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THE CHALLENGE OF BIOLOGICAL TECHNOLOGY

TRANSFER TO DEVELOPING COUNTRIES

BACKGROUND PAPER

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PREFACE

This paper deals with the transfer to developing countries of technology related to the manufacture of biological products.

Since the Second Consultation on the Pharmaceutical Industry in November 1983 and the creation of UNIDO's Advisory Panel on Preventive Medicine in February 1984 much progress has been achieved in the understanding of the various aspects of biological technology transfer . In March 1986, a Model Programme for the Production of Vaccines in Developing Countries was finalised and adopted by the Advisory Panel on Preventive Medicine. The present background document serves as an introductory paper to the Model Programme, highlighting the risks and opportunities presented by the transfer of technology in the field of conventional vaccines. It raises three key issues in this area : the availability of the technology, the feasibility of its transfer and the advisability of actually proceeding with such technology transfer.

These considerations are put forward as issues for discussion under the heading of biologicals at the Third Consultation on the Pharmaceutical Industry, due to take place in Madrid, Spain, in March 1987.

INTRODUCTION

Recognizing that immunization programmes are an essential component of primary health care, especially in developing countries, the Second Consultation on the Pharmaceutical Industry, held in Budapest, Hungary (21-25 November 1983) agreed on a number of points of major importance concerning biological technology transfer(1) :

1) The transfer of biological technology should be offered in stages :

   - The first stage must be the creation and the running of a validated national quality control facility and a quality assurance programme ;

   - The second stage could be the transfer of technology of vaccine packaging, blending and filling. A precondition for that type of technology transfer is often the purchase of bulk vaccine from the supplier of the relevant technology. 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 ;

   - The third stage would be a step by step approach assimilating technologies from packaging and filling to actual manufacture and from the production of classical vaccines to modern ones. Joint ventures were deemed advisable only if they covered industrialized production technologies. It was further postulated by the Second Consultation that production facilities could be developed at subregional or regional levels to achieve economic feasibility ;

2) The vaccine produced must comply with WHO specifications.

It was recommended by the Second Consultation that UNIDO should take a series of actions including :

- Adopt a step-by-step approach for establishing a control and production capability of vaccines in two ways :
  . From packaging and filling towards actual manufacture ;
  . From production of classical (or conventional) vaccines towards modern ones ;

- Implement long term continuous technical assistance and support programmes for effective assimilation of technology and control procedures to be transferred ;

To this end, shortly after the Second Consultation, UNIDO created an Advisory Panel on Preventive Medicine to make recommendations on the technical and economic aspects of the establishment of the Organisation's programme of Industrial Production of Biologicals (IPB). It is the Panel's current role to oversee and give advice on the implementation activities of the IPB programme.

The Advisory Panel has met four times since its inception : in Vienna, Austria (27-28 February 1984) ; Bogota, Colombia (22-23 November 1984) ; Bilthoven, The Netherlands (6-7 June 1985) ; and Ottawa, Canada (11-12 March 1986). The fifth meeting of the Panel is scheduled to take place in Niamey, Niger (30-31 January 1987).

The main conclusions and recommendations of the Advisory Panel are embodied in the Chapters that follow, in so far as they relate to the transfer of technology as described in the Model Programme for the Production of Vaccines in Developing Countries (UC/GLO/84/120).

PRESENT STATUS OF THE BIOLOGICAL INDUSTRY

There are, worldwide, some 20 producers of polio vaccine and measles vaccine, 31 manufacturers of BCG, over forty laboratories that make diphtheria - pertussis - tetanus vaccine and nearly 70 that produce tetanus toxoid (2).

However, only a dozen or so biological manufacturers compete regularly in the UNICEF and PAHO tenders that provide the bulk of vaccines for WHO's Expanded Programme on Immunisation (EPI). These companies are all located in Western Europe or in North America (3).
As a reminder, the objective of the EPI is to provide immunization for every child in the world against diphtheria, whooping cough, tetanus, measles, poliomyelitis and tuberculosis, by the year 1990.

It was feared, a few years ago, that there would be a decreased interest in manufacturing classical vaccines in the industrialized countries and hence a shortage of supply for the vaccination programmes of developing nations (4). This fear has not materialized. While it is true that in the United States, the number of biological manufacturers declined from 11 in 1966 to only 5 in 1981, this phenomenon did not occur in other parts of the industrialized world. The very serious problem of product liability turned out to be a greater disincentive for American producers than diminishing local demand or low profit margins on sales of vaccines in the international market.

To quote from UNIDO Sectoral Studies Series No. 4 : "Nevertheless, the supply situation is satisfactory and there is keen price competition amongst the bidders of international tenders" (5).

Manufacturers in the industrialized countries have repeatedly stated that, provided certain conditions are met, there should be no major difficulty in continuing to supply high quality products, in the required quantities, and at competitive prices, for the vaccination campaigns of developing countries organized under the EPI. The conditions cited include : realistic quantity forecasts by the international procurement agencies (UNICEF and PAHO), reasonable lead times and the adoption of a multi-supplier sourcing policy for each of the EPI vaccines.

Most of these basic conditions currently prevail and there should therefore be no shortfall in the foreseeable future.

This does not mean, however, that the option of local manufacture of biological products should be disregarded by developing nations. As a first step, each country must examine its own supply and demand situation and study the economics and risks involved. These considerations are covered in the following chapters.

THE SUPPLY SITUATION IN DEVELOPING COUNTRIES

The pros and cons of local manufacture, following the step by step strategy recommended by UNIDO's Second Consultation, should be evaluated against the current supply situation for the EPI vaccines and future expectations.

The goal of relative self-reliance so far as conventional vaccines are concerned is a laudable one. However, existing procurement possibilities, economies of scale and public health considerations should not be overlooked.

Many developing countries are currently receiving their EPI vaccines free of charge through donor agencies. Others, who are supplied through the PAHO Revolving Fund or by similar arrangements, purchase the products they need at international tender prices calculated on the basis of worldwide requirements. Countries producing, or contemplating the production of EPI vaccines for their own needs alone, must accept that local manufacture is, or is likely to be, the least economical solution of the three. One of the possible long term effects of donation programmes is the "free of charge" concept of vaccine supply which undermines, from a financial standpoint, future policies of vaccine purchase or local production.

The subject of vaccine donation, within the scope of the Expanded Programme on Immunization of WHO, was touched upon at the Fourth Meeting of UNIDO's Advisory Panel on Preventive Medecine. The Panel remarked that the donation of vaccines may be considered by the responsible authorities of many developing countries as a permanent solution for supply to their national immunization programmes. If free donation is regarded as a final long term solution for the supply of vaccines, local production will never

be feasible for the recipient countries since the cost of donation is zero. The UNIDO Secretariat considered that it would be useful if UNICEF could provide, on a yearly basis, a statement on its donation programme with regard to its size and duration, the conditions required for participating as recipient in the programme, and the market situation for each EPI vaccine with particular reference to the adequation of offer and demand. Such a statement would be of great importance, not only for the authorities of developing countries responsible for planning and implementing national immunization programmes, but also for the biological industry currently supplying the EPI campaigns. This information could also play a key role in UNIDO's IPB Programme.

So far as economies of scale are concerned, countries wishing to engage in local production of vaccines, through technology transfer, should first consider the potential of their own national territory with regard to its population, birthrate, etc.. Then, provided all the necessary competitive criteria are met, and if contractual arrangements permit, these countries may look at the possibilities offered by the international expert or tender market.

It was suggested, at the Second Consultation on the Pharmaceutical Industry, that production facilities could be developed at subregional or regional levels to achieve economic feasibility. Although it is reasonable to expect that larger production batches would lead to a lower cost per dose, special requirements by neighbouring countries might well negate such savings. Above all, political considerations, nationalistic attitudes and unpredictable payment situations could constitute insuperable obstacles to such regional initiatives.
There are, it is true, a few instances of regional bulk procurement for essential medicines and one or two examples of successful regional manufacture of pharmaceuticals. In the vaccine field, PAHO's Revolving Fund is a good example of regional procurement for the EPI. So far as regional manufacture in the developing world is concerned, yellow fever vaccine produced in Senegal is used in the vaccination campaigns for several West African countries.

The main public health concerns relating to pharmaceuticals in general, and to vaccines in particular, are quality, safety and efficacy, whether these products are received free of charge, purchased or locally produced. This implies, of course, the existence of a distribution system and a cold chain capable of ensuring that a vaccine which is safe, potent and of high quality at the end of the production cycle, or upon reception in the country, presents the same indispensable characteristics at the time it is ready to be administered.

The quality control aspects of vaccine production, already identified by the Second Consultation, were highlighted in the Advisory Panel's discussion on the IPB Programme at its First Meeting, held in Vienna in February 1984. It was noted that quality assurance was important in the production of safe and effective biologicals, and also that the quality control of EPI vaccines in particular is of major concern to the World Health Organization. All vaccines used in the Expanded Programme must be safe, effective and stable, and in compliance with WHO's Requirements for Biological Substances. The latter condition is stipulated in WHO's Model List of Essential Drugs, in the section devoted to immunologicals (6).

In its successive meetings and deliberations, UNIDO's Advisory Panel on Preventive Medicine has stressed the importance, from a public health standpoint, of establishing an independent national quality control authority and making sure that this authority is linked up with WHO's network of collaborating quality control centres.

Once it is envisaged to package, fill and ultimately produce vaccines locally, added requirements are the implementation of quality assurance programmes, and the application of Good Manufacturing Practices (GMP). The most recent reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (7) and the WHO Expert Committee on Biological Standardization (8) are useful guides to developing countries in this respect.

CURRENT AND FUTURE DEMAND FOR EPI VACCINES

A few years ago, it was estimated that not more than 20% of the 90 million children born in the developing world each year were fully immunized against the six infectious childhood diseases targeted by the Expanded Programme on Immunization. For lack of protection, some 5 million children under the age of five reportedly died each year and another 5 million were handicapped for life.

The latest Global Status Report on the EPI, however, indicates that all WHO Regions, with the exception of Africa, show an immunization coverage of over 50% for at least one of the EPI vaccines (9). The level of coverage for the African Region is currently about 20%. The Regional Committee, considering that there was reasonable hope of providing immunization for at least 75% of African children by 1990, proclaimed 1986 "Africa Immunization Year".
Appropriately, at its second meeting, in November 1984, UNIDO's Advisory Panel on Preventive Medicine focused on the situation in Africa and made a series of recommendations. The Panel recommended that UNIDO should respond positively to requests for rehabilitation or expansion of existing production facilities in Africa, and that a more comprehensive approach to the production of biologicals in Africa should be taken. In this respect, the Panel discussed a working paper on the Programme for Production of Vaccines in Africa, which stresses, amongst other things, the need for political support involving regional and subregional organizations.

Although the overall immunization situation is improving, a lot remains to be done. Almost 3.5 million deaths are attributable, annually, to the six EPI diseases. There are still over 250,000 cases of poliomyelitis each year. At its eighth meeting, in November 1985, the EPI Global Advisory Group formulated a series of recommendations for the global

EPI programme, with a view to achieving greater immunization coverage and setting targets for reductions in morbidity and mortality (10). If these objectives are to be reached, it goes without saying that greater quantities of vaccine will be required. The problem is how to gauge future demand and determine how much vaccine will be needed between now and the end of the century.

The present and projected demand for immunizing agents included in the EPI were thoroughly analyzed in UNIDO's Sectoral Studies Series No. 4 (5). A comparison of 1980 consumption estimates with 1990 and the year 2000 deman projections for EPI vacines showed a doubling of worldwide requirements by the end of the century, with the developing regions requiring approximately two and a half times the 1980 uptake by the year 2000.

These estimates may well be on the low side, especially in view of PAHO's goal for 1990, i.e. the eradication of poliomyelitis in the Americas, and the hopes, in Europe, of eliminating polio, respiratory diphtheria and neonatal tetanus before the end of the century.

Current trends in UNICEF and PAHO's purchasing patterns do, in fact, reflect the acceleration of vaccination campaigns and the demand for increasing quantities of EPI vaccines.

In view of the above, countries with a large population, a high birthrate and a firm commitment to the Expanded Programme on Immunization may wish to study the option of local production of EPI vaccines. It is with these countries in mind that the Model Programme for the Production of Vaccines was developed.

THE MODEL PROGRAMME FOR THE PRODUCTION OF VACCINES IN DEVELOPING COUNTRIES

At its very first meeting, in February 1984, the Advisory Panel on Preventive Medicine recommended that UNIDO, with the advice of the members of the Panel, should start the preparation of a master plan for projects for industrial production of vaccines in developing countries which should include technical and economic details for the implementation of such projects, at different stages.

At its second meeting, ten months later, the Panel discussed a working paper presented by the Director-General of the Rijksinstituut voor Volksgezondheid en Milieuhygiene (National Institute of Public Health and Environmental Hygiene, The Netherlands) further referred to as the RIVM. The working paper described a model programme for the preparation of BCG vaccine, pertussis vaccine, purified diphtheria toxoid, purified tetanus toxoid ; the controls required for these vaccines and also those for cell culture rabies vaccine, measles vaccine, inactivated poliomyelitis vaccine ; with additional notes on buildings and services, staff members and qualifications, equipment, maintenance and costs. The Panel accepted this first draft and recommended that additional sections be prepared with more detailed reference to training of personnel, animal accommodation, quality control, chemical engineering, local constraints, management, maintenance, priority criteria and cost effectiveness.

Subsequent drafts of the RIVM document were studied and reviewed by Panel members and further items were either added or expanded. These include the addition of standard-cost data relating to the vaccines produced by the unit-processing method with an indication of the cost per immunized child and the importance of on site training for production and control personnel.

The document, in its final form which includes a short Explanatory Memorandum, was adopted by the Advisory Panel in March 1986.

The Model Programme is intended primarily for use by government officials and directors of institutes who are responsible for structuring and implementing national immunization programmes. It may also be of general guidance to the professional staff members in charge of vaccine production. It may, in addition, serve as a basis for comparing different technologies applied in other laboratories for the manufacture and quality control of conventional vaccines.

The Model Programme for the Production of Vaccines in Developing Countries constitutes a summary of the RIVM's experience in the production and control of a series of conventional bacterial and viral vaccines currently used in national immunization programmes. The production of oral poliomyelitis vaccine is not included in the document. The Model Programme therefore offers only one option among a number of technologies : the unit-processing principle as proposed by van Hemert.

The Model Programme comprises 5 sections covering :

1) Vaccine Production Technology ;
2) Quality Control of Vaccines ;
3) Economic Aspects of Vaccine Production and Control ;
4) Lay-out of Technical Facilities for Production of Vaccines ;
5) Staff Training in Production and Control.

The basic information contained in the Model Programme is being completed by a series of UNIDO technical documents covering the production and quality control of BCG vaccine produced on surface culture ; the production and quality control of oral poliomyelitis vaccine ; a paper on technology transfer for biological production and a directory of potential partners in transfer of technology for biological production.

CONDITIONS FOR SUCCESSFUL TECHNOLOGY TRANSFER

Because of the complexities of biological production itself and the difficulties of successfully transferring the relevant technology, the list of prerequisites and conditions is necessarily longer than it would be for the transfer of less sophisticated or non health-related manufacturing procedures.

Some of the basic and preliminary conditions have already been mentioned : a long term commitment to the EPI programme, the acceptance of a stepwise progression in the production process starting with quality control of imported finished goods, and a potential market large enough to justify the investment.

The specific characteristics of biological manufacture were fully recognized by the Second Consultation on the Pharmaceutical Industry, in November 1983. The Consultation noted that the production of vaccines differs significantly from that of other pharmaceutical products. For example :

- The problems of storage and distribution are crucial and a continuous cold chain is essential ;

- The products are rarely subject to patent protection, and established production facilities have the capacity to ensure an adequate supply to the developing world ;

- In an immunization programme, the cost of the product is a minor item in relation to the overall cost of vaccination, and the success of such a programme is entirely dependent on an adequate infrastructure for distribution and administration.

The Explanatory Memorandum to the Model Programme mentions a number of conditions which must be met before, during, and after the actual transfer of the technology. To start with, a preliminary analysis of the local industrial infrastructure and of prevailing economic conditions must be made. Appropriate scientific and technological educational programmes must be devised. A good organizational and managerial infrastructure with the optimal use of human resources is essential for the success of such an undertaking. Additional aspects include the guarantee that the supplier himself shall install the purchased equipment and ensure that all machinery performs according to specifications. Maintenance and training of maintenance personnel are key considerations. As mentioned in Chapter 5, the complete understanding of the concept of quality assurance is of vital importance.

A continuing support services plan should be envisaged at the termination of the execution stage of the project. Such a plan may comprise, on a yearly or two-yearly basis : a GMP audit, spare part procurement, performance of parallel quality control tests, training of new senior staff, raw material testing and implementation of new WHO requirements.

So far as WHO requirements are concerned, the recipient in the developing country and the supplier of technology must make sure that the buildings foreseen for production and control activities, the vaccine seed strains (bacterial or viral), the substrates and the manufacturing processes involved, all meet WHO requirements or specifications.

Finally, two important aspects which should not be overlooked : the political and financial committment to such an investment project and the marketability of the products manufactured locally.

Political will must be demonstrated from start to finish : from the moment the project proposal is drawn up and presented for approval, through

the execution of the project plan, to the time when the quality of successive batches of vaccine is consistently verified by independent audit.

So far as financing is concerned, governments must accept that these are long term projects for which long term funding arrangements have to be sought. A ten-year financial commitment is not exaggerated. UNIDO's Advisory Panel has recommended the establishment of an IPB Fund, suggesting that contributions should come from UNIDO, through its industrial funding, UNDP, World Bank, interested governments and UNICEF which is currently the major supplier of EPI vaccines to the developing countries.

It is commonly believed that the manufacture of goods in developing nations is a highly economical proposition. This does not seem to be the case for vaccines. Although manpower and building materials may be available locally at low cost, up to 80% of the necessary equipment, raw materials and components will have to be purchased abroad, with hard currency. Vials, stoppers and leucosis-free eggs are cases in point.

This brings us to the aspect of marketability of the products. If marketing is defined, concisely, as "achieving consumer satisfaction", this means that the locally manufactured products must be competitive. At the least, they should be of comparable quality, safety and efficacy to the imported products with which doctors, other health care personnel, and patients have become familiar over the years. Although some concessions may be made, for example so far as packaging esthetics are concerned, no compromise on supply and delivery requirements should be tolerated. The locally-made products must always be available in the required quantities, at the right time, and in good condition if national immunization campaigns are to be conducted efficiently and effectively.

CONCLUDING REMARKS

After the preceding chapter which dealt mainly with "caveats", it would seem appropriate to mention that several developing or newly industrialized nations have already launched into extensive programmes of domestic manufacture of vaccines (11). Amongst them : Brazil, Colombia, Cuba, Mexico, India, Indonesia, Pakistan, Algeria and Egypt. Some of these countries are even able to contemplate moving from the production of classical or conventional vaccines towards the manufacture of modern ones, using the advances of biotechnology.

It is the role of UNIDO's Advisory Panel on Preventive Medicine to advise and offer guidance to developing countries on the technical and economic aspects of the establishment of UNIDO's programme of Industrial Production of Biologicals. The Model Programme, introduced in Chapter 6, is proof of the availability of appropriate vaccine technology and the feasibility of the stepwise and comprehensive transfer of such technology.

The various aspects developed in the other chapters of this paper are submitted to governments as "points to be considered" when assessing the advisability of local manufacture of vaccines and other biological products in countries of the developing world. It must be stressed that, in order to launch, at any time that exigencies may require, an endeavour of local manufacture of vaccines in such countries, governments have to devise incentive measures to develop the required capabilities for such an undertaking. These capabilities cover infrastructure and logistics, trained manpower, a quality control authority and facility, university institutes, research and development institutes, etc.

To conclude, it should be understood that the final decision with regard to initiating local production of vaccines must rest with national governments, particularly where a definite immunization programme is to be implemented to achieve definite goals. Considering that fluctuations of price and availability of vaccines may drastically change the policies of local production of immunizing agents, governments have to keep abreast of national, regional and international developments that may affect their long term immunization plans.

REFERENCES

(1) Report of the Second Consultation on the Pharmaceutical Industry (UNIDO/ID/311, 1983)

(2) International List of Availability of Vaccines and Sera Genève : WHO (BLG/1983)

(3) The Biological Industry and World Health (IFPMA, 1985)

(4) The Manufacture of Vaccines in Developing Countries (UNIDO/ID/WG 393/13/Rev.1, 1983)

(5) Prospects for Production of Vaccines and Other Immunizing Agents in Developing Countries (UNIDO/IS/402, 1983)

(6) WHO Technical Report Series, No. 722, 1985

(7) WHO Technical Report Series, No. 704, 1984

(8) WHO Technical Report Series, No. 700, 1984

(9) Weekly Epidemiological Record, 60 (34), 1985

(10) Weekly Epidemiological Record, 61, 13-20, 1986

(11) New Trends for Vaccine Production and UNIDO Programme on Industrial Production of Biologicals (UNIDO/IO.630, 1986)