now regarded as high doses of oestrogens. ADEC's view in September 1965, having considered reports of possible serious untoward effects was that *"This Committee is at present of the opinion that no definite evidence of a cause and effect relationship between oral contraceptives and liver damage, thrombosis, breast and endometrial carcinoma has been demonstrated."*[27] The ADEC 1963-1966 Report, however, highlighted the possible adverse effects of oral contraceptives, which warranted a separate section in the Report. The Committee gave particular attention to reports of thrombo-embolic diseases both in Australia and overseas but was

troubled by the lack of adequate comparative data, stating that *"more evidence must be obtained before a final pronouncement can be made."* The Director-General's Annual Reports for 1965-66 and 1967-68 state that ADEC was maintaining a close scrutiny on these products.

ADEC, in 1968, noted that a survey was being conducted by the then Australian College of General Practitioners and asked the National Health and Medical Research Council to arrange for the inclusion in Hospital Morbidity Statistics of information about oral contraceptive use in cases of thrombo-embolic episodes.[28] In the same year, some overseas requirements for animal toxicity testing were adopted. The Committee recommended that for new systemic contraceptive preparations Australian applications should contain "*similar animal toxicity data to that required by the Food and Drug Administration of the United States of America."* The Committee had noted new requirements in the United States and in Canada and recorded a concern that "*if similar requirements were not introduced in Australia, this country would become the testing ground for clinical investigation of oral contraceptives."* [29] The requirements for clinical studies were updated in 1974 and included in the NDF4 document.

In 1970, ADEC's review of oral contraceptives continued. It was in this year that details of an analysis of reports of thrombo-embolic disorders in UK, Sweden and Denmark showed excesses of reports with higher doses of mestranol and of ethinyloestradiol. As a consequence, ADEC published a statement that included the view that *" ...., the Committee is of the opinion that evidence is suggestive of a causal relationship between the oestrogen content of oral contraceptives and the incidence of thrombo-embolism."* The Committee enumerated factors (including use of the lowest efficacious dose) to be considered when prescribing oral contraceptives. [30]

In the same year, ADEC noted the reporting from toxicology studies of the development of mammary nodules in dogs dosed long-term with some progestogen-containing products. By 1971, ADEC recommended that the development programs for these products should include more toxicology studies before the commencement of human studies and also further animal studies in parallel with the human clinical trials, before marketing. [31]

In 1973, ADEC recommended that the progestogens in systemic contraceptives should be the subject of long term toxicity studies (7 years in dogs; 10 years in monkeys), with interim reports being submitted every three months. Megestrol acetate was one of the progestogens, and because of an association with mammary nodules in beagle bitches and some other results of animal studies, ADEC recommended the withdrawal of contraceptive formulations containing

megestrol acetate from the Australian market.[32] An exception was made for the continued marketing of products for the treatment of some medical conditions.

ADEC took its concerns further in 1975, when it recommended that combined and sequential oral contraceptive formulations should have patient package information inserts and, in addition, detailed patient information booklets, to be available to patients on request from doctors and pharmacists.[33] It took until 1979 before ADEC approved the draft of the patient information book, which had been drawn up by a working party with representatives of obstetricians, consumers, pharmacists, doctors, family planning organisations and the pharmaceutical industry. Unfortunately, the work was to be wasted because, in 1985, the Endocrinology Subcommittee was advised that, since the original drafting of the booklet the information contained therein had become outmoded, the project should be discarded.[34]

In 1979, it was products containing another progestogen (lynoestrol) that were the focus of ADEC's concerns. When administered in high doses to beagle bitches every day for several years, the dogs developed dose-related breast tumours. ADEC recommended withdrawal of products containing higher doses (2.5mg and 5mg) of lynoestrol, leaving open the continued marketing of products containing 1mg, subject to a warning being included in the product information. [35] The sponsor company decided, however, to withdraw all its lynoestrol containing products from the Australian market.

In December 1983, a special meeting of the Endocrinology Subcommittee was called to discuss the recent publication in The Lancet of two papers and an editorial dealing with oral contraception and neoplasia. A study by a group in California had raised the possible association of breast cancer in young women and use of oral contraceptives, while a group in Oxford had raised neoplasia of the cervix uteri as a possible adverse effect of the contraceptive pill. The Chairman of the United Kingdom Committee on Safety of Medicines had written to all UK medical practitioners giving the opinion that the reported study results were inconclusive, but recommending that practitioners prescribe the lowest possible effective dosages of the progestogen and oestrogen active principles. The Subcommittee prepared a statement which was endorsed by ADEC, which recommended that it be provided to the Minister for use as a basis for a Ministerial press release. [36] The full text of the statement is preserved in the filed ADEC minutes.

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14. DRUG EVALUATION AND SAFETY SURVEILLANCE FROM 1963 – THE DRUG EVALUATION SECTION AND DRUG EVALUATION BRANCH

This Section was created in the reorganisation of the Therapeutics Division in 1974 as a *"purely technical group"*, with administrative servicing supported by the Therapeutic Goods Branch, and was headed by the Senior Adviser in Clinical Pharmacology.[1] The medical staff of the Section were responsible for the evaluations of clinical information (described as B3 data) in applications for approval for use in clinical trials or for marketing, and for deciding the outcomes of requests for approval to import unapproved drugs for use in individuals. The senior staff were also responsible for providing summaries for ADEC, incorporating the results of the evaluations of animal pharmacology and toxicology (B2) and of the chemistry and quality control (B1). The evaluators of the B1 and B2 information were initially staff of the NBSL, with the B2 group being co-located in Alexander Building, Woden in January 1975 but not being transferred to the staff of the Section until about 1979. Within a short time of its establishment, the Section was organised into two and then three clinical streams, each headed by a senior medical officer, termed an Adviser in Clinical Pharmacology. Each stream assumed responsibility for a broad band of classes of drugs. The nature of the work of the Section resulted in an intensely symbiotic relationship with the work of the Australian Drug Evaluation Committee.

In liaison with ADEC, guidelines were developed as appendices to the NDF 4 on requirements for information concerning products where applications had been deficient, including parenteral nutrients, non-steroidal anti-inflammatory drugs and slow release formulations.

In addition to the evaluation of applications to market new medicines in Australia, the Section carried responsibility for the authorisation of clinical trials in Australia and the approval of importation and supply of unapproved medicines for use by individuals not participating in clinical trials.

As early as 1968, the ADEC took steps to limit its involvement in the control of clinical trials in Australia. Amongst other things, it recommended that "*It should not be a function of the Australian Drug Evaluation Committee to approve or otherwise comment upon the investigators or the protocol of a proposed clinical trial*" and that "*The function of the Australian Drug Evaluation Committee in relation to clinical trials should be confined to the evaluation of the results of such trials, when requested by the Director-General of Health, in order to determine whether or not approval should be given for the next stage of development."*[2] It may be noted that this has not prevented

ADEC from making valuable contributions to aspects of the conduct of clinical trials in Australia, such as variations to the control procedures and the requirements for ethical approval. But the primary responsibility for the control of clinical trials has been with the Drug Evaluation Section.

The workload issue impacted particularly on the handling of applications for clinical trials of new drugs in the early years. The applications to conduct clinical trials were evaluated in the same way as marketing applications. In 1974, the then newly-formed Drug Evaluation Section implemented an undertaking to give priority to evaluating clinical trial applications over marketing applications and to decide such applications within sixty working days. Shorter timeframes were applied for applications that essentially required only chemistry and quality control assessment. For *"important drugs"*, meetings were introduced at the end of the sixty day period between the medical director of the pharmaceutical company, the proposed clinical investigators and the departmental evaluators, with the aims of increasing the mutual understanding of identified problems and permitting rapid modification of the trial protocol and incorporation of additional monitoring when necessary.[3]

By the end of 1975, however, the industry was notified that the commitment to sixty working day evaluations was withdrawn for late phase clinical trials, which on occasions were being proposed at the same time as the submission of the marketing application. This step was taken to enable the available staff to concentrate on those applications intending to generate genuinely new data in Australia.

By 1980, the Section, working closely with the Anti-Cancer Subcommittee of ADEC, had implemented procedures for early clinical trials of new anti-cancer drugs under set usage protocols at certain approved institutions. The procedures enabled the earlier use in clinical trials in Australia of a number of new drugs developed at the National Cancer Institute in the USA.[4]

The pressure to decide clinical trial applications persisted. At a meeting chaired by the Australian Medical Association in 1981, a number of further changes were suggested and were largely implemented in 1983. The most significant changes included a 45 working day review period for phase I and early phase II trials and for extension from these trials to late phase II or early phase III. A trade-off was the extension of the review time for late phase II and phase III studies to 80 working days.[5] In addition, the Drug Evaluation Section prepared investigational drug profiles at the time of the initial review, further studies within the framework of the data already reviewed by the Drug Evaluation Section were permitted without protocol review and sponsors were required to

maintain registers of their Australian clinical trial programs and to submit annual reports of the status of the programs for each drug in clinical trials.

Despite these changes, there remained continuing concerns over delays in approving clinical trials in Australia compared with some overseas agencies. A working party of ADEC was established in 1984 and discussions held with industry leading to a proposal by the Drug Evaluation Branch to introduce a Clinical Trial Exemption Scheme (CTX), [6] the principal features of which were:

(a) Instead of awaiting Departmental approval, a clinical trial could commence if the Department had not raised an objection within sixty working days (or thirty working days if only pharmaceutical data were involved);

(b) The Departmental requirements for chemistry and quality control information about the active ingredient would involve a checklist. For the clinical experience to date, a review rather than study reports would be required;

(c) Institutional Ethics Committees would take a greater role and responsibility, including review of the design of trials including dosage regimen and duration. Sponsors would be required to provide ethics committees with a set of prescribed documents.

The term "*exemption*" did not refer to any exemption from the approval requirements of the 1966 Therapeutic Goods Act. Rather, the name was borrowed from the United Kingdom Clinical Trial Exemption scheme, introduced in 1981, in which sponsor companies were exempted from submitting the full set of data required to obtain a UK Clinical Trial Certificate. The CTX Scheme started on 1 July 1987, at which time the Branch conducted explanatory seminars in several capital cities. A review was conducted in 1989, after the scheme had been in place for approximately two years. It was considered that the scheme had been a sufficient success for the main elements to be maintained but a number of recommendations for adjustments were made.[7]

From the implementation of the 1966 legislation, both importation of unregistered medicines by individuals and supply of unregistered medicines by Australian pharmaceutical companies for use by individuals outside authorised clinical trials required approval by the Department of Health. The latter was a responsibility of the Drug Evaluation Section which managed the Individual Patient Use (IPU) scheme, involving the consideration by medical staff of the proposed use in each individual case. The product evaluation workload was not aided by the growth in requests under the IPU scheme, from 3467 in 1981-82 to 4121 in 1983-84. In response to this growth, the Section drew up guidelines intended to permit the use of such drugs in circumstances of clinical urgency

and where all accepted conventional therapy had failed or been attended by unacceptable adverse reactions. Particularly with respect to anticancer drugs, the Section had been urged to endeavour to have patients entered into clinical trials or, where the treating physician declined, to require adherence to a protocol for use and reporting of adverse effects that had the approval of the Anti-cancer Subcommittee. On occasions, however, the Director-General of Health or the Minister for Health gave approval for individual patient use contrary to the advice of ADEC. A discontent developed in ADEC over these continuing approvals for use of the substance laetrile, which the Committee had advised should not be used, even in clinical trials.[8]

Against this background, a very public controversy unfolded in 1984. The details of this matter were published in the Medical Journal of Australia September 1, 1984: 317-318. The doctors treating a Mrs Kerry Burke, who had a terminal illness, sought permission to import from China a product containing homoharringtonine. The Chinese source was proposed because these doctors, at this stage, had not met the requirements of the US National Cancer Institute, from which homoharringtonine had became available for clinical trial use. Consistent with the advice of the Anti-Cancer Subcommittee, the Drug Evaluation Section refused to give approval and defended its stance in the face of a growing campaign in the media and involving politicians. In the face of growing media pressure, the Minister for Health, after initially refusing, gave permission for the importation and use. This episode drew attention to what has been described as *"one of the few situations in which approval was justified – i.e., a critically ill patient with no effective standard therapy available."* [9].

The Public Service Board Review in 1987 commented that *"Until now, the Department appears to have viewed IPU applications as being an integral part of the general processes of drug regulation."* After commenting that *"Very few applications for IPU approval are refused"* and that *"The handling of applications consumes a significant proportion of the time of the most expensive of the Department's resources"*, it recommended devolving the approval function to Medical Superintendents of major teaching hospitals. [10] In time, some devolution did occur.

The liaison with the National Cancer Institute in the USA was accompanied by some early initiatives to form a basis for sharing information with other regulatory agencies, including the Food and Drug Administration in the USA and the Canadian agency. For some years, the closest and most fruitful collaboration was in the late eighties and early nineties with the Board of Drugs in Sweden. At that time, many similarities existed between the two countries in the regulation of medicines. Several exchanges of staff occurred, including in 1988 when the Director of the Drug Evaluation Branch worked at the Board of Drugs for a year while the Principal Toxicologist from Sweden worked in the

Drug Evaluation Branch. During this time, the Director led a taskforce in Sweden which evaluated sixteen new drug applications using evaluation reports prepared in Sweden or Australia.[11] An agreement for cooperation in drug evaluation was signed between the two countries in February 1989, with an emphasis on sharing the premarket evaluation of new drugs. [12] The collaboration ceased of necessity when Sweden's drug regulation became tied to the European system after the country joined the European Union on 1 January 1995. A year after the signing of the agreement with Sweden, a similar agreement was made with the Drugs Directorate, Department of Health and Welfare, Canada.

From its creation, the Section had difficulty in handling its workloads, largely because of an inability to recruit suitably qualified medical staff to fill available vacant positions in the Section. This was addressed in part in 1976 by establishing an outpost of medically-qualified clinical evaluators in Sydney. In the reorganisation which created a Therapeutics Division from 1 June 1985, the Section became the Drug Evaluation Branch. A growing backlog in the evaluation of marketing applications led to the establishment of a joint working party of ADEC and the Branch to review clinical trial and marketing application procedures. It is noteworthy, in the light of events that followed, that one of the identified factors impacting on evaluation times was, in addition to the growth in IPU applications, an increase in the number of applications to market "*generic*" products.

The Commonwealth Department of Health Annual Report for 1986-87 included a prominent introductory section headed *"Drug Evaluation - A System under Stress."* It told the story of the Gestalt Matter and the subsequent establishment of a Review of Drug Evaluation Functions by the Public Service Board.

Over a period of years, a number of applications by two firms based in Australia for marketing approval of generic prescription products had relied on results of bioequivalence studies in volunteers conducted at Gestalt Ltd, a clinical facility in South Africa. The evaluators at NBSL and in the Drug Evaluation Branch had on a number of occasions in recent years found difficulty in interpreting the Gestalt data for some drugs and had taken these up with the Australian firms that had submitted the data in their applications.

A senior officer of the Branch had visited the Gestalt facility in February 1985, while in South Africa on other business and, while noting a lack of statistical expertise and raising doubts about competence, did not at that time have reason to suspect improper practices. Late in 1986, the Department advised the Minister for Health that there may be doubts about the veracity of data from Gestalt Ltd. The Department also arranged for external consultants to review the data of concern. The consultants' interim report was considered by a special

meeting of ADEC, which recommended that action be taken to advise doctors not to initiate treatment for new patients with any of the thirty-three drug products involved, pending the generation of new bioequivalence data. For patients already taking any one of these drugs, however, treatment should continue. The sponsor companies were required to submit such data within twelve months or the drugs would be withdrawn. Where repeat bioavailability studies were undertaken bioequivalence was confirmed for all but two products, for which marketing was withdrawn by the manufacturers. Repeat studies were not done for eleven generic products and these, too, were removed from the market.

Investigations related to the Gestalt matter uncovered, in addition, a small number of instances where it appeared that drugs may have been listed on the Pharmaceutical Benefits Scheme (PBS) before marketing approval had been given. [13] This led to suggestions in the media that this was a consequence of a policy of the Department to promote the use of generic products so as to contain the costs to Government of the PBS.

After considering a report from the Department on these two matters, the Minister for Health asked the Public Service Board to establish a review of drug evaluation and related functions of the Department of Health. The review had extensive terms of reference. It was asked to consider and recommend:

- what changes should be made to the Commonwealth's drug evaluation and related procedures to make optimum use of available resources; and
- whether new organisational arrangements were desirable.

The Review was thus of the whole drug evaluation function and not solely the incidents which had provoked its initiation by the Minister. The Review was oversighted by a Steering Committee and in addition had the services for five weeks of the Deputy Director of the Department of Drugs, National Board of Health and Welfare, Sweden. The review also exchanged material with a concurrent Working Party on Drug Evaluation in Canada.

The Report of the Review[14] commented that the Drug Evaluation Branch had not been very successful in reconciling the demands of thorough scientific and medical scrutiny with the requirements for expeditious processing and equitable regulation. The reviewers were charitable enough to add that *"Internationally, they are not alone."* The report also noted that the Branch was not administratively proficient, in part because professional staff *"cannot or will not assume managerial responsibilities."* The Review made sixty-eight recommendations, impacting on many areas of the Therapeutic Division's policies and practices.

In précis form, those that impacted directly on the Drug Evaluation Branch included:

- alignment of data requirements and exchange of information with the agencies in Sweden and Canada, with a view to sharing the workload;
- expediting a proposed Memorandum of Agreement with the Government of Sweden to cooperate in drug regulatory matters;
- making a number of changes to the practices in the evaluation of new chemical entities, and the setting of priorities;
- expanding the use of external evaluators, trialling the use of Expert Reports and the establishing of a "*backlog reduction taskforce*";
- for every drug that is the subject of a general marketing application, a document should be drawn up between the Department and the company reflecting the relevant official standards and/or agreed specifications;
- giving greater weight to Good Manufacturing Practice in the evaluation process;
- introduction of the proposed Clinical Trial Exemption (CTX) scheme, with the time in which the department could object to a trial going ahead reduced to 30 working days;
- devolution of the approval of some IPU requests to Medical Superintendents of major teaching hospitals;
- introduction of a requirement for a plain language patient information sheet to accompany all dispensed products.

The Commonwealth Department of Health Annual Report for 1987-88 stated that consideration of the report had resulted in changes to ADEC procedures including on-going discussions, particularly in relation to assessment of bioavailability, and "*pre-ADEC*" (i.e. prior to consideration by ADEC) consultation with drug companies on new drug applications. An interim system for tracking general marketing applications had been developed and a commitment had been made to provide companies with quarterly reports on their applications. It was reported that new procedures for processing applications should be in place by early 1989.

In addition to its core role in the evaluation of submitted data, the Drug Evaluation Section had from its initiation the responsibility for educational efforts of the Department about medicines. This educational role manifested itself in two major activities of the Branch – the Australian Prescriber and the National Drug Information Service.

From August 1962, Australian medical practitioners were provided with copies of an Australian edition of the Prescribers' Journal, published by the UK Department of Health. In October 1975, this was replaced with the first issue of the Australian Prescriber to fill the need for *"a concise, authoritative, unimpeachably unbiased journal giving guidance to treatment."* From its inception until 1990, the editorship was part of the responsibilities of one of the senior medical advisers in the Drug Evaluation Section. Publication was quarterly. In 1982, publication was suspended by the Federal Government as a cost-cutting measure but was resumed after an absence of about 18 months. In 1991, responsibility for the Australian Prescriber was transferred to the Pharmaceutical Benefits Branch of the then Department of Health, Housing and Community Services. More recently, the journal has become the responsibility of the National Prescribing Service and is published independently of the Government. Co-incident with the celebration of its thirtieth anniversary, a detailed history of the Australian Prescriber was published. [15]

The National Drug Information Service did not share the longevity of the Australian Prescriber. A need for the establishment of a central computerised data bank of information concerning drugs was identified by the Hospital and Allied Services Advisory Council, representing the States and Territories.[16] In 1974 this Council had formed a working party to look at the issue. The data bank was to be at the core of a computerised drug information service which was envisaged as a nationwide co-ordination of drug education services operating by means of a network of hospital-based drug information centres. Also under consideration for disseminating information was a quick reference compendium available to all medical practitioners.

Specially prepared drug data profiles were seen as the means of disseminating objective and reliable information in a comprehensive manner, possibly replacing the then package inserts, and a draft profile was distributed to the medical profession and the pharmaceutical industry for comment. Within about a year, a Technical Secretariat within the Section had begun generation of drug profiles on all new drugs and work had begun on profiles for drugs already on the market.

In time, Drug Information Centres in the States and Territories had on-line access to the growing database of profiles. These Centres varied greatly in their mode of operation and most use of the information was made by hospital specialists, in some instances only within the hospital that hosted the State Centre. The service did not realise its objective of reaching doctors and pharmacists at the community level. The Public Service Board Review observed that there were by that time (1987) 328 completed drug profiles but that in the past two years, the output of profiles had not kept pace with the rate at which ADEC had approved new drugs. *"When compared with the need to*

foster the rational use of drugs in the community, the Review Team considers that the need to maintain an independent source of information about drugs for the use of specialist clinicians is a luxury. Other excellent sources of information, some of them independent of pharmaceutical manufacturers, are available. Compendia based on the Product Information prepared by the manufacturer, and approved by ADEC, are widely available to the general practitioner."

The Review's recommendation that the National Drug Information Service be discontinued and its staff transferred to other duties [17] was accepted and implemented.

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15. DRUG EVALUATION AND SAFETY SURVEILLANCE FROM 1963 – THE ADVERSE DRUG REACTIONS ADVISORY COMMITTEE (ADRAC) AND THE ADVERSE DRUG REACTIONS SECTION.

ADEC itself carried the responsibility for the initial establishment and oversight of the reporting scheme for suspected adverse reactions to medicines in Australia. In August 1964, the Adverse Drug Reactions (ADR) reporting scheme commenced. Copies of a *"Form for reporting Adverse Reactions to Drugs"*, designed by the Committee and filling two foolscap pages, together with a covering letter from the chairman of ADEC, were distributed to all doctors on several occasions. Incoming reports were processed by staff of the Therapeutic Substances Branch, while ADEC was responsible for the expert clinical review. In May 1965, dentists were also invited to report reactions. Between August 1964 and December 1966, 760 reports were received. Reciprocal arrangements were made in that year for the exchange of safety information with the USA, Canada, United Kingdom, Denmark and Switzerland.[1] The reporting increased to a total of 1013 reports by December 31, 1967.

In 1966, Dr Royall attended a conference sponsored by WHO to establish an international system for drug safety monitoring. In the following year, at the World Health Assembly, it was announced that funds, office space and data processing facilities for the conduct of a pilot project had become available at Washington, D.C. The pilot scheme commenced in 1968 with Australia amongst the ten participating countries.[2]

ADEC appreciated the need to feedback information about reporting to the professions. Cumulative lists of the Australian reports were sent to the professional colleges, teaching hospitals, universities and medical institutions on a trial basis in September 1966 and March 1967. This was followed by the issue of the first edition of a booklet titled *"Report of Suspected Adverse Drug Reactions"*, sent to all registered medical practitioners in 1968 and a second edition in April 1969.[3] In 1968, about 70% of reports came from private doctors, 20% from hospitals and 7% from the pharmaceutical industry. At about this time, hospitals were encouraged to submit copies of their discharge summaries when the patient had experienced an adverse reaction as a cause of, or during, admission. Some hospitals continued to contribute these summaries for many years, a problem being that the summaries often contained only limited clinical details of the reaction.

The increasing workload from the reporting scheme led ADEC, in 1970, to obtain the approval of the Minister for Health to establish the Adverse Drug Reactions Advisory Committee (ADRAC), which *"will report to ADEC on all matters relating to adverse drug reactions"*.[4] The operative legislation at the

time was still the Therapeutic Substances Act, which did not provide for the establishment of subcommittees. ADRAC was thus initially established as a committee by Ministerial Instrument, but became a subcommittee of ADEC after the regulations under the Therapeutic Goods Act 1966 came into effect.[5]

ADRAC first met on 26 May 1970. Initially ADRAC met every month, but from the late 1970's it has met at approximately six weekly intervals. The central feature of ADRAC's modus operandi since its foundation has been its very close involvement in the review of incoming Australian adverse reaction reports. Until November 1998, the assessment of every incoming report by the secretariat was reviewed by a member of the committee. This was achieved by sending photocopied allocations of reports to each member for review prior to a committee meeting. At the meetings, members commented on reports that were of concern, warranted further investigation or had been inappropriately assessed. Such close involvement not only kept members in very close touch with the reporting of reactions but gave them a unique and continuing insight into contemporary Australian medical practice. With the current levels of reporting of about 12,000 reports a year, the allocations have been limited to serious and unusual reactions and reactions to new products. The committee's awareness of the overall reporting patterns has been maintained through the provision to it of computerised summaries of the reporting. The initial report forms, illustrated in a paper published in 1968, were lengthy.[6] To facilitate reporting by busy practitioners a simplified report form, in the format of a reply-paid air letter (the "blue card" still used in 2007), was introduced in 1971.

A measure of the value of a national reporting scheme is the number and nature of previously unrecognised adverse reactions that have been detected. A paper about the role of the committee was published in 1990, at which time 65,000 reports had been received.[7]

By 2007, at least 13 instances have been identified where Australian reports to ADRAC have contributed to the early global recognition of a drug-related problem and at least 26 additional instances of Australian reports giving early notice of the occurrence in Australia of a drug-related problem initially described elsewhere.[8] The following table illustrates some of the more notable actions.

Year	Drug	Reaction, comments
1973	Bismuth subgallate	Alert published after consumer reports (from state ostomy association) of neurotoxicity following oral use to deodorise colostomies and ileostomies. Clinical assessment by an ADRAC secretariat medical officer of 24 patients described in additional reports was published. Use for this purpose ceased.
1974	Inhaled adrenaline, isoprenaline, orciprenaline.	Warning of risks published following 5 reports to ADRAC of deaths when inhaled for asthma. These together with a published report from Queensland helped motivate a definitive study in the United Kingdom
1980	Mianserin hydrochloride	Analysis of four Australian reports received in a short period triggered an international alert that this newly marketed antidepressant sometimes caused life threatening suppression of white blood cells (neutropenia; agranulocytosis), especially in elderly patients.
1982	Phenylpropanolamine hydrochloride	Reports to ADRAC and some published Australian case series described severe hypertension caused by use of high-dose allegedly slow release slimming preparations. National dose restrictions and a ban on slimming preparations were introduced. Actions were criticised internationally. In 2000, an epidemiological study in USA reported an association between use of this drug and increased risk of bleeding into the brain and surrounding tissues (haemorrhagic stroke).
1990	Flucloxacillin	Alerts were published about frequent reports of a severe unremitting jaundice associated with the use of this antibiotic, which is valuable in the treatment of staphylococcal infections. Later report in British Medical Journal of research by Melbourne group in association with ADRAC secretariat identified increased age and longer use as risk factors.
1999	Clozapine	Analysis by group in Sydney of reports to ADRAC published in The Lancet. Analysis facilitated by the ADRAC secretariat senior medical officer. Clear evidence of an association between this important drug, used to treat resistant schizophrenia, and severe unwanted effects on the hearts of some patients (myocarditis; cardiomyopathy).
2001	Cervastatin	Alert published in the February 2001 Australian Adverse Drug Reactions Bulletin about 17 reports associating this newly introduced statin with skeletal muscle breakdown (rhabdomyolysis). Noted some patients also taking gemfibrozil and advised against such use. TGA opened dialogue with sponsor. Cervastatin was withdrawn from international market in August 2001 because of this problem. Gemfibrozil was later shown to very greatly increase the risk.

ADRAC has also made a prominent, continuing contribution to the education of doctors, dentists and pharmacists about adverse effects of medicines. In November 1974, the Committee produced the first Australian Adverse Drug Reactions Bulletin. Six more Bulletins, posted to doctors, dentists and pharmacists, followed at monthly intervals from January 1975, and had a marked positive effect on reporting. Independent distribution then ceased as the Bulletin was incorporated into the Australian Prescriber – an action that was of concern to both ADRAC and ADEC, whose fears that the positive effect on reporting would be muted by the loss of a separate identity were realised.[9]

Publication of a separate Bulletin resumed in March 1983. It was distributed separately for a number of years before cost issues forced a move to a co-distribution with Australian Prescriber. In addition to the Bulletin, educational material and research reports have been published in the Medical Journal of Australia. A short film titled "The New Epidemic" was made by 1981 and, together with a companion book, was used widely in schools of medicine and pharmacy for a number of years. [10] A detailed index of published materials is kept in the Adverse Drug Reactions Unit.

In its early years of activity, ADRAC sought to promote supplementary intensified reporting from hospitals and regions. Early in its life, ADRAC commenced exploration of possible intensified monitoring of adverse reactions in several regional centres, including Goulburn, Tamworth and the ACT. Later, considerable work was done towards a regional reporting scheme based in Hamilton, Victoria but the plan fell victim to Government spending constraints in 1974.[11,12]

By the mid nineteen-seventies, there was international concern that the safety of newly-registered drugs should be closely and formally monitored. The concern had been raised in part because of the experience with practolol, which was the first widely used beta-blocker (beta-adrenoreceptor blocking drug), including in Australia. Fortuitously recognised through the publications of the experiences of two United Kingdom dermatologists and, separately, a United Kingdom ophthalmologist, the drug caused severe eye effects (which included blindness in some patients), ulceration of the mouth and other mucosal surfaces and a rash that superficially resembled psoriasis (oculo-muco-cutaneous syndrome), most commonly when the drug had been taken for periods of about eighteen months. Except in an injectable form, practolol was withdrawn from markets worldwide.

At that time computerised medical record systems in general practice and hospitals, which are today widely used for research into the occurrence of adverse reactions to medicines, were uncommon. At a meeting in August 1976, ADEC considered for a second time that year how it might balance the clinical need for the drug dantrolene sodium for the relief of long-standing muscle

spasticity with concerns about the drug's safety. It was agreed to recommend that the drug should be granted a *"limited monitored release to allow its use in appropriate institutions for the treatment of the relatively few sufferers from chronic spasticity. It should not be released to practitioners in general."*[13] At its next meeting (October 1976), the Committee recommended approval for the marketing in Australia of a new beta-blocker (metoprolol) by two separate pharmaceutical companies, each using a different brand name for the drug. Because of concerns that the oculo-muco-cutaneous syndrome might be associated with this newer member of the same drug class as practolol, ADEC recommended that the approvals be made conditional upon the companies negotiating with the Department of Health *" a suitable method of monitoring adverse effects."*[14]

At the December 1976 meeting, ADEC imposed a similar monitoring condition on the marketing recommendation for another new beta-blocker, timolol maleate. [15] These monitoring endeavours came to be known as Monitored Release. The scheme was described by the Chairman of ADEC in a letter to the Australian Prescriber as involving the detailers of the pharmaceutical companies.[16] Through the detailers, special observation cards and reply-paid reporting forms were to be supplied to practitioners. The companies were also responsible for the collation of all data recorded and the provision of consolidated statistical reports on the information thus collated to the Department of Health and ADEC on a three-monthly basis. It was emphasised that the new scheme was not a substitute for the existing reporting scheme. Doctors observing adverse reactions to the monitored products were asked to fill in the customary blue card as well as the special company forms.

When launched, the scheme involved metoprolol, timolol maleate and dantrolene sodium. In early 1978 another beta-blocker, atenolol, was also approved subject to Monitored Release. The initiation of Monitored Release by ADEC caused some initial unhappiness to ADRAC, which had uncertainties about aspects of the methodology.[17]

Overall, the results of the schemes were disappointing and did not justify repetition in an unmodified form. A number of deficiencies were identified, including great dependence on the effort expended by the pharmaceutical company and difficulty in obtaining the co-operation of practitioners.

In the early nineteen eighties, ADRAC proposed the implementation of a system of Recorded Use for Certain Designated Drugs in Australia and canvassed comment widely.[18] The scheme was based on creating registers of patients for who certain drugs had been prescribed, with subsequent follow-up. Aspects of the process had been studied at the Department of Medicine, St Vincent's Hospital, Melbourne. The consultations raised issues to do with

patient consent to the recording of information and the confidentiality of the collected data. Ultimately, funding for the proposal was not forthcoming.

The needs for supplementary intensified research and more formal epidemiological research, including use of medical record databases, have continued to be supported by ADRAC.

Baume, in 1991, found that the existing surveillance system in Australia was generally adequate but recommended that the ADRAC Section should have a budget to enable it to commission a small number of necessary pharmaco-epidemiological studies to determine the nature and risk of some drugs.[19] In the event, only limited funds have been available. Research into flucloxacillin jaundice and into data-mining have been partially funded. In recent years, alternative methods for reporting have been developed. Reporting is possible via a Web-based electronic report form and programs for encrypted e-mail reporting from software used by many general practitioners have been developed. All ADRAC Bulletins from 1995 onwards may be accessed via the TGA Website.

The early involvement in the pilot scheme for international collaboration and pooling of adverse reaction reports under the auspices of WHO has continued. An international collaborative program was introduced at the end of the pilot phase and has been based in Uppsala, Sweden since 1978. Australian reports are contributed to the international database which, in turn, can be accessed by the TGA. Australia has been represented at, and has frequently provided the rapporteur for, most of the Annual Meetings of the program, which has grown to involve National Centres in 83 countries. The WHO Collaborating Centre in Uppsala has for a number of years delivered a two-week training course on pharmacovigilance and introductory pharmacoepidemiology. In 1972 and 1974, the TGA hosted these courses, being the first time they had been delivered outside Uppsala. Each course attracted about twenty-five participants from national centres, principally in South East Asia and the Western Pacific, as well as the Australian pharmaceutical industry. With the support of WHO Fellowships and the Drug Information Association, staff from a number of national centres in Asia, Western Pacific and Africa have had training placements in the ADRAC secretariat (Adverse Drug Reactions Unit).

From 2000, secretariat staff of ADRAC have participated in regular international teleconferences involving counterpart colleagues in the US Food and Drug Administration, Health Canada and Medsafe New Zealand. More recently, regular teleconferences have been held with Medsafe New Zealand, the New Zealand Centre for Adverse Reactions Monitoring and the Pharmacovigilance Unit in the Health Sciences Authority, Singapore.

From its inception, the ADEC and later ADRAC reporting scheme accepted and processed reports of suspected adverse effects of vaccines. In 1995, a separate scheme for the reporting of serious adverse effects of immunisation was established elsewhere in the Department of Health. Incoming reports were to be later forwarded to ADRAC, after processing.

By 1999, the scheme was troubled by insufficient resources and a revised scheme, which operates to this time, was introduced. Reports are sent first to ADRAC, including from State and Territory authorities responsible for immunisation. The ADRAC review processes have been strengthened by the addition of a specialist in paediatric immunisation to the membership. Relevant reports are shared with the State and Territory authorities and reporting patterns are analysed regularly by the National Centre for Immunisation Research and Surveillance in collaboration with the ADRAC secretariat, and published in Communicable Diseases Intelligence. The value to ADRAC of a specialist member in certain areas of medicine has been recognised and extended in 1999 with the addition of a member with expertise about complementary medicines.

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16. REGULATION OF THERAPEUTIC GOODS UNDER THE THERAPEUTIC GOODS ACT 1989 FROM 1991 TO 2007

By the 1980's, there was a mixture of State, Territory and Commonwealth regulation which resulted in both gaps and overlaps. The deficiencies in the *"Band Aid"* approach to the regulation of therapeutic goods became increasingly clear. For domestic supply where the Commonwealth did not want to test its interstate trade powers, there was a patchy framework of controls. For example, Victoria continued to have its Proprietary Medicines Advisory Committee which provided the State Government with advice on over-the-counter medicines for registration in Victoria. New South Wales required manufacturers of medicines to be licensed and conducted an inspection program. However, resourcing for these activities was becoming more stretched.

At the same time, other areas were largely unregulated, as was the case with most therapeutic devices and with complementary medicines for which there were increasing concerns about their quality and safety and the extravagant therapeutic claims that were being made. Reviews of the period covering the regulation of therapeutic goods had a common conclusion of the need for a comprehensive, national approach to the regulatory framework and agreement was reached between governments that the Commonwealth should take responsibility for the regulatory system.

The Therapeutic Goods Act 1989 changed the focus of control from the point of import to the point of supply by using the Commonwealth's powers over imports, exports, interstate trade and corporations. With the support of the States and Territories, this gave the Commonwealth coverage of all therapeutic goods other than those made by unincorporated manufacturers (so-called *"sole traders"*) for supply only within a State or Territory. In order to cover sole traders as well, the States and Territories were to introduce complementary legislation to the Therapeutic Goods Act or to legislatively refer such products to the Commonwealth scheme.

The States and Territories remained responsible for control of the retail supply of therapeutic goods and their scheduling arising from the Uniform Scheduling of Drugs and Poisons as well as the regulation of wholesalers.

The Therapeutic Goods Act introduced:

- a requirement for all therapeutic goods, unless exempted, to be entered on the Australian Register of Therapeutic Goods (ARTG) prior to their supply into the Australian market.

- a risk managed approach to their regulation where products representing a lower level of risk to the public were subject to a lower level of regulation. The premarket evaluation of medicines had arisen from the regulation of prescription medicines and that framework was not appropriate for lower risk products. The Commonwealth used Victoria's experience with regulating over-the-counter medicines and took over the Proprietary Medicines Advisory Committee which later became the Medicines Evaluation Committee. For complementary medicines, a new level of entry into the ARTG was created where they could gain entry as listed medicines through largely a self assessment procedure provided they met certain criteria for low risk including that they complied with quality requirements, contained active ingredients only from a defined list and met restrictions on advertising claims. This also required clarifying the boundary between food and medicines.
- the inspection and licensing of Australian manufacturers of therapeutic goods and inspection or certification of overseas manufacturers against comparable requirements for Good Manufacturing Practice.
- in order to protect the reputation of Australian exports and to be a good international citizen, the expectation that exported goods would meet similar requirements for quality and safety as those expected for Australian citizens unless the regulatory authority in the importing country agreed otherwise.
- more flexibility in access to products not on the ARTG in situations of individual use as distinct from commercial supply where either the individual took responsibility or used the product under the supervision of a health practitioner following informed consent. The Act enabled provision for personal importation of limited quantities of goods, more flexible special access provisions for medical practitioners and more flexible clinical trial provisions.
- introduction of cost recovery for users of the regulatory services of TGA. Initially this was set to recover 50% of the cost of the TGA. A TGA – Industry Consultative Forum was established to provide accountability of the TGA for its performance against performance targets.
- some performance targets were set within the legislation such as those for major evaluations where a financial penalty applied to the TGA if it did not meet the targets. These arose from the review by Baume in 1991.
- definition of the rights of people affected by decisions under the legislation and their mechanisms of recourse.

- stronger penalties and sanctions for breaches of the legislation. This was supported by the creation of a group of surveillance staff.

At the commencement of the legislation in February 1991, a number of products on the market were grandfathered into the ARTG, many of which have not warranted further review by the TGA, whilst others are no longer marketed.

Thus, at the commencement of the operation of the 1989 legislation in February 1991, the Therapeutic Goods Administration had an organisational structure that had been in place for several years, a new set of legislation and the construction of a new laboratories complex well on the way to completion.

Organisational Structure [1]

The five Branch structure put in place when the organisation was designated as the 'Therapeutic Goods Administration' in August 1989 remained unchanged, apart from some rearrangements and changes to the names of two Branches, until 1997.

In 1993, the Virology and Pharmacology Sections of the TGA Laboratories were merged to form the new Molecular Biology Section and in late 1994, an Immunobiology Section with a particular focus on viral and bacterial vaccines and related products was created. The General Administration Branch became the Business and Services Branch on 1 July 1994 and the Drug Evaluation Branch was renamed Drug Safety and Evaluation Branch (DSEB) from 1 January 1995.

In 1996, the National Manager of the TGA became responsible for the management of the Chemicals Policy and Assessment Unit and the Australian Radiation Laboratory, both transferred from the Public Health Division.

In 1997, the Therapeutic Devices Branch was restructured as the Conformity Assessment Branch and the Compliance Branch was restructured as the Chemicals and Non-Prescription Drugs Branch (taking in the Chemicals Policy and Assessment Unit). The responsibility for revaluation of non-prescription medicine products was transferred from the Victorian Department of Human Services to this Branch and a Complementary Medicines Section was established to provide policy advice and technical and secretariat support for the Complementary Medicines Evaluation Committee (CMEC).

For a relatively brief period in 1998-99, the National Manager was also responsible for the management of the Nuclear Safety Bureau and a group charged with setting up the Australian Nuclear Protection and Radiation Safety Agency, which started its operations on 5 February 1999.

Also in 1999, important sections were created within several Branches. The Office of Complementary Medicines was established in the Chemicals and Non-Prescription Medicines Branch, an International Services section in the Business and Services Branch and a group to review Drugs and Poisons Legislation in the Conformity Assessment Branch. In addition the Adverse Drug Reactions Unit was moved from the Drug Safety and Evaluation Branch and reports directly to the National Manager. The National Manager also became responsible for the administrative management of the newly-created Office of Gene Technology, later to become the Office of the Gene Technology Regulator (OGTR).

In 2002, the trans Tasman Group was set up to handle the proposed creation of a joint regulatory agency for therapeutic goods for Australia and New Zealand. In addition, the National Manager of TGA became responsible for the management of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). In 2003, the Conformity Assessment Branch was renamed the Office of Devices, Blood and Tissues (ODBT).

Concerning the on-going regulation of therapeutic goods, including medicines and medical devices, the five Branch plus Adverse Drug Reactions Unit structure was unchanged until 2005, when a sixth Branch (Manufacturers Assessment Branch) was created and took on the functions of the Good Manufacturing Practice section, previously in the ODBT. The trans Tasman Group became the Joint Agency Establishment Group, working with both the TGA and New Zealand Medsafe. The Business and Services Branch (renamed Business Management Group) now includes two substantial groups - Finance and Property Group and Legal Services Group.

The National Manager of the TGA continued to have administrative responsibility for what has come to be termed the TGA Group of Regulators until mid-2007. In addition to therapeutic goods regulation, this Group includes the Office of the Gene Technology Regulator and the Office of Chemical Safety (which includes the Chemicals Policy and Assessment functions, NICNAS, the secretariat of the National Drugs and Poisons Schedule Committee and compliance and monitoring responsibilities to effect Australia's obligations under UN Treaties and the Customs Act and to support the National Drug Strategy for the legitimate end use of controlled substances).

Physical Environment

Occupation of the newly-constructed Therapeutic Goods Administration Laboratories building commenced in September 1992 and it was officially opened by the Minister for Family Services, Senator the Hon. Rosemary A. Crowley on 24 May 1993.

The building, with a fit-out cost of $70 Million, has 18,000 square metres of floor space compared with about 25,000 square metres of the previously planned building. When initially occupied, it housed six major laboratory groups involved in various aspects of chemistry, biology and engineering. Workshops, stores, administrative offices, a scientific library and staff amenities completed the complex. The building received the "Canberra Award" of the ACT Chapter of the Royal Australasian Institute of Architects in 1994.

The TGA Executive and staff involved in the Business and Services and Drug Safety and Evaluation Branches were able to move from Woden to G Block on the Symonston site in 1997. This building was officially opened by Senator Chris Ellison, then Parliamentary Secretary for Health and Family Services on 10 April 1997. A purpose built storage facility housing both laboratory stores and the Records Management Group, with many voluminous applications for registration, was opened in 2000.

In 1996/97 the Commonwealth Government decided to divest itself of ownership of the Commonwealth Special Purpose and Industrial Estate including the TGA Symonston building. The TGA will, however, continue to occupy the building under a 15 year lease back agreement until 2017 with an option for extension. As at mid-2007, work is proceeding on some minor refurbishment to enable the TGA's Manufacturers Assessment Branch to return to the Symonston campus.

Performance and Reviews

At the commencement of the legislation in February 1991, a large number of products then on the market were added to the ARTG ("grandfathered"). At the time, it was indicated by TGA that these products would be reviewed as required and when resources allowed. The great majority have not warranted comprehensive review by TGA, whilst others are no longer marketed.

Soon after the commencement of the 1989 Act, the Clinical Trial Notification (CTN) scheme for clinical trials with unapproved medicines was announced by the Minister for Aged, Family and Health Services, the Hon Peter Staples MHR, in February 1991 and commenced in May 1991 following amendments to Schedule 5 (A) of the Regulations (Statutory Rules 1991, No 84). The link that precluded the acceptance of a marketing application if the first Australian clinical trial for that new entity was still in progress was removed.

In March 1991, the same Minister established an inquiry to advise on any necessary changes to the existing process for evaluation of new chemical entities and prescription drugs for marketing approval which would result in the earliest possible access for consumers to new drugs and the minimum regulatory burden on industry. The reason for the inquiry was said to be

"perceived dissatisfaction with the performance of Australia's drug evaluation system." [2] Dissatisfaction had been expressed in, amongst other places, the Final Report of the Australian National Council on Aids Working Party on the Availability of HIV/AIDS Treatments, December, 1990.

The inquiry was undertaken by the Honourable Professor Peter Baume, Professor and Head of the School of Community Medicine in the University of New South Wales. In addition to being a consultant physician, he had been a Senator for New South Wales from 1974 to 1991 and in that time had been Government Whip, Minister for Aboriginal Affairs, Minister for Health and Minister for Education. In the Terms of Reference, there were ten separate points that the review was asked to consider.[3]

Although titled "*A Question of Balance*", the report is widely known as the Baume Report.

The Report, delivered in June 1991, made 164 recommendations across all aspects of prescription medicines, from individual patient use to evaluation processes and their management, to the role of ADEC and to post-marketing surveillance. All the recommendations were accepted by the Government on 3 July 1991.

The Annual Report of the Department of Health, Housing and Community Services for 1991-1992 includes an extensive listing of the steps taken by the TGA to meet the recommendations. Notable amongst these was an amendment to the Regulations (Statutory Rules 1991, No 485) that changed the nature of the Australian Drug Evaluation Committee, with the long-standing small membership replaced with a core membership of six to seven members (at least 3 being eminent medical practitioners, at least two of whom must be specialists in clinical medicine and at least one being a pharmacologist or having specialised in pharmaceutical science) and between 10 and 20 associate members (including a pharmaceutical chemist with recent experience in manufacturing, a toxicologist, a general practitioner and others either with similar qualifications or with specialist medical qualifications that complement the expertise of the core medical members).

The 'new' ADEC met for the first time on 20 February 1992. A Life-Threatening Diseases Sub-committee was established in lieu of the Anti-Cancer Subcommittee, meeting for the first time on 6 March 1992. In 1995, ADEC renamed it as the Subcommittee for Emerging and Niche Drugs (SEND) on the grounds that the title more closely reflected the nature of enquiries submitted to it by TGA and the Subcommittee's own interest in improving the availability of drugs for all serious diseases. SEND was dissolved by ADEC in October 1997 *"because the work of SEND has been completed successfully."*[4]

In addition to ADEC, constituted under the Regulations, the TGA established two other committees that had been recommended by Baume. A Standing Arbitration Committee (SAC) was established on December 1, 1991. Baume had recommended this committee for the purpose of arbitration on the reasonableness of TGA requests to industry for further data, TGA objections to minor changes of pharmaceutical characteristics of products and in cases where TGA proposed to name, in the Annual Report to Parliament, companies which appeared to be using the Special Access Scheme for *"backdoor marketing.*"

Provision for review by SAC remains in the Australian Regulatory Guidelines for Prescription Medicines but it has not been called upon for many years.

The other of these two committees (Prescription Medicines Advisory Board) was appointed in 1992 to advise the National Manager of the TGA on the external perception of the progress of reform of the drug evaluation system. It was disbanded by the Minister in 1995, having fulfilled the need for its establishment.[5]

The same amendments to the Regulations (1991; 485) put in place the Regulations that enabled the Special Access Scheme as recommended by Baume, creating a more liberal system of access to unapproved medicines. Provision was made for Category A patients, defined as *"a person who is seriously ill with a condition from which death is reasonably likely to occur within a matter of months, or from which premature death is likely to occur in the absence of early treatment"*, to be supplied with an unapproved medicine on the basis of their informed consent and a notification to TGA by their treating doctor, and without a requirement for approval by the TGA. Other amendments supplemented administrative arrangements which put in place the companion arrangements for the approval by TGA of supply of unapproved medicines for less serious ill patients (Category B and C patients, subsequently – in January 2001-fused into a single Category B). (Schedule 5(1) of the Regulations had from their commencement included provisions for the personal importation of therapeutic goods for use by the person or a member of the importer's immediate family).

Also in line with a Baume recommendation, a Backlog Task Force was established to clear a backlog of applications which were at various levels of processing as at December 1989. The task force considered more than 300 applications and by early 1993 had cleared them from the TGA's books.[6] Most applications were accepted, some were rejected and, in some cases, applications were withdrawn after negotiations with the sponsor company.

From September 1992, TGA began accepting new drug applications in the European format and in some circumstances the format defined by the US FDA. By June 1993, the first registration applications to be processed under time

constraints defined in the Baume report were considered by ADEC well within those limits.

For the evaluation of therapeutic devices, evaluation reports were obtained for the first time in 1993 from the US Food and Drug Administration and the Canadian Bureau of Radiation and Medical Devices.

With the commencement of the Act in February 1991, the TGA utilised, under a contractual agreement provided for in section 9 of the Act, the services of the existing Victorian Proprietary Medicines Advisory Committee (PMAC) and its secretariat, located in Melbourne, to evaluate non-prescription registerable goods. In 1995, the Victorian Minister for Health created the Medicines Evaluation Committee to carry out this function. This arrangement concluded in July 1997, when the TGA took over the direct provision of its funding and secretariat. In 2000, amendments to the Therapeutic Goods Regulations 1990 added sections 42ZZA to 42ZZX, thus establishing the Committee under Commonwealth legislation.[7]

A report of a review of the Clinical Trial Notification Scheme, chaired by Professor Richard Day, was received by the TGA in June 1993. The report recommended that the CTN Scheme should be retained as an alternative to the CTX Scheme and as an important contribution to clinical studies and clinical research in Australia. The report included 42 recommendations, including for changes to the CTN Scheme to ensure the integrity of clinical trial activity while providing an expedient alternative to the CTX Scheme. All the recommendations directed at TGA were accepted – some requiring amendment to the Therapeutic Goods regulations to enable implementation.[8]

The Therapeutic Goods Act 1989 retained the provisions for the Minister for Health to make Therapeutic Goods Orders. A new Order (Therapeutic Goods Order No 48) dealing with the requirements for the labelling of drug products in Australia came into effect on July 1, 1994.

After considerable negotiation with industry, agreement was reached in 1993 to phase in over four years new fees and charges that would ensure a 50 percent recovery of the TGA budget. The 50% cost recovery target was reached by 1 July 1996. In the 1997/98 Budget, the Government increased the level of cost recovery from industry, moving to 75% in 1997/98 and to full cost recovery in 1998/99.

In 1996, an important and innovative facility was fully initiated after amendments to the Act that permitted electronic submission of applications came into force on 11 June 1996. The Electronic Lodgement Facility (ELF) had been introduced initially on 1 July 1995 as a means for streamlining the processing of applications for the listing of medicines. A revised version

(ELF 2) was introduced in April 1998 and underwent several upgrades. An on-line facility, replacing the need for submission of floppy discs and renamed as the Electronic Listing Facility (and known at the time as ELF 3), commenced operation in September 2003 and is able to be upgraded constantly. The parallel OTC Medicines Electronic Lodgement System (OPAL) commenced on 6 December 2004 and became obligatory for all OTC medicines applications from 31 January 2005.

In the Foreword to his report, Baume recommended that there should be no further major review of the drug evaluation process before 1996, providing a period for the officers and committees to achieve the outcomes identified in the report. It is remarkable that 1995-96 saw the end of a period of freedom of the TGA, including the drug evaluation function, from external reviews.

The Australian National Audit Office's (ANAO's) Audit Report 12 1995-96 on '*Risk Management by Commonwealth Consumer Product Safety Regulators'* presented to Parliament on 27 November 1995 was complimentary about the TGA. It found that TGA had the most comprehensive post-market regulatory framework reviewed and provided a good example for other regulators to follow. The ANAO Report 14 1995-96 on '*The Sale of C.S.L. : Commonwealth Blood Product Funding and Regulations'*, presented two days later, noted that unlike blood collection centres, blood fractionation was not subject to a specialised Code of Good Manufacturing Practice. Concern was also expressed that TGA audit frequencies did not necessarily reflect the risk of GMP non-compliance and found there was need for improvement in this area. It recommended that TGA should seriously consider conducting a formal evaluation of the merits of adopting such a Code *"as part of its overall risk strategy assessment"*. The Department, in response, indicated that advice had been requested from the Secretariat of the Pharmaceutical Inspection Convention (PIC). The ANAO also recommended a review of the system for regulating processing of foreign sourced blood plasma in Australia.

In May 1996, the Industry Commission released its Report No 51, *"The Pharmaceutical Industry"*. The Commission concluded that some capability to evaluate new products is required, if the Government is to be able to respond to community interests. *"As long as the TGA continues to provide a competent and cost effective service its drug evaluation function should be retained."* In brief, the Report recommended that Australia, through the TGA, continue to pursue harmonisation of standards and data requirements, pursue further exchange of evaluation reports and undertake joint evaluations, place greater weight on overseas approvals by regulators with comparable standards and known expertise in a particular area and in the longer term pursue mutual recognition of drug approvals with countries with similar regulatory standards

while maintaining an independent capacity to conduct evaluations where required *"by unique Australian conditions or where requested by suppliers."*

The Report also recommended that the TGA should be established as a Commonwealth statutory authority to free it of institutional constraints and that all the States and Territories should pass complementary legislation to broaden the application of the Therapeutic Goods Act 1989 by adopting its provisions and future amendments by reference.

The report also addressed issues relating to Over-the-counter medicines, recommending that scheduling become a responsibility of the Commonwealth under the TGA, that research be undertaken into the role of pharmacist counselling as it related to scheduling and that, in some circumstances, advertising of '*Pharmacist Only*' products be permitted.

Therapeutic devices as well as drugs were a focus of inquiry by the Industry Commission. Its December 1996 Report No 56, '*The Medical and Scientific Equipment Industries'* explored the regulation in Australia of what it termed medical devices in considerable detail. The thrust of its recommendations, as far as regulation was concerned, was that the TGA should separate conformance assessment of medical devices from *"its core responsibilities for regulating medical devices and pharmaceuticals"* and assign the assessment responsibilities to a commercially autonomous enterprise funded solely by client fees and charges. It also recommended that the Commonwealth Government should accredit eligible Australian bodies in the public or private sector to assess the conformance to the therapeutic goods legislation of medical devices, their manufacturers and their sponsors. Also recommended were the mandating of the relevant essential requirements in the Directives of the European Union, the keeping to a minimum of any requirements additional to those of the Directives and a discontinuation of the licensing in Australia of manufacturers of medical devices. The Commission showed impatience with progress of a Mutual Recognition Agreement on conformance assessment between Australia and the European Union, initialled on 23 July 1996 and expected to be fully in place on 14 June 1998, urging that the provisions relating to medical devices be implemented *"as soon as practical"*. The formal signing of the agreement took place in Canberra on 24 June 1998 and came into effect later that year.

For certification of Good Manufacturing Practice, the agreement essentially continued the previous arrangements for recognition of audits under the Pharmaceutical Inspection Convention.

For medical devices, the agreement provided that regulatory agencies in the European Union and the TGA would accept the results of assessment procedures on medical devices carried out by designated "*conformity*

assessment bodies" in the other jurisdiction. In Australia, TGA was and remains the only designated conformity assessment body.

The Government of Australia changed at the election of 2 March 1996. The pre-election policies of the Liberal and National Parties, which formed the elected governing coalition, had included a health policy titled "*A Healthy Future"* which promised to ensure that the approval processes of the TGA *"do not present unnecessary barriers to people obtaining 'alternative' therapeutic products where the intrinsic safety of the product is not in doubt, but the therapeutic effectiveness is unproven"*. Drawing on this policy statement , as well as the ANAO reports, the Industry Commission Report No 51 regarding the pharmaceutical industry and the fact that five years had elapsed after the completion of the Baume review, the Parliamentary Secretary with responsibility for the Therapeutic Goods Administration (Senator Bob Woods) directed the Department, in mid-1996, to commission a review of "*Australia's current approach to the regulation of medicinal products" (meaning all therapeutic goods other than devices).*[9]

The review had seven Terms of Reference requiring, in brief, investigation of issues spanning:

1. Restrictions on advertising of medicinal products;
2. Increased use of evaluation reports and decisions of overseas regulatory agencies with comparable regulatory standards;
3. Options for the regulation of orphan drugs;
4. Approval processes for alternative medicines;
5. Removal of unnecessary regulatory obstacles to export from Australia, with still maintaining standards of exports;
6. Appropriate mechanisms for stakeholder input;
7. The food-medicinal products interface.

The review was conducted by KPMG Management Consulting. The Report was released on 24 January 1997 and contained 85 separate recommendations across the seven Terms of Reference.[10] Whilst changes were recommended in many areas, it is important to note that the Review recommended:

- that the Government should re-affirm its commitment to maintain a sovereign, high quality and efficient drug regulation capacity in Australia;
- that Australia's co-regulatory system in relation to advertising of therapeutic goods should be maintained in the long term;

- that there should be clear articulation, including promotion of the strength of the Australian regulatory system, to importing countries particularly in the region of the meaning of the Australian export listing processes and the certification of export drugs.

On 10 April 1997, the Therapeutic Goods Administration hosted the official opening of the new wing of the Symonston building, by Senator the Hon Chris Ellison, Parliamentary Secretary to the Minister for Health and Family Services, who had succeeded Senator Bob Woods in February of that year.

At the opening, Senator Ellison indicated that the Government's commitment to both improve public health while finding real ways to facilitate business, means that the Government has adopted a range of mechanisms which go beyond measures recommended in the TGA review. Senator Ellison acknowledged the changing environment in relation to the community's attitude toward self medication, preventative medicines and the role of complementary therapies and indicated that the Government believes that there is a need to modify the current regulatory model to reflect and respond to these new attitudes. Senator Ellison therefore also released a Government Statement on medicinal products: *'Medicinal Products: Standards, Safety and Security*'.[11] The Government Statement and response set the direction for key areas of TGA for the next five years.

The following sets out major aspects of the Government's agenda:

> *Restrictions on advertising of medicinal products. The Government re-affirms its commitment to industry/Government co-regulation of controls on advertising of therapeutic goods, and therefore supports industry's application to the Australian Competition and Consumer Commission (ACCC) for authorisation to administer the Therapeutic Goods Advertising Code (TGAC). The Government will review current controls on advertising of listable therapeutic goods, with a view to providing greater flexibility and ensuring more appropriate claims. The Government has sought additional information from stakeholders on the effect of advertising therapeutic products containing Schedule 3 substances prior to deciding whether the current prohibition on brand advertising of such products should remain in place, by August 1997.*
>
> *Increased use of medicinal evaluation reports and decisions from overseas regulatory agencies in countries with comparable regulatory standards, with a view to enhancing medicinal product through-put. The Government is committed to maintaining proper Australian scrutiny of the efficacy and safety of therapeutic products, and of encouraging industry investment and growth. The Government re-affirms its commitment to maintaining a sovereign, high quality, effective and efficient drug regulatory capacity in Australia. While it will draw upon overseas evaluations from reputable*

authorities, and pursue harmonisation with New Zealand, the Government will retain the prerogative and the capacity to ensure that products do in fact meet Australia's high safety requirements.

Options for the regulation of orphan drugs. The Government will develop and implement a new program to help ensure proper and affordable treatment for Australians who suffer from rare disabling or life-threatening diseases. The new program will allow waiving of up to 100% of the TGA evaluation fee for an orphan drug and will provide a distinct pathway for processing such products. To improve access and timely availability of orphan drugs in Australia, the new program will examine the use of orphan drug evaluations conducted in the United States as a basis for Australian approvals. Additional criteria will be established for identifying and evaluating orphan drugs within Australia which have not been evaluated in the US or do not meet US criteria.

Approval processes for alternative (or 'complementary') medicines with a view to ensuring any inappropriate existing impediments are removed. The Government has identified a range of initiatives to improve the standard of complementary medicines including new standards for herbal products, a review of all grandfathered products, and an extension of the current adverse reactions reporting scheme. The Government will also establish a new Complementary Medicines Evaluation Committee (CMEC), to evaluate and provide advice to TGA on issues relating to complementary medicines. CMEC will work in conjunction with the Australian Drug Evaluation Committee and the Medicines Evaluation Committee, thereby ensuring independent expert advice across the range of medicinal products. The Government will pursue the accreditation of complementary medicinal practitioners with State and Territory Governments, as this would ensure that consumers can have the same confidence in the standard of training of complementary health practitioners as they do in the standard of medicinal products. The Government will also introduce a range of measures to reduce, where possible, regulatory impact on business.

Export arrangements to remove any unnecessary regulatory obstacles for Australian manufacturers and exporters while maintaining appropriate standards for Australian exports. The Government believes that the potential to facilitate Australian export of medicinal products goes beyond the measures recommended in the TGA review report. The Government has, therefore, established a process whereby industry and the TGA will provide further recommendations on this issue to the Parliamentary Secretary by June 1997.

Appropriate mechanisms for stakeholder input to the regulatory process. The Government supports the concept of increased stakeholder involvement in the TGA evaluation processes (for example, consumer involvement with the Australian Drug Evaluation Committee) where such increased

involvement will enhance the scientific integrity of evaluation processes and ensure company confidentiality.

The food/medicinal products interface. The Government believes that a review of the legislative definition of 'food', as well as greater use of Section 7 powers, under the Therapeutic Goods Act 1989 are appropriate mechanisms for streamlining decisions about whether a product is a 'food' or a medicinal product, addressing the protracted decision making process that industry has, at times in the past, experienced.

Of particular note, in the light of activities in the following years, was the response concerning complementary medicines. While the KPMG Review was in progress, the Minister for Health and Family Services convened an Alternative Medicines Summit, which he opened at Old Parliament House, Canberra on 16 October 1996. The Summit was aimed at *"freeing up access to alternative treatments for seriously ill people"* and was chaired by the then Chair of the Traditional Medicines Evaluation Committee.[12] The KPMG Review subsequently noted discontent in the complementary medicines industry about the performance of the Traditional Medicines Evaluation Committee. It also noted that the Alternative Medicines Summit had proposed that both the TGA and the NHMRC should have a broader range of advice on complementary medicines.

The Review had therefore recommended that the TMEC should be disbanded and replaced with a new broader committee, *"possibly called the Complementary Medicines Evaluation Committee"*. The Review further recommended that this committee should provide policy as well as scientific advice to the Secretary and that it should advise on all complementary medicines, both registered and listed, as well as having a role in evaluating new listable substances for quality and safety. As a corollary, the role of the Medicines Evaluation Committee would be restricted somewhat, to considering all registered products except complementary medicines and those *"handled by the ADEC"*.

The CMEC held its first meeting on December 16 and 17, 1997. In December 1998, a Working Party of industry, consumer and government representatives was established under the Chairmanship of Senator Grant Tambling, Parliamentary Secretary for the Minister of Health and Aged Care, to consider the regulation of complementary medicines by the TGA. Over a period of weeks, the Working Party developed a reform package which was endorsed by all bodies. In addition to making CMEC a statutory body by an amendment to the Therapeutic Goods Act 1989, consequences of the review were the establishment of the Office of Complementary Medicines within the Non-Prescription Medicines Branch and the Complementary Healthcare Consultative Forum. Other outcomes included review of advertising arrangements, review of

fees and charges, enhanced post-market vigilance and review of administrative arrangements for complementary medicines.

The Forum met on five occasions, the last being at Parliament House on 29 June 2001. Its formal discontinuation was recommended in 2003, on the grounds that it had fulfilled its initial purpose and that residual functions could be undertaken by other committees of the Department of Health.

In 1999, Senator Tambling announced a review of Drugs, Poisons and Controlled Substances legislation and the appointment of Ms Rhonda Galbally as independent Chair of the Review. The Review was undertaken under the Competition Principles Agreement by All Australian Governments and was required to examine issues in terms of their costs and benefits. Separate from, but in parallel with, the review chaired by Ms Galbally, the TGA commenced a project to broadly review the labelling requirements of medicines and the process used to determine labelling requirements. The National Drugs and Poisons Schedule Committee (NDPSC) had requested the TGA to consider the issues involved in moving the required warning statements from the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) to the auspices of the TGA. The project produced a discussion paper titles '*Effective by Design*', released in April 2000. A subsequent consultation report titled '*Review of the Labelling Requirements for Medicines – Consumer-focused Labelling - A Way Forward?'* (March 2002) – recommended that the SUSDP labelling statements be transferred to the Medicines Labelling Order, that consideration be given to requiring Consumer Medicines Information for all registered medicines and that a "*consumer-focused*" approach to labelling be adopted under an industry Code of Practice. The Therapeutic Goods Order No 69 was subsequently amended from 1 July 2004 (Statutory Rule 127, 2004) to require the inclusion in labels of statements included in a separate document '*Required Advisory Statements for Medicine Labels' (RASML)*. This document has since been updated twice, most recently in April 2006.

The ANAO again examined the TGA in 1996, presenting its Audit Report No 8, 1996-97 *'Drug Evaluation by the Therapeutic Goods Administration'* to the Parliament on 4 October 1996.

In summary, it found that:

1. the drug evaluation process was efficient but could be increased in effectiveness by more attention to the monitoring of adverse drug reactions, and improving the level of their reporting. It noted a dramatic reduction in the time taken to approve a drug for use, but saw scope for further improvement, *"with the assistance of pharmaceutical companies"*;
2. there were deficiencies in the Information Technology used by TGA;

3. TGA needed to develop an adequate system to assess the cost of its services to the pharmaceutical industry;
4. TGA's performance indicators were not adequately informing the Parliament and consumers of its work.

In its report of a follow-up audit presented on 25 July 2000 (Audit Report No.2 200-2001), the ANAO noted that the TGA had implemented, or partly implemented, 12 of the 14 recommendations in its 1996 Report and was addressing the remaining recommendations through alternative means. *"Generally, TGA's implementation has been consistent with the thrust of that Report to improve TGA's efficiency, effectiveness and reporting to its stakeholders."* The follow-up audit made three additional recommendations. One was that the TGA should develop and publish performance targets for processing reports of adverse reactions to drugs and, in instances where a decision was made to alter the status of a product in response to reported adverse reactions, to provide the sponsor with reasons and the supporting information. The other two recommendations were that TGA should publish performance indicators of the efficiency of its drug evaluation processing and to report performance in calendar days as well as working days.

In his consideration of access to medicines deemed essential, but which for commercial reasons are not marketed in Australia ("*service drugs"*), Baume explicitly did not propose the introduction of incentives towards registration similar to those available under the United States Orphan Drug Program. He saw the role of assuring the supply of service drugs as consistent with the existing role of the Pharmaceutical Benefits Branch in the Department, coupled with a registration evaluation process that was *"easier to negotiate"* and reduced or waived registration fees. A need for consideration of an Orphan Drugs program persisted, however, and the Review of Drug Evaluation by KPMG Consulting included as a Term of Reference *'Options for the regulation of orphan drugs.'* The report of the review recommended the establishment of a program for orphan and essential drugs *"to be administered by an Orphan and Essential Drugs Committee through an appropriate part of the Department."* Other related recommendations dealt with the nature and extent of requirements for data, subsidisation of evaluation fees and the need to publicise such a scheme. Amendments to the Regulations (Statutory Rules 1997 No. 399) added a definition of *"orphan drug"* and provisions for a two step process involving, first, designation as an orphan drug and, second, evaluation and registration at reduced cost through the waiving of application and evaluation fees. The Orphan Drug Program commenced in January 1998. An important aspect was that in instances where the Australian evaluation was favourable and collaborated by unedited US FDA assessment reports, registration could proceed without reference to ADEC.

A review by a consultant was commenced in August 2000 to examine whether the objectives of the Program had been met and to make recommendations for the improvement of the Program. Some months later, the TGA decided that the Terms of Reference should be expanded and the Review was suspended until August 2001. The report of the Review was made in December 2001.[13] Major issues raised were to do with aspects of the requirements for designation but also about strategies which had been adopted by some companies to use the Orphan Drug Program to gain broader registrations whilst avoiding the usually applicable fees. The Program has been continued and by April 2007, 124 drug – orphan disease combinations have been designated, involving 98 different drugs. Forty-three of these combinations have been registered.

Internationally, the regulation of blood products is a relatively recent phenomenon. National regulatory oversight of the manufacture and quality, efficacy and safety of plasma-derived products has followed mainstream pharmaceutical routes for the past thirty years, but the products of blood banking have been under similar rigorous systems for much shorter periods. In Europe, directives which have brought transfusion services under the oversight of the European Commission have only been in place in the past three years. The heightened awareness of blood safety issues precipitated by the transmission of HIV and Hepatitis C virus (HCV) in the 1980's and 1990's were key drivers in increasing regulatory oversight of the blood sector internationally.

This situation has been mirrored in Australia. Plasma derivatives as products of industrial-scale fractionation, and the plasma raw material itself, were included in the scope of the TGA's oversight with the inception of the Therapeutic Goods Act 1989. The government policy of limiting fractionation services to a single domestic manufacturer coupled with a policy of national self sufficiency effectively led to a single supplier on the market for many years. Policy changes in the past five years have led to the establishment of a National Blood Authority charged with assuring supply through, amongst other measures, introducing other players. This has led to a range of other suppliers and an increase in plasma products sourced from overseas being registered.

The issue of TGA involvement in the regulation of the fractionation of plasma was again raised by the ANAO in its 1999-2000 Report *"Commonwealth Management and Regulation of Plasma Fractionation"*. Concern was expressed in relation to how effectively TGA had carried out its auditing of C.S.L. Ltd. The Department of Health accepted a recommendation of the Joint Committee on Public Accounts and Audit (JCPAA) Report No 378, October 2000, that the Department conduct regular internal audits of TGA's performance of this function.

At its meeting in April 1999, the Australian Health Ministers Advisory Committee recommended that TGA should regulate fresh blood components manufactured in Australian blood agencies, in addition to the pooled plasma products that it then regulated. The products of blood banking that do not involve plasma fractionation, such as red cells, platelets and fresh frozen plasma, were largely exempt from regulation until 2000. This had been effected through a blanket exemption from registration (Therapeutic Goods Regulations 1990, Schedule 5, Item 9) of any products of the Australian Red Cross, as well as an exemption from the manufacturer licensing provisions of blood collection centres (Schedule 7, Item 18). In July 2000, the Schedule 9 exemptions were largely removed from the Regulations (Statutory Rules 2000, No 124), and all transfusion activity – referred to as fresh blood in regulatory parlance in Australia – was brought under TGA oversight through requirements for adherence to GMP and submission of information about product quality. Since then the rigour of Australia's regulation of blood has been widely recognised internationally, and the TGA is a member of the WHO's Blood Regulators Network which is specifically restricted to first world blood regulators.

In 2002, Toogoolawa Consulting Pty Ltd was appointed to undertake a wide-ranging review of the advertising of non-prescription medicines and to:

- Develop a trans Tasman therapeutic goods advertising regime;
- Streamline the assessment processes for industry and consumers in dealing with advertising approval and complaints handling processes; ensure that streamlined complaints handling processes appropriately integrated self-and co-regulatory best practice principles; and
- Ensure the new regime offered cost effective and timely processes that delivered ease of access, consistency and transparency to all stakeholders.

The Toogoolawa review was widely consultative in Australia and New Zealand, and it concluded in a report published in March 2003. The report recommended a co-regulatory scheme for the regulation of advertising of therapeutic goods that could be put into place for both Australia and New Zealand, as well as some modifications to the existing Australian scheme. The final recommendation of the report (Recommendation 19) was that a "provisional management board be established to supervise the further development process proposed in this report, including the development of the relevant parts of the parallel legislation. The "*provisional management board*" that was subsequently appointed was known as the Interim Advertising Council (IAC) which was established in May 2003 with 19 members, being broadly representative of Australia and New Zealand. The IAC met nine times between May 2003 and October 2004, when it completed its report that made

recommendations for the key elements of a best practice advertising regulatory model for Australia and New Zealand. That report was published after final consideration by the Therapeutic Products Interim Ministerial Council (TPIMC) in December 2005, along with the regulatory model for advertising that the TPIMC had agreed on after consideration of the IAC's recommendations. The TPIMC broadly accepted the IAC's recommendations with a small number of amendments. That provided the template for a trans-Tasman advertising co-regulatory scheme that had the support of a wide range of stakeholder groups on both sides of the Tasman. Recommendation 16 of the IAC Report included that a small steering group be established to oversee the work required to prepare for the commencement of the new regulatory model. The Advertising Implementation Steering Group was established in mid-2006 to undertake this final piece of work to enable the operation of a joint Australia/New Zealand advertising regulatory scheme.

A series of major events for the TGA started with the receipt by the Adverse Drug Reactions Unit of six reports of suspected adverse reactions to a product sold to prevent and treat travel sickness (Travacalm) in a seven day period in January 2003. Some batches of the product were clearly causing hyoscine toxicity in some consumers and those batches were withdrawn promptly.[14]

Concerns about the practices of the contract manufacturer (Pan Pharmaceuticals, Sydney) led to the recall from 28 April 2003 of 1379 products from the Australian market as well as smaller numbers of products from some European and Asian markets. The products were principally those made by Pan under contract for other sponsors and almost entirely non-prescription products.

As a consequence, the Government promptly introduced legislation to amend the Therapeutic Goods Act 1989 to tighten the existing requirements placed on manufacturers and sponsors and strengthen the offence provisions and penalties. The Therapeutic Goods Amendment Act (No.1) 2003 received Royal Assent on 27 May 2003.

Also as a consequence, the Government established an Expert Committee on Complementary Medicines in the Health System to reassure the public and maintain confidence in Australia's reputation as a supplier of high quality and safe medicines. The Committee reported in September 2003 and made forty-nine recommendations over a wide range of subjects, grouped under the headings *'The National Regulatory Controls for Complementary Medicines', 'Adverse Reactions', 'Information and Advertising', 'Healthcare Practitioners', 'Industry' and 'Administrative and Advisory Mechanisms'*.[15]

The Government in its response in March 2005, after extensive consultation, accepted virtually all of the recommendations within the direct responsibility of the Commonwealth and supported or noted the other recommendations.[16] The

TGA has since released two reports on progress with implementation of the Government response, most recently in October 2006.

The ANAO again audited aspects of the TGA's operations from October 2003, focussing on non-prescription medicines. Its Audit Report No 18 2004-05 was presented to the Parliament on 16 December 2004. Although the Background statement does not mention the recall of Pan Pharmaceutical products, the issue is raised in the Report which has a heavy focus on the TGA's auditing of Good Manufacturing Practice. The Report includes twenty-six recommendations aimed at strengthening the regulation of non-prescription medicinal products.

The Department in response, while noting that a number of issues had been addressed by TGA since the audit commenced in late 2003, accepted all of the recommendations. The Audit Report was later the subject of a consideration on 5 April 2005 by the Parliament's Joint Committee of Public Accounts and Audit, which subsequently made five recommendations – one seeking documentation from TGA for the Committee, the others recommending documentation of procedures for implementation of enforcement action, an increase in post-market laboratory testing for non-prescription medicinal products from overseas manufacturers, an urgent review of TGA information management systems, and continuation of re-accrediting for ISO 9000 and National Association of Testing Authorities standards. Subsequently, a consultant company reviewed TGA's progress on the Audit Report and suggested ways to improve TGA's governance.

From 1991, a Surveillance Unit has aided in ensuring compliance with legislation. Emphasis from the early days has been put on the recruitment of staff with investigative experience. In 2007, the Unit's staff includes eight investigators and two criminal intelligence analysts. The Unit regularly initiates interventions and on occasions prosecutions. In relation to the episode with Travacalm, Pan Pharmaceuticals and an employee were convicted of multiple charges under the Therapeutic Goods Act 1989 of manufacture of a counterfeit medicine and under the New South Wales Crimes Act 1900 of causing grievous bodily harm by negligent act.

The Unit participates in the Permanent Forum on International Pharmaceutical Crime and through it in the WHO's International Medical Products Anti-Counterfeiting Taskforce. The Unit offers an annual training course, held at the TGA, on Counterfeit Medicine Control and Law Enforcement and in 2004, with support from AusAID and the Western Pacific Regional Office of WHO, provided training courses in Vietnam. On 1 July 2007, the Unit's name was changed to Regulatory Compliance Unit, to better describe its role in ensuring compliance with regulatory requirements.

In contrast to some TGA functions, the TGA Laboratories were subject to only one significant review from 1991 to the present time, conducted by Tom Hayes AO in 1999. The Review acknowledged that the laboratories are a large and important part of TGA. *"A TGA without a laboratory would mean a much less capable TGA."* The Review recommended that the TGA should appoint a Regulator for each of four product areas, Prescription drugs; OTC drugs; Complementary Medicines; Devices. (In effect, this would appoint the head of each function responsible for the entry of products onto the ARTG as a Regulator).

The Regulators would be accountable for the regulation delivered in their product area and for the deployment of resources to achieve that; in particular for resources used in pre-market evaluation, batch release monitoring of vaccines and other biologicals, post-market review, post-market testing, collection of data on adverse reactions and problems, industry consultation and public education. The primary role of the Laboratories should be to provide an in-house source of scientific services and support for the regulators.

It was also recommended that the TGA should introduce an internal cross-charging mechanism whereby the costs of services and support provided by the Laboratories would be more transparent.

This approach was subsequently adopted by the TGA. The Review also made recommendations for changed allocation and improved management of some aspects of the work and suggested a greater investment by the Laboratories in the development of its human resources.

The Laboratories today continue to function as a scientific resource for the TGA in both pre-market and post-market spheres. Some long standing functions continue, including consultation on seasonal influenza strains, the annual international collaborative standardisation of reagents for assaying influenza vaccines and the batch release assessments for vaccines and other biologicals, consistent with WHO and European Union recommendations. While testing is perhaps the most visible activity, the Laboratories also remain heavily involved in the evaluation of new biological products, providing specialist auditors for Good Manufacturing Practice inspections and undertaking collaborative laboratory work and the development of standards. The role in the development of standards has moved from the earlier Australian specific standards to contributing to development of international standards. As at April 2007, six TGAL staff were participating as observers on European Pharmacopoeia expert committees while three others were members of various committees of the International Standards Organisation.

Following the changes to the regulation of complementary medicines at the time of the establishment of the Complementary Medicines Evaluation

Committee, there has been an intensification of the TGA Laboratories involvement in post-market vigilance on these products.

In 1997, testing in the Laboratories found that Aristolochia species had been used in manufacture of some imported Chinese medicines in place of Stephania species. Aristolochia species have been shown to cause kidney damage and bladder cancers. Recalls followed and prohibitions were applied, the latter being copied by other major international regulatory agencies. Internationally, tests have been introduced for the presence of aristolochic acid in herbs that might be subject to substitution.

The Laboratories played a key role in elucidating the reason for the puzzling clinical pictures encountered in the Travacalm episode, showing that within single packets some tablets contained none of an active ingredient (hyoscine hydrobromide) whilst other tablets contained more than seven times the amount stated on the label. The Laboratories in recent years have developed an increased capacity for forensic work in support of the Surveillance Unit.

Legislation

Until 2002, the relatively simple structure of the Act was preserved, not withstanding that it was amended on a number of occasions. The following were amongst the more important amendments:

PATIENT INFORMATION (1992)

In line with the report of Professor Baume, the Regulations were amended to require that Patient Information be provided in the packaging of the goods supplied to the consumer, or in such other form as would enable that information to be given to the patient or consumer in written form. An offence was created for goods to be supplied without the information. Schedule 10 described the goods to which the requirements applied, essentially prescription medicines, and the nature of the information to be provided was set out in Schedule 12.

In 1995, the requirement for patient information was extended to include therapeutic goods included in Schedule 3 of the Poisons Standard (Pharmacist Only Medicines), the content being specified in Schedule 13 of the Therapeutic Goods Regulations.

RESTRICTED GOODS AMENDMENT (1996)

This amendment, since repealed, was commonly referred to as the Harradine amendment because it was introduced and supported by the Government following negotiations with Senator Brian Harradine (Independent, Tasmania). A definition of Restricted Goods was added to the Interpretation section of the

Act (s3). Restricted Goods were defined as medicines (including progesterone antagonists and vaccines against human chorionic gonadotrophin) intended for use in women as abortifacients. An added section 6AA (Importation of restricted goods) prohibited the importation into Australia of any restricted goods without the written approval of the Minister. It also required that a written approval shall be laid before each House of the Parliament within 5 sitting days of being given. Unless a written approval is in effect and the Minister has notified the Chief Executive Officer of Customs in writing, restricted goods are to be taken to be prohibited imports under the Customs Act 1901. An added section 23AA required that restricted goods must not be evaluated or registered or listed without the written approval of the Minister, with similar requirements for tabling before each House. The provisions were repealed with effect from 3 March 2006.

MUTUAL RECOGNITION AGREEMENT FOR PHARMACEUTICAL GOOD MANUFACTURING PRACTICE AND MEDICAL DEVICE CONFORMITY ASSESSMENT AMENDMENTS (1997)

Part 2 of the Therapeutic Goods Amendment Bill was necessary to implement the Agreement on Mutual Recognition in relation to Conformity Assessment, Certificates and Markings between Australia and the European Community (EC).

PROTECTED INFORMATION AMENDMENT (1998)

An added section (section 25A) prevents the Secretary using protected information when evaluating another therapeutic good and is designed to protect information that may not necessarily be protected under patent. In brief, protected information is information submitted in an application to register a new therapeutic good (not being a therapeutic device) that contains a novel active component that never before was included in a medicine that was registered or listed on the ARTG. It is required that the information not be used or relied upon in consideration of another application for marketing approval, for a period of five years, unless with the consent of the owner of that information. This legislation does not prevent a competitor submitting a full data package in order the achieve registration of a generic product.

ADVERTISING AMENDMENTS (1999)

When the Act and Regulations commenced in 1991, advertising was covered solely by the Regulations and then only in a limited way. Part 2 of the Regulations, together with Schedule 2, set out a number of *"prohibited and required"* representations and provided for penalties for offences in relation to these representations. Part 2 also provided that the Part did not apply to

advertisements directed exclusively to a number of health professionals including *"herbalists, homeopathic practitioners, chiropractors, naturopaths, nutritionists, practitioners of traditional Chinese medicine or osteopaths registered under a law of a State or Territory"*. Because registration of many of these professions did not occur in many of the States and Territories, provision was made to list a number of professional organisations in Schedule 1. The Part did not apply to members of the organisations listed in Schedule 1.

In the mid 1990s the first step was taken towards creating a co-regulatory environment for advertising of non-prescription medicines, with the delegation by the Secretary of powers to suitable persons employed by the industry associations to pre-approve advertisements that required approval prior to publication or broadcast.

Major changes were made in 1999. The existing provisions in the Regulations described above were moved into the Act and new provisions were added to the Act to require the approval of advertisements to be broadcast or published in the mainstream media, and compliance with the Therapeutic Goods Advertising Code. Extensive new regulations established the Therapeutic Goods Advertising Code Council and the Complaints Resolution Panel and set out procedures for dealing with complaints. The legislation relating to advertising was further amended and clarified by the Therapeutic Goods Amendment Act 2003.

NATIONAL DRUGS AND POISONS SCHEDULE COMMITTEE (NDPSC) (1999)

Part 5B was added to the Act to establish the NDPSC under Commonwealth legislation and to define the Poisons Standard. Previously NDPSC had operated under the NHMRC and more recently under the Australian Health Ministers' Advisory Council. At the same time, the Object of the Act was amended to include as section 4(1) (a) *"to provide a framework for the States and Territories to adopt a uniform approach to control the availability and accessibility, and ensure the safe handling of poisons in Australia."*

COMPLEMENTARY MEDICINES (1999)

As one of a number of reforms recommended by a Working Party which reviewed the regulation of complementary medicines, the Government undertook to make the Complementary Medicines Evaluation Committee (CMEC) a statutory committee. Whereas all other advisory committees had been established under the regulations, CMEC was established by section 53G of the Act. Section 52F incorporated definitions of "*active ingredient*", *"complementary medicine", "designated active ingredient" and "traditional use"*.

UNAPPROVED USE AND CLINICAL TRIALS – AMENDMENTS TO GIVE POWER TO REGULATE CERTAIN ASPECTS (2000)

Concerns had arisen about possible abuses of the liberal provisions for notified unapproved use under Category A of the Special Access Scheme and about the inability of the TGA to audit or adequately monitor clinical trials conducted under the CTN and CTX arrangements. Amendments to the Act gave powers for the setting of conditions relating to the principles to be followed in the use of the goods (for example, National Statement on Human Experimentation), monitoring of use and circumstances under which use of the drug is to stop. There were also powers to require information to be provided about exempt goods when used in category A or under CTN and about unregistered goods approved for use under category B, CTX and the section 19 (5) Authorised Prescriber arrangements. Also included were offence provisions and a power to release information obtained in responses to State and Territory authorities responsible for registration of medical practitioners and pharmacists.

COUNTERFEIT THERAPEUTIC GOODS (2000)

Amendments to the Act by the addition of Section 42E to 42F defined counterfeit therapeutic goods and created offences for manufacturing, supply, importation or exportation. The definition is very broad, encompassing the WHO definition, and, in international terms, is very strict.

PRODUCT TAMPERING (2000)

These amendments were introduced following very highly publicised incidents of product tampering, involving attempted extortion and resulting in very extensive product recalls. An offence for tampering with therapeutic goods was created.

MEDICAL DEVICES AMENDMENTS (2002)

The Therapeutic Goods Amendment (Medical Devices) Bill 2002 was first introduced into the parliament on 29 March 2001 and passed by the House of Representatives on 6 August 2001. The Bill was, however, not debated before the Parliament was prorogued. The Bill was again introduced into the House of Representatives on 14 February 2002. The Bill introduced very extensive changes to the regulation of medical devices and to the format of the Act. The Outline section of the Explanatory Memorandum read as follows:

> "The Bill introduces a new medical device regulatory system which is internationally accepted best practice, harmonising Australia's requirements for quality, safety and performance with the recommendations of the medical devices Global Harmonisation Task Force, which are based on those of the European Community.

The new devices regulatory system has several key features. It provides for specified criteria for safety and performance, (the 'essential principles'), with which devices must conform; increased use of internationally recognised standards for devices as a means of demonstrating that a device conforms with the essential principles; a risk based classification of medical devices; conformity assessment procedures to ensure devices meet the essential principles for safety and performance; and increased emphasis on post-market activities.

The essential principles provide the measures for safety and performance of all devices and will be set out in the regulations.

The classification rules require devices to be classified according to the degree of risk involved in using the device, based on the degree of invasiveness in the human body, duration of use, location of use and whether or not the device is powered. Devices are currently classified as either 'registrable' or 'listable'. The new classification system has several levels of classification which will allow a more appropriate level of regulation to be applied to each class of device proportional to the level of risk posed by its use. It will also be better able to identify and manage risks associated with new and emerging technologies. Details of the classification rules will be set out in the regulations.

The conformity assessment procedures will allow more rigorous pre-market assessment of devices. All manufacturers of all medical devices will be required to meet manufacturing standards and all manufacturers, except those manufacturing the lowest risk devices, will be audited and have their systems certified. The level of assessment will be commensurate with the level and nature of risks posed by the device to the patient or user, ranging from manufacturer self assessment for low risk devices through to full Therapeutic Goods Administration (TGA) assessment with respect to high risk devices (which are to be identified in the regulations). Under the new system there will be increased scrutiny of high risk devices, which are often highly invasive in nature. A conformity assessment certificate, issued by the TGA, will be required before such devices can be marketed in Australia.

Detail of the conformity assessment procedures will be set out in the regulations. Under the new system there is more flexibility as to how devices are assessed as well as a requirement that documentation be held and made available as evidence to verify conformity with the essential principles.

Post market monitoring will include TGA checking evidence of conformity, periodic inspections of manufacturer's quality systems and technical documentation, including documentation held by a sponsor, and specific requirements for manufacturers and sponsors to report, within specified timeframes, adverse events involving their medical devices. Australia will also have increased involvement in the international post market vigilance system and this should reduce the likelihood of repeated adverse events as well as influence the development of new medical devices.

The new harmonised system for medical devices will retain major elements of the current legislation, in particular, the requirement for medical devices to be entered on the Australian Register of Therapeutic Goods (the Register). As medical devices will no longer be 'registered' or 'listed' but rather will be 'included in the Register', a new part of the Register has been created for this purpose. As a consequence, the Therapeutic Goods (Charges) Act 1989 has been amended to provide for annual charges to be imposed in

respect of medical devices 'included in the Register'. Provision has been made for exemptions from inclusion in the Register along similar lines to the current legislation and devices may still be recalled and Register entries cancelled in much the same way as they currently are. Provision has also been made for suspending medical devices from the Register where this is seen as more appropriate in the circumstances.

The Bill also makes provision for applications for 'inclusion' of medical devices in the Register to be made under the new devices electronic application lodgement system. This will allow automatic entry of devices onto the Register once the evidence of conformity has been prepared and a proper application is lodged. However, an important feature is the provision for some applications to be selected for checking prior to entry of devices onto the Register.

The Bill inserts a new part into the Therapeutic Goods Act 1989 (the Act) to provide for the creation of the new devices scheme but a large number of the current administrative provisions of the Act will continue to be used for the new scheme. The Act has been restructured into separate chapters and part numbers have been renumbered as a consequence. There is a separate chapter (Chapter 4) for regulation of medical devices and a separate chapter for medicines and other therapeutic goods that are not medical devices (Chapter 3). The remaining chapters deal with matters common to all therapeutic goods.

Transitional arrangements for the new system allow five years for devices currently on the Register to meet the new requirements. There is also provision for a two year transition period for some specified new devices. These will be specified in the Regulations and will include devices not previously manufactured to a certified quality system and some complementary therapy devices that are currently excluded from regulation. At the end of the transition period, provision has been made in Schedule 2 for further amendments to the Act as a 'clean up' of provisions which will no longer be required once the new scheme has been fully implemented."

The amended Act no longer had the seven Parts of the Act as when first passed. The revised Act is divided into eight Chapters and the previous Parts were in some instances renumbered. This created a separation between "Medicines and other therapeutic goods that are not medical devices" (Chapter 3) and Medical Devices (Chapter 4). The principles of regulation of medical devices had changed, as described above, but those of medicines had not changed.

CIVIL PENALTY PROVISIONS (2005)

The Act was amended to introduce additional enforcement measures to enhance the TGA's ability to secure better compliance with the Therapeutic Goods Act 1989. The Bill introduced civil penalty provisions as an alternative sanction to criminal sanctions for a number of breaches under the Act, in most cases applying to breaches that also attract a parallel criminal offence.

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17. TGA's INTERNATIONAL WORK

International harmonisation of regulatory requirements and cooperation between regulators has become an essential part of TGA's work.

Collaboration with New Zealand

In October 1991, agreement was reached between the TGA and the then Therapeutic Goods Section of the New Zealand Department of Health on exchange of information relating to GMP inspections, testing of therapeutic goods and recalls. In May 1993, the TGA signed an MOU for exchange of regulatory information with New Zealand.

In 1998, the National Drugs and Poisons Schedule Committee set up a Working Party on Trans-Tasman Harmonisation of Scheduling of Drugs and Poisons to examine ways of achieving harmonisation of scheduling and related technical and policy matters. A detailed discussion paper on a proposal for a trans Tasman Regulatory Agency was published in 2002.[1]

The Australian Parliamentary Secretary to the Minister for Health and Ageing and the New Zealand Minister for Health on 12 December 2003 signed a Treaty to establish a single bi-national agency to regulate therapeutic products, including medical devices and prescription, Over-the-Counter and complementary medicines.

To facilitate the establishment of a joint scheme for the regulation of therapeutic products, a Therapeutic Products Interim Ministerial Council comprising the Parliamentary Secretary and the New Zealand Minister was established and held its first meeting on that day. At the time, the agency was expected to commence operation in 2005, but this date was later put back to 2007. A Joint Agency Establishment Group was subsequently created to bring together the work of the Australian and New Zealand project teams then working towards the new agency.

In December 2005 the Australian and New Zealand governments announced agreement on a regulatory model for the advertising of therapeutic products to be applied on commencement of the joint agency. The model followed closely the recommendations in the Report of the Interim Advertising Council presented in October 2004. Also in December 2005, the Therapeutic Products Interim Ministerial Council announced that the title of the new agency would be the Australia New Zealand Therapeutic Products Authority (ANZTPA).

In July 2007, it was announced that the Australian and New Zealand Governments have agreed to postpone negotiations for the establishment of ANZTPA. The New Zealand Government advised that it still supports the

vision of a joint Trans -Tasman therapeutics authority but it does not have the numbers in Parliament to pass its legislation as proposed.

Other International Involvement

In January 1991 TGA was admitted to membership of the scheme for mutual Recognition of Evaluation Reports on Pharmaceutical Products (PER scheme.)

A delegation from the Pharmaceutical Inspection Convention visited Australia in February 1991 and, subsequently, in January 1993 Australia became the first country outside Europe to become a member of the Pharmaceutical Inspection Convention, known from November 1995 as the Pharmaceutical Inspection Cooperation Scheme (PIC/S). From 2001 to 2002, the TGA adopted in turn the Annex 1 of the EU GMP Guide as a Manufacturing Principle for the manufacture of sterile medicinal products, the International Conference on Harmonisation Q7a Guideline on manufacture of active pharmaceutical ingredients and the Pharmaceutical Inspection Cooperation Scheme's Guide for Medicinal Products. This last named document replaced the fifth edition of the Australian Code of Good Manufacturing Practice.

A bilateral inspection agreement for GMP of manufacturers of medicines and medical devices with Japan was signed on 30 April 1993. This was followed in 1996 by an agreement between the TGA GMP Inspectorate and the New Zealand Medsafe GMP Inspectorate to enable reciprocal recognition of the results of inspections.

For the evaluation of therapeutic devices, evaluation reports were obtained for the first time in 1993 from the US Food and Drug Administration and the Canadian Bureau of Radiation and Medical Devices. In 1994 the first formal exchanges of drug evaluation reports with the US Food and Drug Administration occurred. On October 11, 2000 the TGA signed a co-operative agreement with the US FDA regarding the exchange of information on current Good Manufacturing Practice inspections of human pharmaceutical manufacturing facilities.

In December 1999, two senior members of the staff of TGA accompanied Senator Tambling on an official delegation to Vietnam, Thailand and China to advance cooperation in the area of medicines, medical devices and food, including discussions on the development of Memoranda of Mutual Cooperation with the relevant agencies.

In 2001 Australia and Singapore signed a mutual recognition agreement in relation to pharmaceutical manufacturer inspections and, in June 2003, the TGA and Health Sciences Authority, Singapore, announced an initiative for prescription medicine applications.

A bilateral Treaty (the Australia-Canada Mutual Recognition Agreement) was signed on 16 March 2005. The Treaty allows for the recognition of each other's GMP assessments and of the certification of the manufacturer's batch testing certifications. This treaty was in addition to an earlier Memorandum of Understanding signed in April 2004 between the two countries to enhance the information sharing and facilitate cooperation on the regulation of therapeutic products for human use.

In February 2006 the TGA signed an agreement regarding information exchange and future cooperation on therapeutic products regulation with the Indonesian National Agency for Drug and Food Control (NADFC). In March 2006 the TGA signed an agreement regarding information exchange and future cooperation on therapeutic products regulation with the Thai Food and Drug Administration (Thai FDA). The agreements with the Indonesian NADFC and Thai FDA provide a structured framework within which future cooperation between the TGA and the two agencies can occur. The signing of these agreements confirmed the important role of the TGA as a leading regulator of therapeutic products in the Asia-Pacific region.

A Memorandum of Understanding between the TGA and Switzerland's corresponding agency (Swissmedic) was signed on 29 March 2006, formalising their cooperative arrangements to exchange information about regulatory decisions and post-marketing monitoring of therapeutic products. The TGA and Swissmedic already had relations in place through their memberships of the Pharmaceutical Inspection Convention and the Global Harmonization Task Force (GHTF) for medical devices.

The TGA has been active in the international efforts to combat counterfeit products. The technical skills of the TGA Laboratories were recognised with the award of a US Vice-President Al Gore's Hammer Award for the Laboratories' work in developing an analytical method to detect counterfeit and sub-standard ingredients in medicines. Two TGA Laboratories staff members went to Washington DC to accept the award on 29 June 2000. The Hammer is now displayed in the foyer to the TGA building. Other professional recognitions for the TGA have been the holding, by various members of staff, of the Chair of the Pharmaceutical Inspection Cooperation Scheme (1999), the Chair of the Global Harmonization Task Force (GHTF) for medical devices (2000) and the Chair of the Policy Group, WHO Global Collaboration for Blood Safety (2003).

The TGA also assists in the education of regulators in other countries. In 1996, TGA Commercial (later renamed International Services Group) was set up for TGA to provide user pays services internationally. This has seen a continued provision of training courses both at TGA and overseas and many individuals

coming to TGA for individual training placements. A training calendar is now available on the TGA website.

In the 2005-06 year, the TGA provided training in various aspects of the regulation of therapeutic goods to 69 trainees from 19 different countries. During the same period, TGA hosted visits by 24 delegations from regulatory authorities in eleven countries.

In May 1999 the TGA Laboratories and the International Services Group organised a training course on vaccine regulation for staff from other National Control Authorities. The course was arranged as part of the WHO's Global Training Network (GTN) for vaccines, and attendances were funded by WHO and AusAID. Attendees came from China, Thailand, Philippines, Singapore and Brazil. Between 1999 and 2004, four GTN courses were conducted at TGA. The Laboratories continue to provide training for the Australian industry as well as to international groups.

In 1998, the TGA entered into an agreement with the US based not-for-profit Drug Information Association (DIA) to establish a joint DIA-TGA Fellowship Program. This Program supported several individuals from overseas to spend extended periods at TGA as well as the participation of others in training courses at TGA in the period 1999 to 2003.

In November 2000, the TGA staged a Regulators' Forum, in conjunction with the World Self-Medication Industry (WSMI) Fourth Asia Pacific Regional Conference held in Sydney. The Forum was designed to foster closer collaboration in the region between regulatory authorities and lead towards more harmonised approaches in regulation of therapeutic goods.

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18. OTHER MATTERS

In the early 1990's, Australia adopted a National Medicines Policy (NMP) with four arms: the regulation of medicines, the population's access to them such as financially through the Pharmaceutical Benefits Scheme, the quality use of the medicines and having a viable, responsible industry.[1] The national regulatory scheme was a solid basis for TGA's participation in the NMP and the NMP is an important statement of the roles and responsibilities of the variety of bodies involved with medicines.

A theme from Federation has been the need to effectively deal with the division of powers, deriving from the Constitution, between the Commonwealth and the States as they relate to the regulation of therapeutic goods. There was an expectation when the Therapeutic Goods Act 1989 was passed by the Australian Parliament that each State and Territory would pass complementary legislation. As at July 2007, only New South Wales and Tasmania have enacted laws that adopt and automatically update State legislation in accordance with the federal legislation. Victoria adopted the legislation but without the updating provision. Nearly eighteen years after passage of the Act, the other States and Territories have not passed complementary legislation.

Other emerging issues being dealt with by the TGA in mid 2007 are:

- more comprehensive regulation of In Vitro Diagnostic (IVD) kits upon which critical medical decisions can depend.
- the growing variety and complexity of biological products as technology such as genetic engineering and new diseases such as SARS and avian influenza emerge.
- the level of regulation of products manufactured by compounding chemists.
- managing the risks arising from the reuse of devices intended for single use, a practice often driven by cost pressures within hospitals.
- the growing emphasis on post market monitoring as new medicines and medical devices are reaching the market more quickly and often with limited experience of use in patients.
- the need to have suitable products for all age groups including the very young and the very old, and
- the move towards having the products customised to meet the genetic profile of the patient.

Regulation is neither static nor staid.

CHAPTER 18 REFERENCES

1. Murray M. Australian National Drug Policies Facilitating or Fragmenting Health? Development Dialogue 1995; 1: 184-185