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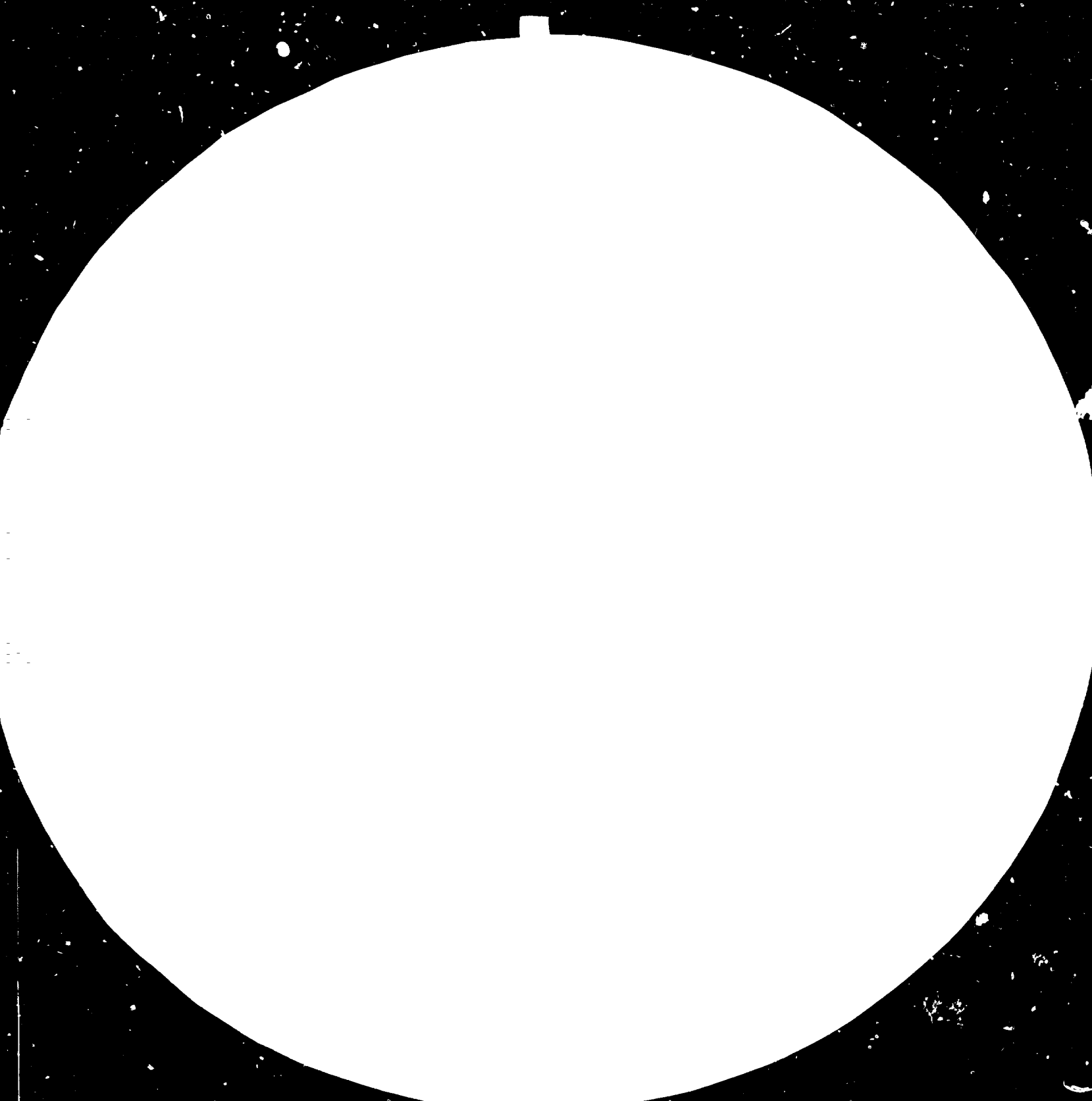

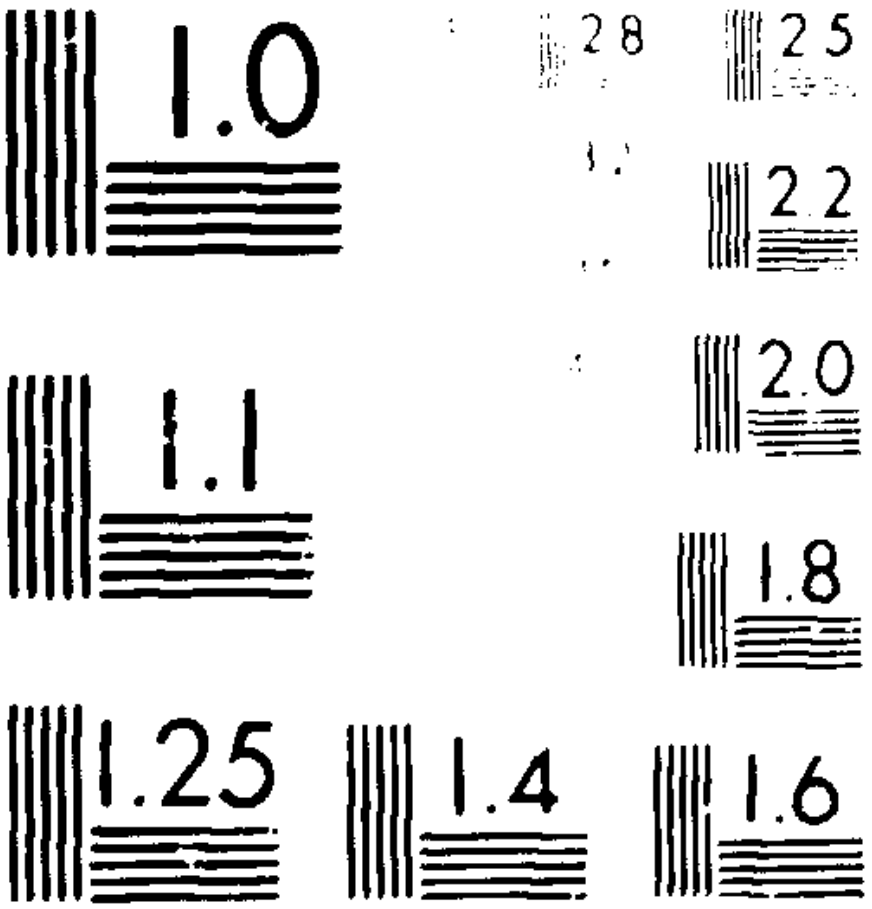
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THE MANUFACTURE OF VACCINES IN DEVELOPING COUNTRIES

Background paper*

prepared by

the UNIDO Secretariat

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INTRODUCTION

1. The disease pattern of developing countries is considerably different from that of developed countries. In the former, especially in the least developed countries, the communicable diseases are still among the leading causes of death or disability. These diseases deeply affect the young in the less developed regions, who are hardly benefitting from the general improvements in mortality characteristic of the more developed regions. A number of communicable diseases can be prevented and controlled by immunization. Since the prevention in most cases is not only the more effective measure for control of these diseases but it is also cheaper than cure, no-one should occupy a hospital bed with a disease that can be prevented by immunization.

2. Historically, from the time of Louis Pasteur and Robert Koch, the manufacture of vaccines was developed on an ethical basis. Although this ethical approach is beneficial for the whole of mankind, the industrial approach of production has, as a consequence, been in most cases missed. With a view to assisting the developing countries in the establishment of pharmaceutical industry, UNIDO has evolved a strategy and elaborated a policy in development of industrial production of biologicals by strengthening the preventive measures to control communicable diseases. The developed industrial capabilities in developing countries can also be utilized for the industrial application of the future results of biotechnological revolution.

3. The two important areas for the local production of active immunization products, vaccines, are the following:

(a) the transfer of technology for the manufacture of classical vaccines, with special reference to the commitments and responsibilities of the licensor;
(b) the availability, terms and conditions for the transfer of technology for the manufacture of improved classical, recently developed and future vaccines.

Annexure A presents a list of the most important classical and improved or recently developed vaccines.

I. TRANSFER OF TECHNOLOGY FOR THE MANUFACTURE OF CLASSICAL VACCINES

A. Prevailing disease patterns in the world

4. In the past 60 years many major infectious diseases of man have been rendered preventable by the development and use of vaccines and by the end of 1977 one of them, smallpox, had been eradicated. Diphtheria, measles, poliomyelitis, tetanus, tuberculosis, whooping cough and yellow fever, are diseases which can be controlled in developed countries due to immunization programmes using highly effective vaccines. Although recently there is a controversy on BCG vaccination, it prevents childhood tuberculosis if potent vaccine is used in a proper way

5. The first mass vaccination programme against diphtheria was started over 50 years ago, and has effectively eliminated the illness in developed countries. Before the era of vaccination against measles and whooping cough 60%-100% of the total population became infected at some time or the other during their lives, but the incidence of the above communicable diseases is now very low in developed countries. Figures per 100,000 inhabitants for the mid-seventies were as follows:

diphtheria 0.01: tetanus 0.3; whooping cough 0.4; measles 1.2: and poliomyelitis 0.03.

6. On the contrary, these diseases are still prevalent in most of the developing countries. Surveys show that whooping cough has a high morbidity (80% of all children contract the disease) and a high mortality (case fatality rate between 4% and 15% is noted), particularly in the first two years of life.

The estimated number of deaths from tetanus is 1 million annually, but the incidence and mortality both vary considerably in different parts of the world. In some areas, rates up to 90-200 per 100,000 inhabitants have been reported, along with neonatal death rates of 100 per 1,000 live births.

Diphtheria is considered a rare disease but the incidence is increasing with urbanization with a case fatality rate of about 10%.

Only in West Africa 500,000 children die from measles each year, mostly between one and two years of age. Throughout the developing countries, 95% of children who survive the first two years develop one or more respiratory, neurological or ophthalmic complications with case fatality rates up to 10%.

The morbidity rate of poliomyelitis varies significantly in different countries, the case fatality rates being generally between 10%-15%. About half of the cases result in some degree of residual paralysis.

According to information from several countries, for each per cent of annual risk of infection with tuberculosis, about 40-60 new smear positive cases can be expected to develop each year per 100,000 of population.

7. All together, the above diseases kill some 5 million children each year and either cripple, blind or cause mental retardation in 5 million more in developing countries, that is 10 children die and another 10 become disabled in each passing minute.

B. The world production of vaccines

8. Since the incidence of dangerous communicable diseases of childhood is very low in developed countries, many of their vaccine manufacturing facilities have closed down in the last twenty years. In the United States the number of biological manufacturers has declined from 11 in 1966 to only 5 in 1981. This decrease has had consequences for developing countries due to the discontinuation of biological products distributed through the subsidiaries of these manufacturers. It should also be noted that half of the production output of a European company (e.g. Lister, UK - which closed down in 1978) was for export purposes. Thus there is a trend of decreased interest in manufacturing classical vaccines in developed countries. The main factors influencing this trend are (a) limited local demand; (b) low profit margins of these products; and (c) the risk involving the administration of vaccines in healthy children.

9. In spite of the fact that a number of vaccine producers have closed down in developed countries, the number of manufacturers, the production per capita and often the volume of production in these countries are significantly higher than in the developing countries. In 1980, the number of manufacturing facilities for BCG, DPT, measles, poliomyelitis vaccines and tetanus toxoid in developed and developing countries were 17, 32, 12, 14, 33 and 10, 10, 2, 2, 13, respectively. The total number of manufacturing facilities in developed and developing countries were 72 and 32, respectively.

10. According to projections made by WHO based on change in the trends of vaccine consumption, the amount of vaccines theoretically required by developing countries will be approximately 5 to 10 times more by 1990 than it was in the mid-seventies. To meet this high requirement, national production facilities must expand and/or new manufacturing facilities be established.

To illustrate the increasing demand, the requirements of DPT vaccine in India could be over 100 million doses by 1990, whereas the production was less than 30 million doses in 1981. Nigeria and Bangladesh would require about 20 million doses of DPT vaccine by 1990 but at present they rely entirely upon government imports and UNICEF and other donor support, in absence of local manufacturing facilities.

11. The decreasing interest in the production of classical vaccines in developed countries contrasts with the increasing requirement for these products in developing countries. The purchasing power of many developing countries cannot sustain the cost of imports in the required measure, leaving no incentive to resume the production of classical vaccines for export purposes in developed countries. To overcome the above UNICEF, as the world's largest buyer and donater of vaccines, may have also a very special and important role in the development of manufacturing capabilities for biologicals in developing countries, since in the long term the donation cannot be the final solution.

12. Local manufacture of classical vaccines, therefore, is the only viable solution for the above paradoxical situation, where these vaccines are produced mainly by developed countries with low demand, while many developing countries, where the need is acute, cannot avail themselves of sufficient quantity and quality. Furthermore, buying vaccines at the cheapest prices does not necessarily improve the efficiency of vaccination programmes because cheap prices could go along with inferior quality.

13. The transfer of technology for the manufacture of classical vaccines has faced many constraints and frustrations and problems relating to the transfer of technology of vaccines should be analyzed in-depth.

14. The technologies of classical vaccines have been developed in the last sixty years, more in an empiric way than by systematic research and development work. These technologies, therefore, customarily have "weak" points which have seldom been systematically investigated, thus making even the industrial scale production of some vaccines more akin to art than to science. For example, the parts of technology for pertussis vaccine which are not exactly defined, are the following:

(a) bacterial strains
(b) culture media
(c) optimal parameters of cultivation
(d) optimal parameters of inactivation
(e) quantity and quality of immunological adjuvants if needed, and
(f) potency tests which can be used for the estimation of efficacy of the vaccines in the field

15. The development of improved classical vaccines is hampered both by financial limitations and by complications of establishing vaccine efficacy in clinical trials. For these reasons, the research and development on classical vaccines in developed countries deals primarily with the development of definitive purified vaccines. If and when this goal is achieved, the problems relating to the transfer of the latter have been presented in paragraphs 26 to 31.

C. Transfer of technology of classical vaccines

16. The technologies of classical vaccines are generally available to developing countries. To assimilate and adopt these, however, requires not only substantial financial resources and organization but also a long manufacturing experience and sufficient confidence to overcome the routine difficulties which arise due to the ill-defined empiric manufacturing processes. Annexure B gives an example of the complexity involved in producing classical vaccines.

17. Developing countries, including more advanced ones, possess little suitable experience or expertise. This problem is more pronounced in the least developed countries, especially in Africa, where diseases preventable by vaccination are the most prevalent. The transfer of technology, therefore, requires special conditions to ensure the assimilation and successful implementation of the technological know-how.

18. The mastering of this technology can be ensured by cooperation between the licensor and the licensee. In this case the licensor is committed to do his best to transfer the technology. To take up this responsibility over a long period may be deemed a rather unusual service of the licensor, but it seems to be the main prerequisite for the successful implementation of the project. The responsibilities of the licensor will differ from country to country depending mainly upon the availability of technical infrastructure for 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.

19. Due to the special requirements for the transfer of technology to manufacture classical vaccines as highlighted above, 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.

II. TRANSFER OF TECHNOLOGY FOR THE MANUFACTURE OF IMPROVED AND RECENTLY DEVELOPED VACCINES

A. The development and production of improved vaccines

20. The price of the improved and/or recently developed vaccines is generally high, and many developing countries cannot afford them with their limited financial resources in public health care.

If these vaccines are at all available in developing countries they can only be obtained through subsidiaries of the large pharmaceutical manufacturers of developed countries, their promotion offices or in some cases from individual retailers. The high prices compounded by foreign currency requirements are major factors limiting the availability of these vaccines, and only a small percentage of the population can afford these highly potent vaccines, which additionally are without adverse effects.

21. The reasons for the high pricing are the following:

(a) the large manufacturers are the exclusive suppliers of vaccines;
(b) the high research and development costs are included in the price, and
(c) the costs of equipment and the general facilities are high.

22. In addition to the above it should be noted that because of the limited amount of starting raw material, the demand for hepatitus B vaccine cannot be met at present even in developed countries. Since the number of asymptomatic hepatitis B virus carriers is limited, the production of the vaccine cannot be increased in line with increasing demand. Hence the export availability of this vaccine is severely restricted if at all possible. The hepatitis B vaccine is not available in most of the developing countries. Its production output cannot be increased by importing the starting raw material (blood) from developing countries. The importing of that type of blood or plasma is restricted since the medical history of donors from developing countries cannot be traced back. However, it should also be mentioned that this type of problem could be solved by the new techniques recently introduced in some developed countries.

23. If the present trend of development of new vaccines continues, these products will be available mainly in developed countries, irrespective of the fact that their utmost benefit would be for developing countries where the diseases preventable by them are prevalent. This paradoxical situation has already been highlighted concerning classical vaccines in paragraph 12. However, there are also some exceptions, e.g. the rabies vaccine produced in vero cell cultures is approximately one hundred times cheaper for developing countries than that produced in human diploid cells.

24. At present development of new vaccines against many infectious and parasitic diseases prevalent in developing countries is in progress. Before 1975, the worldwide expenditure on research in tropical diseases was estimated at about US$ 30 million 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 the above programme is the substantial progress that has been made in fundamental knowledge required to develop an anti-malarial vaccine.

However, it is felt by concerned parties that not enough is being achieved at present in this field. Besides the five most prevalent tropical diseases: malaria, schistosomiasis, filariasis, trypanosomiasis and leprosy - there are other diseases which are common in developing countries 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 children below 5 years of age. These enteric infections are mainly due to Escherichia coli, rotavirus, Vibrio cholerae, Salmonella and Shigella, against which new types of vaccines could be developed. Gonorrhoea also affects millions of people in some developing countries, and since the antibiotic resistant cases of gonorrhoea are steadily increasing, to develop an antigonorrhoeal vaccine seems to be necessary.

25. As paragraphs 20 to 24 show, many new vaccines developed recently by systematic research and development are available, and further research is in progress. No capabilities, however, have been built up for these products in developing countries and this gives a specific role for UNIDO to assist them in establishing their infrastructure and manpower in this specific subsector of pharmaceutical industry. The approach of the production of modern vaccines should be industrial, since only the industrial production based on economic feasibility could provide built-in consistency of these highly sophisticated vaccines.

B. Transfer of technology of improved and recently developed vaccines

26. The technologies for the manufacture of improved and/or recently developed vaccines are not generally available as those of classical ones. These have been developed by systematic research and development work in the past twenty years and most of them have been patented. The royalities and technology fees are high, not only because large manufactures have monopoly but also because the manufacturing processes are expensive and the high research and development costs are included in the price.

27. The technologies of improved and/or recently developed vaccines are sophisticated. The implementation of these on an industrial scale requires a sound and up-to-date technical infrastructure. Operation of the highly specialized manufacturing equipment, in addition, requires careful preventive maintenance.

28. The modification and adaptation of these sophisticated but effective technologies to the local conditions of developing countries would require significant research and development input, which would further increase the cost of transferring the technology and, therefore, this approach does not appear to be realistic.

29. From the above it can be understood that the problems relating to the transfer of technology to manufacture improved and/or recently developed vaccines are completely different from the problems arising in the case of classical vaccines. Even if financial resources to purchase the technology were available, the implementation of the project would be very costly and, therefore, economically not feasible in those developing countries where neither the technical infrastructure nor the trained personnel are available.

30. Some of the more advanced developing countries have the necessary financial resources and technical expertise for these technologies. The conditions for the transfer of technology to the more advanced developing countries could be similar to the ones given in paragraphs 18 and 19. The transfer of technology of improved and/or recently developed vaccines is recommended only to those developing countries which have viable production of classical vaccines. It should be noted that joint-venture seems to be the best way in this case. As a special case, the transfer of technology of the hepatitis B vaccine could be recommended since this product, due to the limited amount of starting raw material in the developed countries, is hardly available in developing countries, even if they could afford to buy it.

31. A special condition for the transfer of technology could be that the transfer is offered in stages. The first stage, in most cases, could include the transfer of know-how of vaccine blending, filling and packaging, and the quality control of the final product. Often a pre-condition for this type of technology transfer is the purchasing of bulk vaccine from the technology supplier. This type of technology transfer if, however, more characteristic of those classical vaccines for which demand is decreasing in developed countries.

III. CONCLUSIONS

32. The infectious diseases preventable by immunization are mostly prevalent in developing countries which, with the exception of the more advanced ones, are without manufacturing facilities. The developing countries without manufacturing facilities cannot be expected to depend indefinitely on imports or donations to meet their entire requirements of vaccines. Likewise, the developing countries with manufacturing facilities cannot be expected to limit themselves to produce only a few classical ones, but they should proceed towards the manufacture of improved and developed vaccines.

33. Since the technologies of classical vaccines are becoming generally available, to assimilate and adopt them requires mainly financing, training and organization. The technologies to manufacture improved and recently developed sophisticated vaccines, however, are often not available besides requiring a high level of technical infrastructure for effective assimilation. The transfer of technology for manufacture of improved classical, recently developed and future vaccines is recommended to be carried out in any of the following three ways:

- stepwise approach of assimilation of technologies in two senses: from filling and packaging towards actual manufacture and from production of classical vaccines towards that of modern of ones;
- joint venture is suggested only if there are industrialized production technologies; and
- production facilities could be developed at subregional or regional levels to achieve economic feasibility.

ANNEXURE A

LIST OF THE MOST IMPORTANT CLASSICAL AND IMPROVED OR 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 measles vaccine
9. Yellow fever vaccine

etc.

IMPROVED, RECENTLY DEVELOPED AND FUTURE VACCINES

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

etc.

ANNEXURE B

Schematic illustration of a process alternative for preparing bulk DPT vaccine in fermenters