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MEDICINE CONTROL IN NEW ZEALAND

manuscript prepared by the

DIVISION OF CLINICAL SERVICES

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DEPARTMENT OF HEALTH

WELLINGTON

NEW ZEALAND

Date _____

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Index

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CHAPTER 1. LEGISLATION

1.1 Historical Background

New Zealand became a British Colony under the Protection of the British Crown, in 1840, when the Treaty of Waitangi was signed.

In 1852 the British parliament enacted a constitution for New Zealand which became effective in the following year. This resulted in self-government, and six regional governments were set up. A Central Government to co-ordinate provincial controls first met in 1854. The provincial governments were abolished in 1876, when effective central government was established for the first time.

Legislation to introduce controls on medicines was an early consideration of Government. The Sale of Food and Drugs Act 1877 which was passed in its first year established conditions under which food and medicines could be manufactured, packed or sold. All medicines had to comply with the British Pharmacopoeia or other standard work. Inspectors were also appointed to take samples and submit them to the Colonial Analyst for analysis. This Act was revoked and a more effective Sale of Food and Drug Act 1907, which was consolidated in 1908, replaced it. This Act was subsequently replaced by the Food and Drug Act 1947, and more recently by the Food and Drug Act 1969.

The first Sale of Poisons Act was enacted in 1866 and was replaced by another in 1871. While this Act only listed 23 substances in

two parts, it prohibited their sale by unregistered persons. It also established Registrars of Poisons, standards of packaging and labelling, and records which could be inspected by any police officer. Labelling did not have to include the word "Poison" if on a medicine prepared by a qualified person, but a prescription book had to be kept. The 1871 Act was revoked and replaced by the Poisons Act 1934.

Certain poisons, known as Prescription Poisons, were first restricted to supply only on the prescription of a medical practitioner, dentist or veterinary surgeon in 1937, with the introduction of the Poisons (General) Regulations 1937. Six poison schedules were created in these regulations, prescription poisons being included in schedule one.

The 1934 Poisons Act was revoked and replaced by the Poisons Act 1960, and new regulations were made in 1964 which are currently in force. In these new regulations, schedule one of the previous regulations was split into the present First Schedule and a new Schedule Seven. Schedule One restricts retail sale to pharmacists and requires certain records to be kept. The Schedule Seven listed all Prescription Poisons in two parts the second of which listed Restricted Drugs. These were first restricted to supply only on prescription, in the Food and Drug Regulations. These restrictions came into force in 1951 for penicillin and streptomycin.

The first official requirement for the notification of new and changed medicines was included in the 1962 Food and Drug Amendment Act which became effective in December of that year.

These provisions were considerably reinforced in the 1969 Act, which became effective in April 1970, and is currently in force.

Narcotics were originally known as Dangerous Drugs. They are now included under the general designation "controlled drugs". Controls on these substances were first introduced in the Customs Law Consolidation Act 1882, which required opium to be imported in quantities of not less than 45 pounds, in ships of not less than 40 tons, and only through approved ports of entry. This Act was followed by the Opium Prohibition Act 1901, which was an attempt to prevent the smoking of opium by Chinese citizens, and was consolidated as the Opium Act 1908. The latter required customs permits for each import and export, and the keeping of records of all quantities bought or sold in a ledger retained for that purpose. It prohibited opium in any form suitable for smoking, prohibited the smoking of opium and permitted search without warrant of any premises occupied by Chinese where smoking of opium was suspected, but required a warrant for premises not occupied by Chinese.

In 1921 and 1922, regulations made under the Opium Act implemented the provisions of the First Opium Convention promulgated at The Hague in 1912. These regulations progressively extended internal control by requiring precise accounting and extended the range of drugs controlled to include the alkaloids of opium (morphine, heroin and codeine), further opium preparations, cocaine, and ecgonine.

The system of international control embodied in the international agreements and conventions of 1925, 1931, 1936, 1946 and 1953

culminating in the Single Convention on Narcotic Drugs 1961, which replaced the foregoing, was incorporated in New Zealand legislation in the Dangerous Drugs Act 1927 and the regulations promulgated under that Act in 1928, 1933 and consolidated in 1951. This Act was revoked and replaced by the Narcotics Act 1965 which incorporated the additional requirements of the Single Convention on Narcotic Drugs 1961.

In 1977, the Misuse of Drugs Act 1975 came into force. This statute incorporates the provisions of the Psychotropic Substances Convention 1971 as well as the Single Convention on Narcotic Drugs 1961, and replaces the Narcotics Act 1965.

A further very effective control over prescribed medicines has followed from the introduction of free medicines under the Social Security health benefit scheme introduced in May 1941. Details of this scheme and its effects are given in the body of this publication.

1.2 Present Legislation and "Codes" Issued by the Department of Health

The control of medicines (therapeutic drugs) is at present covered by four separate Acts and corresponding Regulations - namely the Misuse of Drugs, Restricted Drugs, Food and Drug, and Part II of the Social Security Acts. These are administered by the Department of Health.

The Food and Drug Act 1969 defines "drug" as follows:-

(a) Any substance or mixture of substances used or represented for use, whether internally or externally,

for the purposes of the prevention, diagnosis, or treatment of any disease, ailment, disorder, deformity, defect, or injury of the human body:

(b) Any substance or mixture of substances used or represented for use for the purpose of altering the shape or structure of the human body:

(c) Any substance or mixture of substances, including anaesthetics, used or represented for use for the purposes of influencing, inhibiting, or modifying any physiological process in human beings, or the desires or emotions connected with any such physiological process, or the desire for alcohol or tobacco:

(d) Any chemical contraceptive:

(e) Any material used or represented for use as surgical dressings:

(f) Any disinfectant, germicide, or antiseptic:

(g) Any tobacco prepared for smoking, chewing, or snuffing:

and the term "Therapeutic Drug" is defined as a drug within the meaning of paragraphs (a), (b), (c) or (d) of the above definition. The word "medicine" is for this document synonymous with "therapeutic drug".

While no exemptions to these definitions are recognised in the Food and Drug Act, the Department does, however, scrutinise the advertising claims and related promotional material for homoeopathic and herbal remedies.

The sale or distribution (whether by way of gift, loan, sample or in any other manner) or the advertising of any medicine not sold in New Zealand prior to April 1970, is prohibited before the consent of the Minister of Health to the distribution of the medicine has been notified in the New Zealand Gazette. The penalty for any offence under this part of the Act is substantial: imprisonment for up to six months or a fine not exceeding $5,000, or both. The Minister's consent may be withdrawn and the Restricted Drugs Act provides power for the Minister to prohibit the importation, manufacture, sale or possession of any specified drug for twelve months. The Food and Drug and the Restricted Drugs legislation contain sections on the manufacturers' premises, packaging, handling, labelling, distribution, sale and advertising of medicines. Prosecutions and/or medicine recalls may be instituted if a medicine does not comply with its specifications, or if the conditions of manufacture, packaging, labelling or advertising contravene legislative requirements.

One section of the Act permits an officer to enter and inspect any place where he believes any medicine, medical device, labelling or advertising material is manufactured, packed, stored or kept for sale. This section is the authority for carrying out Good Manufacturing Practice inspections of pharmaceutical manufacturers, wholesalers and retailers of medicines and medical devices. While

not a legislative document, the Department has issued a "Code of Good Practice for Manufacture and Distribution of Medicines". This document is for the guidance of the pharmaceutical industry and hospitals and is used as the basis for the inspection of premises and procedures, methods of distribution and medicine recalls.

Under the Official Secrets Act and State Services Act and Regulations, documents on matters relating to medicine applications and notifications are treated as completely confidential. The only matters made public are the publication in the New Zealand Gazette of the consent of the Minister to the distribution of a new medicine.

Under the controlled drugs legislation (see Misuse of Drugs Act - section 4.2.2.1) the importation, export, dealing in or administration of certain preparations are prohibited except to the extent as may be approved in writing by the Minister either in relation to each specific instance or generally. For instance, no import or export licence may be issued for acetorphine, cannabis, desomorphine, etorphine, heroin, ketobemidone or thalidomide without the written approval of the Minister of Health. Products such as methaqualone, and methylphenidate may be obtained on prescription but only from a hospital pharmacy. Further restrictions and controls relative to supply on prescription, records, delivery and labelling are included in this and the Restricted Drugs legislation. Following a decision to remove anorectics from the Drug Tariff the Pharmacology and Therapeutics Advisory Committee recommended that amphetamines be available as pharmaceutical benefits only for the treatment of a limited number of conditions, the main ones being narcolepsy and confirmed amphetamine dependency. The committee realised, however,

that there may be other rare conditions for which an amphetamine would be regarded as the treatment of choice, but was reluctant to suggest a restricted list of specific conditions. Therefore the committee also advised that the conditions for which supplies should be authorised as pharmaceutical benefits should be at the discretion of the Department of Health with, in certain circumstances, the right of the department to request a specialist recommendation. The Minister of Health delegated to the Division of Clinical Services his power to approve, in particular cases, supply from hospital pharmacies of amphetamine sulphate tablets, dexamphetamine sulphate tablets and long-acting capsules, and methylamphetamine hydrochloride tablets.

Prescriptions for the supply of these medicines are subject to a discretionary approval in every case, but an approval may be granted for an extended period. Applications for approval are made by the medical practitioner to the Director, Division of Clinical Services, and must include the following particulars:

(a) The full name and address of the patient.

(b) The name of the medicine and dosage.

(c) The condition for which the patient is undergoing treatment, including clinical details.

(d) The name of the hospital pharmacy which will be requested to supply the medicine.

If a supply is authorised, the approval is sent to the applicant practitioner, with a copy to the nominated hospital pharmacy.

While any medicine may be sold once the Minister grants his consent, usage is usually very limited until such time as the

product is included as a pharmaceutical benefit under the Social Security Act 1964; this acts as a further control measure.

Restriction of availability free of charge to supply only on the prescription of an appropriate specialist or occasionally only from a hospital pharmacy enable even tighter control to be maintained for any medicines requiring further monitoring for safety reasons.

CHAPTER 2. ORGANISATION OF THE MEDICINE SECTION

2.1 Introduction

When controls over the distribution of new medicines were first instituted in December 1962, medicine control was a function of the Division of Public Health. With the introduction of the Food and Drug Act 1969 and its more comprehensive requirements, control was transferred to the Division of Clinical Services. Approval for remedies used in veterinary practice is granted by the Animal Remedies Board of the Ministry of Agriculture and Fisheries.

2.2 Administrative Structure and Functions

The Division of Clinical Services includes among its functions the evaluation of new and changed medicines and the administration of the pharmaceutical benefits scheme under the Social Security Act 1964. The Division is headed by a Director, but the administration of the Medicine Section is the responsibility of the Deputy Director who is assisted by two Assistant Directors, and two visiting practitioners. All are medical practitioners.

The Medicine Section staff also includes a pharmacologist, three scientists, five pharmacists, (two of which are visiting pharmacists), a statistical officer, an administration officer and seven clerks.

2.3 Co-opted Assistance

Further assistance is co-opted from within the Department of Health or other Government departments as follows:-

(1) Eleven public health pharmacists, based on the major district offices of the department throughout the country, assist with the inspection of manufacturers, wholesalers and distributors of therapeutic products, medicine sampling, licensing procedures and policing of legislation. All inspections are, however, supervised centrally by the Medicine Section.

(2) Four pricing offices headed by pharmacists and employing over 100 clerical workers, price the prescriptions dispensed under the Social Security legislation, make payments to pharmacists and police the various legislative requirements.

(3) Experts from the National Health Institute may be included in inspections of manufacturing premises of sterile products. They may also advise on autoclaves and other sterilisers throughout the country, and help with the testing of biological products.

(4) The Pharmaceutical Branch of Chemistry Division, Department of Scientific and Industrial Research is staffed by eight scientists. The work of the Branch includes the routine testing of medicines and any testing following complaints. All testing is co-ordinated by the Medicine Section.

(5) Radiopharmaceuticals are not evaluated by the Medicine Section. Their safety in use is also under the control

of legislation administered by the National Radiation Laboratory of the Department of Health.

2.4 Committees

2.4.1 Medicine Assessment Advisory Committee

This advisory committee was established in 1970 as the Drug Assessment Advisory Committee when the Division of Clinical Services became responsible for the control of the distribution of new medicines. Membership of the committee is as follows; two nominees of the Medical Association of New Zealand, two nominees of the Pharmaceutical Society of New Zealand, two nominees of the Department of Health (not employees), one member appointed by the Minister of Health, and a departmental chairman.

The original terms of reference of the committee were:

1. To evaluate and advise on the effectiveness and safety of new medicines.

2. To consider and advise the Minister on the suitability of medicines for distribution in New Zealand.

3. To consider and advise on any other matters relative to new medicines or the distribution of medicines.

These responsibilities have since been extended in two ways:

(a) Certain medicines notified as changed medicines are referred to the committee.

(b) Some applications for sale of medicines outside retail pharmacies under the Therapeutic Drugs (Permitted Sales) Regulations 1978 are similarly referred.

(c) Decisions as to which medicines are to be included in the Intensified Adverse Drug Reaction Reporting Scheme.

The committee may request from a recognised specialist in a particular field a report on a medicine of a specialised nature.

A sub-committee of three members was formed in 1972 to report on urgent questions concerning adverse drug reactions referred to it by the Department of Health. This sub-committee is primarily intended to provide expert advice to the Department when this is required with the least possible delay. Such a need arose in 1972, for example, when the toxicity of hexachlorophane became an important issue, and in 1974 when a possible association between rauwolfia and breast cancer was reported. In the normal course of events such matters are referred to the full committee.

The full committee meets three times a year and increasing use is being made of its services. In 1972 consideration was given to 27 new medicines whereas in 1978, 39 new medicines were considered.

Unlike some overseas committees representatives of pharmaceutical firms are never present to make personal representations concerning their products. It should be noted that although the committee

may consider a new medicine suitable for distribution, the responsibility for making a final decision rests with the Minister of Health.

2.4.2 Pharmacology and Therapeutics Advisory Committee

Membership of the committee is as follows; two nominees of the Royal Australasian College of Physicians (two physicians), two nominees of the Royal New Zealand College of General Practitioners (two general practitioners), two nominees of the New Zealand Medical Association (one general practitioner and one physician) and three members appointed by the Minister of Health, at present two clinical pharmacologists and one economist, and a departmental chairman. It advises the Minister of Health about the revision and updating of the Drug Tariff. All medicines considered must have received the prior consent of the Minister for distribution. The committee considers the efficacy of the medicine, the need for it to be made available without charge and any desirable restrictions on its availability as well as its cost to public funds. Restrictions considered by the committee include availability only on the prescription or recommendation of a specialist (either through a hospital or a retail pharmacy), or, limiting supply to hospital pharmacies.

2.4.3 The Restricted Drugs Committee

This is a statutory committee appointed by the Minister of Health to advise him on the scheduling of medicines as prescription drugs and on the making of regulations concerning the dispensing and compounding of restricted drugs. The committee comprises three members of the Department, one of whom is the chairman, two

nominees of the Medical Association of New Zealand and two nominated by the Pharmaceutical Society of New Zealand.

2.4.4 Pharmaceutical Advisory Committee

This committee comprises two officers of the Department of Health (a medical practitioner, who is chairman, and a pharmacist nominated by the Minister), four pharmacists (one each nominated by the Minister of Health, the Pharmaceutical Society of New Zealand, the Chemists' Guild and the Hospital Pharmacists' Association), a medical practitioner nominated by the Medical Association of New Zealand, and a nominee of the Pharmaceutical Manufacturers' Association.

The committee advises on the routine administration of the Pharmaceutical Benefits Scheme particularly as it affects pharmacists.

2.4.5 Committee on Adverse Drug Reactions

The Committee on Adverse Drug Reactions was formed in 1965. It comprises nine members: three nominees of the Royal Australasian College of Physicians, one of whom is chairman, two nominees of the New Zealand College of General Practitioners, one nominee of the New Zealand Dental Association, one nominee of the Otago Medical School, and two nominees of the Department of Health. More recently a nominee of the Accident Compensation Commission has been added. The committee meets three times a year.

Although this is not a departmental committee, the Department of Health provides secretarial services and meets the costs involved in the operation of the Registry of Adverse Drug Reactions. It is believed that autonomy results in a higher rate of reporting

of adverse drug reactions by dentists and medical practitioners. The Department pays the postage on adverse reaction report forms, which are sent to the Committee's Medical Assessor. Practitioners are urged to co-operate in reporting drug reactions, and may also obtain information from the committee on whether or not specific adverse reactions to medicines have been reported or suspected. Annual Reports are published and regular Bulletins distributed as appropriate to developments in the field.

2.4.6 Standing Committee on Therapeutic Trials

This committee is not a departmental committee but has been set up by the Medical Research Council. It reviews all applications made to the Director-General of Health for clinical trials on unregistered medicines. Final responsibility for approval rests with the Department of Health.

2.4.7 Epidemiology Advisory Committee

This committee, set up under the Health Act 1956, deals with any topical questions and measures to control communicable diseases and to influence other aspects of epidemiology. The committee has power to co-opt for special meetings those persons with expertise in particular fields, eg, virology, microbiology, etc. Members represent the University of Otago, the Paediatric Society, the New Zealand Branch of the Royal College of General Practitioners and the Department of Health. Four members are nominated by the Board of Health. This committee advises on the control of marketing of vaccines.

2.4.8 National Poisons Information Centre

This centre, which is located in Dunedin, is quite independent of the Department, but it works in close conjunction with it. Details

of the active constituents of all new medicines and drugs submitted to the Department are referred to the centre which collates them and notes the appropriate antidotes. The centre is on call at all times to advise medical practitioners involved in the treatment of poisoning cases.

2.5 The Use of Consultants

The Department has appointed Consultant Advisers in toxicology, pharmacology, clinical pharmacology, paediatrics, ophthalmology, obstetrics and gynaecology, dentistry, leprology, brucellosis, smallpox, venereal diseases, radiology, dermatology, respiratory diseases and orthopaedics. The advice of any of these consultants may be sought when a particular problem arises in the assessment of new or changed medicines, or in other circumstances where an expert opinion is required.

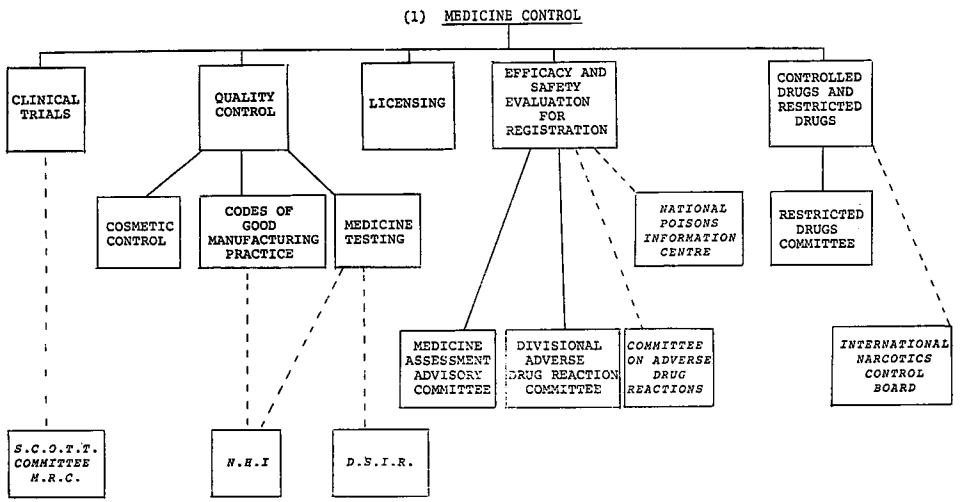
2.6 Fees

No charge is made at present for processing new or changed medicine applications, all expenses being met by the New Zealand Government. While inspections of manufacturing premises are made free of charge, licensing fees may be levied in the future.

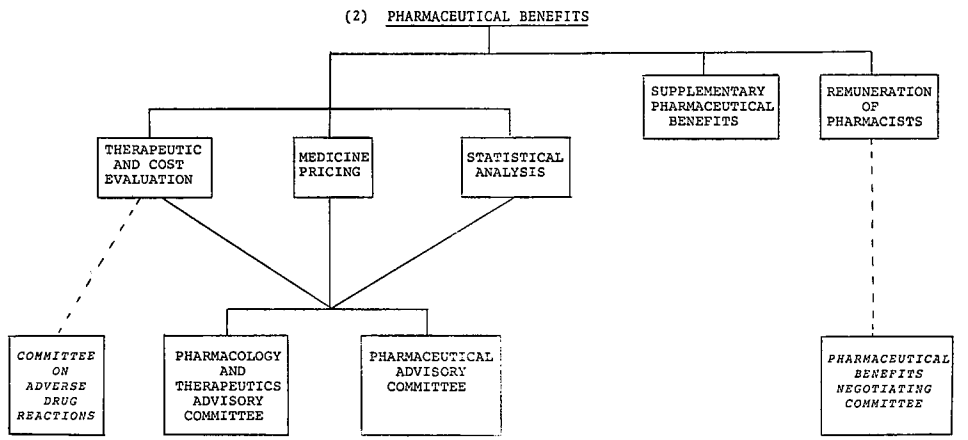
2.7 Location of Clinical Services

The Division is part of the Head Office of the Department of Health, and its offices are in the Air New Zealand Building, 7th Floor, 70 The Terrace, Wellington.

MAJOR FUNCTIONS OF THE MEDICINE SECTION OF THE DIVISION OF CLINICAL SERVICES



Organisations or committees depicted in italics are not administered by the Division of Clinical Services.



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CHAPTER 3. APPROVAL OF CLINICAL TRIALS, NEW MEDICINES AND CHANGED MEDICINES

3.1 Clinical Trials

In December 1962 it became mandatory for the consent of the Director-General of Health to be obtained before any investigator could undertake clinical trials for the purpose of establishing the safety, efficacy, and dosage of new medicines.

A further requirement was included in the Food and Drug Act 1969 whereby the Director-General could approve trialists only if recommended to do so by the Medical Research Council of New Zealand. A sub-committee of the Medical Research Council, the Standing Committee on Therapeutic Trials, was established in 1970 with the responsibility, inter alia, of preparing for the Council recommendations to the Director-General in regard to medicine trial applications. While no legislative procedure is laid down concerning the costs of clinical trials, the promoters of the trial normally meet all the incidental costs. Application forms should be obtained from the Medicine Section.

The following minimum details are supplied to the Department of Health, by manufacturers and importers requesting the approval of persons nominated to carry out a medicine trial, for the consideration of the Standing Committee on Therapeutic Trials:

(a) The nature of the material, its identifying name or mark and its chemical formula.

(b) The purpose of the investigation.

(c) The names and qualifications of the investigators and their curriculum vitae.

(d) The facilities available to the investigators.

(e) A written consent to his nomination from each proposed investigator.

(f) A copy of the information supplied to the investigators, particularly in relation to safety.

(g) A protocol of the trial setting out the number of patients to be involved, the form of the proposed studies including records to be kept, and setting out in particular those who would be excluded from the trial and any other aspects designed tó ensure the safety of the patients.

After the Committee has reviewed the information provided, recommendations are forwarded through the Medical Research Council, to the Director-General. If favourable, the trialist(s) will be given consent to undertake the trial. On occasions, amendments to the trial protocol may be suggested, or the application may be declined.

Medicines to be tested must be imported within 6 months from the date of the trial being approved, or an application must be made for an extension of the time limit.

Medicines used under these provisions must be labelled "To be Used by Qualified Investigators Only". It is the responsibility of the importer or manufacturer to ensure that every person to whom the medicine is supplied is qualified to carry out an investigation and that the medicine will be used only for the

investigation. The importer or manufacturer must keep complete and accurate records of all quantities of the medicine so supplied and of the results of the investigation, and must make copies of those records available to the Director-General when required to do so. Contravention of these conditions renders the offender liable to a fine not exceeding $1,000 and, if the offence is a continuing one, to a further fine not exceeding $100 for every day or part of a day during which the offence has continued.

In the years 1972 - 1978, about 25 applications for approval of investigations have been received each year. In each of the above mentioned years only one application was declined, but several were modified.

3.2 New Medicine Applications

3.2.1 Historical

From December 1962 all new medicines had to be notified to the Director-General and could not be marketed for at least 90 days without his prior consent. The information supplied in the notification was evaluated by the Department of Health and any deficiencies or discrepancies followed up. If any major problems or potential hazards were suspected, the medicine notification could be referred to the Minister of Health and distribution could then not take place until his consent was granted.

Since April 1970, the consent of the Minister to the distribution of a new medicine, and publication of this consent in the

New Zealand Gazette, has been required before any advertising or distribution may take place. Prior to the Minister granting his consent, a comprehensive submission has to be evaluated, and, as far as is practicable, the likely therapeutic value of the medicine weighed against the risk, if any, of the medicine injuring the health of any person. No consent to market any medicine may be deemed to warrant its safety and efficacy, and references to such a consent in promotional material are not permitted.

Although consent to market under the Food and Drug Act may be given, any other restriction invoked by other legislation must be complied with.

3.2.2 Information Requested

The following information lodged by the New Zealand manufacturer, or a manufacturer's agent resident in New Zealand, is required with every application for consent to distribute a new medicine:

(a) The address of that person and, if he is not the manufacturer, the true name and address of the manufacturer. If the medicine is manufactured by more than one manufacturer in New Zealand or overseas, the name and address of each manufacturer must be supplied. "Manufacturer" relates to the manufacturer of the dose form and usually the manufacturer(s) of the active ingredient(s) as well.

(b) The trade name under which the medicine will be distributed.

(c) A full statement of the ingredients, both active and inactive named by the descriptive or non-proprietary names, including details of the quantities in which they are contained in the medicine. For the active ingredient the structural formula, chemical name, official approved name and proprietary names must be supplied.

(d) A description of the form or forms of the medicine; a separate application is requested for each form of medicine, eg, tablets, elixir, injections or suppositories. A quantitative description for each ingredient must be supplied.

(e) The proposed or recommended dosage and frequency of dose, and the manner in which the medicine will be recommended to be administered, applied, or otherwise used.

(f) The purposes for which the medicine will be recommended to be used, and the claims to be made in respect of its usefulness.

(g) Reports of any tests made to establish the safety of the medicine for the purposes for which and in the manner in which it is intended to be used.

(h) Reports of any tests made to control the strength, quality, purity, or safety of the medicine and of the methods of testing.

(i) Any reports tending to demonstrate the efficacy of the medicine.

(j) A translation into the English language, authenticated in such manner as the Director-General may require, of any report referred to in paragraphs (g), (h) or (i) which is not in that language.

(k) Any evidence to show that the distribution of the medicine in the form and for the purposes that it is proposed to be distributed in New Zealand has been approved or consented to by the appropriate authorities in a country or countries other than New Zealand. The status in the United Kingdom, United States of Americ Canada and Australia (copies of approvals are requested) and also on the terms of approval, if any. For example whether the medicine is available for general distribution, restricted to clinical trials, restricted to certain indications, available only on medical practitioners' prescriptions, or only from pharmacies.

(l) The intended method of distribution of the medicine in New Zealand. This includes any restriction on distribution intended by the applicant. For example - on prescription only, to pharmacies, for general sale, to medical practitioners generally, to specialist medical practitioners, or to hospitals.

(m) A specimen of every label and other descriptive matter proposed to be used on or to be included in or to accompany packages containing the medicine.

(n) If the medicine is to be manufactured, prepared, or packed in New Zealand, the name and address of the place or places where the manufacture, preparation or packing is intended to be carried out.

Very detailed information is normally required for the clinical, toxicological, pharmacological and quality control aspects mentioned in the brief summary above. These aspects are expanded below:-

3.2.3 <u>In Vitro and Animal Studies</u>

3.2.3.1 <u>Pharmacology</u>

Full descriptions are required of studies in animals, isolated organs and/or cellular/subcellular systems. The primary pharmaco-dynamic activity forming the basis of the intended clinical use should be described in quantitative terms eg, LD50, and its mode of action explained. Pharmacokinetic data on absorption, distribution, bio-transformation and excretion should include information on first-pass effect, active metabolites and plasma half-life.

3.2.3.2 <u>Toxicology</u>

All information available to the manufacturer which supports the claim that the substance is safe for

administration to human subjects is expected. Full details must be supplied of the investigations carried out on laboratory animals, including acute and chronic toxicity tests. Acute toxicity tests, preferably on three mammalian species, are expected to be done mainly on the active principle, but should also be done on the final presentation where applicable. Chronic toxicity studies on at least two mammalian species are desirable, with the duration of the study related to the proposed length of treatment in humans. Data must include studies intended to establish carcinogenic, embryotoxic or teratogenic properties, and at least two mammalian species must have been included in the studies.

Information supplied should be detailed enough to enable the work to be repeated by an independent investigator and allow proper scientific assessment. The names, affiliations, and qualifications of persons undertaking the studies are required.

Conditions for this work, such as those laid down by the official administrations in the United Kingdom, United States of America, Canada, or Australia or by the World Health Organization, are accepted as appropriate guides.

3.2.4 Studies in Man

3.2.4.1 Pharmacology

Full data are required to confirm that the primary pharmacodynamic activity evident in the in-vitro and animal studies is also reproduced in humans, and should include information on dose-response curves, duration of action and tolerance. The activity should be compared with that of a well-known therapeutic substance of the same pharmacological category whenever possible. Pharmacokinetic data on absorption, distribution, bio-transformation and excretion on plasma half-life, protein binding and therapeutic/toxic plasma concentrations. An animal species with comparable pharmacokinetics as in humans should be specified whenever possible.

3.2.4.2 Clinical Studies

Efficacy is based on differences in responses between treated and control groups. Controls may be treated with another recognised drug or placebo. Studies should be done wherever possible by the double-blind method, and in certain disease states also by the crossover technique. Results should be analysed statistically. Data should include drug dosages, duration of studies, drug interactions and adverse reactions. This body of information should also indicate the safety of the medicine under varying conditions of use so that an assessment of the potential benefits and risks is possible.

3.2.5 Adverse Drug Reactions

Information on all known adverse drug reactions, side-effects, contra-indications and other hazards must be supplied. If there are any precautions to be taken or any specific antidote, these should be stated. If at any time any untoward effects (whether appearing in New Zealand or abroad) become known to the applicant, these must be notified immediately to the Director-General. Adverse drug reactions need not legally be notified if reports describing them have been published by reputable medical or pharmaceutical journals normally circulating in New Zealand but the department prefers to receive this advice.

3.2.6 Bioavailability

The bioavailability of an active ingredient from a medicine may be defined as the rate and extent to which the ingredient is absorbed from the medicine product into the body or to the site of action. Such tests are particularly required for generic medicines (copies of medicines previously protected by patents).

Particular emphasis is given to bioavailability studies for medicaments which exhibit the following characteristics:-

(a) Relatively low solubility and tendency to polymorphism.

(b) Narrow range of therapeutic index (critical concentration drugs), eg, digoxin, levodopa.

(c) Microdose formulations, ie, less than 5 mg.

(d) Substances with suspect availability including medicines known to have a tendency to combine with excipients.

(e) Substances where absorption is undesirable.

(f) Substances whose too-rapid release is undesirable.

3.2.7 Quality Control

Full descriptions of the manufacturing methods of the final product and the actual synthesis or extraction of the active ingredient are required. An outline of the analytical control methods used during stages of manufacture must be supplied including details of sampling.

Reports of any tests carried out during manufacture to ensure quality, strength, and purity of the drug must be submitted. These are expected to include methods of testing and actual specifications for all ingredients including inert excipients and for the final product. If B.P., B.P.C., U.S.P., N.F., European Pharmacopoeia, International Pharmacopoeia or Therapeutic Goods Standards Committee of Australia methods and specifications are used a reference to these standards suffice. If alternative methods and specifications are indicated they must be described in such a way that they may be repeated independently. Details are required for the following factors and must be supplied where applicable: identity, stability, purity of inert ingredients, dissolution characteristics, particle size, pyrogenicity, sterility, and glass or plastic container specifications. Any other tests made for special factors (eg, evidence for prolonged action in appropriate preparations) must also be specified.

Authenticated samples of the pure active ingredient, and of the final product may be required - enquiry should be made with the

Department in this respect. Samples are required for testing where appropriate, for the purpose of identification of unknown tablets or capsules in the case of accidental or deliberate poisoning, and as an aid to toxicologists.

3.2.8 Processing New Medicine Applications

Applications received by the Department include a brief summary, known as Section A, which is supplied to all members of the Medicines Assessment Advisory Committee whether the medicine is to be referred for its consideration or not. Should any member of the committee request that the medicine be considered by the full committee, it is referred accordingly. Vaccines are usually referred to the Epidemiology Advisory Committee.

Often an application to distribute a medicine which has already been accepted for sale in the United Kingdom, United States of America, Canada or Australia, or is included in the B.P., B.P.C., U.S.P., or N.F., is evaluated by the Medicine Section. Medicines which have not received such approval or which are not included in a recognised pharmacopoeia, any radically new medicines and any medicines on which the Department considers further advice is warranted, are referred to the Medicines Assessment Advisory Committee after initial evaluation within the Department (see paragraph 2.4.1). Whenever a medicine is forwarded to the Medicines Assessment Advisory Committee for consideration extra copies of various data are requested for each member.

The committee may recommend that the medicine application be accepted, accepted subject to satisfactory information being provided to the Medicine Section on any outstanding points, declined or the making

of a recommendation may be deferred until some more information is supplied as requested. Recommendations of the committee are taken into consideration by the Minister of Health in making his final decision.

Should a medicine be deferred, it may be referred back to the committee's next meeting, or at any subsequent time, if information is provided which clarifies the matters which caused the deferral. If the medicine is declined, a new application may be lodged but will not be reconsidered sooner than the next but two meetings of the committee.

Should the new medicine application relate to a vaccine, it is evaluated initially by the Medicine Section and the National Health Institute and then referred for consideration to the Epidemiology Advisory Committee for its opinion. This committee advises the Department of Health on topical questions related to the control of communicable diseases, including the safety and efficacy and appropriate use of vaccines.

In no case is the proposed price of the medicine taken into consideration when evaluation for the consent of the Minister is undertaken. This factor, however, is of considerable importance when an application for inclusion in the Drug Tariff is considered.

If the application is processed within the Department, evaluation is usually completed within six months, providing any additional information requested is submitted promptly. Should the application

be referred to the Medicines Assessment Advisory Committee, consideration depends on the date of committee meetings.

Prolonged delay is due to failure of the manufacturer or distributor to supply the data requested by either the Department or the Medicines Assessment Advisory Committee.

The following figures summarise the number of applications for new and changed medicines received during the years 1972, through to 1978:

	New Medicines				Changed Medicines	
Year Ending	Applic-ations Received	Applic-ations Referred to MAAC *	Applic-ations Accepted	Applic-ations Declined	Notific-ations Received	Notific-ations Accepted
31 March 1972	96	27	43	7	135	95
31 March 1973	195	52	75	7	163	119
31 March 1974	161	46	93	23	192	118
31 March 1975	109	39	28	10	226	133
31 March 1976	138	40	97	5	203	203
31 March 1977	111	43	97	6	232	229
31 March 1978	173	39	94	9	355	310

* Medicines Assessment Advisory Committee

3.3 Exemption for Medicines Required by a Medical Practitioner

A general exemption from the provisions for new and changed medicines in the Food and Drug Act, permits the supply of any medicine to a registered medical practitioner, if required by him for the treatment of a particular patient under his care. The purpose of this exemption is to permit a medicine to be used for a patient even though consent to market has not been given, where the practitioner considers this essential for his patient's welfare.

3.4 Changed Medicine Notifications

Any change affecting the following matters requires a changed medicine notification to be lodged with the Department of Health:-

(a) The purpose for which the medicine is represented to be used, or the recommended dosage, or the recommended manner of administration.

(b) The labelling of the medicine or of any package containing it or any descriptive matter accompanying or contained in any such medicine or package.

(c) The pharmaceutical form of the medicine.

(d) The strength, quality, or purity of the medicine.

(e) The methods of manufacture, or the facilities for testing the strength, quality, purity, or safety of the medicine.

(f) The location of manufacture.

(g) The formula under which the medicine is manufactured or intended to be manufactured.

Before any changed medicine is distributed in New Zealand, 90 days must elapse after a notification is lodged which describes the change or changes involved and supplies particulars of any effect that the change might have on the safe consumption or use of the medicine. The Director-General may modify this withholding period by either:-

(i) Giving consent to earlier distribution if this is requested and he is satisfied on all material points; or

(ii) Referring the notification of change to the Minister, in which case the medicine may not be distributed until the consent of the Minister has been notified in the New Zealand Gazette, as with a new medicine submission.

After a changed medicine notification is received, summary details are forwarded to the National Poisons Centre. The notification is evaluated by the Medicines Section and if the information is not considered completely satisfactory, the Director-General may, within 30 days of receipt of the notification of a change, request additional information on any matter relating to the

medicine. The further information requested must be supplied within 30 days of receipt of the request or, at least, an interim reply submitted. Failure to do this may result in the notification of change being referred to the Minister. This may also occur if the further information supplied is not considered sufficient for adequate evaluation.

The Medicines Section takes the opportunity to update its files whenever a changed medicine notification is received for any product sold prior to December 1962. For this reason, further information is frequently requested following receipt of changed medicine notifications, particularly for older preparations. In fact, a number have been withdrawn following discussions between the department and the distributor or manufacturer concerned where safety or efficacy have been in doubt.

3.5 Medicine Distribution Booklet

The Medicines Section has available a comprehensive booklet entitled "Medicine Distribution" which gives in some detail guidelines to assist in the completion of submissions to the department. The booklet is updated as required and supplied free of charge to interested parties.

3.6 Advertising

Applicants submitting new medicines applications and changed medicines notifications must provide copies of labels and other printed packaging including package inserts and all proposed promotional material. This material is examined for conformity with legislative

requirements and also to ensure that all claims made are substantiated in the data provided, that all adverse reactions and precautions listed in the application are included, and that the overall presentation of facts is fairly balanced.

All district offices of the Department, as well as the Medicines Section, scrutinise advertisements appearing in professional journals, newspapers, magazines and similar publications which are available in their respective areas; radio and television advertisements are also examined. Any misleading claims, or contravention of legal requirements observed, results in correspondence with the advertiser concerned. Usually the advertisement is corrected promptly but prosecution is always available although rarely necessary.

The Pharmaceutical Manufacturers' Association, whose members comprise the major manufacturers of pharmaceutical products, has produced a Code of Practice for the Pharmaceutical Industry. Compliance with this code is a condition of membership and amongst the provisions covered are advertising and promotional activities.

Further surveillance is also carried out by the Newspaper Proprietors' Association of New Zealand and the New Zealand Broadcasting Corporation. Both of these organisations have their own ethical standards for advertisements.

Despite these measures, faulty advertisements do appear from time to time. Further restrictions may prove necessary, especially as far as advertisements for medicines sold over the counter are concerned.

CHAPTER 4. CONTROL AND DISTRIBUTION OF MEDICINES AFTER MARKETING

4.1 Pharmaceutical Benefits Scheme

There is no legal restriction on the prescribing of medicines nor to their sale by retail providing the provisions of the Misuse of Drugs, Restricted Drugs and Food and Drug legislation are observed. The use of medicines available on prescription only is, however, often minimal until they have been included in the Drug Tariff. Until that time, the full retail cost must be borne by the patient.

The Drug Tariff lists under official (generic) titles all medicines which may be prescribed by medical practitioners and dentists as a charge to public funds, and sets out the conditions under which they may be ordered. It is a Ministerial Direction under the authority of the Social Security Act 1964; amendments are issued three times a year.

The process whereby medicines are admitted to the Tariff is quite separate from controls on marketing of new medicines. A period of usage in New Zealand is preferred before a medicine is considered by the Pharmacology and Therapeutics Advisory Committee for inclusion in the Tariff.

Factors taken into consideration when evaluating medicines for inclusion in the Tariff are therapeutic value, safety, side effects, the need for the preparation, and cost.

While a medicine may be considered suitable for inclusion in the Tariff, the information available may, in the Committee's

opinion, warrant certain restrictions or conditions being imposed. These restrictions include supply by hospital pharmacies only, or supply only when prescribed on the recommendation of a specialist.

Medicines not included in the Tariff may still be obtained at the cost of public funds, if the doctor applies for a special supply for a particular patient, giving brief clinical details and stating that, in his opinion, it would be unreasonable for the patient to be expected to meet the cost.

4.1.1 Price

Since the Department of Health is the ultimate purchaser of most prescription medicines and also determines whether the medicine will be included in the Drug Tariff, it is in a strong negotiating position when determining the price to be paid. Continuous checks are maintained on prices of drugs in other countries and on other medicines in the same therapeutic class.

Efficacy, both absolute and relative, safety, and price are all explicit considerations in this cost-benefit argument when negotiations between the pharmaceutical industry and Department take place.

Nearly all items in the Tariff are available as a full charge on public funds. Where, however, a manufacturer's price is higher than other items in a similar therapeutic category, the item may be available only as a part-charge in which case, the patient has to pay the difference direct to the pharmacist.

International comparisons have shown that the prices paid for medicines in New Zealand are reasonably low compared with the rest of the world.

4.1.2 Restrictions on Period of Supply

Much thought and trial have gone into seeking the optimal way to regulate the period of supply and, to a lesser extent, the quantity of medicines ordered on a single prescription. At the present time the restrictions are 5 days' supply with one repeat, and extended supply for up to 3 months. A prescription for an extended supply is required to be endorsed in a specified manner by the prescriber. Dental practitioners may not order more than a 5 days' supply plus a repeat for 2 days' supply of medicines used in dentistry. Oral contraceptives may be prescribed for a maximum period of 6 months.

These restrictions are a source of irritation to prescribers but they have kept prescribing costs down, as experiments carried out in New Zealand have demonstrated.

4.1.3 Restriction to Hospital Pharmacy Supply

The supply of certain medicines is restricted to public hospital pharmacies. Medicines restricted in this way are only modestly prescribed, as it is less convenient for the patient to take the prescription to a public hospital than to the nearest pharmacist, and doctors are reluctant to inconvenience their patients unless there is a good reason for doing so.

With new medicines, this restriction is sometimes adopted to ensure that they are used only in moderation for a period to

enable the safety and efficacy to be further evaluated. With few exceptions, the question of safety is the principal reason why medicines are placed in this category.

4.1.4 Restriction to Specialist

This is a tighter category than restriction to hospital pharmacies. Medicines with this restriction may be prescribed only by or on the recommendation of an appropriate specialist. A general practitioner may continue to order such a medicine if he endorses the prescription with the words "Recommended by (name of a recognised specialist plus the year of authorisation)". The authorisation is valid for a period of two years.

In the terms of the Drug Tariff, specialists are accepted for this purpose only in regard to medicines related to their own particular specialties.

There are now two forms of this restriction - "Hospital Pharmacy - Specialist" and "Retail Pharmacy - Specialist", depending on where the prescription may be dispensed. While these restrictions are often resented by general practitioners, they do have beneficial effects. New and expensive medicines tend to be used sparingly and presumably for indications more specific than if use were unrestricted. Medicines that are dangerous, (eg, antimitotic agents), or for which widespread use would impair efficacy (eg, rifampicin) may be used with greater safety or benefit. The safety function is emphasised by the fact that it is not only new medicines that are restricted in this fashion; chloramphenicol, for example, was placed in

this category. Finally, the specialist is placed in the role of an educator to the general practitioner in the use of new medicines when patterns of use are being established.

4.1.5 Restriction Under Certain Circumstances

Contraceptives are available under the Drug Tariff when the medical practitioner is satisfied that the prevention of pregnancy is desirable on medical grounds or that it is inappropriate for the patient to pay. In these cases the prescription is required to be endorsed with the words "approved condition". Tablets used as oral contraceptives are also available free for the treatment of medical conditions, if the prescription is endorsed "approved condition".

4.1.6 Supply Without Prescription

Practitioners may obtain supplies of medicines expected to be required for emergency purposes or for personal administration to a patient on a practitioners supply order form from a retail pharmacy. The majority of medicines listed in the Drug Tariff may be obtained in this way.

Medicines required for the treatment of patients in private hospitals and similar institutions may be obtained from a retail pharmacy on a bulk supply order form.

Certain Drug Tariff items are available only on a wholesale supply order. Supplies are obtained from wholesalers or distributors and the supplier is reimbursed by the Department.

4.1.7 Prescriptions and Payment

All prescriptions dispensed from retail pharmacies as a charge under the Drug Tariff must, upon completion, be forwarded to the Department for pricing and payment.

Pricing offices for this purpose are maintained at Auckland, Hamilton, Wanganui and Christchurch. All prescriptions received are priced, checked for conformity with the legislation, and any trends which may require action by the Department are noted. Within the limits imposed by staffing and time, any survey of prescribed medicines which may be required can be performed, as the Department actually holds all prescriptions.

4.1.8 Conclusion

The Social Security Pharmaceutical Benefits Scheme acts as an additional and effective control on the use of medicines. Unless a prescription medicine is included on the Drug Tariff its use is minimal even though consent to market may have been granted, and with the various restrictions which may be imposed under the Drug Tariff further opportunity is available to evaluate the safety and efficacy of the medicine.

4.2 Further Controls Imposed by the Food and Drug, Misuse of Drugs and Restricted Drugs Legislation

4.2.1 Food and Drugs

Food and Drug legislation sets out the minimum standards required for premises intended for the manufacture, storage, distribution and sale of medicines. In addition, the labelling of medicines and the conditions which must be complied with before a new or

changed medicine may be distributed in New Zealand are defined in detail.

The Food and Drug Act permits homoeopathic and herbal remedies, in non-toxic strengths, to be distributed from any outlet but restricts all other medicaments not specifically exempted by the Therapeutic Drugs (Permitted Sales) Regulations from being sold from other than pharmacies.

4.2.2 Controlled Drugs

New Zealand is a signatory of all conventions on narcotics and psychotropic substances and rigidly enforces the controls which have been agreed upon internationally. The legislative measures presently in force are embodied in the Misuse of Drugs Act and Regulations.

4.2.2.1 Misuse of Drugs Act 1975

The Misuse of Drugs Act 1975 and the Misuse of Drugs Regulations 1977 came into operation on 1 June 1977. This legislation replaced the Narcotics Act 1965 and the Narcotics Regulations 1966, and includes those drugs that were designated "prohibited substances" in the Poisons Regulations 1964 as well as some "prescription poisons" subject to abuse.

The main purpose of the legislation is to give effect to the provisions of the Convention on Psychotropic Substances 1971, as well as the Single Convention on Narcotic Drugs 1961. New Zealand is a signatory to both these treaties.

The legislation updates the law controlling the use and misuse of drugs enacted over a decade ago.

The term "controlled drug" replaces the term "narcotic" and is applied to all preparations listed in the three Schedules to the Misuse of Drugs Act. These include drugs listed in the Single Convention on Narcotic Drugs 1961 and the Convention on Psychotropic Substances 1971. Included are the traditional narcotics as well as amphetamines, barbiturates, hallucinogens and a few tranquillisers. The Schedules contain drugs in descending order of potency and danger. The degree of control also varies downwards from the most restricted drugs which are Class A in the First Schedule, to the least restricted which are Class C drugs in Part VI of the Third Schedule.

The First Schedule comprises the Class A controlled drugs and includes the hallucinogens, cantharidin, heroin, the tetrahydrocannabinols, and thalidomide.

The Second Schedule or Class B controlled drugs include those next in order of potency and abuse potential. The Schedule is divided into three parts.

Part I contains those drugs with a high potential for abuse including cannabis resin and its extracts and tinctures, cocaine, morphine and opium.

Part II contains those "prohibited substances" which are supplied by hospital pharmacies, namely the amphetamines,

methaqualone, and methylphenidate.

Part III contains many of the traditional "narcotics". Examples are dextromoramide, dipipanone, fentanyl, methadone, pethidine and phenoperidine.

The Third Schedule or Class C controlled drugs is divided into six parts.

Part I contains the less potent forms of cannabis (fruit, plant and seed) and the coca leaf.

Part II contains codeine and its isomers, salts, etc, except in preparations found in Part VI.

Part III covers such substances as acetyldihydrocodeine, ethylmorphine, and pholcodine except in preparations contained in Part VI.

Parts IV and V include the barbiturates, glutethimide and meprobamate.

Part VI contains preparations with a limited concentration of certain controlled drugs in combination with other pharmacologically active substances.

4.2.2.1.1 Import and Export of Controlled Drugs

As regards import and export of controlled drugs, but with the exception of Class C Parts IV and V substances,

the new legislation has substantially the same effect as the now revoked Narcotics legislation.

The following table is intended as a useful reminder to persons concerned with the import and export of controlled drugs:

	CONTROLLED DRUGS WITHIN SPECIFIED CLASS									
	A	B			C					
		I	II	III	I	II	III	IV	V	VI
Import/export licence needed (Misuse of Drugs Act 1975, Section 6 (1) (a))	✓	*	✓	✓	✓	✓	✓			
Ministerial approval to import/export also required. (Misuse of Drugs Regulation 7 (2))	✓	**			✓					
Specific notification to Health Department required. (Misuse of Drugs Regulation 49 (1))								✓	✓	

* An import/export licence is needed for controlled drugs in this class except that no licence is available for opium prepared for smoking (Sec. 14 (2)).

** The additional requirement of Ministerial approval to import/export controlled drugs in this class is effectively restricted to cannabis substances, preparations, mixtures or articles as specified or described - see the proviso to Misuse of Drugs Regulation 7 (2).

Two further points should be remembered:

(i) Where controlled drugs are sent to and from Niue, Tokelau Islands or the Ross Dependency, letters of authority are issued in lieu of import/export licences;

(ii) Some overseas countries require import/export licences to be issued for various additional drugs and the Department will provide appropriate papers where requested.

Applications to import controlled drugs are made to the Director-General of Health on form H.502. This same form is readily amended for use in relation to exports, the only additional entry required being identification of the supporting overseas import certificate - see Misuse of Drugs Regulation 7 (3). No fee is required for the issue of licences or letters of authority for the import or export of controlled drugs.

4.2.3 Restricted Drugs Act 1960

This legislation requires that all manufacture, packaging and sale of any restricted drug be carried out by persons who are licensed or otherwise permitted by the Act or regulations. All these operations, including storage, must be completely segregated from foods and must be kept out of reach of the public. Further, the legislation classifies many medicines into three main schedules which impose varying degrees of control.

Those medicines included in the First Schedule may only be sold by retail from pharmacies by qualified pharmacists and records

of the date of sale, the name and amount of medicine sold, name and address of customer, purpose for which the medicine is sold, and name and address of witness to the sale must be kept.

Those medicines included in the Second Schedule may only be sold by retail from pharmacies, but the pharmacist may authorise his sales staff to sell the medicines under his supervision. Records of sale are only required for preparations intended for use in a scientific, educational or commercial laboratory, or for use in a process of manufacture or trade not involving resale of the medicine.

Those medicines included in the Third Schedule are known as Prescription Drugs. They are available from retail pharmacies and hospital dispensaries only pursuant to a prescription from a medical practitioner, dentist, or veterinary surgeon. The pharmacist must provide adequate security for their storage and keep detailed records of all prescriptions dispensed.

4.2.4 Surveillance

Eleven public health pharmacists are employed in the various district offices throughout New Zealand and are principally responsible for the inspection of controlled drug registers in all pharmacies, wholesalers, hospitals and manufacturers. These inspections are carried out to ensure that all aspects of the legislation applicable to the various organisations are complied with.

In addition, apart from the regular monitoring of prescriptions forwarded for pricing, the inspection of controlled drug

registers and restricted drug records by public health pharmacists frequently detect prolonged users, abusers, or persons dependent on controlled drugs and prescription drugs.

Further, over-prescribing or supply of medicines contrary to the legislative requirements is occasionally detected when prescriptions are priced, and by public health pharmacists during inspections. In such cases, the prescribing practitioner or the pharmacist, as may be appropriate, is asked for an explanation. If no good reason is given and the error is gross, the matter may be forwarded to the Disciplinary Committee of the appropriate professional body, or referred to the Court. Usually, the person concerned is warned and subsequent action watched more carefully.

4.2.5 Treatment of Dependents

There is provision in the legislation to prohibit the prescribing of a controlled drug, prescription drug or Schedule One medicine for an individual either entirely or as may be permitted by the Medical Officer of Health or Director-General of Health. Controlled drugs for the treatment of dependency may only be supplied from hospitals and clinics designated in the New Zealand Gazette by the Minister of Health, or from a medical practitioner authorised in writing by a clinic for a specific patient.

At the present time 33 hospitals and clinics have been so designated but, of these, only two, namely Auckland and Wellington, have significant calls on their services with lesser demand at Hamilton, Christchurch and Dunedin.

This restriction has reduced to a considerable extent the excessive use of controlled drugs, particularly methadone and dextromoramide, for the treatment of dependency.

4.3 Control During Manufacture

Inspection of pharmaceutical manufacturing premises was initiated by a team from the Division of Clinical Services in April 1972, with visits being made to commercial pharmaceutical manufacturers, and hospital intravenous solution units. These inspections are carried out approximately annually for general manufacture and 6-monthly for intravenous solution manufacturing premises.

The inspectors adopt the guidelines set out in the Department's "Code of Good Practice for Manufacture and Distribution of Medicines" which was republished and supplied to the pharmaceutical industry in January 1979. Aspects of a pharmaceutical company's operations included in the code are design of buildings, sanitation, calibre of personnel, production procedures and controls, and quality control. The code emphasises that the quality of any pharmaceutical product not only depends on the final analytical testing in the laboratory, but also upon the procedures, precautions and in-process checks carried out at all stages of manufacture. Considerable interest in this code has been expressed by the New Zealand pharmaceutical industry and copies are now being used as an additional reference guide by many manufacturers abroad.

While no legislation exists to enforce licensing of manufacturers, such a step is envisaged in future legislation. In the meantime,

the inspection team acts as educators and recommend ways by which existing standards may be improved before the licensing of medicine manufacturers' premises is introduced.

It is recommended that retention samples of all batches of medicines and active ingredients be retained by the industry for a period of 1 year after the expiry date of the particular medicine concerned. These samples should be available in case problems arise at a later date.

4.4 Quality Control

At the time of processing an application for consent to distribute a new or changed medicine, all quality control aspects are thoroughly examined and checked. Usually no consent is granted until all problems have been resolved.

In addition, an ongoing routine medicine testing programme is carried out on a confidential basis. The results of this are that -

(i) the psychological effect of an active testing programme on the manufacturers is significant;

(ii) the threat of legal or other action in respect of detected substandard batches motivates the manufacturer concerned to improve existing premises and controls;

(iii) the depth of a routine inspection of a pharmaceutical manufacturer is considerably enhanced if medicine testing results are available at the time.

Sampling and testing of medicines is often by therapeutic group. Groups tested have included:-

Simple calcium gluconate products, steroids, antidepressants, sulphonamides, steroidal hormones, penicillins, anticoagulants, oral hypoglycaemic agents, oral diuretics and antihypertensive agents, tranquillisers, quinine preparations, codeine, paracetamol preparations, anticonvulsants, tetracyclines, bronchodilators, oral contraceptives, analgesics and anti-inflammatory agents, erythromycins, and some large volume parenteral solutions.

The testing programme has been extended recently to include tests for sterility and antibiotic microbiological assays.

Some 200-300 samples are tested annually with approximately 15% failure, which is due to a wide variety of reasons. All failures are reported to the local distributor and explanations requested, but in the case of the more serious failures a recall of the batch is requested. Recalls have averaged about 20 per year recently, mainly to retail level but some only to wholesale. The main aim of the testing programme is to check that medicines available on the New Zealand market comply with the specifications claimed whether they be the manufacturer's own standards or pharmacopoeial.

4.5 Recall of Manufacturing Batches

The Code of Good Practice for Manufacture and Distribution of Medicines formalises the procedures to be adopted in the event

of a recall as follows:

(1) Information relative to specific manufacturing batches which have been found to be faulty, whether by the manufacturer, from the routine sampling programme or from any other source, must be referred to the Department of Health for assessment.

(2) The Department, after consideration of all the facts available and discussion with the manufacturer or distributor concerned, will decide on the extent of recall required.

(3) Recalls may be to wholesale level only, to retail level, or, in life-threatening situations, to patient level.

(4) In life-threatening cases, advice of a recall is given by telegram or by telephone, followed by a letter of confirmation. Where the situation does not threaten life, advice is given by letter only. All such letters are dispatched in uniform envelopes marked, in bold red print, with the following words:

"MEDICINE RECALL
ACTION IMMEDIATELY"

(5) All recipients of such notices must reply promptly even if no stocks of the affected medicines are held.

Any medicines belonging to the batch under recall must be returned to the manufacturer or distributor forthwith.

(6) When the recall is completed, the department assesses the effectiveness of the recall and, if necessary, requests further action. In addition, the department attempts to find the cause of the error and where a manufacturing or quality control procedure was at fault, the methods used by the company are studied and recommendations prepared or other appropriate action taken in an attempt to prevent similar occurrences.

4.6 Safety

Prior to granting consent for marketing, all available evidence is examined to substantiate the therapeutic benefit/risk ratio and to ensure that no serious hazard exists. As clinical trials are carried out on a limited number and selective group of patients, and as the period of treatment often does not extend over a prolonged period, there is a low probability that rare or late-appearing reactions will have been suspected and taken into account at the time of approval.

In order to discover, at the earliest possible opportunity, any new adverse reaction, a number of medicine monitoring programmes have been introduced:

(1) The Committee on Adverse Drug Reactions is discussed in section 2.4.5. New Zealand is a participant in the

World Health Organization International Drug Monitoring Project and thus has access to information available in Uppsala. In addition, close ties are maintained with the Adverse Drug Reactions Committee of the Committee on Safety of Medicines in London, and with the Australian Adverse Drug Reaction Advisory Committee; reports are regularly exchanged with other countries participating in the WHO scheme.

(2) All manufacturers are legally bound to advise the Department of Health of any untoward effect occurring anywhere in the world which is not published in reputable medical or pharmaceutical journals normally circulating in New Zealand. A few more responsible companies diligently advise the Department in accordance with their obligations.

(3) The Auckland and Hutt Hospitals have participated in the Boston Collaborative Drug Surveillance Programme.

(4) Intensified Adverse Drug Reaction Reporting Scheme

This scheme was introduced in 1977 with the object of increasing the post marketing surveillance on a limited list of medicines only recently available internationally so that practitioners might detect unexpected adverse reactions and events. A list of medicines affected by the scheme at any time is widely available - the collaboration of practitioners and pharmacists with the Registry of Adverse Reactions is relied upon.

The following actions may be taken to publicise adverse reactions:

(a) The annual report of the Committee on Adverse Drug Reactions is published in the New Zealand Medical Journal, the New Zealand Dental Journal and the New Zealand Pharmaceutical Journal.

The report summarises the deaths apparently due to medicines and congenital abnormalities associated with medicines, interactions between medicines, and includes a summary of the principal medicines used and the most important reactions.

(b) Bulletins relative to adverse reactions prepared by the Committee on Adverse Drug Reactions are circulated to all dentists, medical practitioners and pharmacists as the need arises. The Department frequently draws attention to adverse drug reactions in Clinical Services Letters.

(c) The Department may request manufacturers and distributors to amend their promotional material and package inserts in accordance with new evidence available. In addition, the availability of a medicine on the Drug Tariff may be varied, eg, to restrict supply to prescription or recommendation to a specialist. It may be removed from the Drug Tariff altogether if the particular case warrants this step.

(d) In serious cases, the medicine may be withdrawn from the market by the company. In an extreme case, this might be accompanied by a general medicine recall, to patient level if necessary.

4.7 Withdrawal From Sale

Authority is available to enable the Minister of Health to withdraw his consent to the distribution of a medicine once he has granted it. If the situation is sufficiently urgent or serious, as it was at the time of the thalidomide disaster for instance, the Minister may prohibit the importation, manufacture, sale, possession or use of the medicine in question. This restriction remains in force for up to one year.

The Director-General of Health, for the protection of the public, may publish a privileged statement in respect of a medicine, or in respect of any matter contained or implied in an advertisement relating to a medicine.

Where the situation is less urgent or serious and following discussion with the Department, the company concerned will, in most cases, voluntarily agree to withdraw the product from the market. Practolol was withdrawn in this manner in early 1975.

Alternatively, the medicine may be deleted from the Drug Tariff, which results in greatly reduced usage. This step was taken during 1974 in the case of phenacetin for example.

4.8 Discontinuation of Medicines

There is no legal requirement for any distributor to notify the withdrawal of a medicine under the Food and Drug legislation or the Drug Tariff. It does, however, assist the Department, particularly when a preparation is included in the Drug Tariff, for this information to be supplied.

CHAPTER 5. THE NEW ZEALAND MEDICINE MARKET

New Zealand has a population of just over 3,000,000. The country is divided into 18 Health Districts, but a reorganisation of Health Services is currently under study.

The number of medicines on the New Zealand market is estimated to total approximately 8,000, with the number of different active substances amounting to about 2,000.

All medicines supplied in hospitals to New Zealand citizens, and others who may qualify, are free of charge. Most medicines supplied from retail pharmacies are free of charge, or carry only a small part charge, but those not included in the Drug Tariff are generally paid for in full by the patient.

5.1 Distribution

Distribution is, in the main, left to free enterprise. Many manufacturers and major distributors have their own wholesale section, medical detailers and salesmen. Most also supply wholesale organisations for further distribution to pharmacies and other outlets.

Retail pharmacies in New Zealand are, with one or two exceptions, independently owned by pharmacists. The Pharmaceutical Society and present legislation strongly support the principle of one pharmacist/one pharmacy.

Public hospitals purchase a proportion of their medicines by tender through a bulk purchasing scheme, centred in Dunedin,

which results in significant savings. Individual boards order from the firms concerned.

5.2 The Pharmaceutical Industry

A considerable degree of organisation, while not compulsory, exists within the industry:

(1) The Pharmaceutical Manufacturers' Association, (P.M.A.), represents the majority of the large international manufacturers and companies, particularly those involved in original research. More recently the P.M.A. has introduced associate membership to other companies engaged in the manufacture of pharmaceuticals and those distributors representing overseas manufacturers of generic products. The organisation should eventually be able to represent all components of the manufacturing industry. This will greatly facilitate negotiations between the Department and the pharmaceutical manufacturing industry.

(2) The New Zealand Proprietary Medicines Federation represents distributors of mainly over-the-counter lines.

(3) The Wholesale Druggists' Federation represents the majority of the more traditional companies engaged in the wholesale distribution of pharmaceuticals in New Zealand, while the New Zealand Federation of

Co-operative Pharmaceutical Wholesalers represents the co-operative wholesalers.

(4) The Chemists' Guild of New Zealand (Inc.) represents the retail pharmacists in respect to business and financial considerations. Their activities extend to promotional activities, group purchase schemes, and negotiations with the Department in respect of Drug Tariff payments. The professional aspects of pharmacy are controlled by the Pharmaceutical Society of New Zealand.

5.3 Sales Statistics

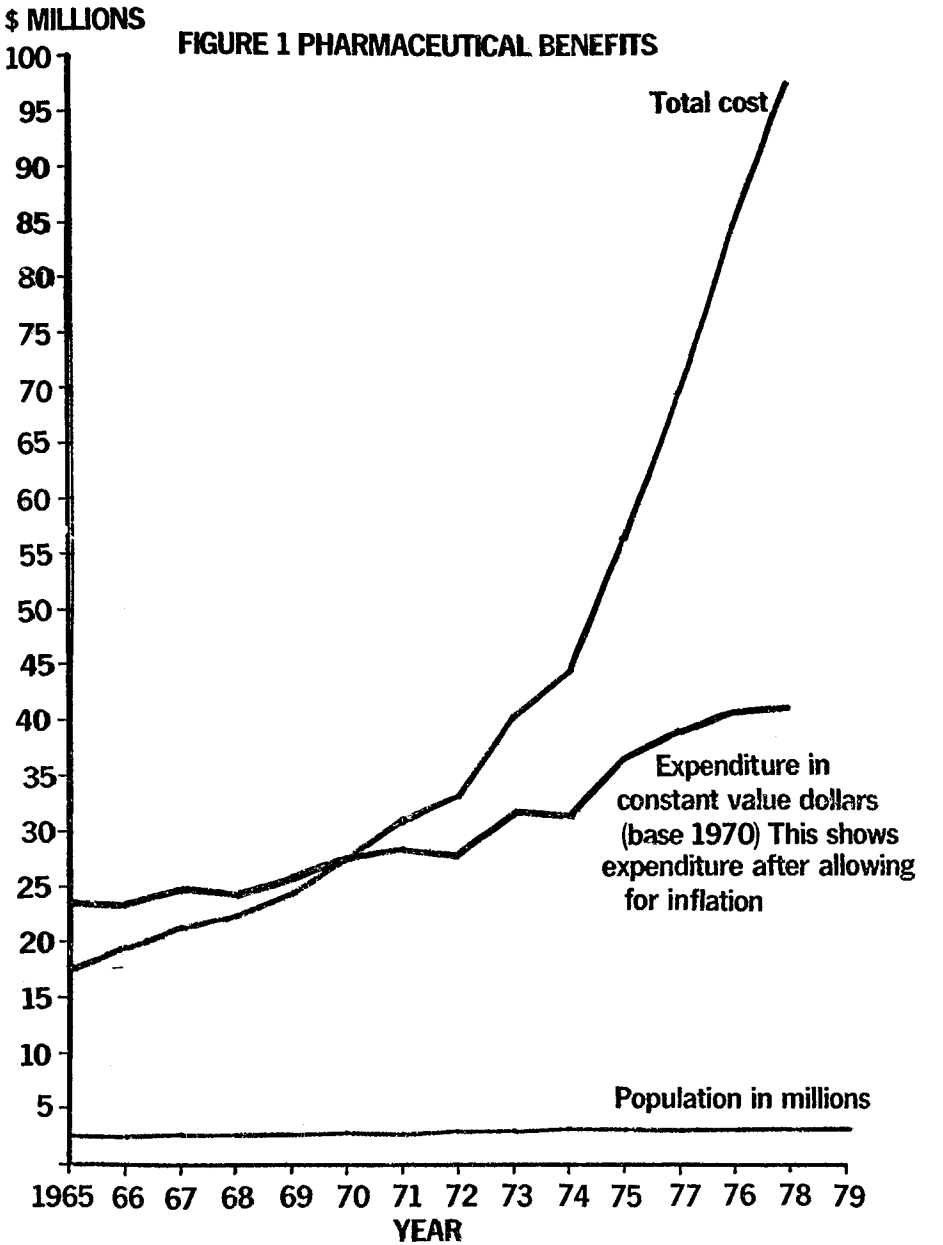
Figure I shows the growth in prescribing costs and population. Figure II shows the increase in the number of prescriptions priced and the cost per head per annum. Between 1946 and 1979 the number of prescriptions increased from 5.4 million to 24.2 million and the cost from $2.26 million to $113.45 million. In the same period the average cost per individual prescription rose from $0.42 to $4.68. Cost of prescriptions per head of population per annum rose from $1.42 to $36.13.

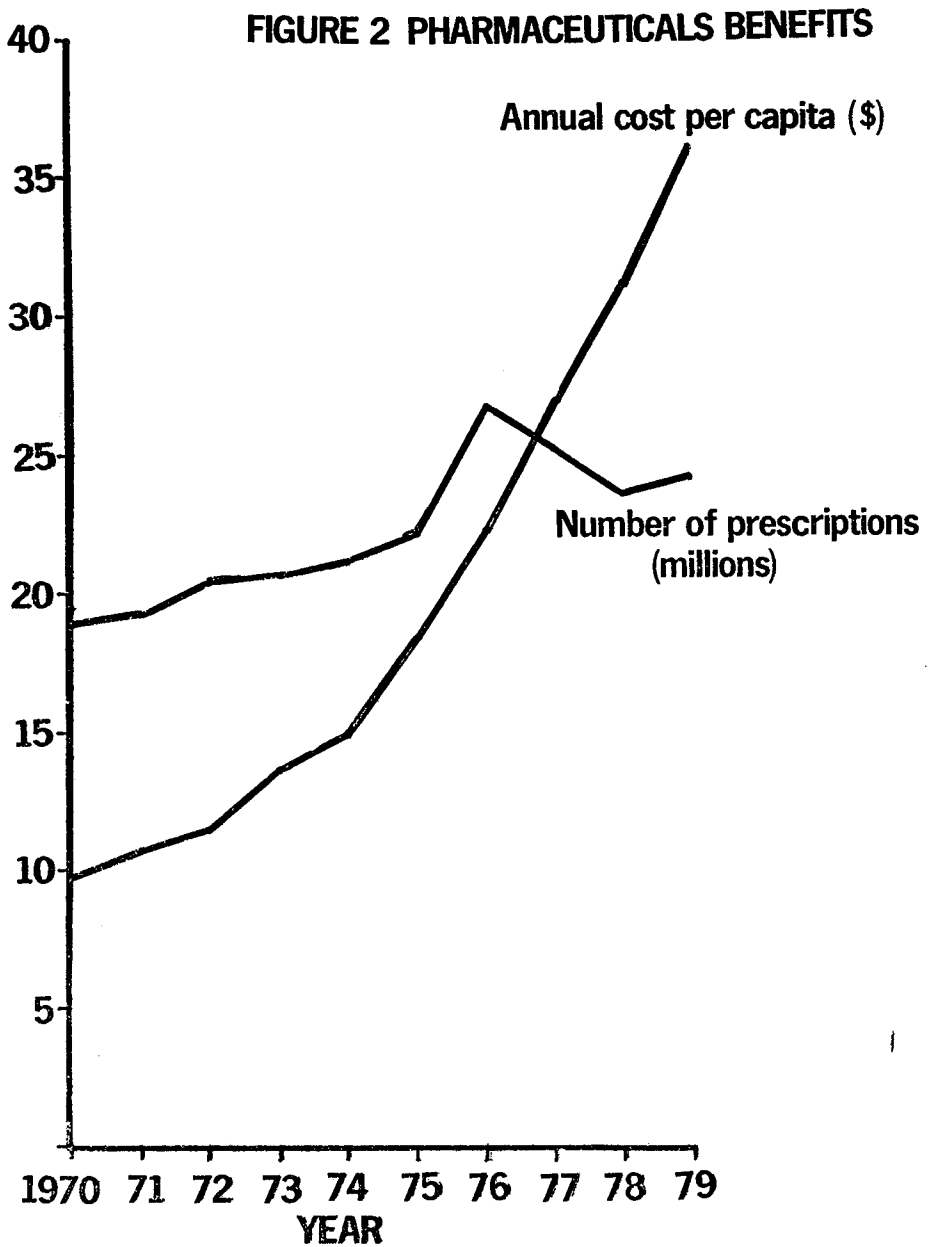
An analysis of the cost and number of prescriptions for the various therapeutic groups of medicines is given in table I.

Table II lists the top thirty medicines in terms of expenditure.

The above information relates only to medicines in the Drug Tariff supplied through retail pharmacies and excludes those supplied through hospitals or paid for by patients.

While no detailed statistics are available for over the counter sales of medicines, the Chemists' Guild estimates that these sales represent approximately 12 per cent of the pharmacist's business. The value of such sales could be as high as $25 million at the present time and includes vitamin preparations, cough and cold remedies, various analgesics and many different types of topical skin applications.





SUMMARY OF PRESCRIPTION SURVEY FOR THE YEAR ENDED 31 MARCH 1978

Preparations Acting on the Alimentary System	Prescriptions	Cost $
Antacids	397,000	1,388,200
Antispasmodics	219,900	603,200
Gastro-intestinal sedatives	221,600	750,900
Other miscellaneous digestive remedies and preparations	37,400	184,300
Tonics	3,700	10,600
Laxatives, purgatives, evacuant enemas, suppositories	373,300	838,800
Sulphonamides acting locally on the rectum	200	2,100
Corticosteroids acting locally on the rectum	130,700	697,700
Other preparations acting locally on the rectum	10,100	34,800
	1,392,800	4,492,900

Preparations Acting on the Cardiovascular System		
Preparations acting locally on the heart	1,295,600	10,033,000
Vasodilators	127,700	1,079,900
Vasoconstrictors	109,900	625,500
Anti-hypertensives	837,200	4,922,900
Anticoagulants and vitamin K	38,600	104,000
Other preparations including sclerosing agents	32,200	281,600
	2,441,200	17,046,700

Preparations Acting on the Nervous System		
Addictive analgesics	39,000	106,400
Antipyretic analgesics	929,800	1,683,100
Specific analgesics	1,403,200	5,661,100

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Preparations Acting on the Nervous System (continued)	Prescriptions	Cost $
Barbiturates	233,600	298,400
Non-barbiturate hypnotics	595,000	1,675,100
Tranquillisers	1,446,300	5,306,100
Anti-emetic preparations	327,300	1,064,900
Anticonvulsants	192,500	836,800
Preparations used in treatment of parkinsonism	82,400	315,700
Muscle relaxants and antagonists	55,500	189,400
Stimulants	300	2,400
Antidepressants	645,100	2,617,300
Local anaesthetics, analgesics and counter irritants	68,600	110,700
Other, including anti-cholinesterase preparations	23,600	180,000
	6,042,200	20,047,300

Preparations Acting on the Genito-Urinary System		
Sex hormones	321,000	976,800
Diuretics	1,679,600	4,448,800
Antibiotics acting locally on vagina or urethra	3,200	12,400
Other anti-infective preparations for vaginal or urethral use	104,900	420,600
Other preparations acting locally on vagina or urethra	4,300	11,300
Preparations acting on the uterus	3,500	4,400
Other preparations acting on genito-urinary system	101,500	356,900
	2,218,000	6,231,100

Preparations Acting Systematically on Infections		
Penicillins	1,787,200	7,948,300
Tetracyclines	542,300	2,564,900
Streptomycins	3,000	7,300

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Preparations Acting Systematically on Infections (continued)	Prescriptions	Cost $
Anti-fungal antibiotics	120,700	699,000
Other antibiotics	387,400	2,022,100
Sulphonamides	697,300	2,610,800
Nitrofurans	19,000	39,600
Anti T.B. preparations	7,200	322,900
Antithelmintics	33,300	99,400
Anti-infectives including antileprotics and antiprotazoals	147,900	676,700
	3,745,300	16,991,000

Preparations Affecting Metabolism and Nutrition		
Insulin	77,800	1,076,100
Oral hypoglycaemics	144,300	700,100
Iron and other erythropoietic preparations	356,200	426,100
Vit. B12 (Unadmixed) parenteral; oral, intrinsic factor	3,500	5,500
Vitamins A and D preparations	19,000	45,300
Vitamin B group preparations	17,300	26,800
Multi-vitamin preparations with or without minerals	174,700	217,500
Other vitamins	33,500	48,300
Corticosteroids for systemic use	171,000	295,500
Anabolic drugs	1,700	10,400
Thyroid and anti-thyroid preparations	209,400	268,600
Antimytotic preparations	12,100	230,000
Calcium preparations	65,000	414,500
Electrolyte and water replacement therapy	220,400	499,100
Other preparations affecting metabolism and nutrition (including A.C.T.H.)	191,300	981,500
	1,696,200	5,245,300

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Preparations Affecting the Respiratory System	Prescriptions	Cost $
Bronchodilators and relaxants	1,016,600	4,293,200
Expectorants and cough suppressants	781,900	1,848,100
Other preparations acting on the upper respiratory tract	745,600	3,148,400
Other preparations including respiratory stimulants	108,600	2,034,000
	2,653,000	11,324,400
Preparations Affecting Allergic Reactions		
Anti-histamines	619,100	1,185,400
Other	12,500	107,100
	631,600	1,292,500
Preparations Acting on the Ear (Not elsewhere specified)		
Antibiotic preparations acting on the ear	24,300	53,200
Corticosteroid preparations acting on the ear	120,300	348,500
Other preparations acting on the ear	15,100	23,400
	159,700	425,100
Preparations Acting on the Eye (Not elsewhere specified)		
Antibiotics acting on the eye	219,600	441,200
Sulphonamides acting on the eye	39,800	75,500
Corticosteroids acting on the eye	58,300	149,600
Other preparations acting on the eye	150,000	456,800
	467,700	1,123,000

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Topical Preparations Acting on the Skin	Prescriptions	Cost $
Sedatives, antipruritics, keratolytics and barriers	195,500	542,700
Antiseptics including surgical antiseptics	144,200	246,500
Antibiotics acting on the skin	320,800	684,600
Sulphonamides acting on the skin	400	700
Corticosteroids acting on the skin	1,055,900	4,388,300
Fungicides and anti-parasitics	224,300	668,800
Other preparations acting on the skin	246,600	784,100
	2,187,800	7,315,700
Other Drugs and Preparations		
Reagents	80,800	280,300
Other (including ingredients used alone or in combination)	14,100	26,300
	94,800	306,600
GRAND TOTAL OF THERAPEUTIC CLASSES:	23,730,400	91,841,600

Note: Data shown for number of prescriptions and cost have been rounded to the nearest 100. Due to rounding, the totals shown may not agree with a total taken of the rounded numbers.

TOP 30 MEDICINES BY COST FOR THE YEAR ENDED 31 MARCH 1978

	GENERIC NAME	TOTAL COST $	NO. OF PRESCRIPTIONS
1	Amoxycillin trihydrate	4,647,200	868,600
2	Diazepam	2,475,900	650,400
3	Propranolol hydrochloride	2,384,000	204,200
4	Co-trimoxazole	2,358,100	621,000
5	Oxprenolol hydrochloride	2,274,800	161,300
6	Sodium cromoglycate capsules	2,034,000	108,600
7	Methyldopa	1,924,600	267,200
8	Beclomethasone aerosol oral inhaler	1,836,100	183,300
9	Alprenolol hydrochloride	1,783,300	105,200
10	Indomethacin	1,614,500	290,700
11	Nitrazepam capsules and tablets	1,528,000	535,500
12	Salbutamol aerosol inhaler	1,466,000	262,000
13	Erythromycin + salts and esters	1,442,700	276,700
14	Cyclopenthiazide + potassium chloride tablets	1,303,100	696,100
15	Doxycycline hydrochloride	1,302,800	157,600
16	Ampicillin + its salts	1,208,900	308,400
17	Ibuprofen tablets	1,096,100	240,300
18	Amiloride + hydrochlorothiazide	1,088,100	325,800
19	Cloxacillin sodium	999,500	134,000
20	Pindolol	990,300	88,700
21	Frusemide	862,300	294,400
22	Timolol maleate tablets	767,500	55,000
23	Allopurinol tablets	742,400	114,600
24	Betamethasone valerate skin preparations	740,200	223,000
25	Amitriptyline hydrochloride	729,100	211,000
26	Clonidine hydrochloride	727,800	85,600
27	Naproxen tablets	688,300	77,900
28	Nystatin	673,600	166,400
29	Debrisoquine sulphate tablets	651,100	138,700
30	Alginic acid mag trisil tablets	636,100	65,600

CHAPTER 6. INFORMATION ON MEDICINE PROVIDED BY DEPARTMENT OF HEALTH

6.1 Prescribers' Notes

In 1957, the Department commenced issuing information leaflets, known as "Prescribers Notes", to medical practitioners. Initially the information was received with suspicion and hostility in some quarters, but the system soon became generally accepted. In a survey conducted in 1973, 75 per cent of general practitioners claimed to read every issue, and 88 per cent of these rated them good to excellent.

About 20 issues of these notes are sent out annually, and they are now supplied not only to doctors, but, where relevant, to pharmacists and dentists. These are three kinds:

(a) Notes on Medicine Costs

Comparative costs of different medicines within given categories, and price lists of selected groups of medicines are well received by doctors, and the Department is constantly being urged to supply more.

(b) Therapeutic Notes

Short practical articles on clinical topics including medicine treatment, aimed in particular at the general practitioner. The majority are specially written by selective experts. Others are based on articles written in the Medical Letter on Drugs and Therapeutics, the British Prescribers Journal or

other periodicals and are reprinted with permission.

(c) Clinical Services Letters

Inter alia these contain information about changes in the regulations by which medicines are controlled, about various aspects of medicine usage and adverse drug reactions. Warnings about sudden rises in the cost of pharmaceutical benefits have been included from time to time with good results.

6.2 Prescribing Costs Survey

General practitioners are provided with tables showing the prescribing costs of practitioners in their own district. Each practitioner can identify his own costs and can compare them with those of his colleagues although he cannot identify the individual practitioners concerned. The survey also enables each prescriber to compare the extent to which he prescribes expensive medicines, repeat medication and combinations of different medicines on the same prescription form. In addition to these publications, the Department of Health facilitates the distribution of relevant information from other sources, including Bulletins published by the Committee on Adverse Drug Reactions and the Annual Reports of the National Poisons Information Centre.

The Department of Health has supplied copies of the British National Formulary free of charge to doctors and dentists and pharmacists. This publication is a remarkably useful compact handbook of practical therapeutics.

6.3 Visiting Practitioners

In 1957, a special committee recommended the appointment of a senior practitioner to visit doctors and advise on prescribing, with special reference to cost. This proposal was implemented in 1959 with the appointment of one doctor. The scheme is successful and currently two doctors are appointed, enabling regular calls to be made to all general practitioners and specialists.

The visiting practitioners have no disciplinary functions, and their present duties may be summarised as follows:

(a) To discuss matters concerning all aspects of medical practice, including medical benefits, maternity benefits and allied health benefits.

(b) Improving liaison between practitioners, both general and specialist, and the Department of Health.

(c) To encourage reductions in prescribing costs.

6.4 Visiting Pharmacist Scheme

In 1976 it was decided to introduce a visiting pharmacist scheme with the prime function of visiting general practitioners to encourage rational, effective and economic prescribing so that expenditure on pharmaceutical benefits might be reduced, or at least contained. This decision followed a State Services Efficiency Review Committee Report of 1974.

Two people are now appointed to cover the North Island. Regular calls are made to general practitioners and specialists and lectures are given to medical students.

The visiting pharmacists have no disciplinary functions. Their main duties may be summarised as follows:

(a) To balance, to some degree, one-sided advertising directed at medical practitioners, and thus foster better prescribing habits.

(b) Improving liaison between medical practitioners and the Department of Health.

(c) To encourage reductions in prescribing costs.

CHAPTER 7. INTERNATIONAL CO-OPERATION

7.1 General Approach

There is a general awareness in New Zealand at government level and in trade and industry that co-operation between nations in the field of medicines is beneficial to all parties concerned. Present New Zealand legislation, however, does not allow for reciprocal recognition of national registration procedures for medicines.

7.2 Countries or International Organisations with whom New Zealand Co-operates

7.2.1 Countries

(a) Australia

(b) United States of America

(c) Canada

(d) United Kingdom

7.3 World Health Organization

7.3.1 Adverse Drug Reaction Programme

New Zealand is a member of the World Health Organization programme. Adverse Drug Reaction Reports have been regularly forwarded to the Research Centre for International Monitoring of Adverse Reactions to Drugs. New Zealand has, in fact, one of the highest reporting rates of all participating countries.

7.3.2 International Information System on Medicines

The Department is participating in the study and supplies data on all new and changed medicines approved for distribution in New Zealand.

7.3.3 W.H.O. Certification Scheme

New Zealand is a signatory to the World Health Organization's resolution which requires states to apply "Good Practices in Manufacturing and Quality Control of Drugs" and to participate in the "Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce". Under the certification scheme we could be called upon to provide certification or assurance of medicines manufactured for export and it would also be possible to use this scheme in relation to any pharmaceuticals imported into New Zealand where any problems or queries arise.

7.4 Organisation for Economic Co-operation and Development

New Zealand is a member of the Organisation for Economic Co-operation and Development. Most of our procedures relating to medicine registration are very similar to O.E.C.D. requirements but our law differs on some aspects. For this reason, New Zealand does not participate in the mutual recognition of medicine licensing.

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