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**MEETING ON FOSTERING
PARTNERSHIPS FOR DTP AND
DPT-BASED COMBINATION
VACCINES**

**TASK FORCE ON SITUATION
ANALYSIS**

23-25 JANUARY 1995



***CVI MEETING
FOSTERING PARTNERSHIPS FOR DTP
AND DTP-BASED COMBINATION VACCINES
23-25 JANUARY, 1995
GENEVA, SWITZERLAND***

INTRODUCTION

The Children's Vaccine Initiative has identified the use of DTP and DTP-based combination vaccines as a major strategy for delivery of current and new antigens in the future. Several recent meetings of DTP producers have recognized the potential for procuring one or more of the components of combination vaccines in bulk as a way for countries to access high quality DTP-based combination vaccines. Production processes based on sharing the primary manufacture and the blending and finishing steps can offer advantages. This is particularly true for developing country producers for whom some type of manufacture is feasible, but for whom ability to invest in facilities and research is limited.

An earlier meeting addressed guidelines for the bulk procurement of oral poliovaccine.¹ At that meeting, Manufacturers² and Finishers³ of bulk oral poliovaccine concluded that of three potential types of agreements describing sale of this product (commodity transactions, partnership agreements, and technology transfer agreements), partnership agreements in general best meet the needs of interested parties. They concluded that the National Control Authority of both Manufacturer and Finisher must be involved in the transaction, and procurement agreements might include mutual monitoring activities and training services. UNICEF as a procuring organization has supported this approach.

The present meeting, "Fostering Partnerships for DTP and DTP-based Combination Vaccines," was called to define mechanisms to facilitate purchase of components of these vaccines and to consider the elements of partnership agreements and the advantages and disadvantages of these partnerships to each of the partners.

¹ Guidelines for Bulk Procurement of Oral Poliovaccine (OPV), CVI/TFSA/94.4

² Manufacturers are defined as the entities which produce and provide the bulk vaccines.

³ Finishers are the entities importing bulk vaccine for the purpose of formulating, filling, and/or distributing the final product so produced.

SUMMARY OF PRESENTATIONS

The list of participants is given in Annex A. A wide range of presentations were given (see Annex B, Agenda), the summary of which follows below.

Experiences with bulk procurement

Participants from manufacturers of components of DTP vaccines in both developing and industrialized countries summarized their experiences with bulk procurement of vaccines. These ranged from simple commodity transactions, in which the bulk component procured could vary from one lot of DTP to the next, to the use of bulk finishing as a conscious strategy to embark on vaccine production. Several technology transfer activities involving bulk procurement were described. The main reasons for importing bulk components were to increase production capacity to meet national demand, and to avoid expensive investment in facilities and quality control needed for production from seed. Generally Finishers published specifications for the desired components, and then tested submitted samples for acceptability. Agreements usually dealt only with agreed payment terms.

Problems cited in these experiences included failure to meet specifications, disputes over test results, problems with the physical characteristics of the bulk, and limitations of choice due to licensing requirements. There may be a mismatch between the legal expertise of large multinational producers and developing country producers. The key issue seen by both Manufacturers and Finishers was quality control. Also noted was the possible impact of changing the final formulation of DTP vaccine, by replacing individual components or adding new components, on the safety and efficacy of the new combination vaccine. The need for field trials and extensive stability studies on these new combinations was considered a major issue.

For most of the transactions described there was no requirement for separate licensing of products made of different components. An exception to the general characteristics of bulk procurement described was the experience of Brazil, in which a shared production strategy had been evolved among national manufacturers of components of DTP.

The Manufacturers of bulk components defined different stages of providing vaccines, with different responsibilities of the respective parties. While the Manufacturer was responsible when the product was supplied in finished form, the Finisher shared responsibility when final bulks ready for filling or bulk components were supplied. Desirable prerequisites for sale of these products included assurances that the Finisher would meet Good Manufacturing Practice and WHO requirements and had an appropriate quality control function.

This shared responsibility implied a bilateral agreement which would consider more than specifications, and would clearly define the mutual division of responsibilities, including those with regard to liability, with a sharing of information on production methods and quality control. Characteristics a Manufacturer might look for in a Finisher were a well-developed management culture, empowered compliance officers, a system of

postmarketing surveillance, and mechanisms for equipment and facility maintenance. The agreement could include exchange of processes and quality control procedures. These agreements would have to be long term of necessity.

Legal and Intellectual Property Issues

As a result of the Uruguay round of the General Agreement on Tariffs and Trade (GATT), the World Trade Organization was formed effective 1 January, 1995. One of its responsibilities is harmonization of national legislation on the protection of intellectual property, including for pharmaceuticals and patents, spelled out in the TRIPS agreement. At this moment there are 76 members of the World Trade Organization. The expected membership is more than 125 countries, including most of the vaccine producers of the world. The TRIPS agreement (1) specifies minimum standards of protection of intellectual property to be provided by each member country, (2) specifies procedures and remedies for effective enforcement, and (3) includes a mechanism to settle disputes. There are provisions in the agreement which allow developing country members to delay their compliance generally for up to five years, and least-developed countries for up to 11 years. There are more complicated arrangements which apply in the situation where developing countries do not presently give product patent protection to pharmaceuticals. Any invention made from now onwards will have to be eligible for protection in such countries, at least by the time that the product gets on the market - either through the grant of a patent after a delay of not more than ten years or through an exclusive marketing right if the product obtains marketing approval before the patent becomes available. Plants and animals may be excluded as patentable subject matter under TRIPS, but microorganisms and microbiological and non-biological processes are included. This is a broader exclusion than found in patent laws of the US, Europe, and Japan, for example.

It is generally felt that Intellectual Property Rights protection is critical to the continuation of industrial investment in research on, and development of, combination vaccines.

There are two sorts of liability which are of concern for vaccine manufacturers: (1) those which stem from manufacturing faults (e.g. a problem of sterility) and (2) design faults (a problem inherent in the vaccine type which might not become apparent until after registration and long term use).

Developing partnerships

The Finisher-Manufacturer partnerships considered at this meeting include those dealing with the vaccines DTP, hepatitis B, and *Hemophilus influenzae b* (Hib), which vary in their use from predominantly public sector to generally private sector, and in their origins from purely public sector production to private sector production. Public sector health products are those which

- should be available regardless of ability to pay,
- are purchased with public sector funds, and
- are driven by public health imperatives.

Public sector vaccine manufacturers in the industrialized world already contribute significantly to the achievement of some of the goals mentioned above. The idea of a public sector consortium of vaccine producers, as developed by Dr George Siber, may be a tool which can assist public sector vaccine producers to participate more effectively in public-private sector partnerships. The development of such a consortium involves changes in the producer's organizational management structure to become more "entrepreneurial". Then, training programmes must be developed and implemented. Demonstration plants could be set up as long range training facilities to improve quality, consistency, and purity of current vaccines. Finally, adequate efforts should be made to develop new products.

SIREVA/PAHO is a regional vaccine system for Latin America and the Caribbean which is developing a public sector consortium of vaccine manufacturers with three major goals: (1) developing networks of quality control and quality assurance laboratories to ensure the procedures used are well-executed, properly standardized and up-to-date, (2) implementing a certification scheme for production laboratories, and (3) promoting research and development on new combination vaccines.

A study of the vaccine industry in South Africa was presented as a useful case study in restructuring a national vaccine industry and setting up a public-private sector partnership. The study, presented by Mr WA Meaney, Acting Chief Executive Officer for South Africa Vaccine Producers Pty Ltd (SAVP), was initiated to answer the question: should vaccines continue to be produced in South Africa, and if so, which ones? More specifically, the study was designed to determine what conditions and ingredients are necessary for South Africa to produce vaccines which meet international requirements and are cost-effective, *versus* what is available by purchasing through UNICEF (UNICEF was used as the benchmark, as the vaccines they purchase meet WHO requirements at very low prices based on international tenders.).

The result of the study was that South Africa needs to do the following to have successful vaccine production:

- Better utilize the current facilities, which means producing approximately twice the requirements for South Africa's demand (DTP, TT, DT, OPV, and BCG);
- Centralize management of the three facilities into one company and install "commercial" type management systems and culture;
- Set up immediately an independent National Control Laboratory as part of the local regulatory system which already includes a National Control Authority;
- Find a suitable international partner for SAVP to secure medium and long-term access to specified and unspecified research and development and an international marketing and sales network.

On this last point, it is felt that to ensure the necessary commitment from an international partner, some portion of SAVP will need to be sold to the partner.

GENERAL PRINCIPLES OF BULK PROCUREMENT AGREEMENTS

After discussion of the presentations and principles involved, the following were agreed by the participants.

General considerations

Vaccine Manufacturers and Finishers should be discouraged from trading in components as commodities. Rather, long term agreements are encouraged to ensure consistency, provide for appropriate information flow, and ensure a successful product.

It is recommended that components not be imported from countries which do not have independent and competent National Control Authorities. Manufacturers are generally encouraged to provide certification that the bulk component(s) are used for an end product which meets the relevant specifications and requirements.

Similarly, it is recommended that adequate mechanisms be established to ensure independent guarantee of quality of the final product in countries importing components for finishing. This can best be ensured by an independent and competent National Control Authority.

It is understood that the respective National Control Authorities would have the right to receive from the Manufacturer and/or the Finisher all information necessary to make fully informed licensing and release decisions.

The following products were covered by the discussion:

Final Product	Components
Products for which considerable experience in combining bulk components exists	
DTP DT TT Td	diphtheria toxoid tetanus toxoid whole cell pertussis (wP) DTP
Products under development as combination products, or for which considerable experience in combining various bulk components does not exist	
hepatitis B - plasma and recombinant Hib conjugates DTaP DTwP combinations with hepatitis B or Hib DTaP combinations with hepatitis B or Hib	whole cell pertussis acellular pertussis (aP) hepatitis B - plasma and recombinant Hib conjugates

For those final products for which there is considerable experience in combining bulk components, acceptable specifications for the component to be used in a specified combination product and for which clinical efficacy has been demonstrated by long experience should include:

- specific final product test results according to WHO requirements, and
- manufacture by a specified process in accord with WHO requirements and Good Manufacturing Practice.

Should the Finisher change the characteristics of the final product, the final container, or the testing methodology from those specified in the agreement, these changes should be validated, and should have the prior agreement of the Manufacturer.

For those products under development, in addition, the Finisher should demonstrate evidence of clinical safety and efficacy, as any combination will constitute a new product. The concern was expressed that this approach could result in many parallel clinical trials of combinations to demonstrate the compatibility of the different components used.

While having a standard product would simplify bulk procurement, such a requirement was generally felt to be neither necessary nor practical.

Choosing a partner

It is recognized that Manufacturers and Finishers can each be either public or private sector entities, and can operate in either industrialized or developing countries. If the Manufacturer is an industrialized country private sector firm, and the Finisher is a public sector organization located in a developing country, the following considerations are especially important.

Prior to the decision to engage in a partnership, it is recommended that the Finisher and the responsible national authority for the Finisher (e.g. the government or the organizational management) undertake a complete economic, technical and operational feasibility study to understand the implications, advantages and disadvantages for the short and long term of entering into a partnership. This study should include:

- *the need and cost of upgrading production and quality control facilities to acceptable levels consistent with Good Manufacturing Practices;*
- *the ability of existing management to institute these changes;*
- *the changes to the structure and legal status required for effective partnership (e.g. hire and fire, budgetary control);*
- *the ability and cost of assuring an effective, independent National Control Authority and Laboratory;*
- *the ability to guarantee functional basic infrastructure.*

The government and the Finisher should have a long-term commitment to institute and invest in the necessary changes. The government or Finisher will then be able to enter into a partnership on an informed and equal basis. This will help to ensure that its objectives will be achieved.

The overall objectives of partnerships may vary. However, many countries aim to have efficient production sharing partnerships with continued local production of DTP and imported bulk antigens. The goal will be to assure a reliable, sustainable supply of quality combined vaccines at an acceptable cost.

The advantages of partnership to the Finisher include ongoing access to new technologies, new vaccines, and technical and managerial skills as well as immediate access to bulk antigens without the need to build new facilities or to invest in expensive research and development capacity. Dependent on the outcome of the above-mentioned feasibility study, a strategic partnership may be the most cost-effective way for the country to assure long term self-sufficiency in vaccine supply. These advantages must be balanced against the cost of investment in the feasibility study, new plant and buildings, the training and recruitment of appropriate staff. Because such a feasibility study will involve senior health management in its execution and any subsequent developments, the costs to country of taking them away from their everyday responsibilities must also be considered.

The advantages of these partnerships for private sector Manufacturers include long term guaranteed economic benefits, expanded global presence, an advantageous position to market other products, competitive advantage, economies of scale, and international good will and visibility. These must be balanced against the costs of diverting limited staff and resources away from their primary production and marketing activities or away from other potential developments. Most Manufacturers will not have the capacity to enter into more than a few partnerships and will therefore choose their partners carefully.

Both the Finisher and the Manufacturer must identify their respective benefits in the partnership in order to have the will to sustain their efforts to obtain a successful end product.

When the Manufacturer is an industrialized country public sector partner and the Finisher a public sector organization located in a developing country, most of the considerations mentioned above are valid, except for the commercial and possibly also some legal issues. In general, considerations of cost-effectiveness of these public-public partnerships are just as important as for private-public sector partnerships, and, in addition, they must have the support of the governments of both partners to be effective.

Role of bridging organizations

Countries have identified a clear need for management and technical support in performing feasibility studies to prepare for partnerships, in evaluating partners, and in conducting negotiations. International public health organizations such as WHO (and certain nongovernmental organizations) can assist in the formation of partnerships by helping the partners better understand each other's objectives. The bridging organizations must not financially benefit from the outcome of partnership negotiations and must maintain confidentiality with the partners. These organizations may also be helpful in providing technical support needed for effective manufacture, licensing, and distribution of final product.

Legal issues to be considered

Successful partnerships require the establishment of a relationship of trust between the partners. This trust is established through frank detailed discussions of all issues related to the partnership in advance of any agreement. Attention must also be paid to how new intellectual property is generated. Patent rights and rights to know-how would normally be reserved to the partner having developed the new intellectual property, but agreements should provide for cross-licensing. As not all information exchanges by the partners need be confidential, partners should exercise reasonable judgement to limit confidential knowledge to the minimum necessary to preserve the vital interests of each.

GUIDELINES TO CONSIDER IN DEVELOPING PARTNERSHIP AGREEMENTS

The following points should be considered by potential partners when developing a partnership agreement:

1. A joint development plan including financial/economic, technical, clinical, and regulatory milestones and targets, and evaluation criteria to monitor the plan's progress
2. The roles of the respective partners in developing a systematic economic assessment of the viability of the project
3. Lines of communication and identities of responsible persons to contact in the case of specific problems
4. The respective roles of the partners in monitoring, data exchange, auditing, and postmarketing surveillance
5. The extent to which details are to be shared on the production process
6. Jointly agreed upon SOP's and protocols
7. How clinical efficacy and safety data for a new product will be assembled
8. Technical support for production and testing
9. The extent to which pilot lots are prepared prior to entering into the partnership agreement
10. The use of joint project teams for problem solving
11. Provision for joint inspections
12. Transfer of know-how and resolution of patent issues
13. Cross-licensing of new intellectual property know-how
14. The definition of territories
15. Responsibilities in seeking and maintaining regulatory approval in all relevant markets
16. Access to both public and private sector markets in the country of production of the final product
17. Established production targets, mechanisms for compensating shortfalls and mechanisms for disposal of excess
18. Means for resolving issues of liability, including warranty of bulk components, liability for manufacturing defects in the final product, and responsibility for design faults in any of the product components, including appropriate hold harmless clauses
19. Resolution of disputes

ANNEX A. LIST OF PARTICIPANTS

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ANNEX B. AGENDA

Presentation of issues:

Summary of Bulk OPV Meeting	Dr J. Milstien
Role of DTP Combinations in CVI Strategy	Dr M. Kane
Bulk Procurement of DTP Components	Mr J. Gilmartin
Objectives of the Meeting	Dr J. Milstien

Presentations by current importers of bulk components: experiences and needs:

Brazil
Indonesia
Pakistan
South Africa
Thailand
Viet Nam

Presentations by current exporters of bulk and technology transfer: experiences and problems:

Behringwerke AG	
Biocine	
Commonwealth Serum Laboratories Ltd. (CSL)	
Human Serum Production and Medicine Manufacturing Company Ltd. (Human Co.)	
Merck, Sharpe and Dohme (MSD)	
Pasteur Mérieux - Merck, Sharpe and Dohme (PM-MSD)	
Pasteur Mérieux Sérums et Vaccins - Connaught (PMSV-Connaught)	
SmithKline Beecham Biologicals s.a. (SKB)	
Institute of Public Health and Environmental Protection Research for Man and Environment (RIVM)	
Legal and Intellectual Property Rights Issues	
World Trade Organization	Mr A. Otten
World Health Organization Legal Department	Ms A. Mazur
International Federation of Pharmaceutical Manufacturers Associations (IFPMA)	Dr R. Arnold
Programme for Appropriate Technology in Health (PATH)	Dr J. Maynard
Approaches to Partnerships	
Public sector consortium	Mr P. Evans
SIREVA approach	Dr A. Homma
South Africa experience	Mr W. Meaney

Presentation of conclusions from Working Groups:

Drafting and consideration of meeting report

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