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ESTABLISHMENT OF PHARMACEUTICAL INDUSTRIES IN DEVELOPING COUNTRIES

Report and Proceedings of Expert Working Group Meeting

Budapest, 5 - 9 May 1969

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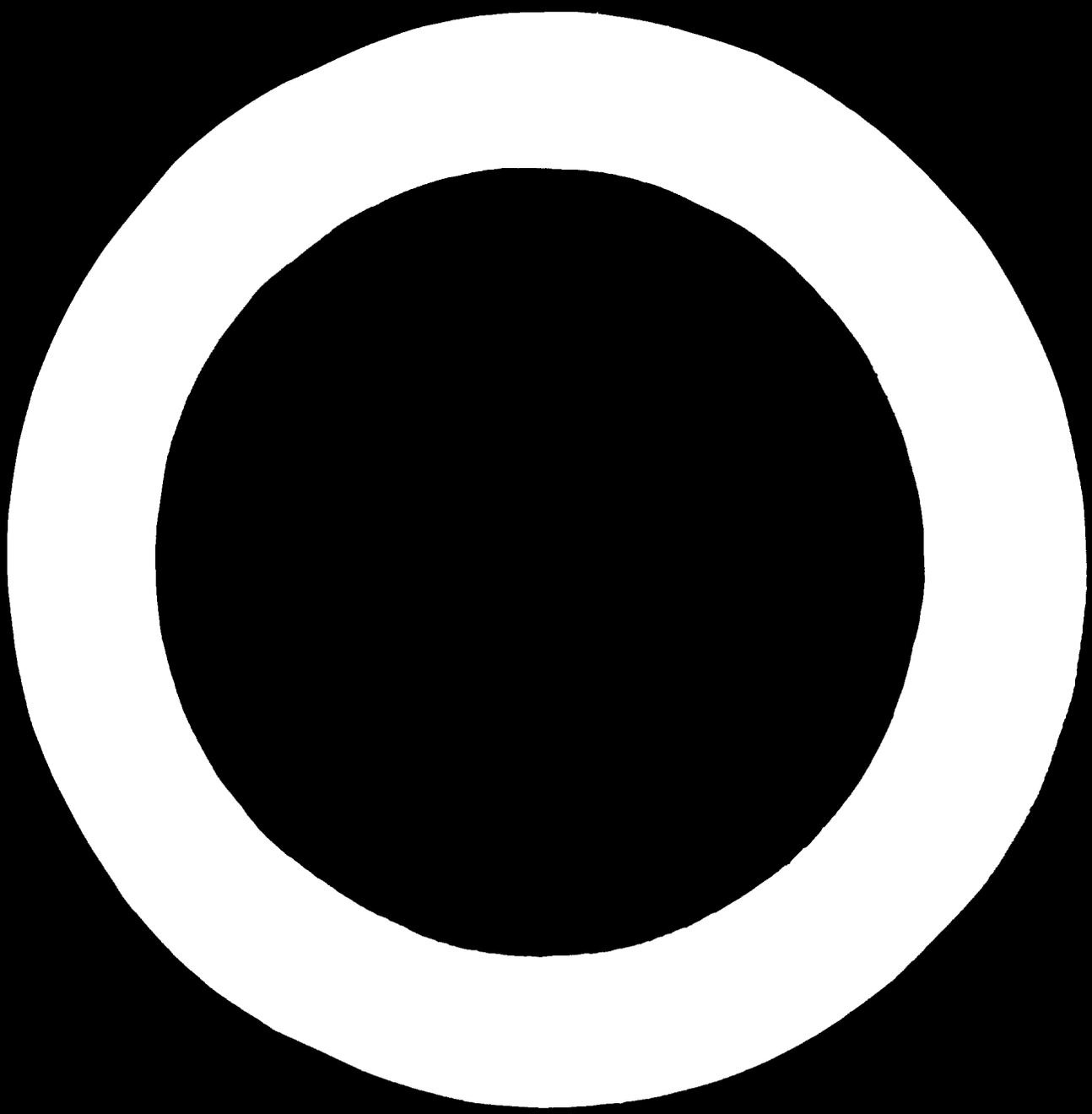
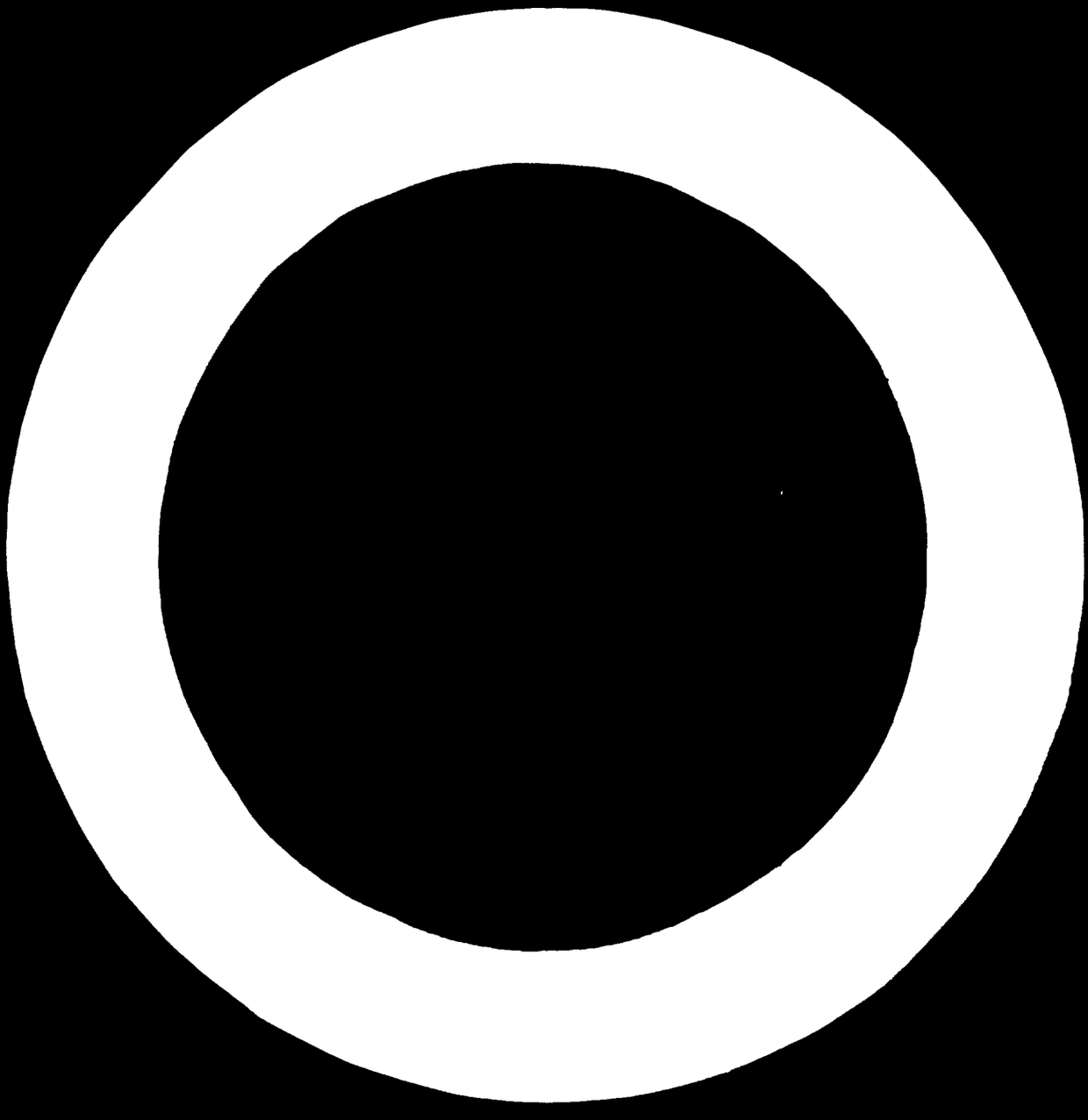
UNITED NATIONS





UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION, VIENNA

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Contents

Contents (cont'd)

Annexes

* Not participating as a member of the Expert Group - paper submitted as a country contribution.

Explanatory notes

References to "billions" indicate thousands of millions.

The following organizations are referred by their initials:

EEC = European Economic Community

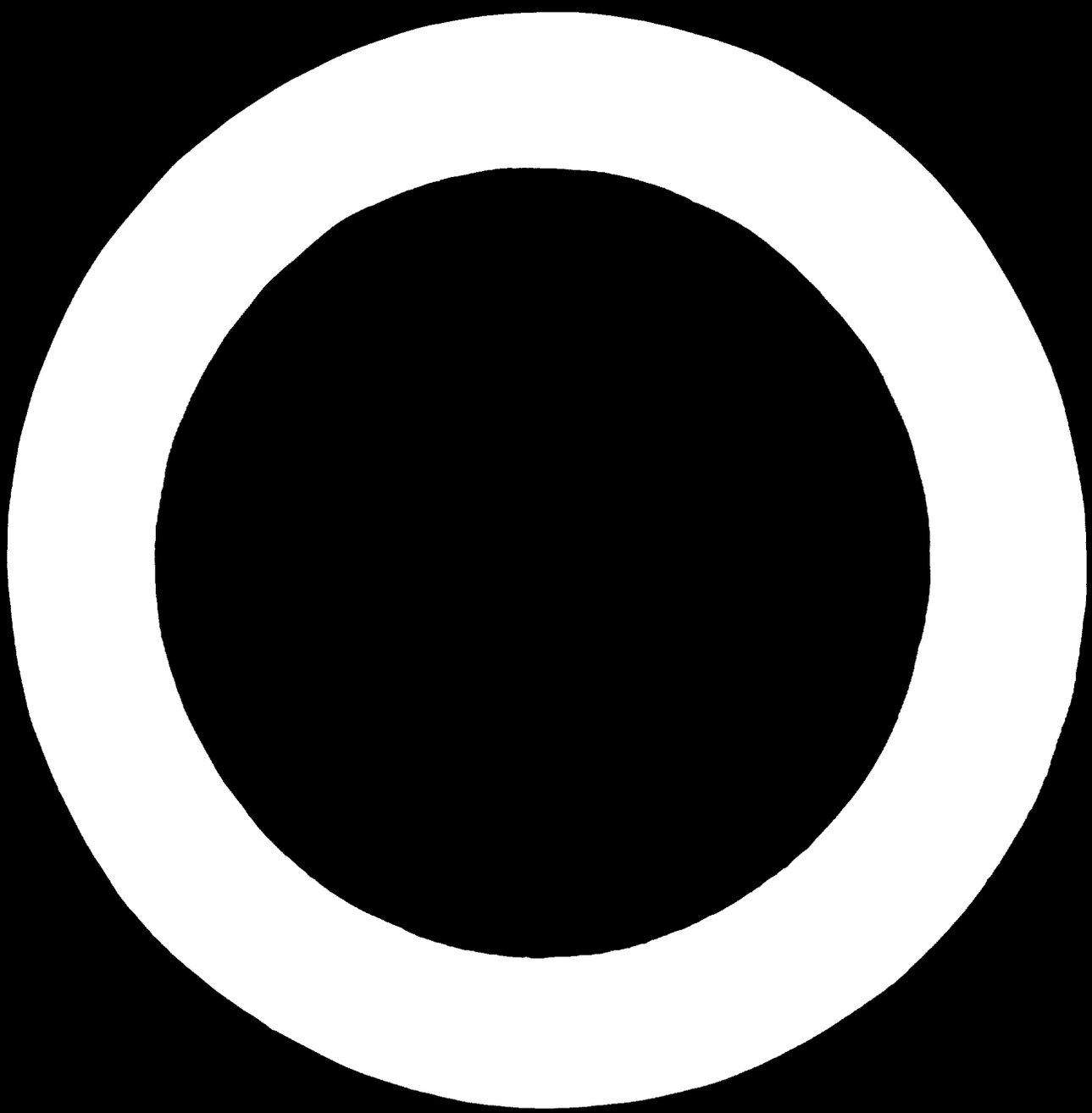
EFTA = European Free Trade Association

FAO = The Food and Agriculture Organization of the United Nations

OECD = Organisation for Economic Co-operation and Development

UNIDO = United Nations Industrial Development Organization

WHO = World Health Organization



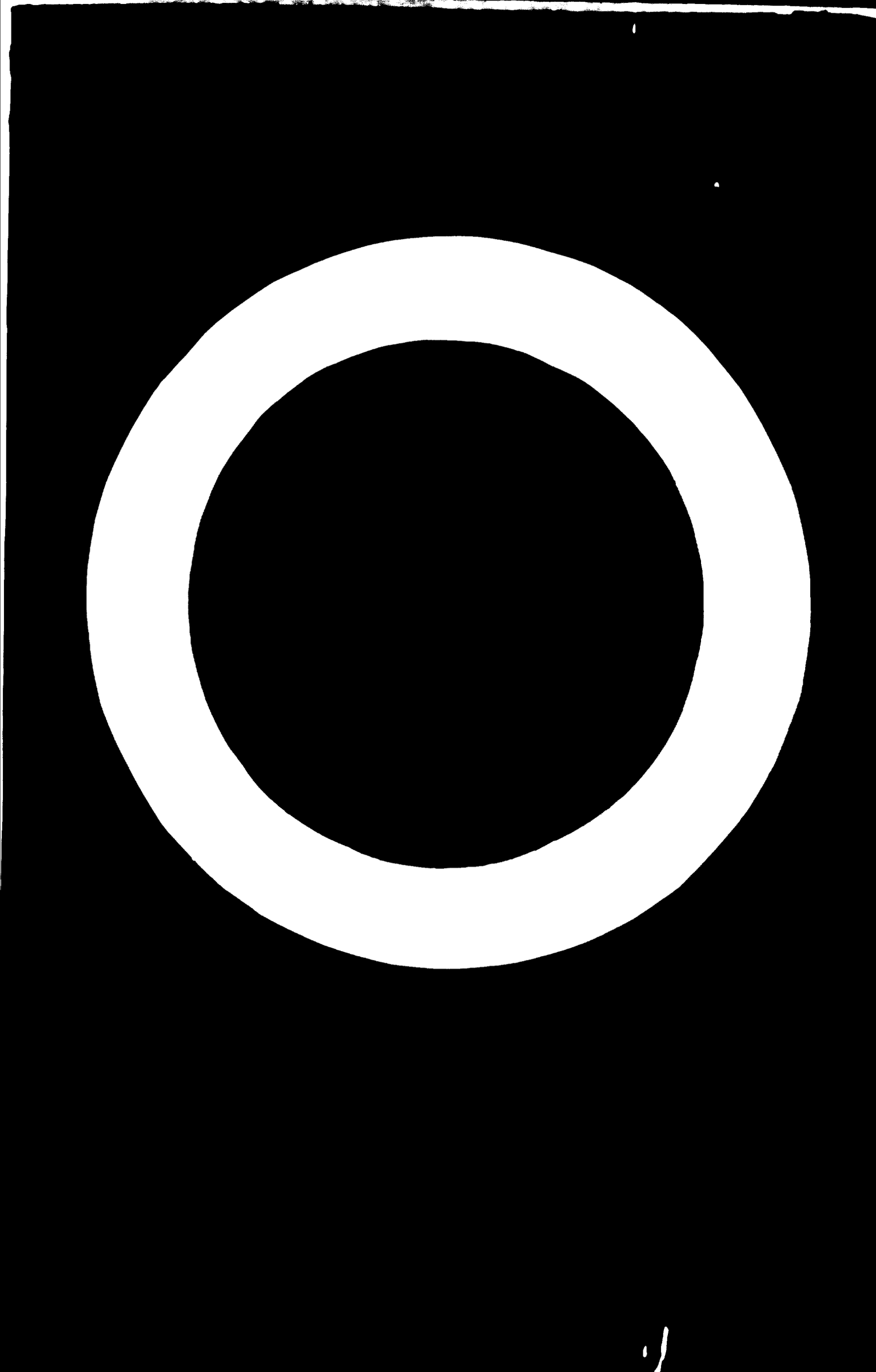
Letter of transmittal to the Executive Director of UNIDO

We have the honour to submit herewith the report of the Expert Working Group on the Establishment of Pharmaceutical Industries in Developing Countries. This report was prepared following the meeting held from 5-9 May 1969 at the headquarters of the Union of the Hungarian Pharmaceutical Industry in Budapest.

The chairman of the group was Mr. G. Horváth, Vice-President and Research Director, Union of the Hungarian Pharmaceutical Industry, and the Vice-chairman was Mr. Pál Székely, Technical and Scientific Director of the Hungarian State Trading Corporation, Medimpex. Mr. W. A. Caldwell and Mr. P. M. Terlizzi of UNIDO acted as Director and Meeting Co-ordinator respectively. Representatives of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) also took part in the meeting. The list of members of the group is given in annex 1 to the report.

The terms of reference for the Expert Working Group were to present and discuss selected papers on the main aspects of the problem facing developing countries wishing to initiate or improve their pharmaceutical industries, and to make relevant recommendations.

Facilities for the meeting were provided by the Hungarian Government through the Union of the Hungarian Pharmaceutical Industry which also arranged visits to the Pharmaceutical Research Institute and to the BIOGAL Pharmaceutical Works in Debrecen. Thanks are due to the Hungarian authorities and to those individuals therein (particularly Mr. G. Horváth, Mr. Pál Székely, Mr. J. Spolarich and Mr. G. Szabó) whose assistance contributed generally to the success of the meeting.



PART I

ORGANIZATION OF THE MEETING

1. The Expert Working Group Meeting on the Establishment of Pharmaceutical Industries in Developing Countries was held in Budapest, Hungary from 5 to 9 May 1969 under the sponsorship of UNIDO.

2. In addition to the discussions, visits were arranged to the Pharmaceutical Research Institute and to the BIOGAL Pharmaceutical Works in Debrecen, which provided the participants with an appreciation of some of the problems involved in pharmacological control. Facilities and arrangements for the meeting and visits were provided by the Union of the Hungarian Pharmaceutical Industry.

3. The purpose of the meeting was to collect and analyse information on the problems facing developing countries wishing to establish or to improve a pharmaceutical industry and to make recommendations to help developing countries in dealing with these problems.

4. The meeting was convened by Mr. W. A. Caldwell of the Industrial Technology Division of UNIDO, who welcomed the participants in the name of UNIDO and outlined the general scope and aims of the meeting. In turn, Mr. J. Lazor, Head of the Pharmacy Department of the Ministry of Health, welcomed the participants to Hungary and emphasized the importance of a pharmaceutical industry to developing countries and the complexity of the problems involved. He then declared the meeting open. A translation of his remarks is given in annex 3.

5. The meeting elected as Chairman Mr. Gyula Horváth, Vice-President and Research Director, Union of the Hungarian Pharmaceutical Industry, and Vice-Chairman, Mr. Pál Székely, Technical and Scientific Director of Medimpex.

6. In addition to Mr. Horváth and Mr. Székely, seven other experts participated in the meeting: one each from Austria, Israel, the Union of Soviet Socialist Republics, the United Kingdom, and three from the United States. Representatives from UNIDO, WHO and FAO also participated and several observers

from Hungary attended. Mr. W. A. Caldwell of UNIDO acted as Director of the meeting and Mr. P. M. Terlizzi of UNIDO served as Meeting Co-ordinator. The participants are listed in annex 1.

7. Presentation of each of the expert papers was followed by a discussion and preliminary consideration of the recommendations made. After a general discussion, the participants joined in formulating a first draft of conclusions and recommendations.

8. The present publication includes the report and conclusions of the group resulting from the meeting and summaries of the expert papers discussed during the meeting. Papers were presented by experts from Austria, Israel, the Union of Soviet Socialist Republics, the United Kingdom, the United States and from FAO and WHO. In addition, UNIDO presented an introductory paper: "Patent aspects of the pharmaceutical industry" and another paper: "Pharmaceutical industries in the Second Development Decade".

9. The views expressed in the papers of the experts are those of the authors and do not necessarily represent the views of the secretariat of UNIDO.

GENERAL RECOMMENDATIONS

10. The proceedings of the meeting resulted in numerous recommendations for action in the establishment of the pharmaceutical industry sector in developing countries, including the following assessments.

Assessments

11. In order to prepare a suitable plan for the introduction of pharmaceutical industry sectors in a developing country, the following should be assessed:

- Data on the general economic and hygienic standards of the country;
- Demographic data, such as the population of the country, average life expectancy, population structure and increases, and general attitudes of the population concerning medical treatment and pharmaceuticals;
- Local patterns of medical treatment and its costs;
- The existence and prevalence of diseases and common ailments, especially those of an infectious and epidemic nature;
- Medical care available, the number of practising physicians, nurses, hospital beds, pharmacies, pharmacists, technicians in the medical area and scientific personnel in sciences related to medicine;
- The size and the nature of the existing local pharmaceutical market, the traditional supply and distribution system, price levels and pricing structures;
- Laws regarding the importation and distribution of pharmaceuticals, company policies and industrial laws, taxation, custom duties and protection of industrial property;
- Local availability of trained and/or trainable manpower for assignments in the pharmaceutical industry;
- Availability of packaging materials for pharmaceutical preparations and the development potential of this area;
- The present and projected demand for pharmaceuticals, classified in therapeutic categories;
- Potential export possibilities and regional and interregional co-operative plans;
- Therapeutic and prophylactic requirements of food-animal and work-animal populations;

- General attitudes towards foreign assistance or investments, and incentives and protection policies, if any;
- Industrial feasibility of the manufacture of selected pharmaceuticals. (Such an assessment should be undertaken jointly by WHO, FAO and UNIDO, and should be carried out not only by pharmaceutical, veterinary, medical, financial and economic advisers of the organizations, but also by specialists resident in the respective developing countries or regions.)
- Data on human therapeutic requirements, treatment patterns, and treatment costs. These can be obtained from:
  - (a) Physicians and veterinarians familiar with the local situation;
  - (b) Statistical data on drug imports;
  - (c) Indicated demand of drug consumption obtained, for example, from local sickness boards or from records of local hospitals and military pharmacies;
  - (d) Representative samples of medical perscriptions by hospital physicians and general practitioners.

12. Under the aegis of the health authorities, a detailed analytical evaluation of such information should be undertaken by therapeutic and clinical pharmacological experts with a view to evaluating demands for pharmaceutical preparations and drugs essential for sound medical care in the region under study, with estimates of annual consumption and, where possible, standard treatment costs per patient per day.

13. From the above assessments an up-to-date evaluation can be made of products essential to sound medical care which could potentially be produced in the country or region.

Pharmaceutical industry and public health service

14. If the production of pharmaceutical preparations is to be based on local therapeutic requirements, the close co-operation of the industry with the public health services of the country or region is desirable. Where a pharmaceutical industry is planned on the basis of a partnership between a foreign enterprise and a government agency, its production programme should reflect the true therapeutic needs of the country and should contribute to the objectives of the national public health service.

15. Close co-operation with public health services should protect a newly established pharmaceutical industry against isolation and thus against a hazardous business situation. Equally important is a permanent minimum level of drug consumption guaranteed by a sufficient number of prescribing physicians as well as a reasonable number of public hospitals and governmental pharmacies.

16. Countries should consider channelling most of their import and domestic buying, especially for government health programmes, through a central agency and purchase commonly used drugs in bulk for greater economy.

Adaptation of production to actual markets

17. Developing countries interested in the establishment of pharmaceutical industries should recognize that, owing to small production runs and other factors influencing production efficiency and product costs, locally manufactured pharmaceutical preparations may well be more expensive than imported equivalents during the first years of operations. Furthermore, the drugs needed for urgent therapeutic requirements are not necessarily those that will be profitable to manufacture.

18. The special conditions required, complicated by an economically unbalanced situation which may exist in a developing country, necessitate careful planning of any material step towards the establishment of a pharmaceutical industry. The permanent availability of advisers on local therapeutic needs and medical progress in general as well as on technological progress in the manufacture and control of drugs is highly desirable. Furthermore, advisers should be well informed on all factors that could affect the local market situation, such as changes in total population, in the average age of the population, in morbidity statistics, in the disease spectrum, in the national income *per capita* and in the numbers of practising physicians, medical auxiliaries, hospital beds, pharmacies and pharmacists, and in the promotional efforts of the pharmaceutical industry itself.

19. Since all data, even that of a highly technical nature, must be considered in relation to local conditions, it would be an error to extrapolate, for example, from marketing figures of other countries, especially developed countries.

20. In developing countries the scale of priorities for drugs is very different from that of most developed countries. Whereas developed countries are concerned with the treatment of diseases of the heart and the central nervous system and psychosomatic conditions, developing countries must give priority to treatment of parasitic and other communicable or infectious diseases, and therefore must develop treatments suitable for the existing situation both in terms of cost of production as well as the level of medical facilities available, particularly in the rural areas.

Selection of items for production

21. If, on the basis of an assessment of actual therapeutic needs, the initiation of a complete pharmaceutical industry is inadvisable, a beginning could be made with a small packaging sector that could be built up gradually as required, depending upon demand, availability of personnel, premises and equipment, availability of utilities and financial resources. For example, since a large proportion of primary drug needs in a developing country concerns such products as solutions, syrups, powders, granules, tablets, and ampoules which can be made from imported raw materials using light equipment, their manufacture may be fully justifiable. If the productive capacity of such an industry is not fully exploited, the production of cosmetics, toiletries and the like can be considered.

22. Since the equipment required for the manufacture of solutions, syrups, powders, granules, tablets and ampoules is generally standardized, easily installed, and readily adaptable to changes in demand, a developing country should not hesitate to consider the early manufacture of those preparations.

23. Since natural products indigenous to a country, such as botanicals and animal organs, can in some cases be a source of active materials for pharmaceutical preparations required to meet therapeutic needs, their exploitation should be considered. Such a programme may provide a training ground for the development of pharmaceutical disciplines.

24. A developing country that wishes to produce certain well established types of antibiotics should consider that, given the low world market prices of most of the non-patented antibiotics, the problems of quality control and the economics of merchandising involved, it will seldom be desirable to encourage the establishment of plants to produce them. Only where the home market is sufficiently large to make such production economic or where substantial export to other countries can be established can a successful development of antibiotic manufacture be expected.

25. A developing country should not consider the complete production of synthetic medicinal chemicals unless it has an advanced fine-chemical industry. Importing fine chemicals from the technically developed countries may be the only economically feasible recourse.

26. In selecting a medicinal agent for production, it should be borne in mind that the therapeutic requirements need not always mean market requirements.

As already noted, the medications most urgently needed may not be those most profitable to produce.

Economic aspects

27. Although the costs of locally produced pharmaceutical preparations during the first years of operation of a newly established industry can be expected to exceed those of comparable foreign products, a reasonable economic status may be reached with growing experience and sales. The rate of consumption of pharmaceutical products tends to continue to increase owing to progressive rises in living standards and level of education and advances in hygiene and medical care. In addition, the required production of auxiliary materials such as cartons, glassware and plastics are sizable activities that can generate supplementary profits.

28. Since the substitution of domestic production for imports would considerably augment the national value added, the loss of customs revenue entailed could be made up by a local tax.

29. The marketing of rational pharmaceutical output, i.e. the choice of distribution channels and the selection and pricing of products, can be rationalized. Where all pharmaceutical products are imported - either by the private or by the public sector - there is a proliferation of competing products and of channels of distribution, with the result that wholesalers and retailers cannot spread their costs over a high volume of sales. A national pharmaceutical industry, having organized the distribution of locally made products, might proceed to refashion the arrangements for distribution of the products that still have to be imported.

30. The establishment of a pharmaceutical industry should be based upon a well directed assessment of the economics, labour supply and markets involved and should not be undertaken merely for reasons of national prestige or to conserve foreign exchange. Wherever feasible, consideration should be given to the consolidation of pharmaceutical production on a regional or interregional basis, to minimize the financial burden in any individual country.

31. The importation of finished biological products may not always be feasible or even the most advantageous choice. For example, vaccines against exotic viruses, produced by well staffed and well equipped laboratories in developed countries, may not be authorized for export by their governments in view of

the high risk of escape of the pathogens involved. In any case, local production, using indigenous and more antigenic strains of viruses or bacteria, is generally preferable, as the vaccines produced therefrom will generally be more efficient.

32. Developing countries interested in the establishment of national pharmaceutical industries may be well advised to encourage experienced foreign pharmaceutical organizations in establishing facilities to initiate sectors of a pharmaceutical industry and should provide adequate incentives and protection.

Legislation

33. In the initial stage of establishing a pharmaceutical industry in a developing country it is of fundamental importance that a legislative and enforcement system should be put into operation which will ensure that the drugs produced are of adequate quality.

34. Anti-monopoly legislation is frequently needed to prevent manufacturing enterprises, indigenous as well as foreign, from misusing their power, for instance by setting prices that are unduly high in relation to the ability of the population to pay, or to deny newcomers access to the market. Developing countries should consider introducing laws or establishing regulations dealing with good manufacturing practice, quality control, and advertising of pharmaceuticals (including the distribution of free samples to both the public and the medical profession).

35. If not already in force, a system requiring the registration of all pharmaceutical products with a government authority should be initiated. The system should require that the registrant, when applying for permission to sell drugs, satisfy the authority as to their safety, efficacy and quality. The system should be designed to take into account the needs of a modern, developing pharmaceutical industry. Experts responsible for supervising the manufacture and control of drugs should possess the qualifications of scientific education and practical experience. The degree of legal control should be commensurate with the status of relevant legislation and its enforcement.

36. Patents play an important role in the pharmaceutical field. Consequently, when establishing a pharmaceutical industry sector, a developing country should institute, if not already in force, conditions whereby protection for patent holders will be provided as regards transfers to domestic producers and their foreign associates of patented technologies, materials and the like.

37. All countries should avoid using their pharmaceutical control systems as a means of raising revenue or to protect home industries. If there is a need to raise revenue or to protect certain industries, this should be done by other means and not be incorporated in legislation designed to ensure the quality, efficacy and safety of pharmaceutical preparations.

Pharmaceutical quality control

38. Whenever possible, pharmaceutical preparation produced in developing countries should be controlled to establish their therapeutic equivalence to standard preparations. Since pharmaceutical control of identity and purity cannot safeguard therapeutic equivalence completely, therapeutic equivalence must be ascertained by clinical studies.

39. The aim of pharmaceutical quality control is to achieve sustained and uniform manufacture of products of desired quality. Once the therapeutic efficacy and safety of a drug has been established, the pharmaceutical quality of the material available in commerce must be judged by measuring its identity, strength, purity and other relevant characteristics. The best and most important means to achieve this is regular production control on the basis of production control specifications.

40. Raw-material and product specifications are necessary to determine the suitability of raw materials and the quality of end-products. Such specifications are usually included in official compendia such as pharmacopoeias, pharmaceutical codices and formularies.

41. Production control should be effective from the first stages in the manufacture and comprise (a) the suitability of equipment, premises and staff; (b) control of manufacturing procedures; and (c) control of starting material, half-finished products and end-products to ensure that they comply with established specifications.

42. A modification in the physical preparation of a drug may alter its blood-level absorption and affect the treatment. Therefore, before altering a formula for a preparation, the effect of the proposed physical modification in its preparation must be tested in the medium in which it is to be used. For example, the activity of a basic drug may be changed so as to make it less effective if it is used as an ingredient in a cough syrup than when it is administered in the usual manner. Any modification of a drug must therefore be checked against the standard for therapeutic activity.

43. FAO and WHO can, within the limitations of their funds and manpower, provide experts and laboratory equipment for the production and quality control of vaccines to control most infectious diseases, and can arrange training courses and seminars and grant fellowships for the study of the quality control of drugs.

44. Requirements for production control are included in the legislation of several countries and serve as a basis for inspection of pharmaceutical manufacturing establishments. A WHO expert committee has adopted the manual Good practices in the manufacture and quality control of drugs,[1/] which can serve as a guide for such inspections.

45. In assessing the alternatives of importing pharmaceutical products or producing them domestically, the relative quality of imported and domestically manufactured items must be taken into account.

46. An important contribution to quality standards is a pharmacopoeia or similar book of published standards. A developing country should have such a specific reference that covers the standards of identity, quality and strength for those medicinals which represent the best practice and teaching of medicine. The provisions of the pharmacopoeia or standards in force should be binding on all those who produce or dispense drugs. The possibility of utilizing national and international pharmacopoeias should be kept in mind.

47. Developing countries in the initial stage of establishing a pharmaceutical industry, must not only have adequate controls for their own manufacture but must ensure that products imported into their territories comply with equivalence standards. Countries without a pharmaceutical industry must take suitable protective quality control measures for pharmaceutical imports.

48. Countries which plan to export pharmaceutical intermediates, raw materials or finished products should be well informed of the quality standards they must maintain, even when exporting such items to countries that do not yet have such standards.

49. The following factors should be considered to help minimize the problems associated with establishing a pharmaceutical manufacturing sector.

1/ See annex 4.

Selection of areas and facilities

50. Pharmaceutical plants are often large enterprises with considerable requirements for electrical power, water and steam and may discharge large amounts of industrial effluents, therefore the auxiliary services required can represent an important problem. Plants should be near good roads and have access to a constant labour supply. Proper maintenance is indispensable.

Equipment

51. All essential equipment should be purchased from a minimum number of manufacturers so that punches, dies and other components will be interchangeable and thus the supply of spare parts can be minimized.

Personnel

52. For the establishment of a pharmaceutical manufacturing sector, it is necessary to determine what skills are needed by the country in order to produce pharmaceuticals. If these skills do not exist or cannot be obtained economically, pharmaceutical production should not be considered until this sector has reached a sufficiently high level of development. In the selection of candidates for the pharmaceutical industry sector, while particular technical competence is required in posts dealing with testing, production, research and the like, developing countries should not overlook the fact that entrepreneurship is a necessity for carrying out the commercial aspect of the industry. As an incentive, special benefits for pharmaceutical workers could be provided, such as free (or reduced cost) medicaments for themselves and their families.

Expansion plans

53. In planning the manufacturing sector of a pharmaceutical industry, a developing country should consider a scheme whereby individual functions such as packaging can be made to expand in steps to a multinational plant as disciplines and know-how are developed. In this consideration, initial planning would include selection of site, purchase of sufficient ground for future expansion, proximity to transportation and utility services and so on. The physical design of the initial plant should be carefully considered to ensure that it can expand both vertically and horizontally to employ the most efficient manufacturing arrangements. These would include storage areas, quality control, raw-material preparation, sterile rooms and the like. In addition,

such information as type of process to be used, the equipment required, capacities, reporting of quality control on special forms, the marking of batches and so on should be carefully developed.

Prerequisites for sound pharmaceutical production

54. Sound pharmaceutical production is affected by:

(a) Availability of specialists and facilities

Permanent availability of specialists who can advise on therapeutic needs and progress, and existence of a number of public hospitals and pharmacies, health centres, clinics and other facilities large enough to provide a permanent minimum level of consumption of the pharmaceutical products and services produced by newly established industries.

(b) The local pharmaceutical market

Population increase; changes in the disease spectrum; urbanization and growing health awareness; increase of national income per capita; activity of the official medical-assistance organizations, medical facilities and personnel; export possibilities; promotional efforts of local pharmaceutical industry; and discovery of new drugs against previously incurable diseases or of better drugs against diseases that are already curable, all significantly influence the local market.

(c) Domestic sector

The establishment of a domestic sector of the pharmaceutical industry in a developing country with relatively small population can effect a saving in foreign exchange, and can facilitate control of production, prices and distribution channels of pharmaceuticals. The most urgent need in a developing country is frequently for effective drugs for control and treatment of parasitic diseases in both man and animals. The development of a pharmaceutical industry will depend upon its purpose, the money available and therapeutic needs. If profit is the only aim, pharmaceutical development would be along one line; if the aim is to satisfy actual needs, therapeutic development will follow another line; if the aim is a combination of both, then yet another plan will have to be followed. Production programmes based only upon therapeutic needs are generally not profitable. A compromise between the realities of the market, public health needs and conditions, and therapeutic needs must be made. Economies of scale play an important role in such calculations.

(d) Consumption rate

Since the rate of increase of consumption of pharmaceutical products continues to rise because of increasingly higher living standards and educational levels, developing countries should plan their pharmaceutical industry to provide for future development.

Training of workers

55. The training of workers is an important factor in establishing a sector of pharmaceutical industries. Such personnel can be trained in a pharmaceutical

enterprise, in courses arranged by associations of pharmacists or pharmaceutical industries, in educational institutions at both undergraduate and graduate levels, through the use of grants or fellowships in foreign countries or by specific training from advisors supplied by the United Nations or other concerned organizations.

56. A training centre, accessible to specific regions, where equipment in various scales for the manufacture of tablets, ampoules and other dosage forms could be made available for practical use and study and for developing experience in repair and maintenance of equipment.

57. A training centre operated in conjunction with an educational institution could be supplied with equipment provided on a loan basis by manufacturers. Such an arrangement would be beneficial to both the trainees and the sponsors who supply the equipment. In addition, the trainees would be advised in the important aspects of necessary pharmaceutical documentation.

Environmental conditions

58. In choosing drugs to be manufactured in a particular country, the environmental conditions of that country have an important effect; for example, sulphathiazole is therapeutically active in temperate zones, whereas in tropical zones this drug can be toxic. Careful consideration should be given to the appropriateness of drugs for a country considering their manufacture.

Efficacy and safety

59. The therapeutic efficacy and safety of drugs should be the concern of all pharmaceutical manufacturers, whether they develop new drugs, produce only established formulations of pharmaceutical preparations or restrict their activities to repackaging.

60. Pharmaceutical manufacturers must be well informed of all potential biological activities of their products. They must be able and willing to inform the medical profession about these effect and also to provide governmental authorities with the necessary documentation on the biological evaluation of their products.

61. Since, in developing countries, therapeutic methods and conditions of drug application often differ from those in developed countries, specific problems are likely to arise in the assessment of efficacy and safety. Deviations from the recognized compatibility of certain drugs from that in countries where the

drugs in question have been investigated in the first instance can occur under conditions of malnutrition or even of different nutritional habits, of different types or incidence of drug resistance, of genetic disorders or average body size and weight, or different climate or other environmental factors that affect the absorption, metabolism and excretion of drugs.

62. The inclusion of "traditional" or "indigenous" drugs into local pharmaceutical preparations may create certain problems of efficacy and safety. The therapeutic value of such drugs is often questionable, and many of them may be no more useful than placebos.

63. The study of efficacy and safety problems requires close co-operation between the pharmaceutical and medical professions. Since developing countries will not always have the necessary personnel trained in pharmacy, pharmacology, clinical pharmacology and experimental therapeutics, WHO can assist in, inter alia, the training of pharmacists, technicians, medical students, post-graduate students and research workers in these medical disciplines. Furthermore, WHO is prepared to assist in the establishment and maintenance of lists of "drugs of choice" on the request of developing countries.

Natural products

64. The natural products available for investigation fall into two groups:

(a) Botanicals

Natural products indigenous to a country or region form a logical exploratory area for the development of sources of therapeutically active materials and/or intermediate preparations for drug or allied products. The field should be considered along the following lines:

(i) A limited qualitative survey and a scientific mapping of natural products containing biologically active materials should be made;

(ii) After assessing the raw material supplies, a preliminary analysis of the market situation and of economics should be carried out with respect to the profitable volume of manufacture, prospective domestic consumption and foreign sales. Analysis should include costs of collection and identification of plants, training in collection techniques, transport, storage of starting materials and the like;

(iii) Plants whose active principles are in demand and of which large quantities must be processed may need to be cultivated in plantations. Such cultivation should be directed by experts, and assistance from FAO may be needed;

(iv) Since some medicinal herbs must be stored in air-conditioned rooms to prevent loss of their active materials, and rapid transportation for plants collected must be available to minimize loss, a developing country wishing to enter this field should be prepared to consider providing such facilities;

(v) Considering the usually poor transportability of vegetable raw materials because of their volume/weight ratio and the often unsatisfactory conditions of roads in developing countries, which cause high transport costs, pharmaceutical phytochemical industries should be brought nearer to the source of raw materials (for example, to plantations).

(b) Animal organs

(i) The collection of animal organs should be undertaken only by well equipped slaughterhouses. After animals are killed, the organs that provide the active material must be separated from other tissues by skilled workmen;

(ii) In an active animal organ collection and processing programme, the material must be kept at deep-freeze or refrigerator temperature for various periods of time therefore the necessary equipment must be provided;

(iii) Since the commercial extraction of many active ingredients of natural substances involves the circulation of great amounts of organic solvents, this requirement must be objectively planned for;

(iv) Some animal organs contain differing quantities of active substances, depending upon the area of the world from which they originate and the local health conditions. Therefore, before initiating the extraction of active substances from animal organs, a thorough study of the raw materials should be undertaken.

Veterinary sectors

65. Pharmaceuticals for veterinary treatment should include those that can be applied in mass treatment and which are aimed at increased animal productivity through improved health, and at preventing the transmission of animal infections to humans.

66. Since parasitism is the greatest single cause of economic loss in livestock, consideration should be given to the production of parasiticides and prophylactics to control internal and external parasitism. These products are to be used for the control of arthropods (insects, ticks and the like) helminths, molluscs which may be helminth carriers, rodents which may be arthropod carriers, and so on.

67. The centralization of all vaccine production in a limited number of fully staffed, well-equipped and strategically located regional laboratories is recommended. Tests for the potency and innocuity of vaccines are a vital part of the work of centralized centres, since there have been instances of vaccines with low potency creating a false sense of security and also of contaminated vaccines contributing to the spread of disease.

68. In view of the dangers involved in handling various viruses or suspected materials submitted for examination, the manipulation of viral strains other than those already present in the countries concerned is not encouraged except by adequately staffed and equipped laboratories.

69. Developing countries are encouraged to consider the relative advantages and disadvantages of initiating vaccine production which involves commitments in building, staffing and maintaining the necessary premises. Comparison between such production with the purchase and importation of the biologicals concerned should be made wherever possible.

70. The establishment in developing countries of laboratories for the production of veterinary biologicals and all the related activities of research and training should be primarily in the hands of the government or other organizations capable of maintaining the high standards necessary.

71. Since parasitic diseases account for the loss of from 10 to 30 per cent of food animals (particularly cattle and buffaloes under one year of age) in developing countries, and this is a heavy burden to bear, a field of considerable interest would be the production of anthelminthics. In some regions of the world, certain food animals such as water buffaloes are also used for work in paddy fields, for ploughing, treading and the like and therefore may become infected by water-borne parasites such as the liver fluke, particularly in areas where new land is being opened up for cultivation through the implementation of irrigation schemes. In such cases, high mortality rates may result, and the infected animals can no longer be used for food.

72. Group treatment of animals must be considered of paramount importance, because it affords great efficiency with a minimum of cost and effort. Specialized treatment of individual animals is generally a luxury that only developed countries can afford. While in developing countries the therapeutic use of antibiotics for valuable animals such as breeding stock, high milk-yielding females and the like has been extended, some misuse of these agents has occurred, leading to the destruction of the intestinal flora in ruminants, particularly milk-producing animals, reducing or even stopping milk production.

73. Since protein of animal origin is badly needed in developing countries, the promotion of growth of food animals is highly desirable. Animals that are unhealthy or that do not thrive normally do not add to the food supply of a country.

74. Because, in such countries, mass vaccination should be resorted to for the control of most of the infectious diseases of animals, the local production of newly developed vaccines, particularly those obtained by tissue-culture techniques, should be encouraged wherever feasible. More extensive use and possible local production of parasiticides and prophylactics should be considered for the control of parasitic diseases.

75. If production facilities for pharmaceuticals for human use are in operation or are planned, their expansion or extension to accommodate some veterinary preparations may be accomplished with minimal changes. The production of feed additives and vitamins for animal nutrition should be considered.

Statistics

76. Statistics on markets should be collected for products whose use is widespread and whose value is relatively high. Estimates of demand should include factors such as increases in population and per capita income, the necessity of achieving a particular health goal and projected changes in the disease spectrum.

77. Because of improper classification, import and export statistics may not always be reliable. For example, imports of pharmaceuticals may be combined with those of soap, cosmetics, surgical supplies and the like. In analysing the types of drugs in which a particular country should be most interested, the prevalence and severity of particular diseases, the number of patients treated and general hygienic standards should be considered.

78. While statistics concerning the health problems of a country usually encompass the entire population, statistics on the consumption of pharmaceutical products may relate to only a limited segment of the population that has access to health services. Accordingly, in the planning of pharmaceutical production goals, such discrepancies must be taken into account.

Advertising and publicity

79. The prestige or image of nationally produced pharmaceutical preparations can be advanced by using high quality labels and packaging as equally attractive as that of imported products.

80. Within the limits imposed by their laws and regulations, developing countries should utilize advertising media such as posters, pamphlets, calendars and local cinemas (film slides and the like) in addition to exhibiting their

national products at fairs or in special shows throughout their territories. Those attending should be able to see models of pharmaceutical preparation procedures and be invited to visit pharmaceutical plants. Regular tours of such plants should be arranged for schools, the military and other significant institutions.

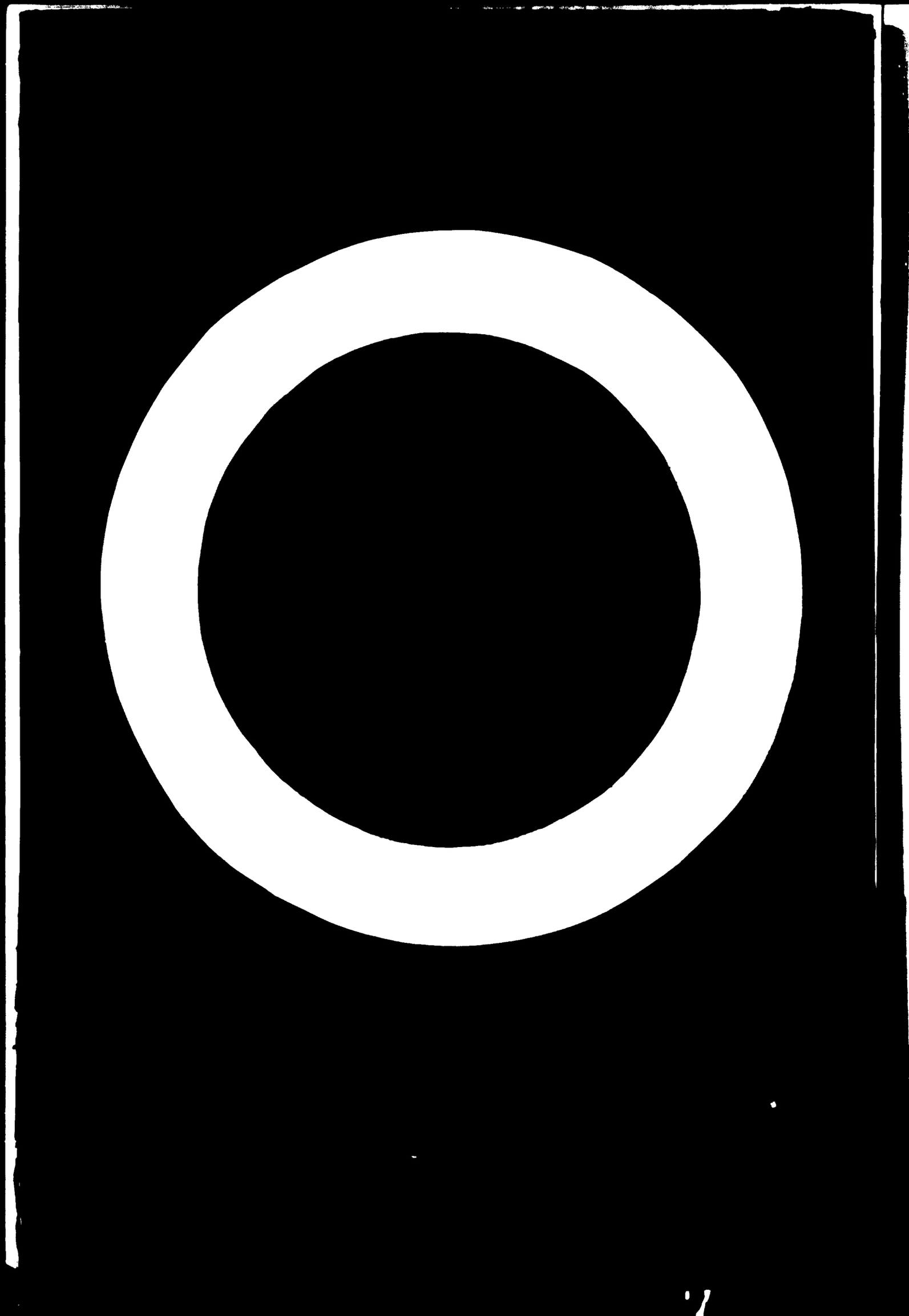
91. It is of the utmost importance that available information regarding pharmaceutical products be made accessible. Reliable and accurate data should be provided by making available reference material which will identify, for the patients as well as the physician, the uses, efficacy and possible hazards of individual drugs.

PART II

SUMMARIES OF PAPERS PRESENTED AT THE MEETING

The papers prepared for the meeting included a statement by Mr. J. Lazor of the Hungarian Ministry of Health (reproduced as annex 3) and reports by experts from Austria, Israel, the Union of Soviet Socialist Republics, the United Kingdom and the United States, as well as from FAO, UNIDO and WHO. These papers, as listed in annex 2, are summarized in the following pages.

India, although not represented on the Expert Panel, submitted a country paper subsequent to the meeting.



The establishment of a pharmaceutical industry in a developing country - a case history

by Yoel Amiran

A description is given of the guiding principles of the Burmese Government for the establishment of the Burma Pharmaceutical Industry in the early 1950s, under a foreign management.

The period preceding the start of the industry is discussed in great detail, with special reference to manpower problems, existing medical services, retail drug outlets, the importation of foreign drugs, and institutions of higher learning. The planning of the factory layout and its long-term influence on the industry is analysed, with special reference to the production of extracts and tinctures and to the fermentation unit for yeast production. The policy governing the choice of medications ultimately to be produced is indicated and reasons given for the integration of product lines such as insecticide formulations and antivenenes. The different departments, as well as the types of medications produced from 1955 to 1959, are then reviewed.

Burmese management of the industry began in 1959 with the termination of the contract with the foreign firm. The senior Burmese staff took over the management of the Burma Pharmaceutical Industry, with the help and guidance of foreign advisers. This period heralded policy changes involving raw material and equipment purchase, know-how agreements with foreign firms and administrative protection of locally manufactured medications. All of these topics are dealt with exhaustively, together with other topics such as public trends concerning medicines, presentation of finished products, publicity and medical detailing.

The interdepartmental relationships within the industry and the role and influence of the various committees are reviewed. External relations with other governmental agencies and scientific institutions are explained.

The role of the worker in the factory and the steps taken to increase his participation in the general effort are reviewed.

Finally, the delicate role of the foreign adviser in a developing country and the importance of human relations are analysed.

How to conduct a realistic marketing, economic and financial study of the growth potential of a pharmaceutical industry in a developing country

by John A. Deering

This paper deals with the evolution and characteristics of the pharmaceutical industry. The stages of its development and the markets that it serves are considered. Figures for the world production of pharmaceutical products during the period 1955-1967 and projections to 1980 are presented. Next, the growth of pharmaceutical production in the developed and developing regions of the world are considered, again with projections to 1980. Also analysed are the growth of *per capita* consumption of pharmaceuticals to present levels and projections of future growth in both the developed and developing regions of the world.

The structure of the industry is studied, stressing the tendency towards concentration and trends in manufacturing, technology, raw materials (their kinds and the sources of supply), research and development, quality control and good manufacturing practices, and manpower requirements. The courses of action open to developing countries to overcome their technological shortcomings, and the cost structure of the industry, with special reference to the developing countries, are explained.

Consideration is given to the factors that influence the market for pharmaceutical products in the developing countries, in terms of the size of the national market and *per capita* consumption of pharmaceuticals. Among them are the following:

(a) Present and past levels of drug consumption, including sources of data and their usual limitations; domestic and foreign suppliers of drugs; national health programmes and their relationship to the effective demand for drugs, showing the reasons why this relationship is not great;

(b) Objectives of national socio-economic development plans, including an assessment of the feasibility of targets set for various economic sectors that have an impact on health; effects of the political environment;

(c) Gross national product, income *per capita*, inequalities of distribution of income and wealth, and the correlation between income *per capita* and consumption of pharmaceuticals *per capita*; differences between urban and rural areas;

(d) Expenditures for health: indirect (governmental), on the central, intermediate and local levels; through third-party systems; and direct (by recipients);

(e) Availability, quality, utilization and distribution of health resources, both governmental and private; medical manpower, including traditional (folk) practitioners; medical facilities, including hospitals, health centres and other out-patient establishments;

(f) Cultural factors that influence demand for health goods and services.

The alternatives open to less-developed countries as regards supplying pharmaceuticals for their populations include the following:

(a) Importation of finished products;

(b) Importation of finished or semi-finished bulk medicinal chemicals and the establishment or expansion of domestic finishing and/or packaging facilities;

(c) Establishment or expansion of self-sufficient manufacturing facilities;

(d) Bearing in mind the implications of foreign trade, some combination of the first three alternatives.

The paper considers the problems faced by pharmaceutical industries in developing countries. Some of these are: economies of scale; the availability of local resources; international and bilateral aid and assistance; considerations of plant size, output and manufacturing costs; research and development; recruitment of manpower for manufacturing and administration; sales promotion and distribution; costs and prices; and quality control.

The advantages of national and foreign ownership and control are compared, and what must be done to induce foreign companies to establish local manufacturing facilities is explained. Conversely, it is set forth what subsidiaries of international companies must do to establish good corporate citizenship in the host country.

The paper concludes with an explanation of how to draw meaningful conclusions from the information presented in it to assess the growth potential of a pharmaceutical industry in a developing country.

Consideration of drug efficacy and safety

by H. Friebel

The therapeutic efficacy as well as the safety of pharmaceutical products must be the concern of the manufacturer. Principles for the biological evaluation of safety and efficacy in pharmacological-toxicological laboratories, as well as in clinics and medical practice, have been worked out by WHO with a view towards their acceptance throughout the world.

Such principles and criteria must also be observed by manufacturers who restrict their activities to the compounding of pharmaceutical products and who are not normally involved in the biological evaluation of new drugs.

In developing countries, the therapeutic methods and the conditions of drug application are often widely different from those in developed countries. Consequently, specific problems are likely to arise in the assessment of efficacy and safety. Some examples are given below.

Local factors such as nutritional habits, malnutrition or certain genetic disorders may lead to adverse reactions which would not have been observed in the country where the drug in question had been developed and tested.

The so-called "traditional" drugs are not usually evaluated for efficacy and safety in a modern and scientific manner. They should, however, be treated in the same way as new drugs even if national law or custom provides certain preferences regarding the registration formalities.

Recently, serious doubts have arisen about the therapeutic equivalence of various proprietary forms of certain generic products. The therapeutic activity of such product varieties should be checked by suitable means whenever possible.

The safeguarding of the biological standards of safety and efficacy requires close co-operation between the pharmaceutical and medical professions. The respective technical units of the WHO Division of Pharmacology and Toxicology are prepared to provide relevant information and to assist in the education and training of the necessary academic and non-academic personnel, for example, by the assignment of consultants and the award of fellowships.

Therapeutic needs and production of drugs

by H. Friebel

The administration of medical care varies in different areas all over the world. Uniformity cannot be expected or achieved because the organization, the facilities, the subjects and the extent of medical care offered to the individual and the community are greatly influenced and modified by the environment. Some of the decisive factors are, for example, the prevalence of infectious and other diseases, the existence of genetic disorders, the health security systems, the availability of physicians, pharmacists, nurses, laboratories and hospitals, and last but not least, an adequate supply of pharmaceutical products.

In a developing country, where the doctor/patient ratio is 1 to 100,000, drug prescription and consumption are totally different from those of countries where the ratio is 1 to 1,000 or less. Together with some other factors, therapeutic practice determines the consumption of pharmaceutical products.

An example is provided in a paper on the role of treatment costs for tuberculosis. Under North American or European living conditions, the choice of drugs to be used in the treatment of tuberculosis would depend, predominantly, on their antibiotic and toxic properties and in the prevalence of drug-resistant strains of pathogenic organisms in the area. Considering both benefit and risk, the anti-tubercular drugs of choice in these areas are isoniazid, para-aminosalicylic acid and streptomycin.

In developing countries of low economic potential, where the patient cannot pay for his own treatment and the government's funds are insufficient to provide adequate care for everyone who requires drug treatment, the minimal amount of money which must be spent for a single patient in order to perform effective treatment becomes the critical figure which determines the choice of drug, since the drug which provides the least costly treatment per person permits the treatment of the greatest number of patients.

The study illustrates the treatment costs for tuberculosis, using four effective drugs, as follows:

Drug	Standard adult daily dose	Cost per year (US$)
Isoniazid	300 mg	0.90
Thiacetazone	150 mg	1.00
Para-aminosalicylic acid	10 g	9.25
Streptomycin	1 g	17.25

It is quite obvious from the above figures that, because of their low price, isoniazid and thiacetazone would be the drugs of choice in a developing country, and that the predominant prescription of them would be advisable. The factor of acquired resistance under such conditions would have to be neglected, since its identification in the individual case would, as a rule, be technically and organizationally impossible.

Active principles, drugs, pharmaceutical intermediates and pharmaceutical preparations extracted or prepared from botanicals, animal organs and agricultural residues

by Gyula Horváth

The paper begins with an historical review of drugs based on such natural organic sources as botanicals, animal organs and agricultural residues. Next, the raw-material basis for biologically active natural substances and its special significance for the developing countries are considered. The required organizational measures for the collection, handling and storage of starting materials are discussed, and the general processes for making galenical preparations, for fermentation, and for the isolation of active medicinal substances are reviewed. Several examples of the processing of the most usual raw materials are presented. The general layout of plants for the manufacture of galenic preparations, phytochemicals and biochemicals is described.

Manufacturing methods for finished pharmaceutical preparations of natural origin, and analytical and biological control methods and laboratories are described. The organizational set-up for an enterprise of this kind is presented, and consideration is given to the training of the required staff.

The most suitable steps in establishing and developing a pharmaceutical industry based on raw materials of natural origin are presented, as are the efforts in research and development needed to maintain and improve the technical and economic level of production.

Some economic aspects of the production of pharmaceuticals of these kinds are presented.

The development and application of veterinary pharmaceuticals

by Richard A. Huebner

The paper includes definitions of the problems of veterinary pharmaceuticals, describes the search for solutions of these problems and points out the goal to be attained. Among the subjects discussed are animal-population surveys; animal diseases, their incidence and transmission; and the classes of drugs and/or other therapeutic agents needed and the potential demand for them.

Also considered are the administration of therapeutic agents by veterinarians or laymen, the use of feed mixes that contain therapeutic agents, and the types of animal diseases prevalent in certain developing regions.

The approximate costs of supplying adequate amounts of the specific therapeutic agents required for some kinds of animals (swine, sheep, cattle, horses, poultry and so on) are estimated, taking into account factors such as total demand and economies of scale. When the requirements have been established, factors to be considered will be the cost and effectiveness of adequate programmes of treatment under the following alternative plans: (a) importing packaged products and bulk materials for repackaging, (b) repackaging partially processed intermediates and (c) undertaking the entire operation after acquiring the requisite licences and patent rights.

Drug research and development and quality control measures are also discussed.

Pharmaceutical plant models and training centres

by Walter Otto

This study deals with two subjects:

1. A scheme for the construction of industrial plants;
2. A scheme for the training of staff in economic and technical matters.

In scheme 1 a pharmaceutical plant is considered to consist of:

(a) Packaging department (i.e., packaging of finished preparations);

(b) Galenic department concerning the manufacture of final products such as tablets, coated tablets, liquids, ointments, capsules and suppositories;

(c) Quality control;

(d) Production of the active substances.

The plant is designed along both horizontal and vertical lines, allowing it to grow in either direction. For example, the packaging department can be divided into two sections. The lower part, at ground level, comprises the packaging area, the delivery department and the cellar, which can be used as a storeroom for semi-finished preparations. The finished preparations are transported with the help of an inclined conveyor belt into the cellar and to the delivery department.

The main floor is allocated to the administration and quality-control departments. The development of a viable scheme for production requires accurate description of the various functions. The production process itself must be described exactly, and information must be provided regarding equipment and its capacity. In addition, such details as quality-control records and the marking of batches must be taken into consideration in the initial planning.

Training may be conducted in three ways:

(a) In a pharmaceutical enterprise;

(b) In courses arranged either by associations of pharmacists, by industry, or by firms engaged in the manufacture and sale of analytical equipment;

(c) By an adviser.

A disadvantage shared by all of these methods is that staff is faced only with specially detailed problems and questions; a general training programme based on a uniform course of instruction does not yet exist. These facts stress the needs to establish a training centre and to a course of education in which technological and economic problems are discussed.

FAO assistance to developing countries in setting up veterinary biological production

by J. G. Rumeau

The first part of the paper reviews the fields of interest to FAO insofar as the veterinary use of pharmaceuticals versus that of vaccines in developing countries is concerned. It is noted that difficulties are being experienced in a certain number of these countries in procuring pharmaceuticals from abroad, particularly those considered most important for the control of internal and external parasitic diseases of domestic livestock. In order to overcome these difficulties, the establishment, wherever possible, of pharmaceutical industries in such countries is strongly encouraged.

The second part of the paper describes the reasons why centralization of vaccine production in a limited number of well staffed and well equipped laboratories is impossible, and why FAO has been requested by many developing countries to assist them in becoming self-sufficient in this respect through the provision of experts, the training of local laboratory specialists and the supply of equipment.

The paper also explains why the production of veterinary biologicals in developing countries should still be regarded, at this stage, as of a rather artisan nature.

Examples are given of assistance being provided by FAO, particularly through its Near East Animal Health Institutes, supported by the United Nations Special Fund and its European Commission for the Control of Foot-and-Mouth Disease. These institutions, among many others, have paved the way for the establishment of veterinary vaccine production on a national basis, thus helping FAO member countries to achieve self-sufficiency in the diagnosis and control of diseases of domestic livestock of major economic significance.

The importance of providing accurate drug information in developing countries

by Julius Segal

The paper begins with a brief history of prescientific use of drugs and attitudes towards them. The scientific use of drugs began only in the last half of the nineteenth century, and understanding of the mechanisms of action of drugs and their clinical use has increased greatly as the science of chemistry has developed and knowledge of how to conduct careful scientific experiments has increased.

It is now clear that the proliferation of drugs and the explosion of data about them challenges our ability to deal effectively and quickly with problems of optimal drug use. The experience of the United States and its citizens in the growing need for better and more available drug information is one which can be used as a guide for avoiding at least some of the pitfalls in the use of drugs and for planning the intelligent dissemination of drug information to citizens of smaller developing countries.

Detailed data are provided for one class of drugs which is growing in its utility and breadth of application. This is the group of drugs used primarily in the treatment of insomnia and related problems.

Accurate information about drugs in general is crucial to protect the consumer from having to spend more than necessary for particular drugs. In addition to such economic considerations, however, the most compelling reason for presenting accurate information on drugs to the consumer in developing countries is to protect his health and welfare. By noting some of the impediments to progress in intelligent drug use in industrialized societies, it may be possible to avoid the negative results brought about by confusion and delayed information that have occurred in the past with regard to drugs. American experience underlines the importance of informing both the clinician and the consumer about the utility and side effects of the drugs that are available for prescription.

The paper discusses an important question which concerns many physicians and drug experts: How much is the patient entitled to know regarding the effects of a drug that has been prescribed for him? The considerations here are whether the patient can use this information to his advantage, whether he

can continue to use the drug without having the psychological impact of the information intrude on the results of the drug treatment and whether he is capable of understanding the information.

The need for comprehensive and accurate drug information outside the control of individual drug companies is highlighted. Here also, the experience of the United States Government, in moving towards a national drug compendium, is used to illustrate some of the lessons learned in this difficult field. Existing sources of information are outlined and their advantage and disadvantages identified.

It is emphasized that intensive research on drugs and their effects, both positive and negative, must continue. Moreover, such research must be increased. In addition to research, however, information flowing from such studies must be provided both to the physician who administers the drug clinically and to the patient who receives it.

The article includes many examples of information, arising out of research, which must be disseminated quickly to both clinicians and patients if drugs are to achieve maximum effectiveness and if the dangers of drug abuse and deleterious side effects are to be avoided.

The pharmaceutical industry in India*

by B. Shah

The pharmaceutical industry in India has grown to be the largest in terms of financial value among the chemical-based industries in that country, with an estimated production value of about 2 billion rupees, a twentyfold increase from the 1947 production value of 100 million rupees.

In any assessment of production an important consideration is whether the industry has developed along the lines of self-sustaining growth. The domestic processing of indigenous raw materials is a key phase in the planned development of a self-sustaining industry. Basic manufacture was therefore accorded first priority in the initial development of the pharmaceutical industry in India, and today the industry is largely self-sufficient in its raw-material requirements.

General production covers a wide range of items, among them antibiotics, sulpha drugs, antileprotics, hormones, analgesics, antipyretics, vitamins, tranquillizers, antihistamines and phytochemicals. The technology employed in production and quality control is on the same level as that in force in the United Kingdom and the United States. The organized sector has provided employment for over 60,000 people, of whom 10 per cent are technically trained. Technicians and administrators receive advanced training abroad.

The development of an industrial base with its own research and product-development centres, quality-control checks and an effective distribution system has brought adequate quantities of modern medicines to India's physicians and hospitals.

In 1953 the Union Ministry of Commerce and Industry set up a pharmaceutical enquiry committee to recommend the lines along which pharmaceutical industry could be developed in an integrated manner. The industry's classification allowed both the Government and private enterprises to establish manufacturing units. The first phase of development was the manufacture of drugs from the basic stages.

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* A country contribution.

The present economic conditions of the country have created a new field, namely, development research to formulate new drugs for the health problems peculiar to India, using indigenously available ingredients, thus replacing or reducing the need for imported materials. This type of research is essentially linked with economic necessities.

Present regulatory statutes involving quality and efficacy in the export and import of pharmaceuticals in selected countries (A)

by Charles C. Stevens

Section I of the paper deals with the need for regulations covering drug quality and efficacy, not only in relation to export and import but also to home manufacture and sale. The importance of the safety of the public and the needs of public health is emphasized, and suitable supporting statements are reproduced. This is followed by a brief review of the history of control of medicines from the time when mainly galenic preparations were controlled on a simple quality basis, through to the development of present regulatory systems, which include product registration, new drug control and, in France and in countries which were formerly French colonial territories, the visa system.

In Section II the work already done in the control field by WHO and other international organizations is summarized and reproduced in part. It is pointed out that WHO through its quality-control, drug-toxicity and expert committees, has studied the matter in general but has not yet drawn up precise, detailed recommendations. The work on quality control and regulations arising from discussions in the International Pharmaceutical Federation and the ad hoc pharmaceutical committees of the Organisation for Economic Co-operation and Development (OECD) is also summarized. Details are given of those parts of the harmonization of regulations in respect of pharmaceuticals carried out by the European Economic Community (EEC), which deal with quality control and the regulation of pharmaceutical products.

This section also emphasizes the importance played by set standards for good manufacturing practice, and it is shown that control is better exercised at the manufacturing stage rather than by inspection and analysis after products have been placed on the market. The recent code established by WHO[2/] is mentioned, and full details are given of basic standards of manufacturing practice adopted by the Pharmaceutical Industries' Association (P.I.A.) in

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2/ Specifications for the quality control of pharmaceutical preparations, Second edition of the International Pharmacopoeia, WHO, Geneva, 1967.

the European Free Trade Association (EFTA),[3/] which already form the basis for standards in some western countries.

Section III deals with existing regulatory statutes and covers the three main systems: new drug submissions, product registrations and the visa system. Full details of the new drug procedure of the United States are given, and a comparative review is made of how these compare with the current new drug provisions in Australia, India and the United Kingdom. As examples of product registration, the detailed system of Sweden is reviewed, being typical of the Nordic countries, and Venezuela is used to illustrate the typical Latin American system, which prevails throughout most of Central and South America. Comparisons are drawn between registration systems that are basically similar to that of Venezuela and those in force in other countries, among them Austria, the Federal Republic of Germany, the Netherlands and Thailand. Finally, the visa system is reviewed in detail.

Section IV reviews the major items to be taken into consideration when framing regulatory statutes for developing countries to cover control of quality and efficacy. Aspects of particular importance to developing countries as regards both imports and exports are considered. The paper concludes with a list of the documentation which may well be considered as basically necessary for approving either the import or sale of a pharmaceutical product in any developing country.

3/ Resolution of P.I.A. Basic Standards of Manufacturing Practice, Pharmaceutical Industries Association in the EFTA (P.I.A.), 1968. P.O. Box 109, 8024 Zurich, Switzerland.

Present regulatory statutes involving quality and efficacy in the export and import of pharmaceuticals in selected countries (R)

by Pál K. Székely

The number of pharmaceuticals becoming commercially available in certain developing countries is increasing rapidly, primarily because they are being manufactured locally. The first part of the paper deals with the politico-economic characteristics of this tendency and gives an estimate of the development to be expected. The requirements for quality and efficacy that must be met for up-to-date manufacture of drugs are stated and the possibilities of their control in countries possessing highly developed drug industries. The roles of governmental organizations and of laws and regulations are examined.

The second part of the paper expounds the relevant statutes and systems existing in Hungary, the Soviet Union and neighbouring countries. It surveys the circumstances prevailing in the developing countries, using as illustrations the legislation and the rules of registration and import in Ethiopia, Lebanon, Nigeria, Pakistan, Peru and Singapore. Its final chapter draws general conclusions and makes recommendations with a special view to the needs and possibilities of developing countries.

Patent aspects of the pharmaceutical industry

by the UNIDO secretariat

This study examines some aspects of the usefulness of patents for the development of pharmaceutical industry sectors. The monopoly nature of this economic institution is generally recognized both in the literature of patents and in that of general economics.

In the United States, for example, pharmaceutical patents can be issued both for new products and new processes. Patented processes, however, constitute a much weaker form of protection and play a less important role in the pharmaceutical industry than patented products. Since the patent itself provides a full description of the process concerned, it is fairly easy for a rival company to modify the process somewhat, thus evading the patent covering it, and to embark on the production of the product in question without risking legal action. Product patents, on the one hand, are a relatively effective means of protection against competing producers.

While patent protection in the United States is complete, in France, the Federal Republic of Germany, Switzerland and the United Kingdom, patent protection is not as comprehensive. For example, in the United Kingdom, patent protection in the pharmaceutical field is available for pharmaceutical products only. Italy, on the other hand, has patent protection neither for products nor for manufacturing processes.

Granting that patent protection is useful to the promotion of technological development, uncertainty as to the protection afforded by patents may be a relevant factor to be considered in connexion with national efforts directed towards the development and exploitation of pharmaceutical technology. In developing countries, over 90 per cent of the patents applied for are issued in the name of foreign nationals. Among the reasons why so few patents are applied for and issued in developing countries are the lack of inventive or entrepreneurial activity in their populations, the unimportance of these countries as markets for patented products, the absence or inadequacy of the legal protection which patents afford inventors and investors, and the relatively greater significance of unpatented, as contrasted with patented technologies.

Because of their shortage of indigenous entrepreneurship and the risks of investment, developing countries should favour monopolistic pharmaceutical situations rather than combat them. The governments of developing countries should show willingness to develop defensive measures for the benefit of new industries in the form of patent protection. Protective measures change their roles in the course of development.

The pharmaceutical industries in the Second Development Decade

by the UNIDO secretariat

This study is a preliminary attempt to formulate suggestions on the objectives that should be pursued by those persons actively engaged in the field of pharmaceutical manufacturing in developing countries. International development strategy should be based on the techno-economic characteristics and morphology of the industry. This study shows that the economic and social development of a country will cause its pharmaceutical industry to become an increasingly integrated industrial sector.

Phytochemical pharmaceutical products today represent only about 5 per cent of the total industrial output. Synthetics take the lead with about 55 per cent of the total, and biologicals, antibiotics and other biochemical preparations constitute about 40 per cent.

In the early 1960s, the average share attributed to pharmaceutical production within the chemical sector, as ascertained for the European Economic Community, Japan, Norway, Poland, Sweden, the Soviet Union and the United States, was between 10 and 11 per cent.

The report divides the development of the pharmaceutical industry within the group of developing countries into these five stages:

(a) Countries without a pharmaceutical industry;

(b) Countries where the pharmaceutical industry is in an early stage (packaging and dosage formulation);

(c) Countries with a well-established pharmaceutical sector, aiming at a particular level of backward (that is, in the direction of chemical processing) integration for at least certain product lines in bulk drug manufacture;

(d) Countries with a high level of self-sufficiency, oriented towards full integration at least for the main sectors of the pharmaceutical industry (starting the development of medicinal-clinical drug manufacture);

(e) Countries with a well-established pharmaceutical industry.

The growth perspectives of the pharmaceutical industry over the medium and long ranges can be described as very favourable, as it profits from the continuous emphasis on the teaching of hygiene in developing countries and from the socialization of medical treatment and the development of preventive medicine. The increase of life expectancy as a consequence of the secular

growth of medical treatment itself, the continuous high rate of population growth in developing countries and the improvement of the quality of pharmaceutical products are all positive factors in the development of the pharmaceutical industry.

UNIDO and the establishment of pharmaceutical industry sectors in developing countries

by the UNIDO secretariat

The definition of a pharmaceutical industry is a broad one that encompasses scientific (pharmacology, biochemistry, quality and efficacy control), technological (synthesis, production, packaging, sterilization, fermentation), economic (marketing costs, pricing, advertising), educational (training, professional personnel), legal (patents, licensing, import and export restriction) and other sector disciplines. Since the degree of sophistication in each of these is high, a developing country with its limited or completely lacking resources in these disciplines would find it difficult to embark on an "across-the-board" effort. For practical purposes, therefore, the advancement of a pharmaceutical industry in a developing country should be conducted through the growth of individual sectors.

The role of UNIDO is to provide assistance to developing countries in those sectors of the pharmaceutical industry which lend themselves to industrialization. This assistance would include, for example, the assessment of the present status of such sectors, detailed evaluation of domestic demand for pharmaceuticals and classes of products, and recommendations concerning the improvement of infrastructures to provide a viable basis for the industrialization of such sectors.

UNIDO works closely with WHO in the development of pharmaceuticals for human use and with FAO in relation to veterinary pharmaceuticals. The therapeutic needs of each country must be evaluated and treatment costs and patterns developed. Based upon the recommendations of WHO and FAO and its regional experts, and with the assistance of the local medical authorities, an estimate of the relative quantities and types of selected classes of pharmaceuticals needed can be attempted.

If, for example, the pharmaceutical products needed by a country are those for the treatment of malaria, tetanus, liver diseases, dysentery and vitamin deficiency, an assessment (based upon the market, production, equipment, labour and so on) would be made of the possibilities of producing some of these pharmaceuticals in the country itself. UNIDO would supply experts to make the technical and economic evaluations. The experts selected and approved by the country and by UNIDO would normally be assigned to an agency

of the requesting Government and would function under its supervision in regard to the terms of reference of the programme. For example, should the expert recommend that the most practical immediate implementation would be to import some basic raw materials, and that the country should produce certain pharmaceutical preparations, the next step of the programme would be to determine how these products could be made.

Upon consultation with WHO and with the country's health authorities, UNIDO would provide assistance to the Government of the country in determining the best method for starting the production of selected pharmaceuticals. Since in many cases the beginning of production is a capital-intensive venture, and available capital may be in short supply, the Government concerned may wish to consider inviting an internationally oriented pharmaceutical organization to establish a small manufacturing plant in the country to produce quantities of selected pharmaceutical preparations. Since profit is a vital factor to be considered in the longevity of an industry, specific guarantees must be given. UNIDO could assist in this phase by reviewing the technical and commercial details of suggested agreements.

If a developing country cannot initially interest a private firm in undertaking such a sector development, the next step to consider would be a Government-industry partnership. However, such a venture can have definite drawbacks, as experience in some developing countries has indicated. In several cases the Government has found itself as the major owner of an unsuccessful undertaking.

A pharmaceutical industry sector must be oriented towards change. It cannot remain static, as its development depends upon new drugs, new techniques of medical application of pharmaceuticals and constant competition from imports. A developing country interested in establishing pharmaceutical industry sectors must be willing to undertake constant improvement of the education and training of the necessary staff, to encourage the establishment of research and development facilities, to direct capital investment to the sectors and to develop confidence in the new products, both domestically and internationally. One of the prerequisites for the success of this type of venture is entrepreneurship, a quality often lacking in many developing countries. The availability of production equipment, of scientific apparatus and of a built-in domestic market are not always enough to assure commercial success.

The role of UNIDO in the development of a pharmaceutical industry sector includes the planning of the enterprise, the initiation of its operation, the development of production, training of the staff needed, organization of marketing and ensuring that there will be adequate motivation for management.

Conditions and prerequisites for the establishment of a pharmaceutical industry in developing countries

by E. R. Valashek

The main types of technical assistance provided by the Soviet Union to the developing countries to help them establish independent national pharmaceutical industries include assistance in the preparation of projects, the provision of equipment and materials, the supervision of building work and the training of personnel.

Characteristically the co-operation of Soviet organizations in the construction of pharmaceutical undertakings in developing countries concerns the establishment of undertakings in the State sector.

The establishment of independent undertakings in the pharmaceutical industry in a developing country has these three aspects:

(a) The organization of production of the pharmaceutical preparations most needed by the public health services for carrying out their task of combating the diseases most prevalent among broad sectors of the population of the country in question;

(b) The establishment of undertakings with a complete production cycle from basic raw materials to finished products, and organization of the production of basic types of raw materials;

(c) The output of finished products, not in the form of powder (bulk form), but as finished medicinal preparations such as tablets, capsules and ampoules.

Before planning such a pharmaceutical undertaking in a developing country, it is necessary to investigate carefully its technical and economic justification. Some of the more important considerations are discussed below.

Arrangements must be made to secure adequate supplies of chemical raw materials, semi-finished products, raw materials of vegetable origin, raw foodstuffs and packaging materials.

Attention must be given to the water requirements of pharmaceutical plants, taking account of the fact that some of them - for example, those producing synthetic preparations and antibiotics - require large amounts of water, some of it at low temperature.

An adequate supply of electrical power must be ensured, especially in connexion with undertakings that produce synthetic preparations and antibiotics,

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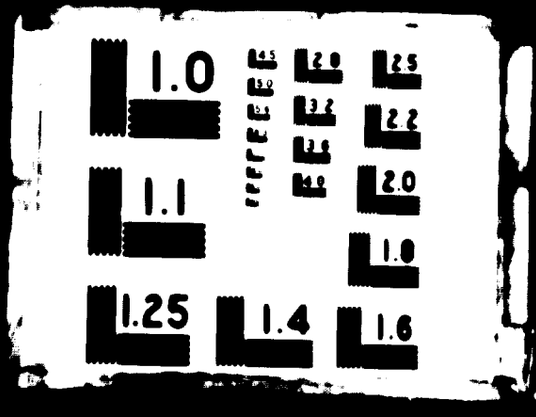


since installations of these kinds require the circulation of cool water for manufacturing processes and for air conditioning and are thus heavy consumers of electrical power.

Attention must be given to problems of waste disposal from various pharmaceutical plants, especially in the case of chemical-synthesis and antibiotics plants, since wastes from such plants must be subjected to preliminary purification in special installations before discharge.

Other conditions which must be taken into account concern the selection of the general area and exact sites for plant construction, taking due note of transport conditions, the availability and level of training of specialist staff, the required residential accommodation, the possibility of producing certain types of equipment in the country concerned and the special characteristics of the construction work.

The study of the local conditions and prerequisites for establishing a pharmaceutical industry provides the technical and economic basis for assessing the advisability and effectiveness of building various types of pharmaceutical plants in a given developing country. It should include consideration of the volume and range of production, the recommended technology, construction times, estimates of the capital investment needed and the anticipated economic efficiency of the plant (production costs at local prices in comparison with existing prices on the local and world markets, profitability, competitiveness).

Our experience shows that the finding of valid technical and economic solutions to all of the above-mentioned problems is critical to the establishment of a national pharmaceutical industry in the State sector in developing countries.

Quality control in pharmaceutical manufacturing

by O. Wallén

The aim of pharmaceutical quality control is to achieve sustained and uniform manufacture of products of defined quality. In order to achieve that aim the raw materials, the semi-finished products or the final dosage forms of drugs must conform to agreed product quality specifications and be subjected to regular production control.

Product quality specifications

The work of WHO in the field of product quality specifications has resulted in two editions of the International Pharmacopoeia.[4/] A brief review of this work is given.

Special attention is drawn to the increasing need for chemical reference substances (about forty such substances needed for the tests and assays described in the second edition of the International Pharmacopoeia are now available).[4/]

In view of the relatively rapid obsolescence of modern drugs, attempts are being made to establish a system by which specifications for drugs can be made available earlier than is possible with the present system of issuing bound volumes at intervals of many years. A suggested solution to this problem is discussed briefly.

Since 1963 the quality control of drugs has been extensively considered by the World Health Assembly and the Executive Board of WHO. During the discussions of the Twentieth World Health Assembly the importance of production control was stressed, and the Assembly requested the Director General inter alia, "to formulate as soon as possible principles for quality control procedures such as should be incorporated in good drug manufacturing practices". This text, Good Practices in the Manufacture and Quality Control of Drugs,[4/] is now available and is reviewed in detail in this paper.

It is the task of the national control authority to supervise drug production by inspection of manufacturing establishments and by laboratory checking of random samples of drugs offered for sale.

4/ See annex 4.

The importance for the national authorities to have at their disposal adequate laboratory facilities and adequately trained expert personnel to perform these duties is stressed, as well as the need for adequate and realistic legal provisions.

Annex 1

LIST OF PARTICIPANTS

Expert Working Group Members

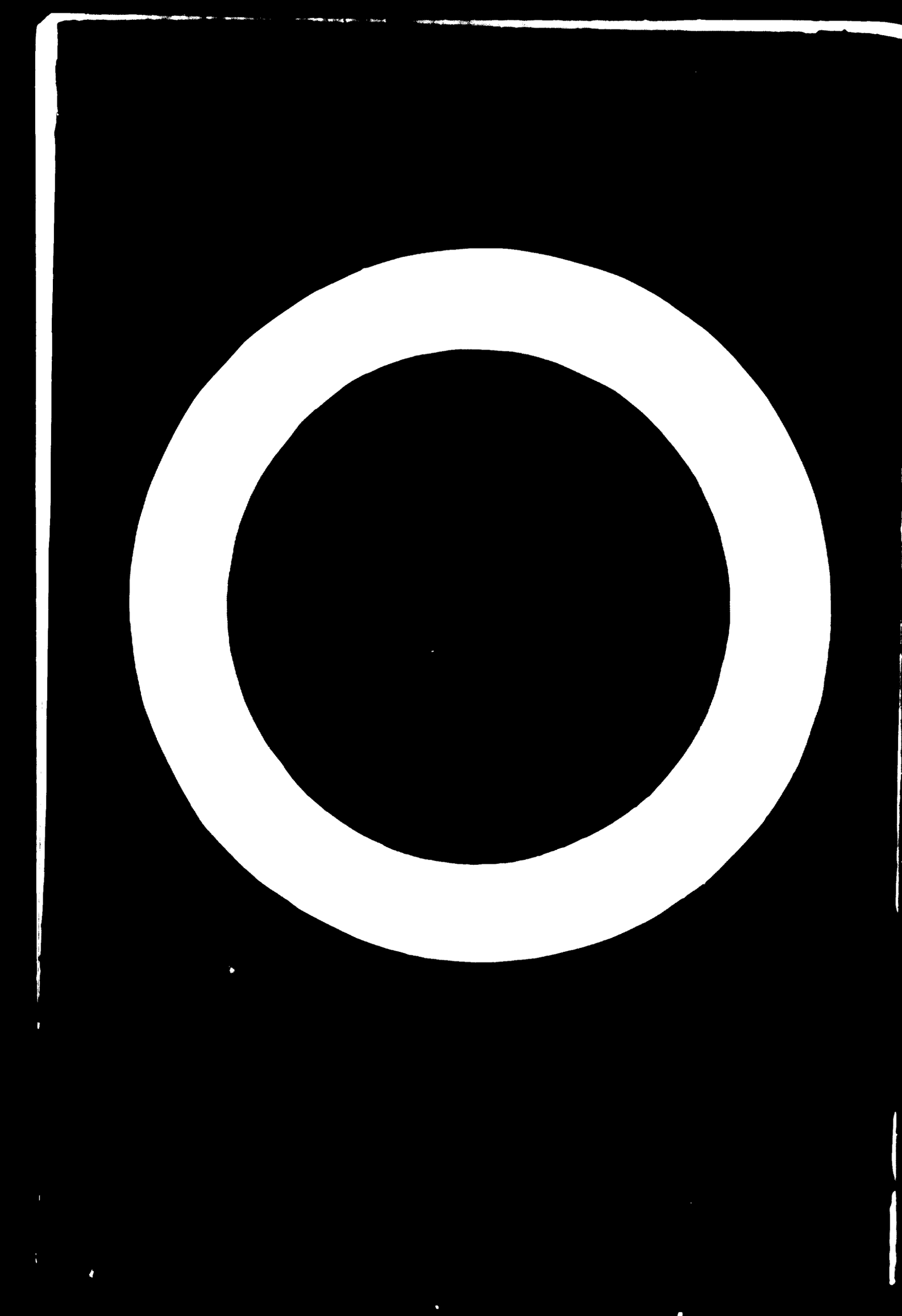
Gyula Horváth	Chairman	Hungary
Pál K. Székely	Vice-chairman	Hungary
Yoel Amiran	Expert	Israel
John A. Deering	Expert	United States
Richard A. Huebner	Expert	United States
Walter G. Otto	Expert	Austria
Julius Segal	Expert	United States
Charles C. Stevens	Expert	United Kingdom
E. R. Valashek	Expert	Union of Soviet Socialist Republics

United Nations Secretariat

Walter A. Caldwell	UNIDO	Meeting Director
Paul M. Terlizzi	UNIDO	Meeting Co-ordinator
Janos Fath	UNIDO	
H. Friebel	WHO	
A. Glutz von Blotzheim	UNIDO	
H. R. Halbach	WHO	
J. G. Rumeau	FAO	
O. Wallén	WHO	

Guest of Honour

Mr. J. Lazor	Head of Pharmacy Department Ministry of Health	Hungary



Annex 2

OPENING STATEMENT BY MR. J. LAZOR,
HEAD OF PHARMACY DEPARTMENT,
MINISTRY OF HEALTH, HUNGARY

It is a great honour to me that UNIDO has chosen Budapest as the place for this meeting of experts, dealing with the establishment of the pharmaceutical industry in developing countries. At the same time I am greatly honoured to have been invited to open the meeting, since this implies recognition of the high level attained by Hungary's public health and its pharmaceutical industry.

The programme, organized by the group of experts, which reflects the noble objective of the welfare of mankind, is of a rather complex character. This complexity arises from the diversity of the general problems in developing countries and the difficulties connected with the establishment of an efficient public health service.

The presence and level of its pharmaceutical industry may influence fundamentally the sanitary conditions of any country, but the pioneering foundation of this industrial branch in any country requires significant investments of intellectual and financial resources. The manufacturing of pharmaceutical preparations is not only a simple economic activity, but it has - because of its social importance - a great many ethical aspects as well. Quite independently of the nature of the social system, there exists the necessity for a regulatory and controlling role of the Government in order to assure that the medicaments will exercise their noble health-giving and healing functions for the benefit of the patients, and that there will be no possibility of marketing any ineffective or dangerous drugs for the sake of unethical economic profits. This regulatory and controlling role has been becoming ever more important all over the world since the regrettable experience with thalidomide.

Hungary has long realized the significance of the control of pharmaceuticals. As early as 1927 an institution for the sanitary control of pharmaceuticals was established. At that time the three most important tasks of this control were the following:

(a) Analytical methods had to be elaborated for testing pharmaceutical preparations, mainly those with more than one ingredient.

(b) Conditions and requirements had to be laid down on the basis of which drugs could be qualified.

(c) Finally, there was the task of organizing control, in the laboratories, in the factories and in use.

Bearing these tasks in mind, our system of registration and control of pharmaceutical products efficiently serves the safety of medications, in accordance with present knowledge.

In the absence of their own pharmaceutical industries, developing countries must supply their demands by import. This does not mean, however, that local control is unnecessary. To organize this control, developing countries need assistance in equipment and in adequate staff. It is the duty of the developed countries to render such assistance.

It is well known that among the countries of the world there are significant differences in the per capita consumption of drugs and in the number of physicians, hospital beds, pharmacies etc. Such statistical data indicate the hygienic standard of a country. In Hungary, for every 600 inhabitants, there is one practising physician, for every 125, there is one hospital bed, and for every 7,000, there is one pharmacy. Compared by these hygienic indexes, developing countries appear to be less fortunate. It is of course true that it would be incorrect for us to suggest to them that they achieve any set indexes for the sake of developing their public health, since the possibility of their doing so will greatly depend on local circumstances. Furthermore, it is well known that the administration of medicaments is a very important factor, but not the only one, for increasing the sanitary standard. This standard is also greatly influenced by the stage of development of the sanitary network, the public health services and, last but not least, by the dimensions of the national product and of private income.

I have enumerated these well-known facts to emphasize the complexity and importance of your work, as well as the beneficial activities of the United Nations, and of its specialized agencies among them UNIDO, by which they strive to promote effectively the availability of good-quality pharmaceuticals and to increase the health standards in the developing countries, which represent a great part of mankind.

Please allow me to convey to you the best regards of our Minister of Health, as well as those of the Hungarian health service employees and to wish you. as participants in this meeting, success in promoting effectively the solution of this very difficult but equally noble task.

I wish all the participants a fruitful and successful meeting and, in addition, a pleasant stay in Hungary.

Annex 3

PAPERS PRESENTED AT THE MEETING

ID/WG.37/1	Patent aspects of the pharmaceutical industry by UNIDO secretariat
ID/WG.37/2	The pharmaceutical industries in the Second Development Decade by UNIDO secretariat
ID/WG.37/4	UNIDO and the establishment of pharmaceutical industry sectors in developing countries by UNIDO secretariat
ID/WG.37/5	Quality control in pharmaceutical manufacture by WHO
ID/WG.37/6	Therapeutic needs and production of drugs by WHO
ID/WG.37/7	FAO assistance to developing countries in the production of veterinary biologicals by FAO
ID/WG.37/8	Present regulatory statutes involving quality and efficacy in the export and import of pharmaceuticals in selected countries (B) by P. K. Székely, Hungary
ID/WG.37/9	The development and application of veterinary pharmaceuticals by R. A. Huebner, USA
ID/WG.37/10	How to conduct a realistic marketing, economic and financial study of the growth potential of a pharmaceutical industry in a developing country by J. A. Deering, USA
ID/WG.37/11	Present regulatory statutes involving quality and efficacy in the export and import of pharmaceuticals in selected countries (A) by C. C. Stevens, U.K.
ID/WG.37/12	Some conditions and prerequisites for establishing pharmaceutical industry in developing countries by E. R. Valashek, USSR
ID/WG.37/13	The establishment of a pharmaceutical industry in a developing country - a case history by J. Amiran, Israel
ID/WG.37/14	Pharmaceutical plant models and training centres by W. Otto, Austria
ID/WG.37/15	Active principles, drugs, pharmaceutical intermediates and pharmaceutical preparations extracted or prepared from botanicals, animal organs, and agricultural residues by G. Horváth, Hungary
ID/WG.37/16	Pharmaceutical industry in India* by B. Shah, India

* Prepared subsequent to the meeting.

ID/WG.37/17	The importance of accurate drug information by J. Segal, USA
ID/WG.37/18	Consideration of drug efficacy and safety by WHO

Annex 4

LIST OF SELECTED WHO PUBLICATIONS

Specifications for reagents mentioned in the International Pharmacopoeia, Geneva, 1963.

Principles for pre-clinical testing of drug safety, report of a WHO scientific group, Technical Report Series No.341, Geneva, 1967.

Principles for the testing of drugs for teratogenicity, report of a WHO scientific group, Technical Report Series No.364, Geneva, 1967.

International non-proprietary names for pharmaceutical preparations, Cumulative List No.2, Geneva, 1967.

Principles for the clinical evaluation of drugs, report of a WHO scientific group, Technical Report Series No.403, Geneva, 1968.

Specifications for the quality control of pharmaceutical preparations, second edition of the International Pharmacopoeia, Geneva, 1967.

Pharmaceutical advertising, a survey of existing legislation, Geneva, 1968 (revision).

Good practices in the manufacture and quality control of drugs, twenty-second report of the WHO Expert Meeting on Specifications for Pharmaceutical Preparations, Technical Report Series No.418, Geneva, 1969.

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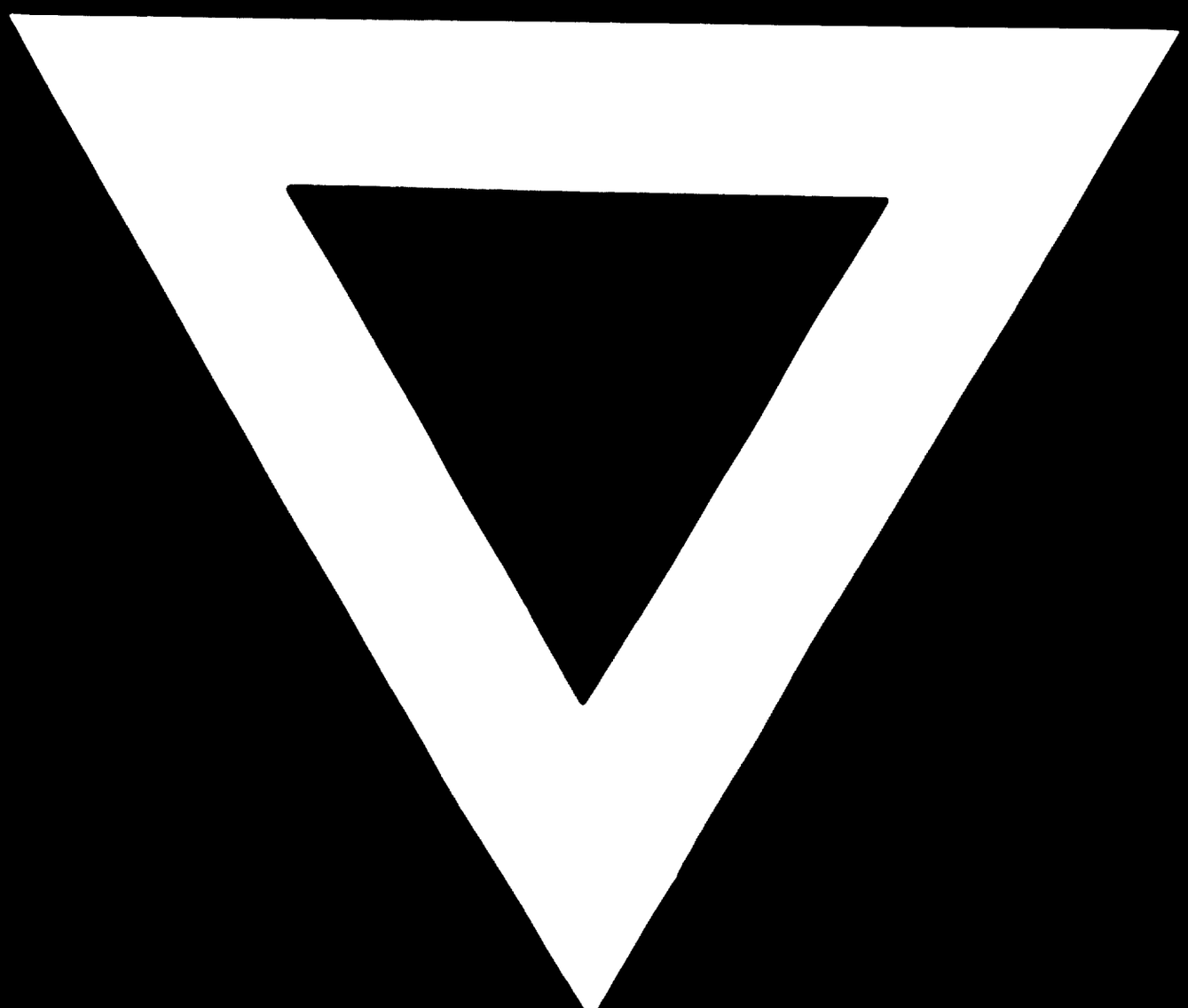

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