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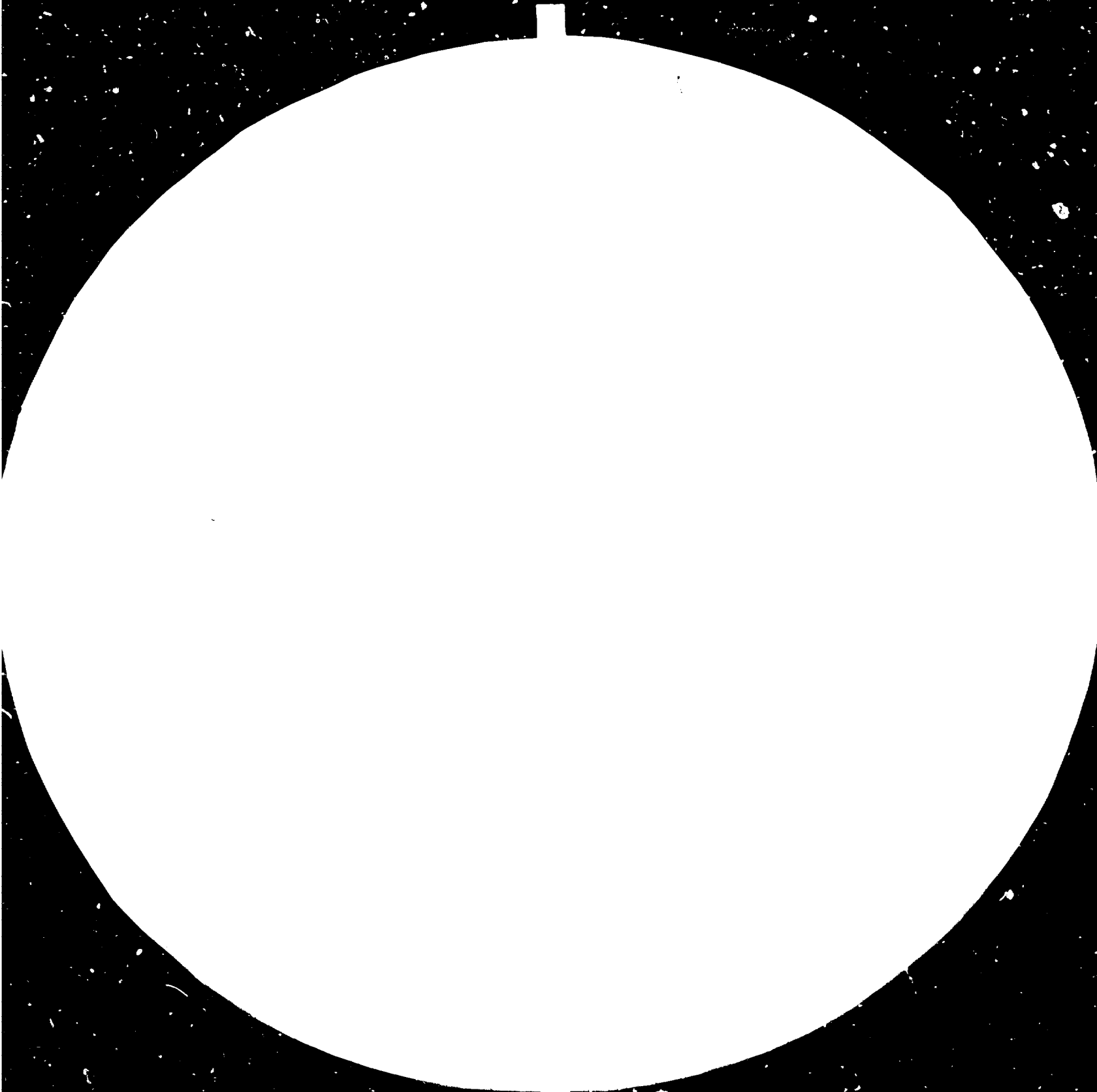

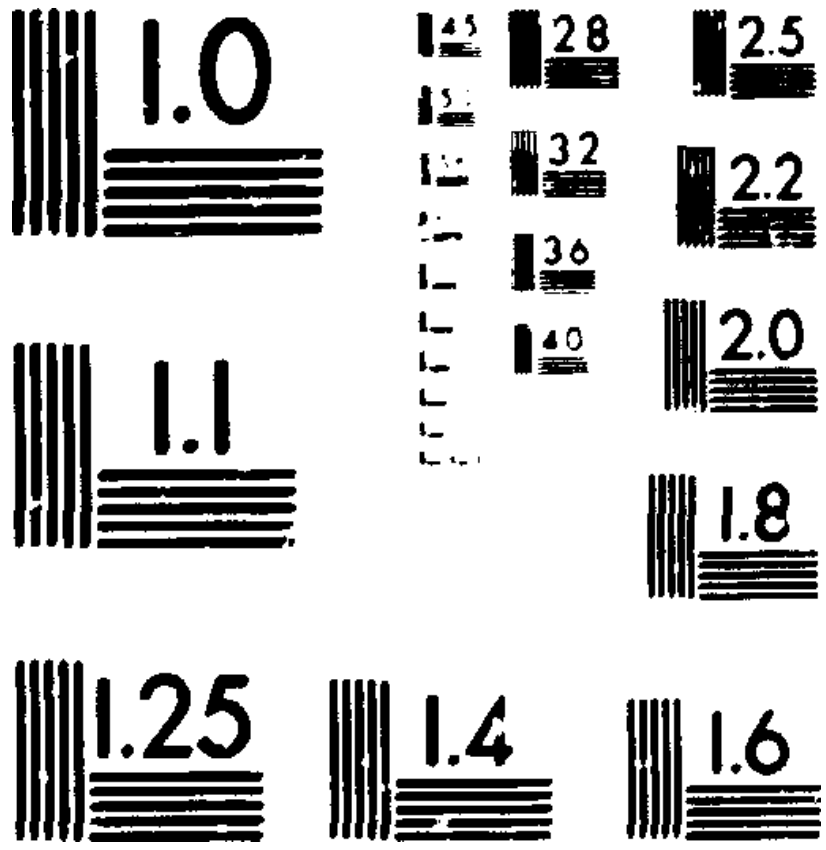

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UNIDO PROGRAMME FOR INDUSTRIAL PRODUCTION OF BIOLOGICALS (IPB)

An introductory paper *

prepared by
Pharmaceutical Industries Unit
Chemical Industries Branch
Division of Industrial Operations

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INTRODUCTION: UNIDO'S INTENTION TO CONTRIBUTE TO THE PREVENTIVE MEASURES OF THE PRIMARY HEALTH CARE.

1. At present, the health state of hundreds of millionsof people throughout the world can be regarded as unacceptable. Approximately half of the world's population does not have the benefit of adequate health care. The 30th World Health Assembly therefore decided already in 1977 that by the year 2000 all people in all countries should have a state of health that will permit them to lead a socially and economically productive life. 1/2/ Health for all, however, does not obviously mean that in 2000 professional health personnel will provide medical care for everybody and it does not mean that by 2000 nobody will be sick or disabled. But it does mean that better approaches will be used than they are used today for preventing disease and alleviating unavoidable disease and disability. Since about 750 million people live in the world in hunger and poverty and if current trends continue this situation will not significantly improve by the year 2000, it has serious adverse effects to the state of world health.3/ At present, 65 developing countries spend less than US$ 8 of public funds per capita per annum on health.4/ To overcome those obstacles which are working against achieving the goals of "Health for all by the year 2000", one of the economically most feasible alternatives is to strengthen the preventive side of medical care at the level of primary health care.

2. The primary health care as the first level contact with the national health system should bring health care as close as possible to where people live and work. However, approximately half of the world population is not even within walking distance (10 km) of a national health facility of any kind. To promote the primary health care in developing countries but in particular in the least developed countries is therefore an absolute necessity.

1/ Resolution WHA 30. 43, 1977

2/ Health is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity". Constitution of the WHO, Basic Documents, 15th edition, 1961.

3/ Brandt Commission, North-South: a programme for survival, Pan Books, London, 1980.

4/ Assessing the march towards health for all, WHO, 1983.

The primary health care includes at least:

- Health education
- Adequate supply of food, safe water and sanitation
- Maternal and child health care
- Immunization against the major infectious diseases
- Preventive care of locally endemic diseases
- Curative care of common diseases and injuries and
- Provision of essential drugs. 5/

The above activities of primary health care are in many senses overlapping and therefore no sound distinction can be drawn between sanitation, preventive medicine, curative medicine, health promotion and improvement of standards of living. 6/

3. The preventive side of primary health care includes different activities such as:

- Health education and training
- Health surveillance (epidemiology)
- Processing of information
- Preventive diagnostic measures
- Adequate food supply and proper nutrition
- Adequate supply of safe water and basic sanitation
- Provision of oral rehydration salts (ORS)
- Chemoprophylaxis (programme on essential drugs)
- Immunization and
- Seroprophylaxis, etc.

Many UN, governmental and non-governmental agencies make their contribution to carrying out the above activities in assisting the developing countries, however, whatever contribution is made, it shall meet the requirements of WHO. Since UNIDO's mandate is to assist in the industrialization of developing countries, the industrial inputs to the preventive medicine should be regarded as a particular contribution of UNIDO to the primary health care. The above UNIDO assistance has its impact not only on the public health but also on the socio- economic conditions of developing countries.

5/ Alma -Ata 1978, Primary Health Care, WHO, 1978

6/ C.-E.A. Winslow, The cost of sickness and the price of health, WHO monograph, no. 7, p. 28, 1951

4. To achieve the goals of "Health for all by the year 2000", UNIDO does not only intend to provide industrial inputs to the preventive side of the national primary health care programmes but for several years has started to assist in creating national industrial capabilities of developing countries by collecting industrial information, training of personnel and developing manufacturing units for essential drugs (chemoprophylaxis), vaccines,blood products (sero-prophylaxis) and oral rehydration salts. It should be noted that UNIDO has already carried out an extensive programme for the production of pharmaceuticals through its technical assistance programme, prepared studies and organized consultation meetings on the pharmaceutical industry. UNIDO has now decided to extend its operation into that particular field of pharmaceutical industry which will provide biologicals to the national primary health care programmes. The scope of the present paper is therefore focused only on the industrial aspects of the manufacture of biologicals, namely immunologicals and blood products.

VACCINES IN THE PRIMARY HEALTH CARE PROGRAMMES: THEIR ECONOMICS AND DELIVERY

5. The analyses of the cost-effectiveness and cost-benefit of vaccines show that immunization programmes against infectious diseases can be among the economically most feasible investments available to developing countries. There is no doubt that the prophylaxis, that is vaccination against those childhood infectious diseases included in the Expanded Programme on Immunization (EPI), has clear advantage over the therapy according to the cost-benefit analyses.

The total costs of the immunization programmes include:

- Capital costs: buildings
  vehicles
  cold-chain
  spare parts, etc., and
- Operating costs: salaries and allowances
  training
  transportation (immunization team travel, fuel, vehicle maintenance, vaccine shipment)
  vaccines and

other operating costs (cold-chain maintenance, electricity/kerosene, jet-injector maintenance, etc.) [7]

There are five main categories of gain from immunization:

- Savings in treatment costs following reduced incidence of disease.
- Reductions in mortality.
- Reductions in morbidity.
- Avoidance of "intagible" costs such as suffering of pain and anguish of illness both of the patients and their families, etc., and
- Supplementary benefits such as strengthening managerial capabilities of national health services, establishing the infrastructure capable of administering new vaccines as they become available, etc. [8]

Valuing a life-saving activity is the most controversial part of cost-benefit analysis in planning of health care programmes. If the value of human life in developing countries were regarded as negative then it seems to be no economic justification for life-saving health programmes. But it is an extreme view, based on a questionable approach to the valuation of human life which naively equates economic welfare with gross national product. There are at least three different approaches to the valuation of life:

- the human capital method is based on the years of life gained from immunization, and therefore gives a lower value to life where formal employment opportunities and salaries are lower as in developing countries.
- Representative samples of population are questioned about there willingness to pay for reduction in the risk of death.
- Actual values of human life obtained from similar decision in the past can be used. [9]

According to the analyses there are immunization programmes which are not only cost-effective, but also save money, they provide net health benefits and reduce net medical costs. Other programmes intended

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7/ Costing guidelines, WHO, EPI/GEN/79/5, 1979

8/ A.L. Creese & R.H. Henderson, Cost-benefit analysis and immunization programmes in developing countries, Bull. WHO, 52. 491-497, 1980.

9/ Cost effectiveness and cost benefit analysis of immunization programmes n developing countries, IFPMA Document, SV 67, p.38, 1983

primarily for specific groups of individuals are cost-effective because they improve the share of health at a low cost, however, these do not result in net medical savings.

6. The results of the cost-benefit and cost-effectiveness analyses of immunization programmes should be regarded as estimates since both the costs and benefits have fixed and variable components, however, the influential factors of the variable costs are different from those of the variable benefits.

Fixed costs can be defined as those expenses which are required to develop and operate a programme of a given capacity. In absolute terms the variable costs depend directly on the number of vaccinations administered during a given period. In relative terms, however, this relationship is indirect, the higher the number of vaccinations administered during a given period , the lower the ratio of the variable costs.

Substantial savings can be achieved by bulk purchases if they can be established on the basis of regular contracts. As much as 500 to 600 per cent savings have been reported by bulk purchases. 10/ The other main component of the variable cost is the intra-country variation. High unit costs in thinly populated rural areas may make immunization against a single infectious disease uneconomic. But since the costs of vaccines represent about or even less than 20 percent of the total costs in the case of EPI vaccines, simultaneous immunization against several diseases provides an economically more feasible alternative for small additional expenses. 11/

10/ P. Carrasco & W. Umstead, EPI in Americas: Benefits from revolving fund, WHO Chron, 37, 81-85, 1983.

11/ M. Rey, Simultaneous administration of vaccines, killed or live, Proc. Int. Conf. Application of Vaccines against Virae, Rickettsial, and Bacterial Diseases of Men, PAHO, p. 407-412, 1971.

It should be however, noted that the distinction between fixed and variable costs is not hard. The global estimate of WHO for an average unit cost, that is the cost for fully immunized infant was approximately US$ 3,00 in 1980, the same value increased to US$ 5,00 by 1983, but the costs of vaccines remained around the same value, that is close to US$ 1,00. 12/ The high inflation rate has not affected the costs of vaccines, however, the costs of delivery have significantly increased.

Finally it is worth to be mentioned that the average unit cost of US$ 5,00 does not include the private costs such as travel expenses and lost work or leisure time of those who attend the vaccination centres.

The main variable component of the benefit side is the value of human life. Depending on the assumptions chosen there can even be a 20-fold difference between the estimated extremes. 13/

The economic evaluation of immunization programmes have recently been carried out in detail by different authors. 14/15/16/

12/ 1984 EPI Revolving Fund Prices, EPI Newsletter, Vol. V, No. 6, p.6-8, 1983.

13/ W.M. Makinen, A social cost-benefit analysis of aunti-measles vaccination in Yaounde, Cameroon, Ph.D. dissertation, University of Michigan, 1979.

14/ A.L. Crease et.al., Cost-effectiveness appraisal of immunization programmes, Bull. WHO, 60, 621-632, 1982.

15/ A. Crease, The economic evaluation of immunization programmes in The economics of health in developing countries, ed. K. Lee & A. Mills, Oxford University Press, 1983.

16/ Prospects for production of vaccines and other immunizing agents in developing countries, UNIDO/IS.402, 1983.

7. In most immunization programmes, as soon as those children within easy reach have been immunized, a greater coverage can usually be obtained only at a higher average unit cost. It can generally be stated that the greater the coverage the higher the average unit cost. However, it is possible to estimate the optimal combination of different approaches that is the use of fixed units, outreach units and mobile units for delivery of vaccines. 17/

One of the most difficult parts of an immunization programme is keeping the vaccine cold during its shipment from the manufacturer to the vaccinee. In a typical vaccine cold chain close to half of the refrigerators and freezers are out of order. 18/

The EPI makes great efforts to improve immunization coverage but it is an extremely difficult task in developing countries. In these countries but in particular in the least developed countries many obstacles have to be overcome during establishing a vaccine delivery system at the managerial, operational and control level. The social acceptance of vaccination is also very low in several developing countries. 19/ In 1983 the immunization coverage was approximately 30 % in developing countries. 20/

HOW TO PRODUCE CONVENTIONAL VACCINES RECOMMENDED FOR USE IN THE EPI IN DEVELOPING AND LEAST DEVELOPED COUNTRIES: MANAGEMENT, TECHNOLOGY, INVESTMENT.

8. For about 30 years many efforts have been made by different UN, governmental and non-governmental agencies and organisations to develop the manufacture of vaccines in developing countries. However, with some exceptions these efforts have failed. Analysing these projects one can identify the most important influential factors which have had their negative effects throughout the implementation and also in the operation resulting in wastage of efforts, time and funds and causing concern and frustration.

17/ K. Lee, Resources and costs in primary health care, in The economics of health in developing countries, ed. K. Lee & A. Mills, Oxford University Press, 1983.

18/ J. Cheyne, Strengthening the vaccine cold chain, World Health Forum, 3, 436-440, 1982.

19/ ICDDRB, Dhaka, Bangladesh, Scientific Report No. 43, 1981.

20/ Immunization, Health Development, WHO, WPR, No. 19, 1983.

Suggestions for successful establishment and operation of manufacturing facilities for vaccines in developing countries have been given in the issue and background papers prepared for the Second Consultation on the Pharmaceutical Industry, Budapest, Hungary, 1983. 21/22/

Many participants to the Second Consultation supported the proposals contained in the issue paper on "The manufacture of vaccines in developing countries". 21/ These participants acknowledged the importance of quality control as even the imported quality vaccines were subject to deterioration during shipment and distribution. Many participants felt that there was no need to set up new production capacity to meet current and anticipated demands in the near future. Further, they suggested that developing countries should first establish national quality control facilities for biologicals and the necessary infrastructure for national vaccination programmes. Finally, they suggested that in case governments of developing countries desired to enter into domestic vaccine production, they should do so in a gradual way by stages, from the checking of imported vaccines to importing concentrated vaccines for blending, filling and packaging to producing domestic vaccines. A number of participants, in support of issues expressed their readiness to provide technology for a wide range of biologicals, such as human and veterinary vaccines and blood products, while several other participants expressed their readiness to transfer technology and offer training on a bilateral basis. 23/

The Second Consultation gave the following recommendations on the subject:

- Use the distinction of classical and modern vaccines for practical purposes as classified in ID/WG.393/12/Rev.1 21/ (see annexure A)
- Consider the addition of vaccines, sera (both for human and veterinary use) and immunoglobulins to the existing biologicals in the UNIDO illustrative list; 24/

21/ The manufacture of vaccines in developing countries, issue paper, UNIDO, ID/WG.393/12/Rev. 1, 1983

22/ The manufacture of vaccines in developing countries, Background paper, UNIDO, ID/WG.393/13/Rev. 1 1983.

23/ Second Consultation on the Pharmaceutical Industry, Budapest, Hungary, 21 - 25 November 1983, Report, UNIDO, ID.311, p. 53-54, 1984.

24/ Progress report of activities taken on consultations on the pharmaceutical industry, Annexure A, UNIDO, ID.WG 393/5,1983.

- Adopt a step-by-step approach for establishing control and production capability of vaccines in two ways: (i) From filling and packaging towards actual manufacture; (ii) from production of classical vaccines towards modern ones;
- Implement long-term continuous technical assistance and support programmes for effective assimilation of technology and control procedures to be transferred;
- Promote the transfer of technology for modern vaccines at national and regional levels where there is adequate technical infrastructure; and
- Promote the manufacture at regional level of certain biologicals other than vaccines that are either difficult to procure or only used in developing countries. 25/

9. Depending on the actual stage of infrastructure of the public health and industry in developing countries, facilities for blending, filling and packaging of bulk vaccines or actual manufacture of vaccines can be established. For the least developed countries the establishment of a blending, filling and packaging unit is a realistic target, while developing countries with solid public health infrastructure and capabilities in the pharmaceutical industry can develop actual manufacture of conventional vaccines. A few more advanced developing countries can enter into the production of modern vaccines. It should be emphasized, if a developing country reached a certain stage, it does not mean that it might automatically enter into the next stage, since the period of each stage even with a continuous technical assistance and support programme can be extended for improving the quality of products and the economic viability of the manufacturing unit.

The basic requirements for manufacture of vaccines in developing countries are as follows:

- National pharmaceutical policy: drug policy and pharmaceutical industrial policy;
- National vaccination policy;
- National control authority and national control laboratory;
- Reliable epidemiological data regarding diseases preventable by immunization;
- Techno-economic feasibility studies and preparatory assistance;

25/ UNIDO, ID/311, p. 11-12, 1984

- Production programme and capacity data;
- Market data: raw materials, bulk vaccines, auxiliary materials, packaging materials, equipment and spare parts, technologies, patents, potential domestic and export market;
- Site of construction;
- Building;
- Technology;
- Trained personnel at managerial, professional and labour level: number and qualifications;
- Logistics: Network for collection of raw materials for blood products and for distribution of finished products, and
- Investment.

The main technical elements of production and quality control facilities for vaccines are given according to the requirements of WHO.[26/] (See annexureB)

10. In case goverrments of the least developed countries desire to enter into domestic vaccine production they should do so in a gradual way by stages. The first stage must be the creation and the running of a validated national quality control facility and a national quality assurance programme. The second could include the transfer of technology of vaccine blending, filling and packaging. A precondition for that type of technology transfer is often the purchasing of bulk vaccine from the technology supplier. Actual manufacture as a starting step does not seem to be a realistic target for the least developed countries. Since the technology is generally available at this stage, the implementation of such projects requires assistance mainly in management and investment. As a preliminary stage the setting up of an infusion and reconstituting fluids plant could be crucial in order to assure the transfer of technology for the water treatment process and sterile operation.

11. The main elements of the implementation of the projects and the ways and means of the recommended technical and financial assistance are as follows:

11.1. The prerequisite for the development of this particular subsector of

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26/ Manual for the design, equipping and staffing of facilities for the production and quality control of bacterial vaccins, WHO, BLG/UNDP/78.1

pharmaceutical industry is the government's promoting policy.
The policy should be established and can be referred to as pharmaceutical policy, which includes besides the drug policy, the pharmaceutical industrial policy. No foreign assistance is required in this phase.

11.2. Based on the national health policy but also on the pharmaceutical policy, the national vaccination policy can be formulated. The vaccination policy includes the immunization schedule and the operational plants. The immunization schedule must be epidemiologically relevant, immunologically effective, operationally feasible and socially acceptable. The operational plans should assure the highest possible coverage of target population, fixed immunization centres and mobile teams. 27/ In this phase a foreign expert, epidemiologist may assist the Government.

11.3. National control authority should be established by the Ministry of Health. The national control laboratory providing the necessary technical services to the national control authority should be also established. The national control authority licenses the manufacturers and their products in the country. The national quality assurance programme is established and controlled also by the above authority. In many cases the director of the laboratory may be the legally empowered authority. 28/ Foreign export in quality control of biologicals may assist the Government in this phase.

11.4. Continuous epidemiological surveillance should be organised and carried out with particular relevance to diseases preventable by immunization.
A foreign expert, epidemiologist may assist the Government in this phase.

11.5. Proposal for production programme and determination of the capacity is given by a foreign expert in production of biologicals to the Government.

11.6. Based on the market research, a techno-economic feasibility study should be prepared to determine the technically and economically most advantageous alternative for investment. In this phase a group of experts (e.g. production, quality control and marketing experts) should assist local counterparts.

27/ Expanded programme on immunization, programme design, WHO, EPI/G.77.1
28/ The national control of vaccines and sera, WHO Techn. Rep. Ser.,658, 1981.

11.7. Selection of size and location for construction. No foreign assistance is required in this phase.

11.8. Selection of technology by a foreign expert in production assisting local counterpart.

11.9. Architectural, mechanical and engineering designs should be prepared in accordance with the Good Manufacturing Practices (GMP). In this phase foreign experts (architect and engineer) may assist the Government.

11.10. Tendering of conditions for execution of the project can result in different agreements as follows: project execution by the technology recipient, implementation of work by a single, independent contractor, implementation of work by a group of contractors of different origin. No foreign assistance is required in this phase.

11.11. Based on the designs, the construction and engineering work is carried out. It should be assured that the capacity of the unit can be increased without major remodelling and/or the premises can be extended with minimum investment when it is necessary. Sources of financing should be identified.

11.12. The project management should be appointed.

11.13. The recruitment and training of personnel for production and quality control should be launched as soon as the construction work has started. Foreign experts, expatriates, local professionals and technicians can be recruited. The training of personnel can be carried out in independent institutions or in the premises of the technology recipient or supplier.

11.14. For purchase of equipment and spare parts for installation of equipment to perform the trial runs and to produce and control the trial batches, foreign experts in production and quality control can be contracted.

11.15 For purchase of bulk vaccines, packaging materials and laboratory animals, sources of supply should be identified. Quality control expert may assist the Government in this phase.

11.16. For the establishment of technical infrastructure the following utilities are required: electric supply, stand-by emergency generator, water supply, drainage and gas supply. In many developing countries it may happen that public utilities do not exist on the site selected for the construction of production facility. In this case there is an option between extending the municipal public utilities to the site of manufacturing plant and establishing them independently. No foreign assistance is required in this phase.

11.17. The logistics for distribution of the products manufactured should be established. Assistance in organisation and funds may be required.

11.18. Sources of financing should be identified. Alternative sources of financing can be: Government's budget, funds of UN organizations and agencies, bank funds, donations, etc.

12. Both professional and labour staff should be highly motivated and disciplined because only this behaviour can assure that during the routine work, the aseptic and sterile conditions will as far as possible be kept. The importance of the above cannot be overemphasized since vaccine production at any stage is based on aseptic and sterile work. Familiarizing with the aseptic and sterile work needs a long-term training aimed not only to teach the techniques themselves but to promote the personal and environmental hygienic conditions and to abandon those unhygienic practices which might occur in developing countries.

13. In 1980 the number of manufacturing facilities in developed and developing countries were 72 and 32, respectively.[29/] Recent information however, shows that at least in developing countries the number of active manufacturers is less than 32, in several cases either the manufacturers do not produce vaccines any more or their products are presently not marketed. The above is particularly true for Africa, where hardly half of the existing and locally licensed manufacturers is active. The quality of vaccines as manufactured differs not only from manufacturer to manufacturer but sometimes from batch to batch. National quality control laboratories for vaccines are still the exception rather than the rule, for example, in 1980 there was only one quality control laboratory capable testing DPT vaccine in Africa. Based on the above, one

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29/ International list of availability of vaccines, WHO, BLG/80.1

participant of the Second Consultation suggested that existing manufacturing and quality control facilities should be evaluated and rehabilitated if needed before setting up new units. 30/ It is recommended that the rehabilitated production units should start with blending, filling and packaging of vaccines before they would enter into the actual manufacture. In the light of the above it is worth mentioning and considering that at present only a few manufacturers in developing countries procure quality vaccines in bulk for blending, filling and packaging in spite of the obvious technical and also economic advantages of this practice.

14. Those developing countries which have certified national quality control facility and have already gained experience in blending, filling and packaging bulk vaccines may enter if desired into the actual manufacture of conventional vaccines. The technology to produce classical vaccines is becoming readily available. According to a recent survey 31/ 20 manufacturers are ready for transfer of technology of vaccine included in the "Revised model list of essential drugs" of WHO 32/. Even 6 manufacturers of 4 developing countries expressed their readyness to make their technologies avialable for developing countries. The latter shows that technical co-operation among developing countries (TCDC) can already be envisaged in this early stage of development of this particular sub-sector of pharmaceutical industry in developing countries.

WHO recognised that a number of developing countries were wishing to produce vaccines at the national level and has prepared manuals for production and quality control of several conventional vaccines to provide the necessary technical information. These excellent manuals intend only to provide general information on methods and they should not be regarded as technologicals descriptions, however, their importance cannot be overemphasized.

30/ UNIDO, ID.311, p. 54, 1984

31/ UNIDO/IS.402, p.46-49, 1983

32/ The use of essential drugs, WHO Techn. Rep. Ser., 685, 1983

They can be used as guidelines for developing of production and quality control facilities and also as tools for training of personnel.[33/34/35/36/37/] Apart from WHO publications, van Hemert's monograph is also available for manufacture of vaccines which contains not only technical and financial considerations but also technological details of production. [38/]

Since the technology is available at this stage, that is the stage of introduction of actual manufacture of conventional vaccines, the implementation of these projects required assistance mainly in management and investment. The technical assistance of a solid partner is recommended not only in the whole period of implementation of the project but also during the first years of operation. Even if the different phases of the project could be executed and/or financed by different foreign or local contractors and organizations, the above partner, that can be also the licensor, would be responsible for supervising all of the activities carried out during the implementation.

15. The main elements of the implementation of the projects and the ways and means of the recommended technical and financial assistance is very similar to the assistance provided to implement projects at the previous stage, that is the transfer of technology for blending, filling and packaging of vaccines. The latter are given in paragraph 11. In the following only those aspects are discussed which are considered as particularly important in the transfer of technology for the actual manufacture of conventional vaccines.

15.1. The sources of supply of technology should be identified and the technology should be selected by a foreign expert or a group of experts who may assist the local counterparts. The type of contract for the transfer of technology should also be determined: foreign investment can be involved in the project or it can be executed without this, it can be "packaged" or "unpackaged" transfer of technology.

33/ Manual for the production and control vaccines, Diphteria toxoid, WHO, BLG/UNDP/77.1/Rev.1

34/ ibid, Tetanus toxoid, WHO, BLG/UNDP/77.2/Rev.1

35/ ibid, Pertussis vaccine, WHO, BLG/UNDP/77.3/Rev.1

36/ Procedure for production of cholera vaccine, WHO, CDD/SER.82.1

37/ Manual of details of tests required on final vaccines used in the WHO Expanded Programme on Immunization, WHO,BLG/UNDP/82.1/Rev.1

38/ P. van Hemert, Vaccine production as a unit process, 19'1.

15.2. The project can be executed by the licensor (technology supplier). This option is highly recommended by UNIDO since the contract in this case could include the licensor's special obligations and responsibilities during the implementation of the project and also during the first years of operation. This period should be long enough for the licensee (technology recipient) to assimilate the technology and gain experience which is needed to master the difficulties which might occur in the processes of production and quality control.

15.3. Training of personnel at different levels of management, production and quality control could be carried out in the licensor's premises. In this way the personnel could gain direct experience from a well established manufacturer and could assimilate the selected technology during an in-plant training course.

15.4. The successful transfer of technology according to UNIDO can be ensured by long-term continuous technical assistance and support programmes of the licensor. The type of this support programme can differ from country to country depending mainly upon the capabilities and availability of technical infrastructure of this particular sub-sector of the pharmaceutical industry. The scope and duration of such a service should be determined at the time of negotiating the conditions for the transfer of technology. Due to the above special requirements for the transfer of technology to manufacture conventional vaccines, the establishment of a joint-venture could be one of the solutions. The setting up of a joint venture reduces the risk of project failure for the licensee, because it directly involves the licensor, thereby ensuring the interest of the technology supplier in the success thereof. Joint-ventures are however advisable only if there were industrial production technologies. In this case the production facilities could also be developed on subregional or regional basis to achieve economic feasibility.

16. The Second Consultation concluded that the transfer of technology for biologicals could be offered in stages. The third stage would be a step-by-step approach assimilating technologies from filling and packaging to actual manufacture and from the production of classical vaccines to modern ones.For modern vaccines the production facilities could be developed at subregional or regional level to achieve economic feasibility.A further step in the transfer of technology can be the treatment of local blood on a regional basis taking into account the differences of the epidemiological situation in the preparation of specific hyperimmune sera and immunoglobulins. According to the recommendations on the subject, the transfer of technology for modern vaccines should be promoted at national and regional levels where there is adequate technical infrastructure. Promoting the manufacture of certain biologicals other than vaccines at regional level is also recommended if they are either difficult to procure or only used in developing countries .[39]

It was also recommended by the Second Consultation that UNIDO should use the distinction of classical and modern vaccines for practical purposes as classified in the issue paper on "The manufacture of vaccines in developing countries" [40] (see annexure A). In the following all of the improved non-EPI vaccines and modern biotechnological vaccines are referred as modern vaccines.

17. The significance of development of an improved poliovaccine is highlighted by the fact that although the oral (Sabin) poliovaccine has been shown to be effective in the control of poliomyelitis in many countries, in some developing countries, especially in the tropical and semitropical areas the immunity induced by the conventional three doses of oral poliovaccine has been incomplete, and as a consequence the incidence of paralytic poliomyelitis has been unacceptably high in vaccinees.[41] Recently an inactivated (Salk) poliovaccine of improved potency has been developed and also its large-scale manufacture has been established.This vaccine can be used in combination with DPT as a quadruple vaccine, and it is said to be no more expensive to use than the present programme involving the cheaper oral polio vaccine.[42]

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[39] UNIDO: ID/311 p. 10-12 , 1984

[40] UNIDO: ID/WG.393/12/Rev.1, 1983

[41] D.M.Horstmann, Control of poliomyelitis:a continuing paradox , World Health Forum , 4, 264-270,1973

[42] Poliovaccine, Lancet, 1, 1022-1023, 1983

The Public Health importance of an improved rabies vaccine should also be emphasized. Hundreds of thousands doses of neural tissue rabies vaccine are distributed annually in developing countries for rabies post-exposure prophylaxis, although the potency of this type of vaccine is questionable. Further it causes paralytic and other adverse reactions which result in close to 50 % default from treatment and, as a consequence in further reduction of its prophylactic value. By contrast, the protective value and safety of human diploid cell rabies vaccine for pre-exposure and post-exposure use are well established. Although the human diploid cell rabies vaccine is expensive, a more economic regimen using 0.1 ml intradermally has been developed . [43] However, the first step towards a worldwide rabies control could only be achieved by the development of a cheap and effective oral vaccine for immunization of canine population.[44]

18. The public health significance of recently developed vaccines in developing countries can be highlighted by two examples. The purified polysaccharide vaccines such as meningococcal and pneumococcal vaccines are the safest biologicals. Up to now hundreds of million doses of meningococcal vaccine have been administred but no single adverse reaction has ever been reported. These vaccines are highly effective either administered alone or in combination, however only above 2 years of age. The purified polysaccharide vaccines could be included in the immunization programmes in those developing countries, but especially in West African countries where the purulent meningitis caused either by Neisseria meningitidis or Streptococcus pneumoniae is endemic .

Primary liver cancer is perhaps the most common cancer in South-East-Asia and Africa, and it is among the ten most common cancers worldwide killing hundreds of thousands of people annually. There is now strong evidence for an association between the carrier state of hepatitis B virus infection and primary liver cancer which justifies the immunization against hepatitis B to prevent this cancer . Since the incidence of primary liver cancer is about 30 new cases for 100.000 population annually in South-East Asia and Africa, the immunisation against it would have a significant impact on the public health situation. However, the present price of the vaccine is very high, even if it was administered intra-

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[43] Intradermal vaccination, Lancet, 2, 1464-1465 , 1983

[44] G.W.Beran & A.J.Cowley, Toward Worldwide Rabies Control, WHO Chronicle 37, 192-196, 1983

dermally. [45]

19. At present development of new vaccines against many infectious and parasitic diseases prevalent in developing countries is in progress. Before 1975 the world-wide expenditure on research in tropical diseases was estimated at about US$ 30 m annually.Since then the annual expenditure has tripled due to the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). One of the major achievements of this programme is the substantial progress that has been made in fundamental knowledge required to develop an anti-malarial vaccine.

Besides the five most prevalent tropical diseases : malaria, schistosomiasis, filariasis, trypanosomiasis and leprosy, there are other diseases which are common and could be theoretically prevented by vaccination . For instance, the diarrhoeal diseases are one of the major causes of childhood morbidity in developing countries and account for some 5 million deaths annually in chidren below 5 years of age. At least those enteric infections which are due to Vibrio cholerae and Salmonella typhi, new types of vaccines could be developed.

20. The price of the improved and recently developed modern vaccines is generally high and therefore most of the developing countries cannot afford them with their limited financial resources of public-health.If these vaccines are at all available in developing countries they can only be obtained through subsidaries of the large pharmaceutical manufacturers of developed countries, their promotion offices or in some cases from individual retailes. The main reasons for the high pricing are the following:

- the high research and development costs are included in the price,
- the costs of equipment and general facilities are high,
- the large manufacturers are the exclusive suppliers of vaccines, etc.

In addition to the above, the promotion of the hepatitis B vaccine presents a special case because of the limited amount of starting raw material. Since the number of asymptomatic hepatitis virus carriers is limited, the production of vaccines cannot be increased in line with the market demand.The production

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[45] Prevention of hepatocellular carcinoma by immunisation Bull. WHO, 61 731-744, 1983

of this vaccine in many developing countries is out of question since they are even without the proper infrastructure for collection of blood and/or plasma. However, it should be mentioned, that this type of problem connected with the shortage of starting raw materials could be solved by the new techniques recently introduced in some developed countries.

21. Blood products, as vital life-saving biologicals,have utmost importance in the health care programmes of any country.However, some developing countries depend entirely on imports of human plasma factions.The cost of imported material is often prohibitive and well beyond the reach of a large segment of population .The developing countries are not able to meet even a fraction of the demand for blood products,since on one hand the import of these items would mean the depletion of their scarce foreign excharge resources,and on the other hand in most cases they do not possess the technical infrastructure and manufacturing capability for collection and processing of human plasma.

In the light of the above, UNIDO and the Committee for National Co-operation on Pharmaceuticals of the Ministry of Health and Social Affairs, Sweden, together with the WHO and the League of Red Cross Societies organised a Seminar on National Self-Reliance in Blood and Blood Fractions for Developing Countries, in Stockholm, Sweden, 1982 with the view to acquaint representatives of developing countries into the various facets of blood transfusion services and the industrial scale of plasma fractionation.Among the recommendations included in the plan of action of this seminar were that UNIDO should carry out a survey of existing facilities, infrastructure and availability of plasma for fractionation in developing countries, and assist in transfer of technology for establishing/expending/improving plasma fractionation on laboratory/pilot/industrial scale.UNIDO could also provide assistance in training of personnel for production of blood derivatives . [46]

22. The problems relating to the transfer of technology to manufacture modern vaccines and blood products are completely different from the problems arising in the case of conventional vaccines. First of all, the technologies for the manufacture of modern vaccines are not generally available as those of conventional vaccines. The modern vaccines have recently been developed and most of them

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[46] Draft Report , UNIDO/ IO, 1983

are patented. The technologies of modern vaccines and blood products are sophisticated.The implementation of the industrial scale technologies require a sound technical infrastructure. The operation of highly specialised manufacturing equipment requires special conditions and in addition careful preventive maintenance. Even if the technologies were available , the implementation of such projects would be very costly and, therefore economically not feasible in those developing countries were neither the technical infrastructure nor the trained personnel are available.According to UNIDO's view, the transfer of technology for manufacturing of modern vaccines is recommended only in those few developing countries which have a certified and economically viable production of conventional vaccines recommended for use in the EPI and a proper infrastructure and trained personnel necessary for the development. It should be noted that joint-venture seems to be the best way in this case. The joint-venture is suggested to be based on an industrial production technology and the production facility is recommended to be developed at subregional or regional level to achieve economic feasibility.

ANNEXURE A

LIST OF THE MOST IMPORTANT CONVENTIONAL AND IMPROVED RECENTLY DEVELOPED VACCINES

CLASSICAL VACCINES

1. BCG vaccine against tuberculosis
2. DPT vaccine against diphtheria, whooping cough and tetanus
3. Tetanus toxoid
4. Diphtheria-Tetanus toxoid
5. Typhoid vaccine
6. Cholera vaccine
7. Oral and inactivated poliomyelitis vaccine
8. Live and inactivated measles vaccine
9. Rabies vaccine prepared in neural tissues
10. Yellow fever vaccine

etc.

IMPROVED OR RECENTLY DEVELOPED VACCINES

1. Rabies vaccine produced in cell cultures
2. Improved poliomyelitis vaccine for parenteral use
3. Hepatitis B vaccine
4. Menongococcal vaccine
5. Pneumococcal polysaccharide vaccine
6. Oral live galactose - epimerase - less typhoid vaccine

etc.

ANNEXURE B

LIST OF TECHNICAL ELEMENTS OF PRODUCTION FACILITIES FOR VACCINES

1. Production:
   a) Building and Services
      Layout and design
      Construction materials
      Clean areas
   b) Equipment and laboratory furnishings
   c) Chemicals and consumables
   d) Staff

2. Quality Control
   a) Buildings and services
      Layout and design
      Construction materials
      Clean areas
   b) Equipment and laboratory furnishings
   c) Chemicals and consumables
   d) Staff

3. Central Services:
   a) Essential services
      Electricity
      Gas
      Boiler House
      Stand-by emergency generator
      Demineralised and distilled water
      Drainage
      Compressed air and vacuum
   b) Administration
      Offices and record keeping
      Library
      Canteen
      Health care
   c) Glassware washing and sterilization
   d) Media and adjuvant preparation
   e) Filling area
      Filling
      Packaging and labelling
      Visual inspection
   f) Cold storage and despatch
   g) Central store and supplies
   h) Maintenance workshop
   i) Staff

4. Animal Housing
   a) Building and services
      Layout and design
      Construction materials
      Isolation
      Disinfection and incineration
   b) Feed and bedding
   c) Storage
   d) Staff