Technical Discussions

St. George's, Grenada
September-October 1978

Provisional Agenda Item 24

CSP20/DT/1 EN
26 July 1978
ORIGINAL: ENGLISH

THE IMPACT OF DRUGS ON HEALTH COSTS: NATIONAL AND INTERNATIONAL PROBLEMS

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1. INTRODUCTION

The Directing Council at its XXV Meeting in Washington, D.C., selected the topic of "The Impact of Drugs on Health Costs: National and International Problems," for the Technical Discussions to be held during the XX Pan American Sanitary Conference.

The selection of this topic evolved from the recognition of the Member Governments at the XXIII Meeting of the Directing Council of the "urgent need to bring about a reduction in the price of high-quality drugs, in order to put them within the reach of the socially and economically less privileged population." Resolution XXIII, adopted at this same meeting, drew the attention of Member Governments to "the desirability of carrying out an analysis of local factors that may contribute to reducing the costs of drugs without sacrificing quality."

Interest in the complex relationships of pharmaceutical products, health costs and national policies is not limited to PAHO. On the contrary, the problems of increasing expenditures on pharmaceutical products and the irrational use of medicines is of concern to many governments. The Technical Discussions at the 31st World Health Assembly in Geneva in May 1978 were on the subject "National Policies and Practices in Regard to Medicinal Products, and Related International Problems."

Although the term, "National Drug Policy," has come into widespread use relatively recently, obviously, national drug policies have existed for a long time. In some countries the policy is a deliberately formulated approach to the problem of providing for the country's demands for drug products while in other countries it has developed as a result of the interaction of the various components making up the system of drug supply and utilization.

A national drug policy, especially one developed in response to perceived needs, should have as its basic objective the satisfaction of the actual drug requirements of the population by products of proven safety and

effectiveness, of high quality, and at a reasonable cost. Although all of these terms have generally accepted meanings, their use in any national drug policy would require specific definition. For instance, the determination of the actual drug requirements entails an assessment by experts knowledgeable about conditions prevalent in the particular country and, usually, a priority listing of the requirements to be met in order of their importance to the public health. Safety and efficacy are relative terms that imply a risk/benefit assessment which may vary from country to country to the extent that a drug product might be acceptable in one country and rejected in another. The cost of a drug product must take into account not only the actual price per dosage unit, but also its effectiveness under the conditions of use in that particular country, especially as compared to other drug products.

Throughout the world, in nations of varying degrees of socioeconomic development and with medical systems of varying sophistication, drug consumption is increasing. While a good percentage of this increased consumption is due to the appropriate prescribing of potent specific medications for serious illnesses, there is also an element of increased desire on the part of patients for medications for less serious conditions; for example, the stress-related problems leading to the use of "mood" drugs, as well as "fads" or poorly founded beliefs in the efficacy of such drug products as tonics and high-potency vitamins. One of the serious problems to be addressed by a national drug policy is the disparity between the frequently inadequate provision of drugs essential to the rural population, and the consumption of less important drugs by a relatively affluent urban population with ready access to medical care.

Drugs constitute a varying but always significant proportion of the national health care costs. Although in the Americas the percentage of health care funds expended on pharmaceuticals is in the range of 10 to 15 per cent in some countries it has been reported as high as 40 per cent.

The cost of pharmaceuticals as a part of health care costs is especially important in countries that depend to a great extent on imported pharmaceuticals. Compared to other parts of the health care costs, imported drugs represent an outflow of hard currency which must be balanced against exports, usually of materials that are not as costly. For this reason, it is important that the imported drugs are carefully matched to the actual need of the country. There is a growing tendency on the part not only of countries dependent on imports, but on the part of drug-producing nations as well, to address the problem of matching drugs to actual needs through the compiling of lists of so-called "essential drugs."

A most important element of a national drug policy is the pharmaceutical supply system which, although varying from country to country, has certain basic components which must be dealt with in any national drug policy. Some of the elements of a pharmaceutical supply system are research, development of new drugs (new chemical entities), the production of the specific drug substance from domestic or imported raw materials, the formulation of drug dosage forms, packaging, labeling, distribution, the development and dissemination of prescribing and dispensing information, and promotion. In a particular country, any or all of these components may be in the hands of private industry subject to varying degrees of governmental intervention, or a direct function of the government.

Although the development of a national drug policy is a matter for each nation to approach in light of its governmental and administrative structures, its history and culture, its human and natural resources, and its state of economic development, there are certain elements that all must consider, particularly those that are international in character.

In summary, the purpose of this document is to consider the problem of drug costs upon total health expenditures on a national and international level. To understand drug costs it is necessary to comprehend how drugs are produced, purchased, distributed and utilized. The legislation and regulation

of drugs must also be considered. Further, the worldwide nature, economic structure and organization of the drug industry must be described, as it is an important determinant of these costs.

This document reviews the factors mentioned above and offers proposals designed to control drug costs and their impact upon total health costs in any nation of the Region. The proposals outlined in section 6 may have to be modified in each nation. However, the Member Governments should direct themselves to these issues in order to control drug costs and at the same time provide essential drugs for high priority health problems--drugs which are safe, efficacious and available at reasonable cost to the general population. The proposals for action and policy suggestions listed in section 6 are based on a careful review of the situation, on economic and administrative studies, and on the experience of a number of countries. The problem of increasing drug costs is remediable and the proposals outlined should aid in its solution.

2. PRODUCTION, PROCUREMENT AND DISTRIBUTION

2.1 General Comments

The production, procurement and distribution of drugs varies widely among the countries of the Region. No uniformity should be anticipated since medical practice, the infrastructure of the health care system, and cultural, economic, geographical and historical factors differ profoundly from one country to another.

The consumption of pharmaceutical products is influenced by diseases which are prevalent as well as by the number of physicians, pharmacists, nurses, and health facilities. The availability of the required drugs is also an important factor.

2.2 Production

2.2.1 Factors in the Development of a Local Pharmaceutical Industry

Developing countries should produce locally at least part of the drugs they need and consume, for several reasons: from the economic

standpoint it would help them to save foreign exchange by cutting down their imports and from the professional standpoint it would stimulate the creative energies of nationals of the country to lay the foundations for a local (or regional) pharmaceutical industry economically and technologically independent of the outside world.

The technology of drug production is closely linked to that of chemicals in general, for today most pharmaceuticals are derived from chemicals and not from plant or animal substances. In turn, these chemicals come from three primary sources: alcohol, coal and petroleum, with the latter the chief source of raw materials for the manufacture of synthetic drugs. The production of the basic chemicals needed for the manufacture of pharmaceuticals requires that the country involved has an established chemical industry. Self-sufficiency can only be achieved by dint of a protracted period of capital investment, transfer of production technology and the training of local personnel. The process is a lengthy one and therefore should be started as soon as possible.

There are three stages of pharmaceutical production which can be readily identified. These are:

a) the production of basic chemicals and intermediates;
b) the production of finished dosage forms from such basic chemicals; and
c) the packaging of dosage forms bought in bulk.

Countries which do not have a fully-developed chemical industry are forced to start with the packaging of dosage forms and gradually work up to the production of the basic chemicals and intermediates. One of the major stumbling blocks in this process is the lack of production technology available to the developing countries. Such information is currently held by the large transnational pharmaceutical firms. Some developing countries have been able to establish license agreements whereby the foreign company will provide the necessary

technology in order to develop their own industry. Such agreements, however, usually contain restrictive clauses which prove a hindrance to the full-scale development of local production. For example, the licensee may be required to purchase the active ingredients from the foreign firm at a specified price and in many instances sales of the finished product are restricted to the domestic market.

The feasibility of establishing a viable pharmaceutical industry, with the aim of becoming self-reliant in regard to drugs, depends on a number of factors, including:

a) the population and per capita income;
b) the availability of technical manpower;
c) access to the required technology and equipment;
d) adequate water and energy supplies; and
e) the possibility of export markets.

Thus careful studies should be conducted before embarking on a major program to develop a domestic pharmaceutical industry.

2.2.2 Regional Production

As indicated in section 2.2.1, there may be technological, economic and other restraints which make it impracticable for every country to develop a fully integrated pharmaceutical industry. Thus it has been necessary to consider the possibility of co-operative activities in the pharmaceutical area. Venezuela, Colombia, Ecuador, Peru and Bolivia are members of the Andean Pact. These countries have started to integrate their activities in the drug field. They have designated two areas in which they propose to cooperate, namely

a) the production of raw materials for the pharmaceutical industry; and
b) the manufacture of pharmaceutical products.

Another example is the establishment of the Central American Common Market, designed for the purpose of dividing the tasks and

commitments among its Member Countries in accordance with the contributions that each may offer in the development of a truly integrated pharmaceutical industry suited to the Region.

2.2.3 Utilization of Medicinal Plants and Other Natural Products

Almost all of the Latin American countries have had hundreds of years of experience with traditional medicine based on native plants. Tradition and familiarity have established their local acceptance for certain ailments. Extracts of such plants in water, alcohol or other solvents are not expensive. Initial studies should be made on plants which have been widely used with beneficial effects. Research should be conducted to identify the active ingredients and specifications established for these medicines. However, their safety and efficacy should be confirmed clinically in scientifically conducted studies. The cost/benefit ratio as compared to synthetic drugs must also be taken into consideration in regard to the use of such products.

Work of this type has been carried out by the Botanical Institute for Therapeutic Plant Resources in San Marcos University in Peru. Scientists have collected several thousand species of Peruvian plants and studied approximately 300 of these from the pharmaceutical point of view. The stage of clinical application has been reached in the case of 17 of these plants. Another example of a drug being obtained from plant sources is the production of steroids from the barbasco, a plant that grows wild in much of Mexico.

In Mexico, the Medical Institute for the Study of Medicinal Plants, A.C. (INMEPLAN), was founded in March 1975 under the sponsorship of the Mexican Government. It now has twenty researchers working in the areas of medical history and anthropology, ethnobotany, phytochemistry, experimental and clinical pharmacology, and data processing.

Since that time two colloquia have been held, the first on the national level: "The Present State of the Knowledge of Mexican Medicine or Plants," in April 1976, and the second on the international level: "The Evolution of Traditional Medicines in Contemporary Society," in April 1977.

The objectives of this Institute are:

a) to collate all the traditional knowledge of medicinal plants in Mexico;
b) to investigate such information scientifically and complement it with what has been done in research laboratories both at home and abroad;
c) to restore this traditional knowledge to the community, validated by scientific research carried out in its own chemical and pharmacological laboratories; and
d) to implement, within the capabilities of INMEPLAN, rural medicine programs based on the traditional plants.

It can be seen from the foregoing that Mexico has embarked on the development of drugs from natural sources that, in some cases, can complement "western medicine."

It should not be assumed that this new therapeutic armamentarium will be ready for use in the near future, much less supplant therapies currently in use. But it should be noted that the synthetic drugs are not available to millions of people chiefly because they cannot afford them.

In Argentina, in view of the large numbers of cattle in that country, consideration could be given to the production of glandular extracts, such as anterior pituitary extracts and insulin.

2.3 Procurement

2.3.1 Methods of Procurement

The major objectives of a procurement system are to ensure a supply of high quality drugs at the lowest price obtainable and the delivery at the time specified. Great care must be taken in selecting the suppliers in order to ensure the continuing availability of drugs of uniformly high quality. All suppliers and their individual products must be registered with the appropriate office of the health ministry. Dependence on a single suppliers should be avoided. In the case of large orders, they should be broken down into smaller lots, provided they are still large enough to obtain the best price.

In the case of purchases by the government, the bidding should be open in order that all approved suppliers who process or manufacture the desired product may submit quotations. The mechanics of this competitive bidding, which has been practiced for years in several countries of the area, are very briefly as follows:

a) the list of drugs to be acquired, including the quantities needed, is published or made available to suppliers, and a deadline is established for the presentation of bids (in some countries it is required that the quotations be accompanied by samples);

b) on the deadline date the competition is closed and the date is announced on which the bids will be opened publicly;

c) when the bids have been opened, the order is awarded to the supplier who has offered the best quotation. If two or more have offered the same price in their respective bids, the quantity ordered may be divided between them;

d) agencies that request samples along with quotations proceed as follows (as in the case of the Social Security Institute of Costa Rica):

i) all samples provided are analyzed, beginning with the samples quoted at the lowest price;

ii) if all quality control requirements are met, the supplier of the samples analyzed first is selected and no other samples are analyzed;

iii) if, however, the lowest-price sample does not meet the quality requirements, the sample of the next higher price is analyzed, and this procedure is continued until a satisfactory sample is obtained.

There are several problems which may arise in this system of competitive bidding. The suppliers of a particular product may agree informally to submit the same price in order to be sure of sharing equally in the order. In instances where samples are required to be submitted, the sample accompanying the quotation may be found to meet all quality control specifications. However, it is subsequently discovered that the bulk of the order is of a lower quality. Thus it is necessary to analyze random samples of all shipments as delivered. This type of situation points up the importance of the careful selection of the approved suppliers.

2.3.2 Establishment of a Central Procurement Office

It is highly desirable that all government procurement of pharmaceutical products be centralized in one agency. All purchases of drugs, regardless of the unit that will use them in a given country, should be channeled through a central procurement office headed by a committee consisting of representatives of the various government agencies involved in the process: the ministry of health, the treasury or ministry of finance, the agency concerned with trademarks and patents, and customs, in order to harmonize the work and deal with problems as they arise. This procedure has obvious advantages: larger orders at lower prices, a single office to deal with reports on drug quality and a single office to take whatever action is required against

suppliers who do not meet contract requirements. To be able to perform these functions, the Central Drug Procurement Office must maintain close and continuous liason with the administrative units or agencies responsible for:

a) the registration of manufacturers and their products; and
b) maintaining surveillance of the quality of all drugs purchased by the government.

In the same way, the Central Drug Procurement Office must be in contact with other government agencies which have an impact on the procurement of drugs in order to expedite the procedures involved. These include the unit in charge of import procedures, the unit in charge of customs to allow the rapid clearance of shipments particularly of products requiring refrigeration, e.g. vaccines, and even the unit that makes payments for orders, in order not to keep suppliers waiting for their money.

2.3.3 List of Essential Drugs

The development and the advantages of a list of drugs which are necessary to meet the basic needs of health care of the population of a country are discussed in detail in section 3. A World Health Organization Expert Committee has developed a "model" list of essential drugs consisting of approximately 200 substances by generic name.(1) The establishment of such a list in a country, while not covering all drugs required, will nevertheless greatly facilitate the operation of a Central Drug Procurement Office.

It is, of course, recognized that the national list of essential or basic drugs will not include substances registered and authorized as research products, such as cytotoxins, or new products that are approved after the list has been printed. In these and other circumstances, procurements may be effected outside the basic list provided there is a therapeutically sound and scientific reason for doing so.

2.3.4 Emergency Needs

Any country may experience a disaster (an earthquake, a flood, an epidemic, etc.), in which case the procurement office must be prepared to make emergency purchases, either for prevention, (vaccines, or toxoids) or for curative purposes (sulpha drugs and antibiotics, or substances to purify water). For this reason it is advisable to maintain a standing reserve of drugs that may be indispensable for the launching of an emergency operation.

2.4 Distribution

2.4.1 Objectives

The objectives of the pharmaceutical distribution system is to ensure the availability of products necessary to meet the health needs of the population in all parts of a country. The distribution should be conducted in a manner that will maintain adequate inventories and at the same time provide proper storage. It is at this point that the advantages of the establishment of a basic or essential list of drugs becomes even more apparent. With a smaller number of products to handle, inventory and storage conditions are much easier to control. At the present time the distribution system for drugs to both the public and private sectors varies widely within the Region.

2.4.2 Types of Distribution Systems

The types of distribution system or pattern depend to a considerable extent on the economic system under which the government is operating, i.e., a controlled economy, a free market economy, or some combination of the two. The following examples of distribution patterns can be identified within the Region:

a) private manufacturers and drug wholesalers who supply both the public and the private sectors without direct governmental involvement;

b) a combination of distribution by private manufacturers and wholesalers to the private sector, with a governmental

agency, e.g., the Ministry of Health, responsible for procurement and distribution within the public sector;

c) a central governmental procurement agency which has responsibility for procurement and distribution of all drugs to both the public and private sectors;

d) a state monopoly which has full responsibility for procurement, distribution and sale of all pharmaceutical products.

It is recognized, of course, that there can be additional combinations of the foregoing patterns.

2.4.3 Distribution by Means of a Central Drug Procurement Office

In this section, distribution by a Central Drug Procurement Office to the public sector will be discussed. No attempt has been made to analyze the distribution patterns which involve private manufacturers and wholesalers or systems operating under a State monopoly. Nevertheless, many of the aspects discussed would apply to all patterns of drug distribution.

In a situation where the Central Drug Procurement Office has been assigned full responsibility for the procurement of all drugs for the public sector, this same office should be given responsibility for their distribution and for ensuring their quality until used.

The types and quantities of drugs required for primary hospitals, intermediate institutions and peripheral facilities will vary widely. Therefore, it is essential to establish a basic list of the drugs necessary for each of the foregoing levels. Normally the hospitals are located in the large cities and have all the requisite types of health manpower. The intermediate institutions are generally situated in smaller towns and do not have on their

staff personnel with all types of medical specialization. The peripheral centers are staffed with less-qualified personnel and provide chiefly outpatient consultations and home care.

In order to provide the drugs required at the levels of health care indicated in the previous paragraph, an effective distribution system should be able to undertake the following functions:

a) to store and distribute at regular intervals the medical commodities necessary to support the public health program at all levels;
b) to collect data at regular intervals from the communities on public health program activity and the utilization of medical commodities;
c) to establish and maintain a proper inventory system;
d) to transport the personnel and information needed for the training of staff;
e) to support field staff members by serving as a regular two-way channel of communication; and
f) to ensure that the system itself has the transport capacity it needs and to prevent breakdowns by providing for regular maintenance of the vehicles used.

2.4.4 Storage Facilities

To carry out its responsibilities relating to the storage of drugs, the Central Drug Procurement Office should have under its jurisdiction a central drug warehouse as well as responsibility for the supervision of storage facilities at the intermediate and peripheral levels. Since these storage facilities are a critical factor in the distribution of drugs, it is recommended that a small manual be developed on proper storage operations. This manual should include information on:

a) rotation of stocks;
b) arrangement of drugs on shelves;

c) procedures for making returns of drugs that have reached their expiration date or have spoiled;
d) protection of drugs against excessive heat; and
e) special precautions for products requiring refrigeration.

All staff should undertand the rationale for the standardized operating procedures and follow the directions in the manual.

2.5 Other Factors

In order to decrease the inventory of drugs at all levels the sizes and dosage forms should be standardized. Care must be taken to ensure that drugs that are easily damaged are appropriately packed. Personnel responsible for transportation must be informed of the types of drugs they are handling in order that special precaution may be taken, e.g., drugs which require refrigeration. A stock of natural or traditional medicines should be maintained at the peripheral centers, since the patients at this level will be familiar with such medicines and will accept them readily.

3. DRUG SELECTION AND DRUG UTILIZATION

3.1 General Comments

Drug utilization and the total expenditure for drugs are rising throughout the world. While much of this increase is for drugs of proven safety and efficacy, unfortunately some of the increase is accounted for by drugs of little or no efficacy and occasionally by drugs that are unsafe. Furthermore, some drug utilization is for symptomatic complaints that may be relatively trivial ("running nose" or "apathy"), vague or self-limiting and often not requiring drug therapy. The epidemiologically important diseases such as cancer, arthritis, coronary heart disease or certain parasitic diseases are not entirely responsive to drug therapy but other important diseases such as hypertension and tuberculosis are treatable by drugs.

A nation with limited resources for either drug production or purchase must realistically adopt a policy which tries to bring drug utilization in line with important treatable diseases or illnesses and discourage unnecessary drug expenditure. This can be done without adversely affecting the health of a population; indeed, by encouraging appropriate prescribing and drug use, adverse drug reactions can be reduced and persons with diseases treatable by drugs can be identified and brought into therapy.

3.2 Assessing the Drug Needs of Populations

3.2.1 Developed Countries

Developed countries are in a fortunate position in that most of their public health agencies conduct periodic morbidity and mortality surveys of random samples of their populations and thereby have reasonably accurate estimates of the incidence of diseases responsive to drug therapy. Of course, many of the most highly prevalent diseases (coronary heart diseases, upper respiratory viral infections, adult-onset diabetes) are presently untreatable by means of oral drugs; however, many drugs are marketed for these indications in spite of an absence of adequate proof of efficacy. Pharmaceutical firms in developed countries have expended much money in an effort to promote drugs for the treatment of highly prevalent conditions that are either presently unresponsive to therapy or are trivial and self-limiting conditions that may be better left untreated. (2) This has contributed to an over-utilization of drugs of questionable efficacy (or even significant toxicity with no concomitant proof of efficacy). Examples of this situation include the wide promotion and use or oral hypoglycemics (3,4), "long-acting" nitrites for ischemic heart disease, clofibrate for hypercholesterolemia (5) and antihistamines for respiratory infections of non-allergic etiology.

It is fair to summarize the situation in many of the developed countries as follows:

a) Over-utilization

Research and promotional activities of large pharmaceutical companies are often directed at perceived lucrative markets (that frequently do not reflect the basic health needs of the country).

Promotional activities of large pharmaceutical companies are often designed to widen the indications for certain therapeutic drug classes, such as the psychotropics, so that the exigencies and difficulties of daily living become "redefined" or labeled as disease treatable by psychoactive agents. (6) This effort has led to a striking increase in psychoactive drug utilization so that there exists the phenomenon in the U.S.A. of about 80 million prescriptions for diazepam and chlordiazopoxide issued during 1974 for a population of about 225 million. (7)

The research activities of pharmaceutical companies are directed frequently to the development of drugs for the symptomatic relief of such essentially trivial and self-limited conditions as viral colds (where no real progress has been made) rather than to the development of agents for more serious illnesses such as epilepsy, where the market for a useful drug would be smaller.

Patient "demand" for drugs also contributes to over-utilization but much of this desire for medication is probably stimulated by drug company promotion, lack of knowledge about risks of drugs and the desire of busy physicians to terminate patient interviews by the issuance of a prescription. (8)

The practice of allowing the licensing of drugs with minor structural modifications but with different proprietary names has produced a confusing drug nomenclature which makes physician education about drugs and drug action far more difficult than it would otherwise be.

Efforts to exploit lucrative drug markets and take advantage of the patent laws have led large drug firms to excessive research efforts aimed toward altering molecules sufficiently to gain a patent although the new slightly modified drug may often offer no therapeutic advantages. (9)

b) Under-utilization

On the other hand, problems of under-utilization of drugs do exist in developed countries. It is reported that many hypertensives go untreated in spite of the proven efficacy of certain antihypertensive agents in preventing morbidity and mortality from the disease. (10) Part of this under-utilization is due to poor patient compliance (possibly because of some of these drugs' undesirable side-effects, such as impotence or orthostatic hypotension); other reasons include cost, lack of education and lack of screening programs to detect treatable hypertensives.

3.2.2 Developing Countries

Developing countries often lack needed resources required to accurately assess health needs as related to necessary drugs, and thus establishing priorities for drug requirements may be difficult. Nonetheless, morbidity surveys and extant health records and information usually permit the setting of health care priorities although the quantitative data used may be of questionable accuracy.

Like the developed countries, over-utilization of drugs and adverse drug reactions may exist but are lower priority problems for countries with limited economic and material resources or where severe shortages of health personnel exist.

3.3 Drug Utilization Studies

Drug utilization provides a surveillance system for monitoring the efficiency of drug distribution and consumption, provides a data base for the interpretation of adverse drug reaction frequencies and helps identify gaps in the delivery of a crucial aspect of health services: the provision of safe and efficacious medicines. Malconsumption (either over- or under-utilization, or needless prescribing) can be identified and economies achieved once these problems are corrected. Linking drug utilization with standard health indices (morbidity and mortality rates) can help evaluate the efficiency of drug delivery systems and ultimate drug consumption and may also help evaluate the adverse or beneficial effects of widely used drugs. Drug utilization review can be considered an essential activity of a well-organized health delivery system,which offers great potential for both health planning and evaluation.

3.3.1 Drug Utilization Review Methods

Drug utilization review is the activity of measuring drug use and consumption among defined populations and/or within defined geographic areas. Its purposes are to:

a) establish denominator data for use in the calculation of adverse drug reaction rates;

b) estimate drug utilization in populations by age, race, social class and disease-specific rates to identify areas of possible over- or under-utilization;

c) estimate drug expenditure on the basis of utilization data;

d) monitor utilization of specific therapeutic categories where particular problems can be anticipated, e.g., use of amphetamines, hypnotics or sedatives, and other psychoactive drugs;

e) gauge the appropriateness of drug utilization by linking prescriptions to reasons for prescription issuance (therapeutic indications listed);
f) monitor the promotional activities of pharmaceutical firms by following utilization trends and patterns;
g) use utilization data to help estimate disease prevalence (digitalis utilization and congestive heart failure are closely correlated, for example); and
h) project future utilization trends so that needed drug productive capacity can be planned to meet important demand.

3.3.2 Sources of Data for Drug Utilization Studies

The following sources can provide useful information in drug utilization studies.

a) manufacturers' production and sales figures;
b) marketing research estimates;
c) national samples where drug reimbursement schemes operate;
d) ad hoc surveys and special studies;
e) hospital utilization;
f) pharmacy audits; and
g) prescriber audits or diaries.

In summary, drug utilization studies can contribute greatly to:

a) the identification of under- and over-consumption of drugs
b) crude methods of assessing efficacy and efficiency of dist tion, and
c) detection of adverse drug reactions.

3.4 Essential Drugs

As indicated previously, a recent report of a WHO Expert Committee on "The Selection of Essential Drugs."(1) includes a list of approximately 200 drugs which the Committee considered are the drugs most needed for the heal care of the majority of the population. The adoption of an "essential dru

by a country permits advantages of economy, and their organized procurement is possible. Furthermore, countries can be assured that drugs on the list are effective for their recommended uses. The drug list must be revised and adjusted to the particular health needs and health priorities of individual nations, but the advantages of such a list are clear.

Education provided to health care personnel can concentrate on those drugs thought essential to the health needs of the population. Drug advertising can correspondingly be more carefully controlled and monitored. Pharmaceutical companies will have greater incentives to direct their new drug research and development activities toward important new agents for diseases of public health importance. Local drug production could concentrate on developing capacity to manufacture those drugs essential to the national health. The problem of quality assurance is greatly simplified with fewer drugs available; furthermore, the quality assurance activity is directed toward the really beneficial and important drugs.

3.5 Drug Information and Education

In order for health professionals to prescribe drugs both appropriately and rationally, it is necessary that they have access to unbiased and accurate information. In the Region at present, much drug information received by prescribers comes from drug company detailmen, advertisements or similar promotional activities. The accuracy of this information varies depending on the drug regulatory agency activities in each nation.

To decrease unnecessary prescribing and drug utilization, it is essential that a reliable, accurate and unbiased source of drug information be made available to prescribers and patients alike. Furthermore, the national drug regulatory agency must develop some means of regulating drug promotion to prevent inaccurate and misleading promotional activities.

Continuing education in therapeutics is a helpful adjunct for keeping the prescriber abreast of new developments in clinical pharmacology and therapeutics. A national "drug compendium" and a drug bulletin or newsletter are useful methods for accomplishing these aims.

Once again, the primacy of an "essential drugs" list is paramount as the job of supplying accurate and unbiased drug information is simplified with the elimination of redundant and ineffective drugs.

Another important function of providing accurate information about drugs concerns the question of comparative efficacy in the choice of one drug over another. It is important for the prescriber to have a reliable source of information concerning the cost and efficacy of alternative drugs for a given indication. This information can be supplied by government agencies and should lead to more appropriate prescribing and lower drug expenditures.

The use of generic nomenclature is to be encouraged as it counteracts the tendency of the prescriber to use "brand names" which may be more costly and yet no more reliable than the generic equivalent. Prescribers are influenced to write prescriptions using brand names while drugs are under patent, and that habit may persist even after termination of the monoply patent and subsequent availability of less-expensive generic equivalents.

3.6 The Over-the-Counter Market (OTC)

Much drug consumption within a population is comprised of over-the-counter (OTC) purchases for less-serious illnesses. These drug purchases do not require a prescription and the range of remedies covers a large variety of illnesses, such as headache, arthritis and insomnia. In many nations, the manufacturers' claims for these products are extravagant and only recently has there been an attempt to regulate the sales of these drugs. In the U.S.A. the Food and Drug Administration has established panels to judge the safety and efficacy of these OTC drugs by therapeutic categories.

While OTC drugs are a necessary part of primary medical care, it is essential that the claims of the manufacturers be substantiated by proper clinical trials, lest consumer expenditure be wasted upon inefficacious remedi

Model laws to regulate OTC drugs should be developed in the Region and adopted by each nation.

3.7 Role of Pharmacists

Traditionally, pharmacists in developed countries have devoted much of their time to filling prescriptions and have spent little time as "drug information specialists," counseling prescribing physician and patient as to appropriate drug use. It is generally acknowledged that this represents a waste of the pharmacists' training and skills and a variety of plans to expand the role of the pharmacist have been proposed.

The situation in Latin America is quite different. In most countries, the pharmacist readily diagnoses and prescribes, although his training and experience is not adequate for this role. Nevertheless, the pharmacist represents a valuable resource that could potentially be utilized to improve drug utilization patterns and prescribing appropriateness. The expanded role of the pharmacist as drug information specialist, patient counselor and monitor for adverse drug reactions should be explored and developed. A decrease in unnecessary drug utilization and drug costs should result from this expanded role.

3.8 International Cooperation

The nations that are Members of the Pan American Health Organization have much to gain by actively cooperating in the field of drug utilization and drug regulation. Areas which could be productive include:

a) cooperative efforts to develop model laws to regulate and control drug promotion;
b) cooperative efforts in the purchase of drugs;
c) cooperative efforts to develop drug information systems to monitor drug utilization;
d) development of regional systems for the monitoring of adverse drug reactions;

e) joint efforts to develop lists of essential drugs and then purchase them at minimal costs;

f) joint efforts to develop unbiased and accurate information sources about drugs for distribution to prescribers.

4. DRUG COSTS

4.1 General Comments

The topic of drug costs should not be considered in isolation from a number of other facets of a national drug policy. These relevant aspects have been discussed in the previous sections. It is particularly important that any consideration of drug costs include the necessary requirements and procedures to ensure their quality, safety and efficacy. A poor quality, harmful or ineffective drug is an expensive drug at any price.

4.2 World Pharmaceutical Industry

4.2.1 Structure

It has been estimated that throughout the world there are over 10,000 companies that consider themselves as "pharmaceutical manufacturers." However, not more than 2,000 to 3,000 can be considered as fully competent dosage form pharmaceutical operations. Probably no more than 100 of these companies play a significant role in international trade. It is believed that these 100 companies supply approximately 90 per cent of total world shipments. Among the non-socialist countries, the top 50 companies are estimated to supply over 60 per cent of manufacturers' sales.(11,p.17) The 14 leading pharmaceutical companies, based on sales in 1974, are shown in Table 1.

The structure of the world pharmaceutical industry has major implications for the transfer of technology to the developing countries. It not only raises the direct financial and indirect social costs but also creates important constraints upon the establishment of pharmaceutical industries. The direct costs include the profits earned by

the transnational companies that result in a transfer of scarce foreign exchange resources from the developing countries to the headquarters of the transnationals. The research and development costs are borne by all consumers, including the poor in developing countries, although such expenditures at present contribute little to the solution of their major health problems. The indirect social and economic costs include the introduction of drugs that are inappropriate in terms of price and therapeutic effects to the basic needs of the developing countries. (12,p.VI)

It should be noted, however, that the pharmaceutical industry in many developed countries is also dominated by the transnational corporations. The share of the pharmaceutical market held by the domestic industry in 25 selected countries in 1975 is shown in Table 2. These data indicate that less than 10 countries in the non-socialist world possess a domestic pharmaceutical industry that supplies 50 per cent or more of the countries' requirements. (11,p.13)

4.2.2 Pharmaceutical Markets

During the 1960's and the early 1970's the growth in the world pharmaceutical market was approximately 15 per cent annually. This rate of growth has persisted through 1976 and it is assumed that the increase in 1977 will be of the same order. If this growth rate continues it will mean that the value of the world sales of pharmaceuticals will double every five years. The estimated world pharmaceutical market, broken down by regions, is shown in Table 3.

These data reveal that Western Europe is the largest market, with 30.0 per cent of the total. The market in North America, Eastern Asia and Eastern Europe ranges from 16.0 to 19.7. These four regions account for 83.6 per cent of the total. South America has sales representing 7.0 per cent. The remaining four regions, i.e., Central and Southeastern Asia, Africa, Middle East and Oceania, represent only 9.4 per cent of the total sales.

The twenty countries with the largest sales of pharmaceuticals, excluding the socialist countries of Eastern Europe, and China, are shown in Table 4. These data reflect in greater detail the regional figures given in Table 3. It will be noted that six of these countries, i.e., the United States, Brazil, Argentina, Mexico, Canada and Venezuela are in the region of the Americas.

Pharmaceutical sales in selected countries of the Region of the Americas are given in Table 5. Total sales range from US$7,800 million in the United States to US$23 million in Chile. The per capita sales also vary widely. The increase in sales in 1977 over those in 1976 is well above the world average increase of 15 per cent, i.e., 53 per cent in Chile, 50 per cent in Argentina and 35 per cent in Brazil.

The per capita consumption of pharmaceuticals in eleven CARICOM countries is shown in Table 6. It will be noted that the consumption in Barbados is higher than in any of the other territories.

4.2.3 Imports and Exports

International trade in pharmaceutical products has increased in recent years even more rapidly than production. Between 1968 and 1971, world exports of medicinal products, excluding exports by the socialist countries of Eastern Europe, increased from US$1,900 million to US$3,000 million. The magnitude of world trade in pharmaceutical products in 1971 for the major economic groups is shown in Table 7. These data indicate that the developed market economy countries account for over 80 per cent of the exports and 56 per cent of the imports. While the developed market economy countries and Eastern Europe are net exporters of drugs, the developing countries and the countries of Southern Europe import about 4 to 5 times more drugs than they export. (12,p.8)

The leading exporters among the developed countries are the Federal Republic of Germany, which in 1971 exported 28 per cent of its production; the United Kingdom, 51 per cent; the United States, 5 per cent, a relatively small exporter in relation to its large domestic production; and Switzerland with 72 per cent. The balance of trade in pharmaceuticals for the leading exporting and importing countries for the years 1971 and 1974 is given in Table 8. These data show clearly the domination of the world pharmaceutical market by the drug companies of the Federal Republic of Germany, the United Kingdom, the United States and Switzerland. They also reflect increasing trade in active ingredients between developed countries.

The figures for imports and exports of pharmaceuticals in eleven CARICOM countries are given in Table 9. With the exception of Guyana the exports are insignificant compared to the imports.

4.2.4 Research and Development

The pharmaceutical industry expends a relatively high proportion of annual sales on research and development. On a global basis it has been estimated that companies allocate 5 to 8 per cent of their sales to such activities and some of the leaders in the industry may spend from 13 to 15 per cent. (11,p.21)

In the United States, research conducted by the pharmaceutical industry has been concentrated on the search for drugs to treat central nervous system diseases, infections, neoplasms and cardiovascular problems. (13,p.6) These are undoubtedly major areas of concern for the developed countries but they do not meet the priority health needs of the developing countries. Despite the prevalence of parasitic and other communicable tropical diseases and the very large numbers of persons at risk, investment in research and development by the pharmaceutical industry directed to the control of these diseases has not increased significantly in real terms over the past decade.

Faced with this critical situation, WHO, in collaboration with UNDP, has developed a Special Programme for Research and Training in Tropical Diseases. An important element in this program is the promotion of the development of new prophylactic and chemotherapeutic substances for the treatment and control of each of six diseases which have been given priority. If this objective is to be achieved collaboration with the industry is of critical importance. Universities and other research institutions have been responsible for valuable advances in the understanding of these diseases, and have contributed to the discovery of promising therapeutic approaches. However, only the pharmaceutical industry has the financial and technical resources to translate these discoveries into large-scale production of new products for general use.

An appeal to the pharmaceutical industry to intensify its efforts to develop drugs for the control of parasitic tropical diseases was officially presented by WHO to the International Federation of Pharmaceutical Manufacturers Associations (IFPMA). At the General Assembly of this organization, in which the top executives of leading research-based pharmaceutical firms participated, the following views were expressed:

a) investment of the pharmaceutical industry in the field of tropical diseases must be considered substantial in relation to financial returns;
b) the industry is faced with the problem of whether a market can be found for this type of product, since so much depends on health authorities rather than individual purchasers;
c) since patent protection is "loosely managed" or non-existent in many developing countries, an inventor may be unable to reap any financial reward that could be forthcoming; and
d) the products already available are often under-utilized and some recently developed products have not found a market, presumably because they were too expensive.

Following the appeal by WHO, the Council of IFPMA decided to set up a committee to explore collaboration with WHO in the area of the Special Programme.

It can be concluded that research and development of new and better drugs for the control of parasitic and other communicable tropical diseases is not receiving adequate support from the pharmaceutical industry because these drugs are uneconomic to develop in spite of a widespread need. WHO and PAHO are in a unique position to help reverse this situation provided that adequate resources are made available, and employed in a well-designed program.

4.3 National Expenditures on Pharmaceuticals

In attempting to assess the impact of drugs on health costs, it is useful to examine the proportion of the national expenditures on health care which are required for the purchase of drugs. The expenditures on pharmaceuticals as a proportion of total health costs in seven developed countries are given in Table 10. It will be noted from these data that, while the percentage of the GNP spent on health care was relatively constant, the proportion of health care costs devoted to the purchase of pharmaceuticals varied widely. The proportion of the GNP spent on health care ranged from 5.5 per cent in Japan and the United Kingdom to 8.0 per cent in Italy and West Germany. On the other hand, the proportion of health costs devoted to pharmaceuticals varied from 10.5 per cent in Sweden to a high of 33.2 per cent in Japan.

The estimated average per capita expenditure on pharmaceuticals in 14 selected countries of the world is given in Table 11. The data show a range of per capita expenditures from US$53.35 in West Germany to US$0.75 in India, compared to a world average of US$9.60. There are obviously major differences in this respect between the developed and the developing countries. In developed countries where the whole population has relatively easy access to essential drugs there is concern about over-consumption, misuse and the rising costs

to governments or health insurance organizations. On the other hand, in developing countries the lack of funds to purchase essential drugs is the major problem. In these countries expenditures on drugs may represent as much as 40 to 60 per cent of a very limited budget for health care. These governments consider, therefore, that expenditures on drugs not only affect the balance of payments but constitute a serious limiting factor in the development of their health programs.

4.4 Factors Affecting Drug Costs

4.4.1 Policies of the Pharmaceutical Industry

The pharmaceutical industry in the developed world is characterized by a large number of small companies supplying a relatively minor proportion of the market and a few very large firms, mostly multinational in their operation, supplying the major portion. (12,p.14) As indicated previously, no more than 100 companies are believed to supply about 90 per cent of total world shipments. (11,p.17) Available data indicate that the extent of concentration in the industry has been increasing in every major producing country, as a result both of the disappearance of the small companies and the merger of larger firms. (12, p.14) In the United States the number of pharmaceutical establishments has decreased from 1,114 in 1958 to 756 in 1972. In view of this concentration of the industry, the leading drug companies possess a high degree of market power.

In the case of new drugs being introduced to the market, which in most instances are covered by patents, the prices are normally set by the larger companies at a level which, based on anticipated sales, will return to the company research and development costs within a reasonable period. However, the period of patent protection in many countries extends for 15 or more years. In the case of a widely used drug, the initial price levels may be maintained for the life of the patent or as long as the price structure will assure the company a significant share of the market. The concentration of the industry

and patent protection thus provide for considerable flexibility in pricing with the result that the price of the same product manufactured by the same company will differ widely in various countries of the world depending on the market situation within the country.

A distinctive feature of the pharmaceutical industry is the fact that marketing expenses constitute a very high proportion of net sales as compared to other industries. In 1976, 36 Canadian pharmaceutical companies expended 21.8 per cent of net sales on such promotional activities as medical sales representatives, advertising, promotional literature and samples. (14) The proportion of net sales devoted to such activities vary from country to country and between companies. There is no doubt, however, that marketing expenses have a significant impact on the price of drugs.

Profits in the pharmaceutical industry are, in general, higher than average. In the United States in 1975, after-tax earnings, as a percentage of stockholders equity, were 17.5 per cent, as compared to 11.5 per cent for all manufacturing industries. (13,p.41) Similar figures for Canada for the years 1968-1971 averaged 12.7 per cent, as compared to 7.6 per cent for all manufacturing. (15,p.17)

All the foregoing factors, i.e., the pricing policies of the industry, patent protection, relatively heavy investment in research and development, large expenditures on promotional activities, and higher than average profits, have an upward impact on drug prices.

4.4.2 Governmental Regulations

The studies that are required to demonstrate adequately the safety and efficacy of new drugs are referred to in section 5. There is no doubt that these requirements have become more stringent during the past 15 years as our scientific and medical knowledge has increased. This in turn has resulted in a large increase in the

research and development costs for each new drug approved. Because a large part of the research and development costs cannot be allocated to specific products, e.g., basic research and the cost of development on projects which must be abandoned owing to inadequate efficacy or excessive risk, it is not practicable to estimate the full research and development costs identified with a particular new drug. But one can divide the total industry research and development expenditures by the number of new single chemical entities introduced in any year. On this basis it has been calculated that in the United States this amounted to US$1.3 million in 1960 and rose to US$24.4 million for a typical new single chemical entity started in 1972. (13,p.2) It should be noted, however, that there were 50 new single entity drugs introduced to the U.S. market in 1960 and only 10 in 1972. Thus the figure for 1972 is much higher per drug entity. However, research and development expenditures as a percentage of net pharmaceutical sales have remained relatively constant in the U.S., varying between 10.5 to 12.0 per cent over the period from 1965 to 1974. (13,p.5)

On a global basis such expenditures have been reported to vary from 5 to 15 per cent of net sales. (11,p.21) These expenditures are passed on to the public as a portion of the price of drugs. However, there is no evidence to indicate that government regulations pertaining to new drugs have resulted in an overall increase in the percentage of sales devoted to research and development.

4.4.3 Customs Duties and Sales Taxes

Customs duties and sales taxes contribute significantly to the cost of drugs in many countries of the Region. In Guyana, for example, there is a 15 per cent tariff on all imported pharmaceuticals, with the exception of antibiotics, vaccines and insulin. In addition there is a 10 per cent consumption tax on vitamin preparations and an 8 per cent tax on all other pharmaceuticals. Obviously, governments must obtain

revenues from some source, and traditionally import duties and sales taxes have provided a significant proportion of such revenues. However, consideration should be given to shifting the burden of such taxes to other less essential items.

4.4.4 Wholesale and Retail Pricing Practices

There is a tendency in any consideration of drug costs to concentrate on the price of drugs at the level of the manufacturer and to ignore the fact that in many instances the mark-ups imposed in the distribution chain are equally, if not more important. In countries operating under a free-market economy, the increases applied at the wholesale and retail levels vary widely and depend largely on the competition within the market. In countries with a mixed or a controlled economy, the distribution system may either be owned and operated by the State, or the government may set limits on the mark-ups which may be applied at each level of distribution. In Guyana, a maximum increase of 20 per cent has been established for both the wholesale and retail levels. It should be noted that such increases apply to the manufacturer's price plus customs duties. In Guyana, these increases combined with import duties and consumption taxes result in an average mark-up on imported drugs of approximately 85 per cent. There is no doubt that even greater increases apply in some countries of the Region.

4.5 Procedures Designed to Decrease Expenditures on Drugs

4.5.1 Use of a National Formulary

Estimates of the number of pharmaceutical products on the market in different countries range from a low of 950 to 35,000 or more. The lowest estimates are from countries with a controlled economy, or from countries in which the government has employed price and relative efficacy as a basis for drug registration.

The numbers are also much lower in countries which have developed a list of drugs which are essential to meet their health needs. The advantages which can be derived from the use of an essential list of drugs have been discussed in section 4. In some countries the essential list has been published as a national or regional formulary with the intention of restricting the drugs allowed to be sold in the country or region to those on the list. In other cases, it is a list of drugs which are covered by a drug benefit program.

The Guyana National Formulary, which contains approximately 1,200 dosage forms, was published late in 1977. It is essentially a list of drugs which are required to meet the health needs of that country. Only those drugs listed may be imported into, or sold, in Guyana. No data on the price of the drugs is included.

A number of provinces of Canada have issued drug formularies in connection with their drug benefit programs. The Saskatchewan Formulary contains 1,320 entries while the Ontario Drug Benefit Formulary lists approximately 1,700 pharmaceutical products. The two publications include the unit price of the drugs. All these governments believe that the drug programs, of which the formularies are an essential part, have decreased their expenditures on drugs.

4.5.2 Certification of Quality

As has been emphasized previously, it is absolutely essential that any program designed to control expenditures on drugs must include procedures to ensure the quality of the products in question. The procedures required at the national level are discussed in section 5. It is recognized, however, that a number of developing countries may not be in a position to establish and maintain their own quality control facilities for the testing of imported drugs

To meet this situation the World Health Organization has been working for a number of years on procedures to ensure the quality of pharmaceutical products moving in international commerce, and has recently published a pamphlet on the subject. (16)

This pamphlet includes a detailed description of practices required in the manufacture and quality control of drugs as well as a proposed form for the certification of the quality of pharmaceutical products. The certificate is intended to define the status of the pharmaceutical product and its manufacturer in the exporting country. It should be issued by the drug control authority in the exporting country in accordance with the requirements of the competent authority in the importing country.

If certificates of individual batches of products are required, such certificates could be issued either by the manufacturer or the competent authority of the exporting country. The batch certificate should provide information to identify the batch, a statement that the batch meets certain specifications, and data on such matters as date of manufacture and results of analyses. The form of the certificate and explanatory notes are shown in Annex 1.

4.5.3 Bulk Purchasing

Most pharmaceutical firms will quote a lower unit price for a large order of a drug, e.g., one million tablets, than they will for an order of 10,000 tablets. The reasons are obvious. The larger lots will permit a company to reduce production and distribution costs and to obtain a guaranteed market for their product. A description of two bulk purchasing plans which are currently proposed or are in operation in the Region will illustrate the principles and procedures involved.

a) A Canadian Bulk Purchasing Plan

Under the Canadian Constitution, responsibility for health services has been assigned to the provinces. Thus the major drug purchasers in the public sector are the provincial governments. At the request of the provinces, a federal-provincial meeting was convened in 1973 to consider procedures for the bulk purchasing of drugs used extensively in provincial institutions. A plan was developed which was acceptable to the provinces and bulk purchasing was initiated in 1974. The following major steps are involved in the development of the annual agreements:

i) The federal-provincial coordinating committee meets and agrees on the list of drugs to be included in the bulk purchasing plan;

ii) The Federal Department of Supply and Services requests the provincial governments to provide them with their anticipated requirements for the next year for each drug, indicating the dosage form and strength;

iii) The provincial governments name suppliers acceptable to them for each drug;

iv) The Department of Supply and Services collates the requirements by acceptable suppliers, and calls for tenders; and

v) The lowest bidder is awarded a contract which remains in effect for one year.

The provincial governments receive a copy of the agreements and from that point forward all transactions are between the provinces and the suppliers. The provincial governments place orders for the amount of the drug required at various times during the year for delive to not more than 10 points within the province. The drugs in the agree ments are chiefly those employed in mental institutions, in sanatoria f

the treatment of tuberculosis, and for vaccines employed in public health programs. In 1977-78, a total of 28 drugs and 139 dosage forms and potencies are included in the program.

b) Master Contract Purchasing of Drugs, Caribbean Community Secretariat

This Caribbean program for the bulk purchasing of drugs has been developed by the Caribbean Community Secretariat in response to a request from the Conference of Ministers Responsible for Health. The current status of the project was outlined in a paper presented to the Third Conference, held in St. Kitts, June 1977. (17)

The basic principles involved are essentially the same as those to be found in the Canadian bulk purchasing plan described in the previous section. From the various pharmaceutical products proposed by the participating territories, 10 drug entities in 39 dosage forms were selected for inclusion in the program. The requirements for these pharmaceutical products were collated and the forms inviting tenders were submitted to approved suppliers. Quotations were received from 15 pharmaceutical firms. These quotations were summarized and submitted to all participating governments.

4.5.4 Regulation of Procurement and Distribution

In recent years, governments concerned with increasing expenditures on drugs have given attention to procedures for limiting the availability of drugs to those which are essential for the health needs of the country (section 3) and to the centralization of drug purchasing (section 2). Thus the Second Conference of Ministers Responsible for Health in the Caribbean meeting in Monserrat in 1976 passed a resolution (18) calling upon health administrations:

a) as a first stage,

to prepare, as soon as possible, a list of drugs by generic name for use in government institutions, thus providing the basis for a Caribbean Formulary, and

b) as a second stage,

i) to establish a State buying service to undertake the purchase of pharmaceuticals for the entire public and private sectors, and

ii) to restrict the importation and domestic production of drugs to those listed in the national formulary.

Guyana has already implemented these recommendations. A revised and enlarged edition of the Guyana National Formulary was published in November 1977. It contains 850 drug entities and 1,200 dosage forms. The drugs are listed by generic name. A National Drug Ordering Committee has been appointed which has responsibility for placing orders and maintaining stocks of all imported pharmaceuticals for both the public and the private sectors. Purchases for 1978 are restricted to those drugs listed in the Formulary or which have been specifically approved by the Government.

In some countries, operating under a free-market or a mixed economy, the distribution of drugs is controlled by the government. In Sweden, for example, all drugs are sold through "Apoteksbolaget," which is the national corporation of Swedish pharmacies, established in 1970 by the Swedish Government. It has responsibility for ensuring an adequate supply of drugs at a reasonable price for both the public and the private sectors in Sweden. It also issues objective information on drugs and provides statistics on drug consumption.

4.5.5 Development of a Domestic Pharmaceutical Industry

Any comprehensive discussion of procedures designed to decrease expenditures on drugs should include consideration of domestic drug production. If a local drug industry can be established on a viable economic basis, it should have a desirable effect on drug costs, as well as other economic and social benefits. The various aspects of pharmaceutical production have already been discussed in section 2 and require nc further elaboration in this section.

4.6 Patent Legislation

The technological domination of the pharmaceutical industry by a limited number of companies with headquarters in six or seven countries is further illustrated by the ownership of patents. The number and country of origin of new patents issued in the U.S.A. in 1975 are shown in Table 12.

These figures reveal that of the 4,557 new patents for pharmaceuticals issued in the U.S. in 1975, 2,483 or 54.5 per cent of the inventions originated in that country. A further 1,758 or 38.6 per cent originated in six additional countries, which are all major producers of pharmaceuticals. The remaining 6.9 per cent include patents originating in many developed countries. It can be concluded that very few of the pharmaceutical patents in force in developing countries are the property of local industries; for example, it is reported that in Chile in 1975, 98.4 per cent were foreign owned. (12, p.21)

The pharmaceutical industries argue that they could not continue to invest large sums of money in research and development unless the new products which result from such activities are given patent protection. On the other hand, both developed and developing countries which do not have a major pharmaceutical industry must pay a full share of these costs despite the fact that the countries in which the research and development is conducted are the greatest beneficiaries. In addition, patents permit pharmaceutical firms to

maintain monopolistic control over the price of certain essential drugs for periods up to 15 or more years. In view of this situation, a number of countries have taken action to modify their patent legislation relating to pharmaceutical products.

In Canada during the 1960's serious concern was expressed, particularly by consumer groups, in regard to the cost of drugs. This concern led the Canadian Government to conduct a comprehensive investigation ot drug costs and prices. (19) The report of this study included a recommendation that the Patent Act be amended to include applications for compulsory licences to import drug products in all forms. The Government acted on this recommendation in 1969. Section 41.(4) of the Patent Act now reads as follows:

> "41.(4) Where, in the case of any patent for an invention intended or capable of being used for medicine or for the preparation or production of medicine, an application is made by any person for a licence to do one or more of the following things as specified in the application, namely:
>
> a) where the invention is a process, to use the invention for the preparation or production of medicine, import any medicine in the preparation or production of which the invention has been used or sell any medicine in the preparation or production of which the invention has been used, or
>
> b) where the invention is other than a process, to import, make, use or sell the invention for medicine or for the preparation or production of medicine,
>
> the Commissioner shall grant to the applicant a licence to do the things specified in the application except such, if any, of those things in respect of which he sees good reason not to grant such a license; and, in settling the terms of

> the license and fixing the amount of royalty or other consideration payable, the Commissioner shall have regard to the desirability of making the medicine available to the public at the lowest possible price consistent with giving to the patentee due reward for the research leading to the invention and for such other factors as may be prescribed."

From June 1969 to June 1976, 158 compulsory licenses to import and/or manufacture drugs have been issued. A total of 149 licenses, covering importation only, were issued to 24 different companies for 44 different chemical entities. Five companies received more than 10 licenses. (20) Since June 1976, a further 52 licenses have been issued giving a total of 210, as of September 1977.

As might be anticipated, opinions with regard to the impact of the issuance of compulsory licenses for drugs vary widely. The Pharmaceutical Manufacturers Association of Canada considers that the legislation has had an adverse effect on investment by the pharmaceutical industry in research and development and production facilities in the country. (20) On the other hand, there are numerous instances of widely used drugs being sold under compulsory license at prices much lower than those quoted by the original patent holder. In any event, there is no indication that the government is considering changes in the present legislation.

In Guyana, drugs may be patented under the Patent and Designs Act. In this Act an invention is defined as "any manner of new manufacture", i.e., a "process" patent. Provision has been made for the issue of compulsory licenses under certain conditions. In addition, any government department may use an invention for the services of the State, on such terms as may be agreed upon, with the approval of the Minister responsible for the department. The prevention of

abuse of monopoly rights under any patent is provided for under Section 31 of the Act, which comes into effect at any time after the expiration of three years from the date of sealing of a patent.

4.7 Example of a Comprehensive Prescription Drug Plan

Saskatchewan is one of the mid-western provinces of Canada, with a population as of June 1976 of 909,714 persons. The Saskatchewan Prescription Drug Plan was established to:

a) provide coverage to Saskatchewan residents for quality pharmaceutical products of proven therapeutic effectiveness;
b) reduce the direct cost of prescription drugs to Saskatchewan residents;
c) reduce the cost of drug materials by encouraging effective price competition and quantity discounts;
d) encourage the rational use of prescription drugs through research, consultation with professional associations and educational programs directed at physicians, pharmacists and the general public. (21,p.3

The major design criteria, as given in the annual report of the Plan for 1976-77 were: (21,p.3)

a) the Drug Plan should be a universal program;
b) the consumer should pay a portion of the cost of each prescription;
c) a drug formulary system should be used. Only drugs proven to be therapeutically effective and made by competent manufacturers should be covered;
d) there should be government involvement in the purchasing of drugs to reduce drug material cost;
e) the existing wholesale and pharmacy retail distribution system should be used;

The Plan began providing benefits on 1 September 1975.

The Saskatchewan Formulary lists the drugs which are covered by the plant. A Formulary Committee was established by the Minister of Health to

compile and maintain this list of drugs. The range of drugs listed in the Formulary is considered to be sufficient to enable physicians to select a course of therapy for most patients. Only products formulated and produced in accordance with good manufacturing practices and which comply with official standards are listed. The price per unit of the drug is also shown in the Formulary. A representative page is given in Table 13. An asterisk to the left of the drug strength and dosage form, e.g., chlordiazepoxide, 5 mg. capsule, indicates that the brand name products under this heading are interchangeable. An asterisk to the right of the price indicates to pharmacists that the Drug Plan has negotiated a contract price for that product. Pharmacists are required to dispense such products except where a prescriber indicates "no substitution" for a product in an interchangeable category.

The main features of the Drug Plan are as follows: (21,p.8)

i) all Saskatchewan residents are eligible for benefits under the plan;

ii) the consumer pays a maximum of Can $2.25 per prescription for most drugs covered by the Plan, and a maximum of Can $1.00 per package of insulin or urine testing agents. The balance of the prescription cost is paid by the Drug Plan;

iii) the Drug Plan pays the pharmacy the drug material cost as listed in the Formulary, plus a dispensing fee subsidy of Can $0.75 per prescription (Can $0.50 after the first 20,000 prescriptions);

iv) the Saskatchewan Formulary Committee has identified approximately 175 interchangeable drug groups. Products in an interchangeable group are considered to be equivalent in therapeutic effectiveness; however, their price can vary widely. The Drug Plan utilizes compulsory product substitution to reduce the cost of drug materials. When a prescription is filled for a drug in an interchangeable category, payment is based on the lowest-priced product in that category; and

v) if a physician belives that a particular brand is necessary for the specific need for a patient, he or she must indicate

"no substitution" on the prescription. The pharmacist must, in these circumstances, dispense the brand specified and he will be reimbursed by the Drug Plan at the rate specified in the Formulary for that brand.

The methods employed in obtaining the price of drugs for listing in the Formulary are "Maximum Allowable Cost" and "Standing Offer Contracts." The main features of the two methods used for obtaining the price of drugs are as follows: (21,p.10)

i) Maximum Allowable Cost

This method is used where low volume requirements do not justify establishing a Standing Offer Contract. Drug manufacturers must provide firm price quotations for each drug which they have listed in the Formulary, effective for a period of six months. For drugs listed in an interchangeable category, the Drug Plan will reimburse the pharmacy for its acquisition cost up to the lowest guaranteed price in the Formulary for that category;

ii) Standing Offer Contract

A Standing Offer Contract is a contract between a manufacturer and the Drug Plan to supply certain drug products to approved wholesalers and warehouses at a contracted price. These distributors will purchase the drugs from the manufacturer and will distribute to pharmacies at the Formulary price. Two suppliers are normally used for each interchangeable Standing Offer Contract category to ensure a continuous supply and to allow more manufacturers to participate in the Saskatchewan market. The pharmacist must dispense a Standing Offer Contract drug in an interchangeable category unless the prescriber has specified "no substitution." Standing Offer Contracts are also used to obtain quantity discounts for single supplier drug products.

It is difficult to determine if savings have been achieved in drug material costs through the intervention of the Saskatchewan Government in the

acquisition of drugs through the use of the "Maximum Allowable Cost" or "Standing Offer Contracts." It is evident however that the retail price of a number of selected drugs in Saskatchewan has decreased between December 1974 (prior to the implementation of the Drug Plan) and July 1977, as shown in Table 14. These drugs are all widely used and, with the exception of "Slow K," there are a number of suppliers. Thus the acquisition procedures employed by the Saskatchewan Government have been effective in increasing competition and reducing significantly the unit price of eight out of the nine drugs shown in Table 14. Similar reductions in price have not been achieved in the case of the majority of the drugs listed in the Formulary since, in most instances, there is only one supplier.

In the fiscal year 1976-77, 583,358 persons or 64.1 per cent of the covered population benefited from the Drug Plan. Additional statistics of interest are:

Number of Prescriptions		3,653,506
Total Drug Plan Payments	Can	$14,908,077
Total Consumer Payments		$ 7,163,610
Administrative Expenses		$ 1,585,465

It will be noted that the administrative expenses amount to Can $0.43 per prescription.

There is no way of assessing in any quantitative manner the longer-term economic and social benefits of the Saskatchewan Prescription Drug Plan. But, undoubtedly, the beneficial effects on the health and welfare of the people of Saskatchewan would be significant. The Drug Plan has achieved most of the objectives outlined at the beginning of this section. It has:

i) provided coverage to all Saskatchewan residents for prescribed drugs of established quality and proven therapeutic effectiveness;

ii) reduced the direct cost to Saskatchewan residents of prescribed drugs; and

iii) reduced the cost of drug materials by encouraging effective price competition and quantity discounts.

5. DRUG LEGISLATION AND REGULATORY CONTROL

5.1 Legislation

5.1.1 General Comments

It is important that the national drug control program have a firm legal basis expressed in a comprehensive statute that addresses the basic aims of the national government, defines the authorities of the regulatory agency, provides for the promulgation of specific regulations without requirement of further legislative process, and firmly fixes the responsibilities of the government, the industry, the health professions, and other interested and affected groups. Where political, legal, or administrative subdivisions exist, delegation or reservation of authorities or responsibilities should be clearly defined.

The basic purpose of a national drug control program and its underlying legislation is to protect and enhance the health of the population by assuring that drugs and related products used in the country, whether imported or domestic, are safe and effective, of high quality, properly packaged and labeled, and promoted and distributed in such a way that safety and efficacy are not impaired. PAHO has addressed itself to this problem on several occasions. A seminar on drug control in the Americas in Maracay, Venezuela, in November 1970 resulted in a report that included a model "national drug control law" which today could still serve its intended purpose. (22) More recently, a document prepared by the Division of Disease Control, PAHO, entitled "Guidelines for the Development of a National Drug Control Program," provides an even more comprehensive approach to legislation and the format of a national drug control agency. (23)

The drug legislation of a country, in pursuit of the basic aim of protection of the population against unsafe or hazardous drugs, as well as the promotion of public health through the ready availability

of safe and effective drugs of high quality, will determine the degree of control which the government considers necessary to exercise over the various elements of the pharmaceutical supply system. This system ranges from research and development, production, importation, distribution, sale, licensing and registration, quality, safety and efficacy, labeling, advertising and other promotional activities, procurement and utilization of drugs and other medicinal supplies, and price. A WHO document providing background material for the Technical Discussions at the 31st World Health Assembly contains an outline of the technical and administrative components of drug policies and management of the pharmaceutical supply system. (24)

5.1.2 Definitions

Precise definitions of important terms used in the law are required for enforcement purposes, especially in the face of legal challenge. The terms to be defined will depend on the scope of the legislation and the definitions will vary depending on the intent of the drafters.

5.1.3 Prohibition of Sale of Adulterated Drugs

This section of the national law would prohibit the sale of drugs that, either because of the conditions under which they are manufactured or produced, or because upon analysis it is determined that they do not comply with specifications of identity, strength, quality, and purity, could present a hazard. This section of the law could also contain a prohibition against sale of a drug that has been manufactured or processed under conditions not in conformity with current good manufacturing practices.

5.1.4 Prohibition of Sale of Misbranded Drugs

As in the preceding paragraph, the law should prohibit the sale of drugs which are misbranded because labeling or advertising is false

or deceptive; or fails to conform with the requirements imposed by the law, or in any other way misrepresents the product.

5.1.5 Licensing of Manufacturers, Wholesalers and Distributors

The authority to license manufacturers, wholesalers, and distributors of drugs provides the assurance that the facilities, practices and procedures of all those involved in the pharmaceutical supply system conform to the law and especially to the good manufacturing practices provisions. Refusal to grant a licence is a preventive measure which has been shown to be more effective and more economical than corrective action after an undesirable situation has developed.

5.1.6 Registration of Drugs

The drug control legislation should include a requirement that all drugs be registered before they may be imported, manufactured, distributed or sold. The application for registration of a new drug should include, in addition to other information:

(a) a description of the drug, its proper (generic, INN) name and the name under which it is proposed to be sold;

(b) a list of all ingredients and specifications for both the ingredients and the final dosage form;

(c) a description of the manufacturing process and evidence that the conditions of manufacture and the quality control procedures are satisfactory;

(d) data to establish the safety and efficacy of the drug for its recommended use; and

(e) its recommended route of administration, proposed dosage, claims and contraindications.

The legislation should establish the period for which the registration is valid as well as the fees for the initial and subsequent registrations.

5.1.7 Establishment of Nonproprietary Names

The use of established nonproprietary names is essential to the safe and effective use of drugs, especially in a situation where a number of "brand names" may be presented to prescribers and consumers. Where possible, the name selected should be the "International Nonproprietary Name (INN)" recommended by the World Health Organization. The law should be specific about the manner in which the common, proper, or generic name (INN) is to be used in labeling and in promotion, such as advertisements in journals and mailing pieces.

5.1.8 Establishment of Schedules of Drugs for Control Purposes

The national drug law should provide for varying levels of controls of different classes of drugs depending on such factors as the inherent toxicity of the drug, ancillary measures necessary for the safe and effective use of the drug and the potential for abuse or misuse of the drug. Some national laws provide for separate schedules of drugs with abuse potential such as narcotics, psychotropic agents, hypnotics and sedatives partly because diversion and illegal production and trafficking in such drugs are considered matters to be dealt with, in part at least, by government agencies with police authority, distinct from that of the drug regulatory agency. However, the range of restriction of drugs can be dealt with in a hierarchy of schedules ranging from drugs which are prohibited because of an unacceptable risk or the lack of recognized medical use, through drugs restricted to use by or on the prescription of a licensed practitioner, to drugs which are permitted to be sold directly to the consumer with only general control of their quality and labeling.

Two international conventions provide guidance in regard to those substances whose use represents the greatest abuse risk; these are the Single Convention on Narcotic Drugs, 1961, and the Convention on Psychotropic Substances. Over 100 countries are now parties to the Single Convention. The Convention on Psychotropic Substances came into effect in August 1976. The following categories of drugs should be placed in different schedules with varying degrees of control.

a) Prohibited Drugs

Examples of drugs which might be prohibited from sale except for very limited scientific investigational and medical use are lysergide (LSD), psilocybine, and certain amphetamine derivatives.

b) Narcotic Drugs

Because of the potential for abuse of narcotic drugs, with detrimental effect on the public health, these drugs should be placed in a schedule in the national law which provides for adequate controls. Nations which are parties to the Single Convention and Narcotic Drugs, 1961, should provide for a legal basis to acquire data required under the Convention.

c) Hypnotic-Sedatives

This category includes the barbiturates and drugs, such as glutethimide, which require strict control in view of their liability to abuse and dependence-producing properties.

d) CNS Stimulants

This category includes the amphetamines and drugs, such as methylphenidate and phenmetrazine, which require strict control for the same reasons as the hypnotic-sedatives.

e) Drugs Available on Prescription Only

The restriction of drugs to use by or on the prescription of a medical doctor or other licensed practitioner is generally advisable in the case of drugs that are inherently toxic, subject to abuse or habituation, or that require ancillary measures such as precise diagnosis for their safe and effective use. The actual list of restricted drugs, however, will reflect, to a great extent, the conditions of medical practice and drug distribution in any particular country. Where there is a shortage of qualified medical practitioners, drugs that would ordinarily be restricted to prescription use may be permitted to be distributed by paramedical personnel.

f) Drugs Available on Batch Release Basis

For certain types of drugs, such as vaccines, toxoids, antisera, and sometimes antibiotics, it has been found advisable to make the release of each batch contingent upon the meeting of all specifications established for the drugs. The testing of such batches prior to release is usually the responsibility of the regulatory agency but may be carried out by the laboratories which have been determined to be qualified.

g) Drugs Available Without Prescription

This list would include all of the drugs not listed under the more restrictive schedules. Such drugs are regulated as to quality, safety, efficacy, and labeling, and are usually permitted to be sold directly to consumers for the relief of minor symptomatic conditions.

5.1.9 List of Diseases for Which Drugs May Not Be Promoted to the General Public

It may be desirable to restrict the promotion to the general public of drugs for certain illnesses which are extremely difficult of diagnosis, or for which self-treatment is extremely hazardous, or for which there may not be any really effective drug available. This provision of the law not only protects the public health, but also protects the population against economic loss by promoters of fraudulent or ineffective remedies.

5.1.10 Requirements for Medical Devices

Medical devices cover an even wider spectrum of products than do drugs, ranging from extremely simple devices requiring only the most general of controls relating to quality and labeling, through sophisticated electronic life-supporting devices requiring high standards of quality and performance. In addition, the device area provides a fertile field for promotion of fraudulent gadgets that may be

relatively harmless but which may be inherently hazardous or may cause diversion of patients with serious illness from effective medical treatment. The device provisions can be relatively simple providing that, in addition to meeting the general requirements of the drug control legislation, no device shall be sold that:

a) when used as recommended causes injury to the user;

b) is sold or advertised in a misleading manner; and

c) where a standard has been prescribed for a device, fails to meet that standard.

5.1.11 Powers of Inspectors

Agents of the drug control agency should have precisely defined authority which would include the right at reasonable times to make appropriate inspections of premises covered by the law, to examine, copy, or abstract any relevant records, and sample or detain any article he believes may be in violation of the law.

5.1.12 Authority to Establish a List of Essential Drugs

In recent years, there has been a movement, fostered to some extent by WHO activity, to establish lists of "essential drugs." These lists are of many types and may include drugs that:

a) are considered necessary to meet all the health needs of the country;

b) drugs that are considered essential for the national health services and that are available for use in such services;

c) drugs that are provided free of charge or with a nominal charge through a national drug or pharmaceutical benefit plan.

Where drugs are provided as part of a national health service or a drug benefits plan, or where the national or regional government provides full or partial payment or reimbursement for drugs under certain conditions, there has also been a tendency for national governments to establish maximum prices for such drugs.

Where either or both of these activities are contemplated, national drug law should provide for the establishment of appropriate criteria, and delegate the authority to an appropriate agency. It should be recognized that the selection of essential drugs requires expertise not usually confined to the national drug regulatory agency, and that there are good reasons for separating the functions of selection of essential drugs from the registration of safe and effective drugs. Likewise, it is probably better to lodge the responsibility for the establishment of drug prices in an agency other than the one responsible for registration.

5.1.13 Authority to Promulgate Regulations

Effective implementation of the broad provisions of a statute generally requires the promulgation of specific regulations for the guidance of the regulated industry and others affected by the legislation. Specific regulations established after due process also provide a basis for immediate administrative action without the necessity of establishing in each case the importance and relevance of the matter covered by the regulation. It is, therefore, essential that the regulatory agency have the authority to establish, within limits established by the basic law, regulations regarding such matters as labeling, packaging, promotion of drugs, specifications for drugs, the conditions of manufacturing, importation, distribution of drugs, methods employed for the testing of drugs, authority of inspectors, requirements for recordkeeping and reporting, and procedures, criteria and fees for the registration of drugs, as well as regulations relating to any other provisions of the law.

5.1.14 Export of Drugs and Related Medical Materials

If the country produces for export drugs or other medical materials, the law should cover the conditions under which such materials may be exported. Generally speaking, if a product satisfies the law of the country of origin and meets the requirement of the importing country there is no bar to international commerce. Where the requirements are significantly different, the national law must specify the criteria for exportation in order to protect the ultimate consumer and prevent exploitation of the population of a country having less demanding standards. The requirement of permits for exportation provides the opportunity for the application of such criteria.

5.1.15 Penalties

Provision should be made for appropriate penalties for violations of the act or regulations. These penalties should include:

a) authority to seize and dispose of articles in violation; and

b) fines or imprisonment for persons convicted, by the courts, of violations of any provisions of the law.

5.2 National Drug Control Agency

5.2.1. General Comments

Implementation of the national drug control law and its attendant regulations requires an effective, well-organized national drug control agency. The exact format of the agency will depend not only on the intended provisions of the national law but also on such factors as the availability of manpower, the economic system of the country, the status of the health professions vis-a-vis the government, administrative and geographical subdivisions, and the resources which the government is prepared to commit to drug control. As a bare minimum, however, the drug control agency should be so organized as to deal effectively with the registration and licensing of drugs,

quality assurance and regulatory activities. These aspects of drug control are dealt with in the following sections.

5.2.2 Registration and Licensing

a) Safety and Efficacy

The national drug law that provides for the registration of drugs should include criteria relating to safety, efficacy, and quality, which would guide the drug regulatory agency. Whether, as in the case of a country with research and drug production capabilities, there is a requirement for scientific evidence of efficacy based on studies conducted in that country or, as in the case of a country primarily dependent on importation, the requirement is for registration in the country of origin, there is a need for close evaluation of documentation of safety and efficacy prior to registration.

b) Specifications

Effective drug control requires that the registration process include precise specifications or standards for identity, strength, purity, and quality of the drug. Where they exist, specifications in compendia, such as the United States Pharmacopeia, British Pharmacopeia, or the International Pharmacopeia may be used. Otherwise the specifications must be provided by the applicant for registration and accepted after review by the control agency.

c) Labeling

Safe and effective use of a drug product requires that it be properly labeled with clearly stated indications, cautionary material, and directions for use including dosage and administration. Those responsible for registration of a drug must establish that the labeling does not exceed the claims warranted by the available scientific evidence, that all appropriate warnings, contraindications, and precautions are included. Attention must be paid to the use of the proper or generic name of the drug in

the various segments of labeling, especially where the law establishes the labeling as the basis for advertising and other promotional efforts.

d) Post-marketing Surveillance

Because the risk/benefit assessment established upon initial review of safety and efficacy data is subject to change over time, it is essential that there be a system for continuing review of this assessment by the reponsible agency. Revisions of labeling and dissemination of new information, particularly adverse information, through health professionals and officials, depends on this surveillance activity. Frequently overlooked are reports of lack of efficacy, which may indicate a problem with the quality of the drug product, particularly in the area of bioavailability.

e) Licensing

The term "licensing" in most countries refers to the granting of permission for the manufacturing, warehousing, distribution, or selling of drug products by the regulatory agency upon documentation of compliance with the appropriate regulations (in some countries, a "product license" is granted for some drug products: this is the equivalent to "registration"). It is important that the license not be granted until a thorough inspection of the establishment has been conducted and a favorable report submitted.

5.2.3 Quality Assurance

Continuing surveillance of the quality of drug products is perhaps the most important and fundamental activity of a national drug control agency. Registration of a drug product produced domestically should not be granted without verification of the ability of the applicant to consistently produce a drug within the appropriate specifications. This would usually require, in addition

to documentary evidence of the applicant's capability, an on-site inspection of the facilities for production and quality control. Basic elements of the quality assurance program include:

a) Inspection of establishments

This includes manufacturing sites, warehouses, wholesalers, and retail outlets, and any other points in the production-distribution chain.

b) Sampling of drug products

Although drug quality assurance depends largely upon validation of the production processes, end-product testing continues to be extremely important. Sampling of drugs at various points in the production-distribution chain according to a statistically valid plan is vital to quality assurance.

c) Laboratory services

The two major activities of the drug control laboratories would be analysis of the samples obtained at inspection of domestic establishments or at the dockside in case of imported drug products, and the analysis of drugs submitted for batch release if this is provided for in the national law. Laboratory services can be provided by laboratories directly under the control of the agency or by laboratories determined to be qualified whether independent or part of academic institutions. A further function of quality assurance laboratories in many countries is research into methodology for the testing of drug products. Bioavailability of drugs has become an important matter in recent years and frequently the laboratories of the regulatory agency are involved in the testing of drug products for this important attribute.

5.2.4. Regulatory Activities

The effectiveness of the national drug law depends on the ability of the national control agency to take prompt and appropriate action when violations of the law or regulations are found. The national law and the attendant regulations usually provide an array of regulatory options, ranging from requesting a manufacturer or other member of the regulated industry to make a correction or desist from an activity through seizure and destruction of the violative product, to provision for civil or criminal penalties on the responsible individuals.

It is essential, in order to avoid arbitrary and capricious actions, as well as to provide firm guidance to the regulated industry and health professions, that the national control agency promulgate their regulations and other guidelines and that it be consistent and equitable in their enforcement.

5.2.5. Organization and Status

There is no typical or standard format for the organization of a drug control agency. Factors such as the availability of trained manpower, the socio-economic development of the country, the economic system, and the historical background of drug control will all have a significant effect on the organization.

It is essential, however, that one agency be assigned overall responsibility for the drug control program, including registration and licensing of drugs, quality assurance, and regulatory activities. If the responsibilities are divided among several agencies or departments, the direction, coordination and efficiency of the program will suffer.

The drug control agency should be accorded a significant place in the governmental hierarchy with the head of the agency reporting to the ministerial level. The salaries of the personnel, their level of training, and the facilities and equipment available to them, should reflect the importance of this activity.

6. CONCLUSIONS

The problems of increasing expenditures on pharmaceutical products and the irrational use of medicines is a concern of most governments. This situation has led to the conclusion that each country should have a comprehensive national drug policy dealing with these issues. The particular aspects discussed in this paper include drug legislation and regulatory control; drug production, procurement and distribution; drug selection and utilization; and drug costs. In order to reduce expenditures on drugs, improve drug utilization, and reduce unnecessary drug use, it is proposed that governments:

a) review present drug legislation to ensure that it is adequate to meet the current situation within the country;

b) ensure that the national drug control agency has the staff and the facilities to enforce the drug legislation, and that the head of the agency reports to the ministerial level;

c) develop, if economically feasible, the local production of pharmaceutical products;

d) establish a central drug procurement agency with responsibility for procuring and distributing all drugs used in the public sector;

e) develop a list of essential drugs to meet the health needs of the majority of the population;

f) provide accurate and unbiased information on drugs and monitor their use;

g) regulate advertising and other promotional activities relating to drugs;

h) encourage the use of traditional medicines of proven safety and efficacy;

i) expand the role of the pharmacist to include activities as a drug information specialist;

j) restrict, as far as practicable the purchase of drugs for the public sector to those products on the list of essential drugs or included in the national formulary;

k) consider deleting or reducing excise duties and sales taxes on essential drugs;

l) develop purchasing procedures which significantly increase the competition among suppliers; and

m) review patent laws and amend such legislation if there is evidence that such legislation is unjustifiably increasing the price of essential drugs.

TABLE 1. FOURTEEN LEADING PHARMACEUTICAL COMPANIES, 1974

Company	Headquarters Location	Estimated Pharmaceutical Sales (millions US$)
Hoffmann-La Roche	Switzerland	$1,112
Hoechst	West Germany	1,100(a)
Ciba-Geiby	Switzerland	974
American Home Products	U.S.A.	950
Merck & Co.	U.S.A.	890
Sandoz	Switzerland	808
Bayer	West Germany	750
Warner Lambert	U.S.A.	675
Eli Lilly	U.S.A.	634
Pfizer	U.S.A.	575
Bristol-Myers	U.S.A.	550
Boehringer-Ingelheim	West Germany	535(b)
Takeda	Japan	511
Schering-Plough	U.S.A.	500

Note: "Pharmaceutical" includes only ethical and proprietary specialties, in dose form, for human use; proprietary products included are only those with a recognized therapeutic activity. Where applicable, foreign currency conversions into U.S. dollars have been made at IMF rates at fiscal year end. Dollar volumes are believed to be accurate within 5%.

(a) Including Roussel-Uclaf
(b) Excluding de Angeli and Sturge

Sources: Annual reports, Trade journals and industry reports. Private communications and SRI estimates.

Source: Schaumann, L., Pharmaceutical Industry Dynamics to 1985, Health Industries Department, Stanford Research Institute, Menlo Park, Cal., U.S.A., July 1976, p.18.

TABLE 2. PHARMACEUTICAL MARKET SHARES HELD BY THE DOMESTIC INDUSTRY IN 25 SELECTED COUNTRIES, 1975

Country	Estimated Share %
Argentina	30
Australia	15
Belgium	10
Brazil	15
Canada	15
France	55
India	25
Indonesia	15
Iran	25
Italy	40
Japan	87
Mexico	18
Netherlands	40
Nigeria	3
Philippines	35
Saudi Arabia	0
South Africa	40
Spain	55
Sweden	50
Switzerland	72
United Kingdom	40
U. S. A.	85
U. S. S. R.	100
Venezuela	12
West Germany	65

Note: The "domestic" share accounts for sales (at manufacturer's level) invoiced by more than 50% nationally owned manufacturing companies; products under license by these companies from foreign companies are included in domestic sales. By contrast, the foreign share includes both sales by companies that are over 50% owned by foreign companies (including companies that have only a pro forma domestic majority shareholding) and sales by domestic companies that function as contrac marketing,distribution, and,in rare cases, manufacturing agents for foreign companies. In short, "foreign" companies are those whose policies, in the final analysis, are dictated by foreign interests. Sources: Internal SRI data and projections. Industry sources.

Source: Schaumann, L., Pharmaceutical Industry Dynamics to 1985, Health Industries Department, Stanford Research Institute, Menlo Park, Cal., U.S.A., July 1976, p.13.

TABLE 3. ESTIMATED WORLD PHARMACEUTICAL MARKET, 1977

	Total Sales (millions US$)	World Market %
World Total	$48,700	
Western Europe	14,600	30.0
North America	9,600	19.7
Eastern Asia (including Japan and China)	8,700	17.9
Eastern Europe	7,800	16.0
South America	3,400	7.0
Central and Southeastern Asia	1,700	3.5
Africa	1,300	2.7
Middle East	1,000	2.1
Oceania (including Australia)	530	1.1

Source: IMS World Publications, manufacturers' sales at 1976 exchange rates.

TABLE 4. THE TWENTY COUNTRIES WITH THE LARGEST PHARMACEUTICAL MARKETS, 1977

	US$ Millions	Percentage of World Market		US$ Millions	Percentage of World Market
United States	$7,800	16.0	Canada	$695	1.5
Japan	5,400	11.1	India	570	1.2
West Germany	3,640	7.5	Belgium	505	1.1
France	3,100	6.4	South Korea	480	1.0
Italy	2,200	4.5	Australia	450	0.9
Brazil	1,500	3.1	Sweden	430	0.9
Spain	1,480	3.0	Netherlands	422	0.9
United Kingdom	1,200	2.5	Iran	400	0.8
Argentina	960	2.0	Switzerland	365	0.8
Mexico	806	1.7	Venezuela	320	0.7

* Socialist countries of Eastern Europe and China excluded.

Source: IMS World Publications, manufacturers' sales at 1976 exchange rates.

TABLE 5. PHARMACEUTICAL SALES IN SELECTED COUNTRIES OF THE REGION OF THE AMERICAS, 1977

	Total Sales (millions US$)	Per Capita (a) (US$)	Increase over 1976 %
Argentina	$ 960	US$37	50
Brazil	1,500	14	35
Canada	695	31	11
Central America and Panama	135	6	13
Chile	23	2(b)	53
Colombia	217	9	20
Ecuador	70	10	15
Mexico	806	13	17
Peru	214	13	22
U.S.A.	7,800	36	10
Venezuela	320	26	13

(a) Based on estimated 1976 population.
(b) This figure may be low. According to other data available to PAHO the per capita consumption is US$9.

Source: IMS International

TABLE 6. THE PER CAPITA CONSUMPTION OF PHARMACEUTICALS IN ELEVEN CARICOM COUNTRIES (a) 1976

	Population	Per Capita US$
Antigua	72,000	$ 4.82
Barbados	246,000	17.60
Dominica	85,000	6.45
Grenada	110,000	2.42
Guyana	809,000	3.96
Jamaica	2,210,000	5.97
Montserrat	13,000	8.07
St. Kitts	48,000	6.19
St. Lucia	120,000	3.38
St. Vincent	100,000	3.47
Trinidad & Tobago	1,200,000	5.30(b)
Total	5,013,000	

(a) Consumption = Production + Imports - Exports
(b) Tentative figure.

TABLE 7. INTERNATIONAL TRADE IN MEDICINAL PRODUCTS, 1971 (US$ MILLIONS)

	Exports	Imports	Balance	Percentage of total Exports	Imports
Developed market-economy countries	US$2,757	US$1,833	US$ 924	81.1%	56.5%
Southern European countries	36	182	-146	1.1	5.6
Developing countries and territories	231	905	-674	6.8	27.9
Socialist countries of Eastern Europe	375	327	48	11.0	10.1
Total	3,399	3,247	152	100.0	100.0

Source: Lall, S.Major Issues in the Transfer of Technology to Developing Countries, A Case Study of the Pharmaceutical Industry, Institute of Economics and Statistics, Oxford University, Oxford, U.K., UNCTAD Document TD/B/C.6/4, 8 October 1975, p.8.

TABLE 8. BALANCE OF TRADE IN PHARMACEUTICALS (MILLIONS US$)

Leading Exporting Countries	1971(a)	1974(b)
Federal Republic of Germany	US$ 332.4	US$ 603.2
United Kingdom	318.8	490.4
United States	283.1	592.3
Switzerland	270.6	589.7
France	96.6	193.0
Italy	50.6	25.8
Netherlands	38.6	64.7(c)
Denmark	19.1	31.4
Totals	US$1,409.8	US$2,590.5
Leading Importing Countries		
Japan	-146.8	-318.6
Spain	- 58.6	-126.0
Canada	- 52.5	-107.7
Belgium/Luxembourg	- 45.5	- 47.1
Austria	- 41.5	- 68.2
Sweden	- 41.7	- 66.9
Australia	- 40.3	- 52.6(d)
Totals	-426.9	-787.1

(a) Source: Lall, S., Major Issues in the Transfer of Technology to Developing Countries, A Case Study of the Pharmaceutical Industry, Institute of Economics and Statistics, Oxford University, Oxford, U.K., UNCTAD Document TD/B/C.6/4, 8 October 1975, Annex p.4.

(b) Source: Pharmaceutical Manufacturers Association, Fact Book 1976 Edition, Washington, D.C., U.S.A., p.64.

(c), (d) 1973 data.

TABLE 9. IMPORT AND EXPORT OF PHARMACEUTICALS IN ELEVEN CARICOM COUNTRIES 1976

	IMPORTS (000's US$)	EXPORTS (000's US$)
Antigua	$ 347	
Barbados	4,105	$ 336(a)
Dominica	549	
Grenada	267	
Guyana	7,200	5,500
Jamaica	17,077	1,216
Montserrat	106	
St. Kitts	300	
St. Lucia	405	
St. Vincent	347	
Trinidad & Tobago	6,360	

(a) estimate

Source: UNAPEC Report on Caribbean Regional Drug Policy, 1978

TABLE 10. NATIONAL EXPENDITURES ON HEALTH CARE AND PHARMACEUTICALS IN SEVEN DEVELOPED COUNTRIES 1974 (BILLIONS US$)

	GNP	Per cent spent on health care(b)	Expenditures on Pharmaceuticals (a)		
			% of GNP	% of health care	Total
France	279	7.8%	1.6%	20.7%	4.5
Italy	150	8.0	1.9	23.3	2.8
Japan	438	5.5	1.8	33.2	8.0
Sweden	61	7.8	0.8	10.5	0.5
U.K.	195	5.5	0.9	16.8	1.8
U.S.	1397	7.9	1.0	12.2	13.5
West Germany	420	8.0	1.6	20.2	6.8

Note: Because of definitional uncertainties, lack of comparable statistics possible double counting, currency fluctuations, and differences in inflation rates, the data in this table reflect rough estimates only The estimates for West Germany include phyto and homeophatic preparations, and indigenous medicine is included in the case of Japan.

(a) Ethicals and proprietaries for human therapeutic health care, at retail level.
(b) Includes costs of facilities construction, public health expenditures and medical research.

SRI estimates based on public data and private information.

Source: Adapted from Schaumann, L., Pharmaceutical Industry Dynamics and Outlook to 1985, Health Industries Research Department, Stanford [illegible] California. U.S.A., July, 1976, I

TABLE 11. ESTIMATED PURCHASES OF HUMAN PHARMACEUTICALS IN SELECTED COUNTRIES, 1975 (US DOLLARS, MANUFACTURERS' PRICES)

	Average Per Capita Purchases	
World	US$	9.60
West Germany		53.35
France		51.90
Japan		38.45
Sweden		36.60
U.S.A.		35.05
Australia		29.65
Argentina		26.10
U.K.		19.50
Mexico		13.70
U.S.S.R.		13.70
South Africa		11.10
Brazil		9.30
Nigeria		1.20
India		0.75

Note: Owing to uncertainties of definition, lack of comparable statistics, possible double counting, currency fluctuations and differences in inflation rates, the data in this table reflect rough estimates only. Data based on UN, IMF and SRI estimates including internal data, industry data and trade information.

Source: Adapted from Schaumann, L., Pharmaceutical Industry Dynamics and Outlook to 1985, Health Industries Research Department, Stanford Research Institute, Menlo Park, California, U.S.A., July 1976, p.16.

TABLE 12. NEW PATENTS ISSUED FOR DRUGS AND MEDICINES, U.S.A., 1975

	Number of Patents	Per Cent
U.S.A.	2,483	54.5
Federal Republic of Germany	507	11.1
Japan	447	9.8
U.K.	255	5.6
Switzerland	246	5.4
France	222	4.9
Italy	81	1.8
Others	316	6.9
	Total 4,557	100.0

Source: Pharmaceutical Manufacturers Association, Fact Book, 1976 Edition, Washington, D.C. U.S.A., pp. 14-16.

TABLE 13. REPRESENTATIVE PAGE FROM THE SASKATCHEWAN FORMULARY

28:00 CENTRAL NERVOUS SYSTEM DRUGS

28:16.08 PSYCHOTHERAPEUTIC AGENTS (TRANQUILIZERS)

CHLORDIAZEPOXIDE

**5MG CAPSULE*

020915	NOVOPOXIDE	NOP	$0.0102*
007374	PROTENSIN	ELL	0.0347
018066	C-TRAN	MOM	0.0350
314498	NACK	CPN	0.0388
013463	SOLIUM	HOR	0.0414
012629	LIBRIUM	HLR	0.0496

**10MG CAPSULE*

007382	PROTENSIN	ELL	0.0083*
020923	NOVOPOXIDE	NOP	0.0087*
018074	C-TRAN	MOM	0.0440
314471	NACK	CPN	0.0490
013471	SOLIUM	HOR	0.0528
012637	LIBRIUM	HLR	0.0663

**25MG CAPSULE*

020931	NOVOPOXIDE	NOP	0.0216*
018082	C-TRAN	MOM	0.0640
007390	PROTENSIN	ELL	0.0695
314528	NACK	CPN	0.0790
013498	SOLIUM	HOR	0.0851
012645	LIBRIUM	HLR	0.1022

CHLORMEZANONE

100MG TABLET

033618	TRANCOPAL	WIN	0.0863

200MG TABLET

033626	TRANCOPAL	WIN	0.1010

CHLORPROMAZINE

10MG TABLET

025453	LARGACTIL	POU	0.0325

**25MG TABLET*

232823	NOVOCHLORPROMAZINE	NOP	0.0128
295086	CHLORPROM	ICN	0.0191
025461	LARGACTIL	POU	0.0356

**50MG TABLET*

232807	NOVOCHLORPROMAZINE	NOP	0.0153
271101	CHLORPROM	ION	0.0241
025488	LARGACTIL	POU	0.0527

Source: Saskatchewan Formulary, Fifth Edition, July 1977, Saskatchewan Prescription Drug Plan, Department of Health, Regina, Saskatchewan

TABLE 14. COMPARISON OF PRICES OF SELECTED DRUGS, DECEMBER 1974 AND JULY 1977

	Unit Prices		Estimated Annual Utilization (000's)	Annual Savings
	Dec. 1974	July 1977		
Tetracycline, 250mg cap	Can $.0458	Can $.0140	4,480	Can $142,464
Diazepam, 5mg tab	.0596	.0040	10,870	604,372
Slow K, 600mg tab*	.0479	.0422	2,140	12,198
Ampcillin 250mg cap	.1094	.0437	2,760	181,332
Sulfisoxazole, 500mg tab	.0361	.0150	1,710	361,081
Chlorpropamide, 250mg tab	.0662	.0152	1,030	52,530
Amitriptyline, 25mg tab	.0727	.0132	2,140	127,330
Imipramine, 25mg tab	.0812	.0131	770	52,437
Chlordiazepoxide, 10mg cap	.0579	.0083	1,930	95,728
				Total $1,304,472

* This product is available only from one manufacturer, therefore substitution or price competition is not possible.

Source: Saskatchewan Prescription Drug Plan, Regina, Saskatchewan, Canada, October 1977.

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ANNEX 1. WHO CERTIFICATE ON THE QUALITY OF PHARMACEUTICAL PRODUCTS MOVING IN INTERNATIONAL COMMERCE

CERTIFICATE OF PHARMACEUTICAL PRODUCT(S) [1]

Name and dosage form of product: .....

Name and amount of each active ingredient: [2] .....

.....

.....

.....

.....

Manufacturer, and/or when applicable, the person responsible for placing the product on the market:

.....

.....

.....

Address(es): .....

It is certified that:

☐ This product has been authorized to be placed on the market for use in this country.

Number of permit and date of issue (if applicable): .....

.....

☐ This product has not been authorized to be placed on the market for use in this country for the following reasons:

.....

.....

.....

It is also certified that (a) the manufacturing plant in which the product is produced is subject to inspections at suitable intervals, and (b) the manufacturer conforms to requirements for good practices in the manufacture and quality control, as recommended by the World Health Organization, in respect of products to be sold or distributed within the country of origin or to be exported. (See Explanatory Notes.)

.....
(Place and date)

.....
(Signature of designated authority)

[1] This form may be adapted to cover several products of the same manufacturer.
[2] Use, whenever possible, international nonproprietary names (INN) or national nonproprietary names.

EXPLANATORY NOTES

Certificate of Pharmaceutical Product(s)

This certificate is intended to define the status of the pharmaceutical product and its manufacturer in the exporting country. It is issued by the competent authority in the exporting country in accordance with the requirements of the competent authority of the importing country. It may be required by the importing country at the time of the first importation and subsequently if confirmation or updating is required.

The requirements for good practices in the manufacture and quality control of drugs mentioned in the certificate refer to the text adopted by the Twenty-eighth World Health Assembly in its resolution WHA28.65 (see *Official Records* No. 226, Annex 12, Part. 1).

Batch certificates

If certificates of individual batches of products covered by a Certificate of Pharmaceutical Products are required, such certificates could be issued either by the manufacturer or by the competent authority of the exporting Member State, according to the nature of the product and the requirements of the exporting Member State or of the importing Member State. The batch certificate would indicate the name and dosage form of the product, the batch number, the expiry date and storage conditions, a reference to the Certificate of Pharmaceutical Products and a statement that the batch conforms either to the requirements of the competent authority for sale or distribution within the exporting Member State (with reference to the authorization) or, where appropriate, to published specifications, or to established specifications to be provided by the manufacturer. The certificate could also include data on packaging, labelling, nature of the container, the date of manufacture, results of analysis, and other data.