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PRESENT REGULATORY STATUTES INVOLVING QUALITY AND EFFICACY IN THE EXPORT AND IMPORT OF PHARMACEUTICALS IN SELECTED COUNTRIES 1/

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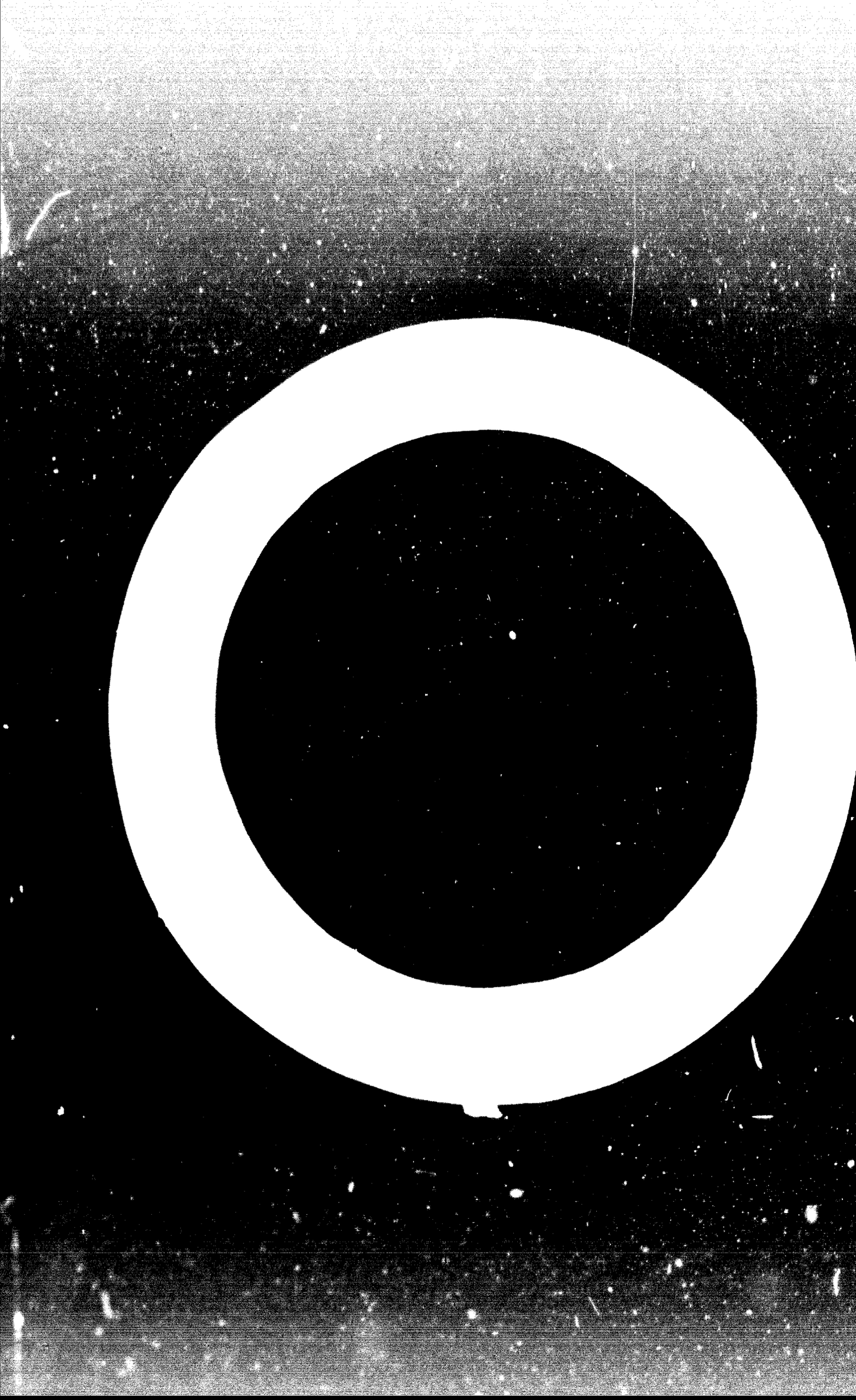

INTRODUCTION

On the occasion of the twentieth anniversary of the coming into force of the Constitution of the World Health Organization, the 7th April 1968, Dr. M.G. Candau, Director General of WHO issued a special message saying :

"The seventh of April this year marks the twentieth anniversary of WHO. It also provides an opportunity to review the past and to anticipate the future.

Looking back, the Organization and its Member States have witnessed the general improvement in world health which is largely due to their combined efforts.

There have been disappointments; there still remain the inequalities between the developed and the developing countries which it is the Organization's aim to reduce."

It is not necessary to emphasize that this general statement refers also to drugs, substances of extremely great importance in public health; a definite discrepancy can be shown between assortment, quality and availability of medicaments circulating in developed and developing countries.

Since the turn of the last century in the developed countries there is hardly a branch of industry which would have developed insomuch as the pharmaceutical industry. The reason lies - first of all - in the rapid development of the natural sciences : medical science, pharmacology and chemistry, further in the fact that in these countries the drug manufacturing became the task of the industry and in our days the manufacturing of pharmaceutical preparations takes place in very well equipped and large research group employing factories where more and more potent preparations come to light.

As a result of all these the variety of drugs being placed on the market nowadays increased to a hardly measurable number and simultaneously the drug consumption per capita rises too. In Switzerland for instance more than 20.000 pharmaceutical preparations are on the market and in certain countries the per capita drug consumption exceeds $ 20,- a year. We may say that in this respect the offer is strongly exaggerated.

This immense development was not free of unforeseen complications in spite of the invested vast mental and financial efforts and one should not be prophet to say that notwithstanding the continually growing control and cautiousness of the manufacturers and the state we have to take into account similar accidents like the Thalidomide one, for the simple reason because there are not at our disposal methods by the help of which - on basis of laboratory experiments on animals - all the effects of the new active substances could be exactly predicted on human organism.

All over the world there is an endeavour to consider the efficacy and quality of drugs public matter and the state has definite obligatory tasks in this field. The state wishes to meet its responsibilities by the use of laws and orders, and by establishing institutions and central organizations.

The rapid expansion of, and changes within the drug arsenal, beginning in the middle of the 20th century, have throughout the world added new demands to the existing requirements of drug control. The number of drugs has considerably increased. The early botanical drugs have successively been replaced by active principles isolated from them; the inorganic compounds have been, to an ever growing extent, succeeded by organic molecules; biochemical preparations have emerged, etc. This process of extension and exchange is likely to produce drugs which are not only more active than the old traditional ones, but are potentially more toxic as well. Therefore, their therapeutic use will not only result in advantages, but will, more or less, be accompanied by harmful side-effects. As drug therapy today is potentially more dangerous than it ever was, drug control should be extended to cover the peculiar problems of drug safety (introduction, field of application, dosage). Drug control, thus, has to cover some general aspects which have been realized in industrial countries for some decades, e.g. the control of finished pharmaceutical preparations, testing methods used in the assessment of new drugs, the follow-up of the side-effects of drugs already in current use, the supervision of drug information, the exact regulation and checking of the introduction of new drugs by the health authorities and, last not least, the specification of stability, purity, and activity.

In developed countries the regulating power of legislation comprises every phases of drug manufacturing including research too. Laws and instructions direct the conditions the manufacturer should satisfy realizing the fact that the pharmaceutical manufacturer is in a position to prevent mistakes by adequate care in the various manufacturing procedures and he has the first opportunity to detect any mistakes that occur by analysis in his own control laboratory. The quality of a pharmaceutical preparation depends on the purity of the materials

used in its formulation, the care with which the ingredients are measured, and the precision with which they are mixed. Care must also be taken to ensure that the correct labels are used and that the final container and package are suitable for their purpose. Another requirement for the satisfactory production of pharmaceutical preparations is the cleanliness and fitness of the premises in which they are prepared. Well-kept premises, good organization with strictly enforced rules, well-trained and conscientious personnel and the quality control described above, will ensure the production of reliable pharmaceutical preparations.

The other efficient instrument of regulation on national level is the publication of collected standards i.e. pharmacopoeias, equally compulsory for everybody. Nowadays the modern pharmacopoeias contain quite unique quantities of information concerning not only the continually growing number of pharmaceutical preparations but also definite instructions for the execution of different examinations. The value of these publications is extremely increased by the fact that they are easily accessible and in consequence of this quality they are utilised, in our days, beyond their original function, that is not only in the issuing country but they also have a fundamental role in the international trade of drugs; moreover they are regularly brought into practice in countries which are not in a position to compose their own pharmacopoeia.

The developed countries possessing pharmaceutical industry take special care of the regulations of putting drugs on the market. In most countries the legislation requires the obtaining of a licence prior launching a new drug.

In order to obtain the licences the manufacturer has to present an extraordinary thorough and all embracing - therefore extremely expensive - information which proves to the present state of knowledge - that the pharmaceutical product will from its introduction into practice is in the first place safe, consequently besides the supposed curative effect it has no other unknown and possibly dangerous effects, in the second place it is effective, i.e. it really has the indicated therapeutic effect supposing the drug is properly applied.

The observation of requirements prescribed in pharmacopoeias, marketing licences or special orders by the state is being controlled by her suitable laboratories, by restriction of sale to pharmacies meeting the requirements, by limiting the quantity of medicaments on medical prescriptions or by special inspections.

Generally speaking, methods of control are becoming more and more sensitive and precise. This may result in more and more stringent requirements that do not always stand in reasonable relation. A practical commonsense approach must therefore be adopted, if only to prevent unnecessary increase of costs.

To all these it is added yet that most countries - beside the above mentioned facts - regulate, by orders, the possibilities of promotion of pharmaceuticals. It refers first of all to advertisments.

One must confess that the result of this extremely complicated legislation and regulating systems - enumerated above only in part - is rather poor and disillusioning. Though it is true that the manufacturer generally respects almost both in his own and in the interest of the product put on the market, incorrect in conformity to the established standards, at the same time the national organizations are not able to cope with the task, in lack of material resources, staff or effective information, not even in the rich countries.

The WHO dealt with these problems at several technical meetings and reports. Many suggestions were made for the liquidation of the unsatisfactory situation, for instance the introduction of so called information sheets for the accentuation of the further responsibility of the manufacturers, the establishment of international, non profit making control laboratories, the education of experts etc., all the [illegible] unification, specification of pharmaceuticals and quality control is an unsolved problem even today. All these problems [illegible] with particular importance in the developing countries.

SECTION I

The manufacture and import of drugs in the developing countries

[illegible] of the developing countries the number of the home products [illegible] extremely rapid increase. The establishment of the home [illegible] supported by the step by step starting of [illegible] production [illegible] have drawn attention to the [illegible] of compulsory [illegible] and also of [illegible] instead. Moreover in many [illegible] the governments [illegible] to adjust manufacturing works of [illegible] are [illegible] every industrializing [illegible] this process into [illegible] much the more be- [illegible] developing countries started [illegible] way [illegible]

[illegible] most [illegible] raise [illegible] United States, [illegible] [illegible] production of drugs [illegible] generally

found in the programmes of governments.

There is no doubt that because of the rapid increase of research expenses, excessively increased requirements and often of unusually short span of life, the price of the majority of drugs - mostly that of the new ones - exceeds the purchasing power of the wide layers of the population in the developing countries. At the same time it should be stated that a sufficient number of pharmaceuticals appropriate for treatment of the most frequently widespread diseases are put on the market already in a few years after their launch at an acceptable price in consequence of the competition among the large manufacturers.

Considering the problems of the developing countries we must separately examine two drug groups which are distinguished on the basis of the difference between retail price and costs of production in order to come to right conclusions. This difference is usually big with the new "brand" products, being results of long and expensive research, and low with the traditional commercial items. One must admit that even the manufacturing of specialities belonging to the second group of "low" price level is profitable - here the expression "manufacturing" covers the meaning of formulating, processing, filling etc., only which can be realized in the developing countries for the first time - especially if the manufacturing is accomplished with proper equipment and in great series. These two conditions generally do not exist in the developing countries because machines and equipments of this kind are rather expensive - their capacity significantly surpasses the demands - and also because of the little consumption there is no possibility for producing in great lots. It is well-known that the per capita drug consumption per annum in the developing countries makes 1/10-1/20 of the developed countries', that is the annual drug consumption in a country of 20 million inhabitants is the same in value like the consumption in a developed "country" of 1-2 million inhabitants.

Generally all these economical viewpoints are not considered properly but they become acute problems only in the practice. The undisputable advantages of the establishment of local pharmaceutical industry is the fact that it contributes to realization of industrialization plans of the country, it creates new opportunity of work, increases the number of employees in industry of higher demand and culture, and to a certain degree it eases the troubled balance of payments. All things considered the enterprises working under the described conditions are actually only rarely profitable and consequently their equipment, quality, also of their staff and the speed of their development fall behind the developed countries, not mentioned the control facilities which are rather expensive because they require

instruments and experts. In the developing countries beside the above factors the endeavour for independence often influences the establishment of the indigenous pharmaceutical industry significantly. In most cases the countries try to emancipate themselves from the distant suppliers because of the long delivery time. This endeavour often has political sense and it can aim at awaking of national pride.

On the basis of the formers - looking ahead - we should take into consideration the fact by all means that the developing countries shall continue the realisation of their projects and in spite of the known difficulties more and more pharmaceutical works will come into being in these states. As a result of that the import of the ready made pharmaceuticals in dosage form will decrease and the purchase of the active ingredients necessary for their manufacturing will increase. As for the distant future as well as the manufacturing of this substances will certainly start first of all with utilization of material of animal and plant origin available in the country.

The expectable course of this development, the division of the complete drug manufacturing process into this two parts further the development in the structure of the drug import should be considered by all means if we deal with the evolution of the drug legislation in developing countries.

Legislation in some selected developing countries

The viewpoints enumerated in the previous section become valid at the selection of the quoted countries which are : Ethiopia, Pakistan, Lebanon, Peru, Singapore and Egypt. Every of them lies on one of the most remarkable continents from the viewpoint of the subject that is in Asia, Africa and South-America. Their history and formation are quite different. They constructed their establishments under different cultural influences and the legislation of various developed countries formed the basis of shaping of the local orders. A great difference shows, however, in the date of publication of the valid laws in the selected countries; in Singapore the Poisons Ordinance issued in 1938 is in force even today with many modifications and additions while the Rule of Ethiopia, the Pharmacy Regulations was dated in 1964. There is a difference also in number of inhabitants in the selected countries. The population of Pakistan is around 80 million while in Singapore about 2 million people live. A similarly great

difference appears at per capita consumption per annum also in case of Ethiopia and Lebanon. The selected countries are far not on the same degree of industrialization, for instance, in Ethiopia the local drug manufacturing goes on actually in one single factory. It means that the country is forced to cover practically the whole drug consumption by imported preparations. At the same time in Pakistan several pharmaceutical works operate and Egypt stands in need of import of ready made pharmaceuticals only in a small degree.

Ethiopia

Pursuant the Proclamation No. 100 of 1948, the Minister of Public Health issued a new Pharmacy Regulations in 1964. The Regulation defines medicinal preparation as "any drug, biological product or other parenteral medication and any combination of such items intended for use in the diagnosis, treatment or prevention of disease in men or animals." Under the provisions of these Regulations the general Advisory Board of Health and the Pharmacy and Laboratory Department led by the Chief Pharmacist were established. This Department performs all the functions and discharges all the duties set forth in the Regulations. The Department keeps Registers of licensed pharmacists, druggists, pharmacy technicians, retail and hospital pharmacies, drug shops and manufacturing laboratories and issues registration certificates, permits and licences. Pharmacists, druggists and pharmacy technicians are adequately college or high school qualified persons with clean record. In areas without pharmacies or druggists' shops rural medicine vendors are licensed to sell prepacked pharmaceuticals. Pharmacies can be established on the condition that the responsible manager is a registered pharmacist, the establishment and the location of the pharmacy serves the public interest and the pharmacy has adequate facilities and a minimum stock. The establishment of druggists shops is analogously regulated. The permit for the establishment of local manufacturing laboratory is issued to qualified and experienced persons only. The manufacturing facilities, equipments, buildings etc., are to be investigated and approved by the Board.

Imported pharmaceutical preparations cannot be sold, distributed or offered for sale and distribution unless permitted by the Minister. Permits for sale are issued basically upon submitting official certificates of the country of origin on the registration and free sale of the product in the producer's country. Wholesalers must also be authorized by the Minister. The Minister may forbid, in the pharmacies and druggist shops, the sale of any specified article which would not be compatible with the proper conduct of the enterprise. The compounding

or any kind of preparation or prepackage of drugs are strictly limited to licensed and registered pharmacies. Manufacturing activities in the laboratories are at all time to be supervised by the registered pharmacist or his assistant. The manufacture of biological preparations and sterile products are subject to special regulations as the Minister may issue. The manufacture, dispensing, purchase, storage and [illegible] of narcotics are regulated according to the international import quota allocated by the WHO Narcotics Commission. The Minister may prohibit the manufacturing, import, sale or distribution of preparations which are or are likely to prove injurious or harmful.

All medicinal preparations must meet the requirements of any Pharmacopoeia accepted by the Minister. The label of the preparations must bear the following data: name, active ingredients and their amounts, directions for use, the name and address of the manufacturer, the name and address of the establishment at which it is sold and finally the name and address of the patient in the case of dispensed preparations. Adulterations or mislabelling are punishable. Drug advertising has to follow the standards fixed by the Ministry. The Ministry has the right to examine any pharmaceutical preparation and to ban the sale of it if it fails to conform with the standard of quality or is adulterated or mislabelled. New and experimental drugs - hitherto unknown in Ethiopia - must be investigated by export, before release for public sale.

By the force of the Regulations the Minister appoints qualified inspectors for regular inspection of pharmacies, drug shops, storage facilities etc. Any licences or permits can be suspended, restricted or revoked in the case of violation of the provisions of the Regulations.

The country has a central body, the Central Medical Stores Corporation. All the governmental purchases are effectuated by this corporation; the sale and distribution of narcotics are restricted to the same.

On the basis of a duly authenticated certificate, the Ministry issues a provisional registration, valid for two years. The Department of Pharmacy then sends samples to the Imperial Central Laboratory to establish its consistency with the requirements. In the case of a failure, the drug is banned from Ethiopia.

The Imperial Central Laboratory was founded by the Ministry of Public Health about two years ago. It does not have adequate facilities to test every drug which enters Ethiopia - for the time being approximately 10.000 different brands, the value of this import is some $ 5 million per annum. To complete the picture: the population is 24 million, there are in the country 408 doctors, 41 pro-

fessional pharmacists, 44 pharmacies, 32 hospitals, 536 clinics, 64 health centres, 10 drug shops and 624 licensed rural vendors.

The country has one manufacturing unit, the Ethiopian Drug Manufacturing Share Company, under the control (84 %) of the Government. The supplies made by the Company make about 1 percent of the total import.

Pakistan

The rules regulating the supply of drugs are included first of all in the 1940 Drugs Act and in several different ordinances of the Government.

Pakistan has three kinds of pharmacists. The first category includes the pharmacy graduates who received their education at the Dingas National Institute in Punjab University. This course takes three years after they receive the F. Sc. (premedical) or preferably the B. Sc. (chemistry) degree.

The courses offered and the system of teaching is just the same as at the London School of Pharmacy. The first exhaustive examination which is in physiology, pharmacology and pharmacognosy takes place after two years of study. The final examination in pharmaceutics and pharmaceutical chemistry is held at the end of the third year. They graduates are largely engaged in industrial pharmacy. Last year Peshawar University opened another College of Pharmacy for under graduate studies.

The second kind of pharmacists in Pakistan are the pharmacy licenciates. They receive two years of schooling at Dow Medical College in Karachi after high school graduation. They study basic physical sciences with specialization in laboratory techniques and dispensing.

The third and the largest pharmaceutical force is that of compounders.

Drug stores in Pakistan sell only drugs. Those which have tried to introduce other items have been unsuccessful. This evidently is because of the trend to purchase other merchandise at specialized stores.

The owner, opening a new drug store, should be at least a compounder or he should engage one. Other persons who are ligible to open drug stores are pharmacists, doctors, nurses and health assistants. Licenses

[illegible], pharmacists are alone entitled to manufacture [illegible] that they possess the necessary equipment. [illegible] of pharmaceutical specialities [illegible] the imported pharmaceutical packages and [illegible] in the country of [illegible] being [illegible].

[illegible] ban [illegible] by the Ministry [illegible] manufacturer, the [illegible] names of all [illegible] as the [illegible] number of [illegible] the price to the [illegible] approval [illegible] Ministry of Health can [illegible] which would be [illegible] without any therapeutic [illegible] such as [illegible].

[illegible] specialities [illegible] other than the pharmaceutical [illegible] preparations and [illegible].

[illegible] factory must examine the [illegible] chemical composition [illegible] with the data [illegible] information. Where [illegible] informs the Ministry [illegible] and must retain [illegible].

[illegible] must in turn examine [illegible] pharmaceutical compound, [illegible] has been completed, [illegible] factory.

[illegible] pharmaceutical products, [illegible] pharmacists. The owners [illegible] by pharmacists.

An analytical laboratory was established in 1956, the function of which is to carry out the examination of pharmaceutical preparations and of foodstuffs.

In Lebanon the supply with medicines bases practically on the import, in 1964 about 200 importers bought medicaments in total value of about $ 9 million but also the local production has begun, however, this production covers appr. 5 % only of the whole demand. The import is extremely liberal. As a result of that in 1964 the products of some 650 different, even unknown, manufacturers were on the market of the country. To prevent this in 1966 the Ministry of Health, Directorate of Drugs obliged the manufacturers to supply a very thorough information and the products only of those companies were admitted which were able to testify adequately that they dispose of appropriate research as well as of own well-equipped analytical, biological and pharmacological control laboratories. Calculation of prices of the imported preparations bases on the price of the product accepted in the country of origin. (Decree No. 151/1 of 1967)

Peru

The Decree of 31. December 1960 defines a pharmaceutical speciality as being any medicament of known composition, stable pharmaceutical form, demonstrated therapeutic effects, uniformly packaged, intended for individual or hospital use, distinguished by a conventional name or by the name of the product coupled with that of the manufacturer, and affording advantages over official preparations by reason of the form of its preparation and the constancy of its effects. Sera, vaccines, antigens, culture media and other biological products intended for human or veterinary diagnosis or therapeutic treatment, substances used in radiography, as well as dietetic preparations, are also regarded as specialities. Galenical products are subject to the formalities of registration, recording and control by the Pharmacy Directorate of the Ministry of Public Health, in compliance with the same standards as for the pharmaceutical specialities themselves.

The Decree distinguishes between national and foreign pharmaceutical specialities. Products processed abroad and finished in Peru may not bear the descriptions "packaged in Peru" or "repackaged in Peru". Only such national or foreign pharmaceutical specialities may be supplied or utilized as have been recorded, registered and licensed by the Pharmacy Directorate pursuant to the provisions of the Decree,

with the approval of the Advisory Board of the Directorate. No samples of pharmaceutical specialities may be supplied or distributed if they have not been previously licensed.

The most important requirements which must be satisfied when an application for registration is made, are as follows: two samples of the specialty or class of product, which is to be used or intended to be placed on the market and the signature of the Pharmacy Directorate, together with [illegible] the name of the manufacturer of the material. In the case of a foreign pharmaceutical specialty, the price in the country of origin must also be stated. The price is one of the most important requirements for the granting of registration.

Applications for the registration of foreign specialities must be made by the pharmaceutical chemist, whether Peruvian or foreign, in charge of the authorized pharmaceutical undertaking or firm of importers. In the case of national specialities, applications must be submitted by the technical director of the laboratory producing them.

In the case of foreign specialities, applications must be accompanied by a certificate issued by the health authorities of the country of origin, to the effect that the laboratories producing such specialities are duly licensed and that the specialty itself is produced and supplied in the country of origin, or is produced for the purpose of dealing with the health problems arising from the diseases prevalent locally. Applications in connexion with national pharmaceutical specialities or galenical products must be accompanied by the control certificate signed by the pharmaceutical director of the control laboratory of the establishment or of the control laboratory authorized to carry out analyses. In the case of foreign specialities, specifications of the technical control methods which are used to test the quality of the specialty concerned must be given.

The Pharmacy Directorate studies the various documents submitted to it within a period of 15 days at the most from the date of submission of the application. In granting the licence, it takes into account the accuracy of the formula, the presentation of the specialty, the justification for its presentation as a specialty or galenical product, and a comparative study of the price of similar products of national or foreign manufacture which have already been licensed. The decision as to therapeutic similarity is taken by the Advisory Committee of the Pharmacy Directorate. Similar pharmaceutical specialities are considered to be those which, disregarding their chemical composition, possess analogous therapeutic properties, their constituents being evaluated pharmacologically, particularly from the point of view of their usefulness, application and therapeutic properties. The Advisory Committee also decides as to the acceptance or rejection of the documents and pamphlets which accompany the specialty. The Peruvian Decree specifies that, for purposes of the approval of the name of the specialty, care must be taken to ensure that the said name indicates, as far as possible,

the composition of the product, and its properties as to [illegible] indications.

With regard to the [illegible] stipulates that [illegible] accepted, [illegible] that [illegible] special [illegible] foreign [illegible] registered [illegible] where [illegible] the [illegible] pharma [illegible] three years.

The [illegible] the last mentioned [illegible] Pharmacy, [illegible] application for [illegible] commercially [illegible].

The [illegible] the local [illegible] vity. The import data [illegible] customs [illegible] chemical agents [illegible] about [illegible].

Singapore

The drug regulations of Singapore can be traced back to the Poisons Ordinance No. 19 of 1934. Among the [illegible] issued under the [illegible] important ones.

This law [illegible] and trade [illegible] to worth [illegible] poisons [illegible] in the [illegible] The main [illegible] prescription [illegible] dictions [illegible] indicated [illegible] must be kept at [illegible].

[illegible]

Hungary

The Public Health Act No XIV. of 1876 was the first that put the manufacture and sale of pharmaceutical products under official supervision. [illegible] as early as 1933 [illegible] regulates the [illegible] animal origin [illegible]

[illegible]

[illegible]

new product is therapeutically justified.

Thereafter the National Institute of Pharmacy refers the application supplemented with its own expertise to the Scientific Health Council's Committee for Drug Research and Registration. The Committee discusses the proposal and as a result, makes a decision on the admission for clinical trials. In some cases it asks the applicant to supplement preclinical data. In accordance with the decision taken by the Committee, the National Institute of Pharmacy makes arrangements for the pharmacological and clinical investigations requested.

The Hungarian health authorities recognize the importance of clinical pharmacology for safe drug therapy and for the smooth expansion of the pharmaceutical industry. Therefore, it set up a network concerned with clinical pharmacology. Within the scope of this network clinical investigation of new preparations proposed for trials by the Scientific Health Council is carried out on the basis of determined methods. At present 11 institutes are involved in the activities of this network. Parallel with the investigations taking place in institutes outside the network of clinical pharmacology are, as a rule, supervised and coordinated by the competent institute of the network. The institutes send their comprehensive expert opinions including detailed suggestions as far as the production of the drug is concerned to the Committee for Drug Research and Registration of the Scientific Health Council. This expert opinion has to include a suggestion concerning the dosage schedule, and the possible side-effects and contra-indications which have to be mentioned in the directions for use and in the pamphlets compiled by the manufacturer are also indicated. The session of the Scientific Health Council, after evaluating the clinical reports, takes its decision concerning the introduction of the preparation. Thereafter, the National Institute of Pharmacy delivers its approval in principle for the manufacture of the item and solicits the producer to apply for registration to the National Institute of Public Hygiene.

For the registration and launching of pharmaceutical products the manufacturer has to apply to the Ministry of Health; the application is directed to the National Institute of Public Hygiene.

The application for registration is required to contain full data of the preparation by the completion of the appropriate forms attached, specimens of the proposed labelling of the preparation, the text of the directions for its use approved by the National Institute of Pharmacy and the scientific papers and reports dealing with its preparation or with some of its active components.

On the occasion of registration an exact statement of the speciality's composition is made by the National Institute of Public Hygiene including the auxiliary constituents present in the preparation. Any deviation from the composition declared is only allowable upon a special permit by the National Institute of Public Hygiene, or when the manufacturer has announced his intention to modify the composition and the Institute has given its approval and carried out the necessary amendments in the registration files. The specimen for labelling has to comply with the standards laid down by the National Institute of Public Hygiene. No data other than those specified in the standards may appear on the labels. The relevant regulation provides for the following data:

a) the name, quantity and dosage form of the preparation;
b) the active principles, their quantities and their potencies;
c) The name and address of the manufacturer and the distributor;
d) the registration number;
e) the production number;
f) the mode of employing and the route of application;
g) the term of expiration (if any),
h) the retail price;
i) a clear indication whether the preparation may only be dispensed upon prescription;
j) the conditions of storage if they are important.

The directions for use are compiled by the medical department of the manufacturer and are subject to the approval of the National Institute for Pharmacy.

The manufacturer has to send samples of the finished preparation as well as of the substances used as components to the application for registration. Should the Institute of Public Hygiene ask for further data or information the manufacturer is obliged to furnish them.

The National Institute of Public Hygiene tests the drug in question for composition, activity, stability, sterility, etc. by chemical, biological, and bacteriological methods, as applicable. Only those preparations will be accepted for registration which, when tested, have satisfactory results in every respect.

After registration procedure has been accomplished marketing licence can be given. The marketing licence is granted to the manufacturer or the distributor after the price of the drug has been fixed by the Ministry of Health.

Should any preparation prove, even at a later date, not to comply with the conditions established in the marketing licence, the National Institute of Public Hygiene is authorized to withdraw it from the market.

It should be remarked here that the permission of the Ministry of Health is also required for the production and sale of sero-bacteriological products. Prior to their introduction, the products are adequately checked by the National Institute of Public Hygiene.

Medicated nutrients are submitted to a preliminary check in the National Institute of Nutrition and Food Hygiene and are licenced by the Ministry of Health. In cases of quality complaints the National Institute of Nutrition and Food Hygiene is entitled to withdraw certain batches of nutrients from sale.

In Hungary today a new collective codification of all the laws, ordinances and rules issued hitherto is under preparation. This new law is expected to come into force by the end of this year and it will contain more and stricter requirement in the first phase of the registration, at the stage of the manufacturing licence.

Hungary has a well developed pharmaceutical industry. The first factory was founded in 1867. The annual per capita consumption is about $ 10,- and over 90 percent of this demand is covered by the local industry which has a total production in bulk substances and specialities appr. $ 140 million per year. The annual import in dosage form pharmaceutical preparations is about $ 1 million. The manufacturing of drugs and biologicals is concentrated in 7 large state owned companies. The pharmaceutical export - two thirds of the total production - ranks Hungary in the seventh or eighth place in the list of the drug exporting countries. The total staff of the drug industry is about 17 thousand, 10 percent out of it holding university or equivalent degrees. The population is little more than 10 millions, the number of practising doctors is appr. 19 thousand and that of hospital beds 80.000. The distribution and sale of pharmaceuticals is restricted to a national organization of the 1400 pharmacies and hospital dispensaries. The number of pharmacists is 3600 at the present within this organization.

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible] the [illegible] further [illegible] quantity necessary [illegible] purposes [illegible] the decision of the [illegible] organization [illegible] will be advised [illegible] Committee and confirmed by the [illegible] Soviet Union.

[illegible]

[illegible] of marketing and [illegible] name and address of [illegible] chemical [illegible] the [illegible] Ministry [illegible] to [illegible] and [illegible] coordinated [illegible]

[illegible] at the [illegible] by the [illegible] [illegible] arguments [illegible]

[illegible] mutual [illegible] the [illegible] and [illegible] principle [illegible] to [illegible]

SECTION 3

Conclusions and Recommendations

Surveying the legislation of the selected countries and considering the quality of the circulating medicines in these states one can draw the remarkable conclusion that the existence of the law is primary and indispensable but this alone doesn't represent a complete solution. In certain countries the situation is not satisfactory in spite of the newly framed, precise legislation, in other countries, at the same time, the situation is reassuring though the regulations are outdated. This is not surprising as the quality of the available medicines - besides the legislation - is determined by other factors too: the stage of development of the local industry; the general financial situation of the country; the level of the general culture, the number of hospitals, pharmacies, doctors and pharmacists; and traditions of the local pharmaceutical industry; the general law-abiding moral etc. The achievement of a certain level can only be imagined as the result of a long development process where the legislation itself plays an important part but it cannot replace the presence of other factors.

The different international organizations, especially the WHO, have done a good deal in this field. The several reports and recommendations of WHO for standardization, control, working out of uniform specifications, regulating of distribution and trade of pharmaceuticals, further for education of experts, establishment of laboratories, organization of control and introduction of information sheets etc. are all well-known. The results of these efforts are undeniable even if we know that one can hardly keep level with the extremely rapid development in the pharmaceutical industry and research, and even if it is known that the costs of the appropriate control increased in such a way that they became important factors in the price calculation and the purchase of the special control instruments is a real trouble today also for institutions with good finances. At the same time it is well-known too that in the developing countries the demand for drugs increases from day to day and one can count with the fact that in these countries pharmaceutical factories will be established in growing number without satisfying - even partly - the above mentioned conditions.

Essential change can be expected, of course, only as a result of the conjugate effects of all the factors, especially, if the drug law appears as a primary impulse because of it's progressive quality and if it is not satisfied with the formulation of the prevailing situation created by the existing fundamentals.

From all these comes that the legislation should adopt itself to the changing circumstances and must keep level with the development. To what extent had it been accomplished we could approach mostly by studying the circumstances, that is which considerable discrepancies are to be found between the real situation and world of the legislation, the introduction of what sort of new definitions are necessary and to which new fields the regulations should be extended.

One of the deficiency of the present laws is that they are not adopted to one of the most important changes went on in the drug manufacturing; they do not make distinction between the manufacturing of chemical substances forming the active ingredients of pharmaceuticals and the production of specialities made by use of the formers. The first process is the task of the chemical industry the realization of which goes on almost only in factories established with immense material and mental investment in the developed countries while the actual production of pharmaceutical preparations and specialities known under the name of processing, compounding, formulating, filling etc., can be done also on smaller scale, in "manufactural" plants because it requires mainly physical processes.

An other deficiency is that in the factories making chemical transformations the pharmacist was replaced by the chemist, biologist, engineer, mechanic, physicist and pharmacologist. At the same time the pharmacist plays the role of the educated tradesman in the pharmacies. Practically he does not make medicine, still less he examines them but he is satisfied mostly with the observation of the outer marks of the label and packings. So the general "pharmacist" concept in the laws should be adjusted too.

The division of the complete manufacturing process into two parts exists even if both phases will be carried out by the same enterprise; the "processing" workshops are mostly isolated, possibly on another settlement. The quality of the drug will be determined primarily in the first, "manufacturing" phase. If the active ingredient is not adequate the result even of the most precise "processing" can be only a substandard drug. Because of his capabilities only the "manufacturer" can be obliged to

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