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PRODUCTION OF BIOLOGICALS (PHASE I), A SURVEY

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Technical report: The supply of EPI vaccines in the ASEAN countries*

Prepared for the Governments of Indonesia,
Malaysia, Singapore, Thailand, The Philippines
by the United Nations Industrial Development Organization

Based on the work of Basil Gibson
Expert in vaccine Production

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1. INTRODUCTION

As part of a survey of the production of biologicals in the ASEAN countries (Indonesia, Singapore, Malaysia, Thailand and the Philippines), the Commonwealth Serum Laboratories was asked to provide an expert to carry out a survey of the production and supply of EPI vaccines. I was appointed as the expert and undertook the mission from 6th April to 25th April 1986.

Unfortunately, it was not possible for all of the necessary arrangements to be completed in time for the inclusion of the Philippines in the mission. UNIDO therefore agreed that the mission should commence on the 6th April and proceed to the other four countries. The future of the Philippines part of this survey was discussed with UNIDO during debriefing in Vienna and it was decided that this would proceed as soon as possible. The Manila visit took place from 19th May to 24th May 1986.

Some months prior to the commencement of the mission, I prepared a questionnaire (Appendix 1) and UNIDO pre-circulated it to either appropriate officers of the Ministry of Health or to directors of manufacturing institutions in each country. The information from the questionnaires was to be used, in advance of the mission, to calculate volumes of vaccines required and hence the scale of the manufacturing equipment and facilities and quality control requirements. Thailand completed the questionnaire while Indonesia indicated that it would provide the information during the visit. Copies of questionnaires with answers are placed at the end of this report (Appendix 22). As Malaysia and Singapore stated that they do not produce EPI vaccines, it was agreed that for these two countries only the first Term of Reference (Section 2) would apply and the necesary information would be sought from the appropriate persons during the mission. Appointments were made in each country so that I could meet Ministry of Health officials responsible for ensuring that there are adequate supplies of vaccines either locally manufactured or imported, and for the national quality control of the vaccines. Arrangements were also made for me to meet the directors and visit manufacturing institutions in Indonesia, Thailand and the Philippines.

I wish to acknowledge that I was made most welcome and received willing co-operation during the various discussions and laboratory visits which took place.

2. TERMS OF REFERENCE

The purpose of the assignment was to visit the ASEAN countries in order to:

(1) Identify demands for EPI vaccines and costs of locally produced and purchased vaccines.

(2) Examine existing manufacturing facilities and devise a program to:

- (a) expand and improve facilities to GMP standards and increase vaccine production output to meet the country's needs.
- (b) improve quality control if necessary.

(3) Advise on the development of new facilities for the formulation and packaging of vaccines which are not currently produced in the country.

(4) Identify present levels of experienced and trained staff available for vaccine production and advise on needs in order to develop trained manpower for the production of vaccines.

As neither Malaysia nor Singapore manufacture EPI vaccines, only the first term of reference relating to purchased vaccines applied in those countries although I also proposed to obtain information about the level of quality control testing which might be carried out by their authorities.

It was also agreed that in carrying out the mission any recommendations should only be considered for implementation provided that they are not contrary to the wishes or policy of the country concerned.

The EPI vaccines to be considered are:

DPT vaccines
BCG vaccine
Measles vaccine
Poliomyelitis vaccine.

3. SUMMARY AND RECOMMENDATIONS

3.1 Perum Bio Farma: Bandung: Indonesia

This Institute has a long history of successful vaccine production. Of its own initiative and with some overseas aid, it has moved to expand it activities to meet the demands of the EPI. Forward planning is good and there is an ongoing staff training program. Compliance with GMP is only fair but efforts are being made and need to be made to improve in this area.

(a) Diphtheria Antigen

Bio Farma is currently upgrading this department. I have suggested a number of improvements which should be made to the design. Additional equipment to the value of 152,000 US$ (Appendix 1) is required to bring the area into compliance with GMP.

(b) Pertussis Antigen

This is a well managed department which is functioning very satisfactorily. I recommended that the building should be extended on one side to overcome a number of deficiencies in relation to GMP. Some additional equipment is required (Appendix 1) to the value of 177,000 US$.

(c) Tetanus Antigen

Production has been recently upgraded to fermentor technology with ADAB assistance. Some building modifications are needed to improve culture handling and reduce the contamination rate. A proposed plan is at Appendix 2. Additional equipment is listed (Appendix 1) to the estimated value of 55,000 US$.

(d) BCG Vaccine

Production method and capacity are satisfactory. Repositioning of the air-conditioning duct work is needed.

(e) Formulation of DPT, DT and T Vaccines

The room in current use for this work is badly designed and too small for its purpose. It was suggested that a new facility should be built alongside this building and it should have cold room space also for the storage of final packed products. The additional equipment needed is at Appendix 3 and a proposed floor plan is given at Appendix 4. Estimated cost of equipment is 53,000 US$.

(d) Dispensing and Packaging

Additional cold room space is needed for the storage of packaged products - see Appendix 4. Provision of distilled water is needed at a cost of 57,000 US$ - Appendix 3.

(g) Measles and Poliomyelitis Vaccines

Approximately 30% of the LPV is being obtained as concentrate for dilution, dispensing and testing at Bio Farma. The rest of the vaccines are obtained as dispensed products. some staff have received overseas training and are able to carry out virus culture work and completely test these vaccines to WHO standards.

A team from USAID, WHO And UNICEF has carried out a study and concluded that Bio Farma could produce these vaccines. I support that conclusion and have recommended that UNIDO should consult with the other agencies and satisfy itself that the project is economically sound. If it is, UNIDO should assist. Reports by the study team and by Bio Farma are at Appendices 5 to 7. The estimated total cost is 5 to 6,000,000 US$ and Bio Farma is seeking aid to the value of 5,300,000 US$.

(h) Engineering Services

The level of expertise needs to be improved by the appointment of a professionally qualified engineer to take over the running of this Section. There is a definite requirement to improve the steam supply which is not as dry as it should be and delivery pressures fluctuate. New stills are needed so that both distilled water and hot water can be reticulated to all of the production laboratories. Water treatment plants are also needed. Bio Farma is aware of the need for all these services but has been unable to include them in the current budget. The estimated cost is 180,000 US$ and UNIDO should assist if possible.

(i) Total Value of Aid

I have recommended that assistance in the form of equipment to the value fo 674,000 US$ be given in addition to the 5,300,000 US$ being sought for virus vaccine manufacture.

3.2 Singapore and Malaysia

Quantities used and prices of vaccines were obtained. There is no vaccine manufacture nor is this being considered in view of the small population to be vaccinated.

3.3 Government Pharmaceutical Organization: Bangkok: Thailand

The Biological Division of the GPO is endeavouring to meet Thailand's vaccine needs in the line with government policy. This Division seems to have been neglected in the past in favour of the more profitable Pharmaceutical Division although now because of the demands of the EPI, funding is becoming available. A number of new buildings have been constructed in recent years and a new facility for diphtheria and pertussis is currently being built. The expertise of middle and senior management requires strengthening but nevertheless, it is felt that any aid assistance to the GPO would be put to good use.

(a) Diphtheria and Pertussis Antigens

The most pressing Thai need for aid is in the production of these antigens. Some years ago, the GPO sought assistance from WHO and UNICEF and funding to the extent of 300,000 US$ for equipment has been obtained. This funding is not sufficient to purchase all of the new equipment that is needed and UNIDO should assist by meeting the shortfall which will be about 84,000 US$.

(b) Tetanus Antigen

The present facility, while able to meet the requirement so the EPI, falls far short of an acceptable standard. The GPO recognizes this fact and plans to construct a new facility. I have recommended that construction should not start until the plan has been approved by an expert. Aid in the form of equipment costing 329,300 US$ and overseas training of the OIC in tetanus fermentation are recommended.

(c) BCG Vaccine

This vaccine is currently manufactured at the Queen Saovabha Memorial Institute (Section 3.4) but Thailand government policy appears to favour production at the GPO. It is recommended, as a low priority item, that this vaccine be added to the production range of the GPO. A new laboratory must be constructed by the GPO at an estimated cost of 150,000 US$ and it is recommended that equipment costing 318,750 US$ should be funded by UNIDO.

(d) Measles and Poliomyelitis Vaccines

There is no production expertise at the GPO but the Department of Medical Sciences, Ministry of Health is able to fully test these vaccines. It is felt that the GPO has too many problems with the other vaccines which must be addressed before the production of these virus vaccines can be considered.

(e) Vaccine Formulation and Dispensing

The GPO must increase batch sizes in order to meet the EPI demand and increase the efficiency of both quality control testing and dispensing. To carry out this function, the GPO should construct a new equipment preparation area and a new vaccine formulation area (Suggested plans are at Appendix 14 and 15). A list of equipment required is given at Appendix 16 and the estimated cost is 152,500 US$. With large batches, dispensing must be carried out by automatic high speed machines. The GPO has a suitable area in its Injections section to do this work and the cost of equipping the area for the task is estimated at 179,000 US$. I have also recommended that a suitable male be given training in cleaning, preparing and operating mixing tanks as well as aseptic vaccine formulation and sampling.

(f) Engineering Services

There needs to be improvement in all areas of supply and maintenance. I have recommended that staff should be selected for overseas training in the operation and maintenance of steam generation and distribution plant and also servicing of autoclaves and distilled water stills. Training in the servicing of air-conditioning and refrigeration plant including freeze dryers is also needed.

(g) Total Value of Aid

I have recommended that assistance in the form of equipment to the value of 1,063,050 US$ be provided to the GPO by UNIDO.

3.4 Queen Saovabha Memorial Institute: Bangkok: Thailand

This Institute was set up in 1917 to produce vaccines and other biological products. As far as I was able to establish, Thai policy is for EPI vaccine production to be at the GPO. However the QSMI does not appear to share this view and continues to produce BCG vaccine which is not produced at the GPO. They have invested a considerable amount of money to upgrade the production department and regardless of government policy, appear most likely to be the only BCG producer in Thailand for some time to come. Staff have been well trained in Copenhagen on production and testing precedures. I have recommended that UNIDO supply equipment (Appendix 16) to the value of 74,000 US$.

Note: The upgrading of the production facilities of both the GPO and the QSMI was considered under an ADAB project in 1983. UNIDO should discuss this report with ADAB before moving towards arranging aid to either institute.

3.5 Serum and Vaccine Laboratory: Alabang: Philippines

This institute has been allowed to deteriorate to a very depressed state. Most buildings are inadequate and along with most engineering services, need replacing. There is no evidence of any long term planning to upgrade and this is probably due to the absolute uncertainty of the money supply. The first priority before any aid is decided upon is for an expression of complete commitment to be given by the government of the Philippines. It must want to have a vaccine manufacturing facility and be prepared to fund a building program and the provision of services, to ensure that there is sound management at the top level and to ensure that there are adequate funds for the proper maintenance, servicing and replacement of equipment as necesssary. On the basis that this commitment will be given, I have made a number of recommendations.

(a) BCG Vaccine

The building needs renovation to bring it into compliance with GMP. It needs air-conditioning and the provision of reticulated services. A list of equipment estimated to cost 144,000 US$ to be provided by UNIDO is at Appendix 18.

(b) Tetanus Vaccine

A new building is needed and equipment (Appendix 20) costing 289,500 US$ is recommended.

(c) Diphtheria and Pertussis

These antigens are not being produced at Alabang at present. The building needs redesigning and renovating and existing equipment has to be rendered operative. Essential services such as distilled water and hot water, need to be reticulated to the building. An additional fermentor is needed costing about 70,000 US$ and a pass through autoclave costing 56,000 US$.

(d) Measles and Poliomyelitis Vaccines

These are obtained from overseas. There is no production or testing expertise at Alabang. It will be well into the future before the production of these vaccines can be contemplated.

(e) Vaccine Dispensing

The design of a recently renovated area on the first floor of the Bacterial Vaccine Building needs altering so that dispensing can be done in compliance with GMP. New equipment already on site needs to be made operative and batch sizes need to be increased to make dispensing runs more efficient and to reduce the level of quality control testing. A list of equipment required and estimated cost (222,500 US$) is at Appendix 19.

(f) Engineering Department

This department is badly run down, has not got proper facilities or equipment and lacks expertise in most areas. The services which it provides are unsatisfactory for a biological manufacturing laboratory. I have recommended recruitment of a professionally qualified engineer to take over this Department. Plannning must commence then to either upgrade or renew all of the present services.

(g) Quality Control

This Section is operating in a satisfactory manner. As a lower priority, it needs new laboratories. There is a need for training in GMP so that a quality assurance program can get underway under the control of this Section.

(h) Total Value of Aid

I have recommended assistance in the form of equipment to the value of 782,000 US$ be provided by UNIDO.

It is emphasized that this list is only of minimal essential items and undoubtedly much more equipment will be needed to make the laboratories function properly. A contingency fund of at least 500,000 US$ would not be excessive for this purpose.

I wish to stress again, that any aid should be on the basis of complete commitment by the government of the Philippines.

4. INDONESIA

4.1 Directorate of Epidemiology and Immunization: Ministry of Health

Discussion was held with the following persons:

Dr. S Gunawan	Head of Directorate
Dr. Elnaggar	WHO consultant
Mr R.J. Hatfield	UNICEF (Project Officer EPI)
Mr. Jones	USAID

The Directorate is responsible for deciding dose regimes for the vaccines and for determining the number of doses that will be given over the whole population in any one year; usually this is set out as a five year plan.

The planned schedule of doses is:-

DPT Vaccine	3 doses
DT Vaccine	1 dose
Tetanus Vaccine	2 doses - pregnant women and girls about to marry 1 dose - secondary school girls
BCG Vaccine	1 dose
Poliomyelitis Vaccine	3 doses
Measles Vaccine	1 dose

The table below gives the current 5 year plan in terms of the number of doses to be given each year and makes no allowance for losses which will be incurred during administration. It is expected that there will be a minimum coverage of 65% of target vaccinations. The birth rate in 1988/89 is expected to be about 28% and the annual number of new borns will be approximately 5×10^6.

	Millions of Doses					
Antigen	1984/1985	1985/1986	1986/1987	1987/1988	1988/1989	
BCG	2.97	3.50	3.89	4.45	4.90	≡ 98% cover
DPT	5.62	9.10	10.21	11.70	13.43	≡ 90% cover
POLIO (LPV)	2.81	5.60	7.85	9.85	12.97	≡ 87% cover
MEASLES	0.63	1.70	2.36	3.00	3.98	≡ 80% cover
T	4.76	9.21	13.40	13.60	14.00	
DT	5.10	6.50	5.20	7.10	7.10	

At the present time Bio Farma manufactures all of the BCG, DTP, DT and T vaccines and purchases all of the Measles vaccine as dispensed, freeze dried product. Bio Farma also purchases live Poliomyelitis Vaccine about 70% as dispensed product and about 30% as bulk concentrate which is diluted and dispensed at Bio Farma. In addition to the MOH requirements, Bio Farma also sells some vaccines to private practitioners. This is one reason why there are apparent discrepancies between the table above and the answers given to the questionnaire.

The prices which are charged to the Government of Indonesia are as follows per dose:-

DPT Vaccine	10 dose (5 mL)	641.5 Rph approx	5.8c (US)
DT Vaccine	10 dose (5 mL)	641.5 Rph approx	5.8c (US)
T Vaccine	10 dose (5 mL)	520.5 Rph approx	4.7c (US)
BCG Vaccine	(20 dose)	907.5 Rph approx	4.1c (US)
Measles	(10 dose)	1562.0 Rph approx	14.2c (US)
Poliomyelitis Vaccine (LPV)	(10 dose)	913.0 Rph approx	8.3 c (US)

The price of the virus vaccines is high in comparison to world prices and is mainly due to the limited buying power of Bio Farma which purchases in relatively small lots. From 1986/87 they will be purchased through UNICEF and prices will be:-

Measles Vaccine	10.0c (US)/dose
LPV	3.3c (US)/dose

It is possible that International Rotary may donate LPV through UNICEF for the next 5 years.

4.2 Quantities of Vaccines Needed

Calculation of the quantities of different EPI vaccines needed is based on the proposed immunization schedule and table of expected doses to be given in 1988/89 as presented in Section 4.1. It is assumed that all Measles vaccine is freeze-dried, that the BCG vaccine is freeze-dried and administered intradermally and that the Poliomyelitis vaccine will be live attenuated vaccine administered orally.

Factors involved in the calculation are allowances for 20% losses during formulation, dispensing and testing. In addition, there is an allowance for wastage and breakage during administration as follows:

DPT, DT and T vaccines	20%
BCG vaccine	50%
Measles and Polio vaccines	25%

Taking all these factors into account, the calculated annual requirements are:

DPT	13.43×10^6	x	1.2 x 1.20 =	19.34×10^6	doses
DT	7.10×10^6	x	1.2 x 1.20 =	10.22×10^6	doses
T	14.00×10^6	x	1.2 x 1.20 =	20.16×10^6	doses
BCG	4.90×10^6	x	1.2 x 1.50 =	8.82×10^6	doses
Measles	3.98×10^6	x	1.2 x 1.25 =	5.97×10^6	doses
Polio	12.97×10^6	x	1.2 x 1.25 =	19.46×10^6	doses

4.3 Center of Drug and Food Control: Ministry of Health

This Center is responsible for the national quality control of vaccines.

Bio Farma tried to arrange for me to see Dr. Charles Siregar, Head of the Center but it did not prove possible. I was unable to meet his Deputy, Dr. Iskak Koiman either as he was in hospital. Consequently, I did not visit the Center but discussed various matters with Dr. Gunawan and Dr. Elnaggar who appeared to be quite familiar with the Center's operations.

The National Control Laboratories are now being established on good grounds with Japanese co-operation. New laboratories built in 1985 are not yet fully operational but should be before the end of 1986. Various staff members have received training overseas including at NBSL Australia and State Serum Institute, Copenhagen. The training program has been supported by WHO and equipment has been supplied by the Indonesian government.

4.4 Bio Farma: Bandung

4.4.1 Introduction

I visited Bio Farma from 8th to 10th April and discussions took place with:

Dr. M.S. Nasution	Director
Mrs. Soeharto	Commercial Director
Dr. Sutaryo	Production Director
Dr. G. Hartono	Secretary

The Pasteur Institute was established in Jakarta in 1890 and has a long history of successful vaccine and anti-serum production. In 1923, the Institute was moved to its present site in Bandung. In 1955, the name was changed to Perusahaan Negara Pasteur which eventually was altered to Perusahaan Umum Bio Farma. The name is now usually abbreviated as Perum Bio Farma.

The Institute produces a range of vaccines, antisera, diagnostic reagents, sterile infusions etc and acts as a national reference laboratory in a number of fields of microbiology.

The Management has an ongoing policy to ensure thorough staff training assisted by overseas fellowships and to continually upgrade facilities and improve compliance with GMP. In the latter regard, the cleanliness of the site was exemplary.

4.4.2 Diphtheria Antigen

4.4.2.1 Production Method

The system used is that published by RIVM: Bilthoven and involves fermentor technology utilizing Lingards' medium which is meat based. This was discussed and it was agreed that they should move towards using a fully synthetic medium. Currently final product is not tested for meat protein which is a test required by WHO. The toxin is concentrated using an Amicon system, toxoided and purified in the usual way by ammonium sulphate fractionation. Final purity is greater than 1500 Lf/mg protein nitrogen which complies with British Pharmacopoeia.

4.4.2.2 Production Requirement 1988/89

The quantities of vaccines required are calculated in Section 4.2.

DPT Vaccine 19.34×10^6 doses
DT Vaccine 10.22×10^6 doses

Each formulation contains 20 Lf per 0.5 mL dose
Diphtheria toxoid required = $29.56 \times 20 \times 10^6$ Lf
= 591.2 million Lf

4.4.2.3 Capacity

The department has a Novo-Paljas fermentor with two 90 litre vessels and one 250 litre New Brunswick fermentor. In June 1986, it will also have a Magno-Paljas fermentor with one 500 litre and one 90 litre vessel.

Total fermentor volume will be 1020 litres which will handle 710 litres of medium and successful ferments will yield (after filtration losses) 635 litres toxin.

After allowance for contamination rate (20 to 25%) there can be 30 successful ferments per year yielding 120 Lf/mL.

Therefore, total toxin yield = $30 \times 635 \times 120$
= 2286×10^6 Lf.

Assuming 50% losses during purification, the annual yield of purified toxoid could be 1143×10^6 Lf. Capacity therefore in June 1986 will exceed the 1988/89 requirement (Section 4.4.3.2) of 591.2×10^6 Lf by a large margin.

4.4.2.4 GMP

There was no production during my visit as the laboratories are being modified and refurbished I made some suggestions which I believe would improve the new area, particularly the flow of the culture through the department and the separation of culture areas from clean work areas. The media preparation area should be partitioned off from the culture area and a new entrance to the media room should be constructed through the outer wall. Entry lock facilities are needed for both staff and portable tanks. Infected material will still have to be transported outside the new culture area for decontamination. this is unsatisfactory and the problem would be solved by the provision of a pass through autoclave.

The accepted contamination rate (20 to 25%) is very high and is probably due to inadequate facilities which have been used and perhaps greater attention to good aseptic techniques is needed. Bio Farma plan to provide sterile filtered air to the new laboratories but this is not included in the present budget. I believe this is the most essential item required to reduce the contamination rate and comply with GMP. Filtration must be terminal ie. at point of entry to each room. Culture work should be done under vertical laminar flow cover and a new cabinet should be provided.

Additional equipment required and cost estimates are given at Appendix 1. Mr Ketut Japa who is in charge of diphtheria production would benefit from 2 to 3 months training in fermentation technology. As the fermentors he will use are Novo-Paljas type, it is recommended that training should be at RIVM, Bilthoven, Holland. Bio Farma will fund this if necessary but would prefer to receive assistance. I recommend that UNIDO should provide funding and arrange this training.

4.4.3 Pertussis Antigen

4.4.3.1 Production Method

They use one strain of B.pertussis which is designated MAENO and was obtained from the Kitisato Institute in Japan. Production is in fermentors using the procedure published by RIVM Bilthoven, Holland.

Harvests are centrifuged using Sharples centrifuges because they are much cheaper and simpler to use than the Westfalia recommended by RIVM. The organisms are resuspended in saline and inactivated by heating at 56°C for 30 minutes. The harvests have exceptionally good potency in that the vaccine can be formulated at 24 x 10^9 organisms per mL (most use 40 x 10^9 per mL) and pass the WHO potency test quite well.

4.4.3.2 Production Requirements

The quantities of vaccines required are calculated in Section 4.3.

DPT Vaccine 19.34×10^6 doses

The formulation contains 24×10^9 organisms/mL

ie. 12×10^9 organisms per $^1/_2$ mL dose

Pertussis required = 9,670 litres at 24×10^9 organisms/mL.

4.4.3.3 Capacity

The department has the following fermentors:

1 x Super-Paljas = 1 x 70 litre medium
2 x Novo-Paljas = 3 x 70 litre medium
1 x Novo-Paljas = 2 x 70 litre medium will be installed in June 1986

Therefore 6 vessels will ferment 420 litre medium and after 15% processing losses will yield 360 litre at 12×10^9 organisms per mL.

After allowance for contamination rate (20%) assume there can be 32 successful ferments per year from each vessel which will produce 32 x 360 litres at 21×10^9 organisms/mL

ie. 11520 litres at 21×10^9 organisms/mL

Vaccine contains 24×10^9 organisms/mL

Therefore Vaccine equivalent = $\frac{11520}{1} \times \frac{21}{24}$ litres

= 10,080 litres at 24×10^9 organsims/mL

= 20.16×10^6 doses

Capacity in June 1986 will exceed the 1988/89 requirements (Section 4.4.3.2) of 19.34×10^6 doses. The calculations above are based on 32 ferments per vessel per year. Staff indicated that many more ferments could be achieved, however the capacity will ensure that this will not be necessary.

4.4.3.4 GMP

The department is very capably managed by Mrs Peggy Sunotoredjo who has had the benefit of overseas training. The laboratories are fairly well set out, clean and uncluttered.

The fermentors are housed in rooms which are separated from one another by aluminium framed glass partitions. The rooms are very good but do not have a filtered air supply which I believe is the main cause of the unacceptably high contamination rate (20%). Removal of the harvests from the Sharples centrifuge bowls is done without the protection of laminar flow cover. I suggested that the bowls should be transferred back to the culture room laminar flow cabinet for this part of the process. Cultures are handled under horizontal laminar flow and safety would be improved by changing to vertical laminar flow.

Some significant changes are required for the room lay-out to improve the flow of cultures through the area at each stage of processing. There needs to be a clean room for aseptic work separated from the culture room. Some seed cultures are transported across an open area to a fermentor. It would be reasonably easy to avoid this problem by enclosing the open area.

There appears to be an adequate number of portable tanks and processing equipment but the department needs to be modified to allow for personnel and tank entry locks and needs a pass through autoclave for entry of sterile equipment and decontamination of infected material which is currently transported to another building for autoclaving. There is sufficient space at the back of the building to allow an extension to be built to house the pass through autoclave and a new clean room for general aseptic work. The present clean room must be traversed with living cultures regularly and therefore the work done in this room should be shifted away from the culture path. The major requirement is terminally HEPA filtered air conditioning.

Additional equipment required and cost estimates are given in Appendix 1.

4.4.4 Tetanus Antigen

4.4.4.1 Production Method

This department has received the benefit of assistance for the Australian Development Assistance Bureau (ADAB) to redevelop toxin production. The program which was managed by the Commonwealth Serum Laboratories, included the installation of a fermentor and training for the Head of the Department in Australia.

Production is by fermentation in tryptic digest of casein which is the commonly used medium for tetanus. The toxin is separated from the culture by filtration using a large plate and frame filter press. Formalin is added and when toxoiding is completed, purification by ammonium sulphate fractionation and then concentration using an Amicon unit are performed. Final purity is well in excess of 1000 Lf per mg protein nitrogen which is the WHO minimum requirement.

At the present time some toxin is being produced also by static culture in bottles but this is only to establish a reserve quickly and when this is achieved, production by this method will cease.

4.4.4.2 Production Requirements

The quantities of vaccines required are calculated in Section 4.3.

DPT Vaccine 19.34×10^6 doses ($^1/_2$ mL)
DT Vaccine 10.22×10^6 doses ($^1/_2$ mL)
T Vaccine 20.16×10^6 doses ($^1/_2$ mL)
DPT Vaccine contains 15 Lf tetanus toxoid/mL
DT Vaccine contains 15 Lf tetanus toxoid/mL
T Vaccine contains 20 Lf tetanus toxoid/mL

DPT and DT vaccines require $(19.34 + 10.22) \times 10^6 \times 7.5$ Lf toxoid.
$= 221.7 \times 10^6$ Lf
T vaccine requires $20.16 \times 10^6 \times 10$ Lf toxoid
$= 201.6 \times 10^6$ Lf
Total requirement = 423.3×10^6 Lf of purified tetanus toxoid

4.4.4.3 Capacity

The 1000 litre fermentor vessel cultures 800 litres of medium which yields about 730 litres of toxin at an average of 45 Lf per mL this being the yield stated to me during the visit. (Recent runs have yielded 60 Lf/mL). The yield per ferment is 32.8×10^6 Lf. After allowing for 16% contaminated runs, there can be 27 successful ferments per year yielding approximately 440×10^6 Lf.

This capacity exceeds the requirement (Section 4.5.4.2) for 1988/89 by a small margin. If the reply in the questionnaire (7.5) is accepted ie. 40 Lf/mL fermentor yield, then capacity becomes 391×10^6 Lf. The department is able to produce up to 100×10^6 Lf per year by static culture if necessary so that I do not consider the provision of another fermentor is a matter of high priority. It is something which could be considered for the future. In the shorter term I am optimistic that the contamination rate can be reduced to improve the overall capacity and possibly a slightly better recovery after purification can be achieved.

4.4.4.4 GMP

The building is separate from all others as required by WHO and the fermentor is housed in a room which was said to have filtered air supply. I did not ascertain the type of filtration in use but it was noted that terminal HEPA filtration was not installed. Materials and equipment enter via a pass through autoclave and contaminated equipment passes out via the autoclave. There is a tank outside the building piped to the fermentor for decontaminating material ex fermentor before discharge to sewer. The entry area for staff is unsatisfactory and I have suggested that a new entry lock should be built and the present one should only be used for transfer of portable tanks. The culture can then be completely contained in this area provided that a doorway is built between the seed culture room and the fermentor room. At present living culture is transported outside the culture areas through a clean area.

Toxin is transported to a warm room in a separate building for detoxification. I pointed out that this is contrary to WHO requirements and suggested that there is adequate space on one side of the tetanus laboratory to allow an extension containing a warm room to be constructed there. If the department eventually moves to a process involving concentration and purification of toxin before toxoiding, then probably the existing warm room adjacent to the culture room will be large enough for this purpose. I understand that this new process and associated equipment will be provided under the ADAB aid project which is not yet finalized.

The doorway at the back of the room should be sealed and steam lines used for sterilizing portable tanks should be extended from outside the fermenter room to the clean area on the other side of the building.

To improve staff safety, the horizontal laminar flow cabinet should be replaced by a vertical flow safety cabinet and a new incubator is needed in the seed culture room to obviate the requirement to transport seed cultures to the warm room for incubation. In order to improve compliance with GMP, there should be a staff entry lock at the seed culture room and a new doorway needs to be provided between there and the fermentor room. The existing staff entry should be used only as a portable tank entry lock. A sketch of my proposal to modify the area is given at Appendix 2 and the list of equipment required is at Appendix 1.

4.4.5 BCG Vaccine

4.4.5.1 Production Method

The Pasteur Strain 1173P2 is cultivated and harvested by the Copenhagen process which is used very widely throughout the world. A new secondary seed lot is obtained each year from the State Serum Institute, Copenhagen. The harvest is suspended in 1% sodium glutamate and freeze dried in a Vertis Freeze Dryer in amber coloured ampoules. The ampoules are sealed under vacuum in the Japanese ampoule sealing machine.

The vaccine is dispensed as 1.5 mg which is reconstituted after freeze drying into 2 mL saline to give 20 doses at 0.075 mg per dose. The viable count per dose is 0.2 to 0.5 x 10^6 colonies which although lower than usual, is probably satisfactory. I understand that if a greater dose is given the reaction rate becomes unacceptably high.

4.4.5.2 Production Requirements

The quantity of vaccine required is calculated in Section 4.3.

BCG Vaccine required = 8.82 x 10^6 doses.

4.4.5.3 Capacity

The limiting factor at the moment is the capacity of the freeze dryer. The maximum batch size is 8500 x 20 dose ampoules and the department can do 70 batches per year, the capacity therefore is 70 x 8500 x 20 doses = 11.9 x 10^6 doses. After allowing for a low contamination rate of about 5% production capacity is 11.3 x 10^6 doses. This is adequate to meet the country's total requirements of 8.82 x 10^6 doses (Section 4.4.6.2) but in any case Bio Farma intends to install another Vertis Freeze Dryer which will double the production capacity.

4.4.5.4 GMP

I was unable to enter the department culture areas for inspection but as far as I could ascertain compliance with GMP is good. Product is tested to WHO requirements. The building is separate from all others and is air conditioned with HEPA filtered air and my only criticism is that it is via exposed duct work below the ceiling. This should be replaced above the ceiling with terminal HEPA air filtration and I recommended to Bio Farma that they should arrange for this to be done.

4.4.6 Formulation of DPT, DT and T Vaccines

The sterile components including aluminium phosphate are mixed aseptically into large sterile glass vessels or portable stainless steel tanks. The bulk batches are sampled for sterility testing but all other tests are carried out on samples of the dispensed product. Batches are tested and must comply with WHO requirements.

The present mixing room has HEPA filtered air which is not terminal. There is no proper change room for staff nor a satisfactory entrance for materials and no laminar flow cover. I discussed this with staff of Bio Farma who agreed that a larger area complying with GMP is needed. A floor plan is given at Appendix 4. There is a suitable area beside the present room on which a new facility could be built. This facility would also house a new 2° to 8°C cold room for the storage of packed vaccines. New equipment needed is listed at Appendix 3.

4.4.7 Dispensing and Packaging

These areas were given new equipment and were upgraded with the assistance of ADAB some years ago. Equipment, vials, stoppers etc pass from the wash up area via either an autoclave, a hot air sterilizer or a UV pass through into the dispensing area. This dispensing room has HEPA filtered air and has Cozzoli dispensing and stoppering machines each of which is installed under vertical laminar flow cover. There are entry locks for staff entry. I was informed that the current capacity is more than adequate to handle all of the requirements of the EPI.

The wash up area has a machine for washing ampoules and vials. The area does not have hot water nor reticulated distilled water but Bio Farma has planned in its current budget to supply these services. I recommend that assistance be given by UNIDO to do this work. Equipment required and cost estimates are given at Appendix 3.

The packaging room has Cozzoli labelling machines and while being fairly crowded, is able to quite readily meet all demands. The department is in need of additional cold room space and it was suggested that an additional facility could be provided in conjunction with the proposed new mixing area discussed in Section 4.4.7. See Appendix 4.

4.4.8 Measles and Poliomyelitis Vaccines

Indonesia imports dispensed freeze dried Measles Vaccine and Live (Oral) Poliomyelitis Vaccine (LPV); in the latter case about 30% is purchased as bulk concentrate which is diluted and dispensed at Bio Farma. Full testing is carried out to WHO requirements. There are three staff members who have received overseas training for this purpose and in this regard Bio Farma is in advance of the Center of Drug and Food Control which is responsible for national quality control - refer Section 4.2.

Bio Farma is currently growing both measles and poliomyelitis viruses on a small scale and wishes to eventually manufacture both vaccines, the projected requirements being 20×10^6 doses of LPV and 6×10^8 doses of Measles Vaccine after allowing for losses during dispensing and vaccination programs.

In 1984, Bio Farma received a visit from a project team made up of members from USAID, WHO and UNICEF. This team undertook a feasibility study on the production of Measles Vaccine and LPV in Indonesia. It concluded that Bio Farma could produce these vaccines and suggested a step wise plan for its implementation. A copy of this report is at Appendix 5.

Bio Farma is an impressive organization which has good management and well trained efficient staff. There is an ongoing commitment to ensuring staff expertise in areas of production and quality control by selection of suitable people for overseas training. This has been funded either by Bio Farma or where possible, by aid agencies. The various people I discussed this project with appeared to agree that Bio Farma has the capability to do this work. All agree that it is in the country's best interests to do so provided it can produce at close to world prices. The project team concluded that it could and the cost of the project would be 5 to 6,000,000 US$.

It is most important that the economics of the plan are correct. I suggest that UNIDO should discuss this with USAID, WHO and UNICEF and, if satisfied, participate in some way in the project.

At Appendix 6 and 7 are proposals put forward by Bio Farma which is seeking aid amounting to 5,300,000 US$ and indicating its intentions to provide about 1,400,000 US$ in the form of buildings and services.

4.4.9 Engineering Services

The Head of the maintenance team has had a long period of overseas training and appears reasonably competent. Most maintenance work can be carried out by his team with reasonable efficiency. Boiler capacity is in excess of present requirements and will be able to provide all the energy needed for the provision of reticulated hot water and distilled water. Some aspects of the steam supply need attention as the supply tended to have fluctuating pressure and excessive in line condensation causing the steam to be too "wet" at the point of delivery.

Bio Farma requires a supply of dry steam at reasonably constant pressure. There is a need for a water treatment plant and the provision of reticulated hot water and distilled water throughout the laboratories. Wherever it doesn't exist now, production laboratories require air conditioning with terminal HEPA filtration. There are buildings to be constructed or refurbished. All of these things in addition to warm rooms, cold rooms and fermentors will require constant maintenance and repair work. There is a large enough area of responsibility to warrant the appointment of a full time professionally qualified engineer to plan, co-ordinate and supervise this work. I recommend that Bio Farma appoint such a person.

The estimated costs are

		US$
Water softener plant	25,000 litre/hour	12,000
Water treatment plant	2,500 litre/hour	56,000
Water distillation plant	1,200 litre/hour	90,000
Stainless steel piping to BCG diphtheria pertussis and tetanus buildings		22,000
		180,000

4.4.10 Quality Control

Bio Farma has well trained and equipped staff who carry out this work to WHO requirements. A WHO consultant for vaccine quality control has visited Bio Farma and approved it for inclusion in a global network of vaccine testing laboratories (including viral vaccines).

5. SINGAPORE

5.1 Pharmaceutical Department: Ministry of Health

Discussion was held with the following persons:

Mr. K.K Tan	Director
Dr. C.C Tang	Microbiologist, Department of Pathology
Ms. T.L Keng	Pharmacist in Charge, Quality Control

This Department is responsible for obtaining the quantities of vaccines required to meet the program each year. Singapore does not manufacture vaccines as this would be most uneconomical because of the small target population. Each year tenders are called with overseas manufacturers for the supply of vaccines.

The population is 2.6×10^6.
The birth rate is 1.6%
The target population is approximately 42,000
Dose regimes are:-

DPT	3 doses
DT	1 dose
T	Trauma cases only
BCG	2 doses (with 10 years between)
Measles	1 dose
LPV	3 doses

Tabulated below is the number of doses required annually, the amount purchased which includes an allowance for wastage and the price per dose.

	Require	Purchase (1986)	Price
DPT	126,000	150,000	6.7 c (US)
DT	42,000	50,000	5.6 c (US)
T	-	70,000	3.1 c (US)
BCG	84,000	110,000	NA
Measles	42,000	60,000	NA
LPV	126,000	200,000	NA

The Department requires vaccines to be supplied with a WHO protocol and insists on rigid compliance with the cold chain. This is stipulated in the tender document and if the indicator shows that the chain has been broken, the batch is rejected.

The only testing performed by the Department is sterility testing of samples of DPT, DT and T vaccines. Occasionally samples are sent overseas (Australia and Japan) for potency and safety testing.

The Quality Control Department monitors vaccine immunogenicity by carrying out serological testing from time to time.

The population of Singapore is too small to warrant local production of vaccines and therefore the current policy of purchasing vaccines as required should continue.

6. MALAYSIA

6.1 Institute for Medical Research: Ministry of Health

My appointment with Dr. Lim Teong Wah, Director was cancelled because he received an unexpected visit from the Malaysian Director-General of Health. I discussed matters with Mrs Tan Yoke Soon, Head of the Vaccine Division.

EPI vaccines are imported by the General Medical Stores, Ministry of Health. A WHO protocol must be supplied for each batch and strict compliance with the cold chain is required.

The population is 14×10^6
The birth rate is 2.9%
The target population is approximately 450,000
Dose regimes are:-

	DPT	3 doses (in 1st year)
	DT	2 doses (1 to 6 years)
	T	Trauma cases only
	BCG	1 dose
*	Measles	1 dose
	LPV	3 doses

* Occasionally, the University Hospital checks antibody titres of vaccinated babies and if deemed necessary, another dose is given.

Tabulated below is an estimate of the number of doses required annually, the amount purchased which includes an allowance for wastage plus a build up of reserve and the price per dose.

	Require	Purchase (1986)	Price (US $)
DPT	1,350,000	2,242,000	0.069
DT	900,000	1,087,000	0.043
T	-	2,636,000	0.043
BCG	450,000	NA	0.071
Measles	450,000	1,096,000	0.093
LPV	1,350,000	2,996,000	0.072

There is a National Pharmaceutical Control Laboratory which occasionally tests vaccines for sterility and toxicity but has not developed the capacity to perform potency testing.

As for Singapore, the population of Malaysia is not sufficient to warrant attempting production of any of the EPI vaccines within the country.

7. THAILAND

7.1 Department of Communicable Disease Control

Discussion was held with the following persons:

Dr. Sawat Ramaboot	Chief of Bacterial Section
Ms Sumana	Chief of Medical Supplies

The EPI is under the administration of the Ministry of Public Health (MOPH). The Department of Communicable Disease Control is responsible for carrying out the policy of the MOPH on the EPI including the provision of vaccines and equipment for vaccinations. Some of the vaccines are manufactured in Thailand and the remainder are obtained from outside the country with the assistance of UNICEF either by purchase or donation.

The planned schedule of doses is:

DPT Vaccine	3 doses
DT Vaccine	1 dose - as booster after at least 2 doses DPT 2 doses - as primary vaccination
Tetanus Vaccine	2 doses - pregnant women and girls about to marry
BCG Vaccine	1 dose
LPV Vaccine	3 doses
Measles Vaccine	1 dose

The plan is to have a 100% coverage of target vaccinations by 1990. The current birth rate is 1.8% which is expected to reduce to about 1.5% by 2000 and the population is expected to increase from the current 50×10^6 to about 60×10^6 by that time. The number of doses to be given in 1990 and 2000 is based on the annual number of new borns being 900,000 and is tabulated below.

	Million of Doses	
	1990	2000
DPT Vaccine	2.7	2.7
DT Vaccine	1.8	0.9
T Vaccine	1.8	1.8
BCG Vaccine	0.9	0.9
LPV Vaccine	2.7	2.7
Measles Vaccine	0.9	0.9

The prices which are charged to the Government of Thailand are as follows per dose:

DPT Vaccine	5.7¢ (US) but 12.9¢ (US) when supplied by the Government Pharmaceutical Organization in Thailand
DT Vaccine	5.7¢ (US)
T Vaccine	4.1¢ (US)
BCG Vaccine	6.5¢ (US) when purchased from Thailand Red Cross but 7.9¢ (US) from overseas.
LPV Vaccine	5.9¢ (US)
Measles Vaccine	11.4¢ (US)

7.2 Quantities of Vaccines Required

Calculations are based on the dose requirements listed in Section 7.1 making the same assumptions as in Section 4.2. Allowance has been made for 20% losses in formulation, dispensing and testing plus allowance as follows for wastage and breakage during administration. For the virus vaccines, allowance is only made for administration losses on the basis that these vaccines will not be manufactured in Thailand in the near future.

DPT, DT and T Vaccines	25% (NB Indonesia 20%)
BCG Vaccine	50%

Taking all of these factors into account, the calculated annual requirements from 1990 to 2000 are:

DPT	$2.7 \times 10_6^6 \times 1.2 \times 1.25$	$= 4.05 \times 10_6^6$ doses
DT	$1.8 \times 10_6^6 \times 1.2 \times 1.25$	$= 2.70 \times 10_6^6$ doses
T	$1.8 \times 10_6^6 \times 1.2 \times 1.25$	$= 2.70 \times 10_6^6$ doses
BCG	$0.9 \times 10_6^6 \times 1.2 \times 1.50$	$= 1.62 \times 10_6^6$ doses
LPV	$2.7 \times 10_6^6 \times 1.2$	$= 3.24 \times 10_6^6$ doses
Measles	$0.9 \times 10^6 \times 1.2$	$= 1.08 \times 10^6$ doses

7.3 Department of Medical Services: MOPH

Discussion was held with the following persons:

Dr K Chatiyanonda	Virus Research Institute
Mrs V Ngarmvat	Chief of Medical Research Division
Mrs K Leelasiri	National Control Laboratory for Biologicals

This Department is responsible for ensuring that all biological products used in Thailand are of acceptable quality. Its officers are fully trained and capable of carrying out all of the WHO tests required for the EPI vaccines including LPV and Measles Vaccine. The Department has been using laboratories at the Government Pharmaceutical Organization but is about to move into new laboratories which are being constructed in Bangkok and are nearing completion.

7.4 Government Pharmaceutical Organization

7.4.1 Introduction

I visited the GPO on 16th to 17th April and discussions took place with:

Dr Y Sujjavanich	Director
Mrs A Vichitnant	Director Biological Products Division
Mr S Pongpairoj	Head, Quality Control Section

In 1966, the Ministry of Public Health established the GPO by the combination of the Government Pharmaceutical Laboratories with the Division of Medical Depot, Department of Medical Sciences. Previously, the Government Pharmaceutical Laboratories (established in 1941) was a manufacturer, and the Division of Medical Depot (established in 1902) was a distributor. These two units were completely independent of each other. The GPO is invested with the following functions:

1. Production of pharmaceuticals and medicinals.
2. Promotion of study and research of local raw materials to be made into pharmaceutical and medicinal productions.
3. Controlling the quality of production.
4. Controlling price level.
5. Establishment of reserve stocks to prevent shortage in case of emergencies.

The GPO generates its own funds for new building and equipment programmes as far as possible but from time to time seeks aid either from the Government of Thailand or from external agencies.

7.4.2 Diphtheria and Pertussis

Some years ago an approach was made by the GPO to UNICEF for help with the production of these two vaccines. UNICEF requested consultant help from WHO and subsequently Dr Gaitonde, from the WHO regional office at Delhi, visited the GPO. This project will introduce fermentor technology into the GPO for these two products. The provision of all services is to be funded by the GPO and equipment to the value of 300,000 US$ is to be provided through UNICEF. The project's activities include the training of GPO staff in fermentation techniques, GMP, management, and laboratory animals breeding technology and also the provision of a consultant to introduce the fermentor technology once the new equipment is installed. A copy of Dr. Gaitonde's report is at Appendix 8.

Modification of a building to house the new equipment for the production of these antigens is well advanced. While there are some aspects of the design (staff and equipment entries, decontamination of infected and flow of culture work through the area) which could be improved, I have not addressed this matter here but have confined my observations to the equipment list funded by UNICEF (see Appendix 9) and have recommended additional funding of 84,000 US$ to be provided by UNIDO.

The current processes in use are static culture for diphtheria and roller bottles for pertussis and both have suffered for a long period from a very high contamination rate due at least in part to poor facilities but possibly also to poor techniques. The sooner the new facilities with fermentor technology are introduced, the better.

7.4.2.1 Production Requirements

The quantities of vaccines required annually from 1990 to 2000 are calculated in Section 7.2.

DPT Vaccine 4.05×10^6 doses
DT Vaccine 2.7×10^6 doses
DPT contains 30 Lf purified diphtheria toxoid per dose
∴ Require 121.5×10^6 Lf purified diphtheria toxoid
DT contains 2 Lf purified diphtheria toxoid per dose
∴ Require 5.4×10^6 Lf purified diphtheria toxoid
TOTAL purified diphtheria toxoid required per year = 127×10^6 Lf.
DPT contains 20×10^9 pertussis organisms per 1/2 mL dose.
TOTAL pertussis organisms required = 2025 litres at 40×10^9 organisms/mL

7.4.2.2 Capacity

Diphtheria Toxoid

The WHO report recommends 1 x 75 litre capacity fermentor. After allowing for a 20% contamination rate, it is assumed that there can be 25 successful ferments per year, each yielding 70 litres at 140 Lf/mL.

Total toxin yield = $25 \times 70{,}000 \times 140$ Lf
= 245×10^6 Lf.

Assuming 50% losses during purification, the annual yield of purified toxoid = 122.5×10^6 Lf. This is barely sufficient to meet demand but probably can be increased by a reduction in the contamination rate, a small increase in yield and by performing a few extra ferments per year. I would have preferred the fermentor to have a capacity of at least 100 litres.

Pertussis

The WHO report recommends 1 x 75 litre capacity fermentor.

Assuming that each ferment yields 65 litres at 60×10^9 pertussis organisms per mL, it would require 21 satisfactory ferments to yield the annual demand of 2025 litres at 40×10^9 organisms per mL.

Capacity is satisfactory and there is probably a margin which would allow this fermentor to be used for diphtheria toxoid production. Again I would have chosen a fermentor of 100 litre capacity.

7.4.3 Tetanus Antigen

7.4.3.1 Production Method

Tetanus production is carried out in a fairly old building that is not in a very good state of repair. The building is not air-conditioned except for small wall units in some rooms. There was evidence of the roof leaking in some places and the building is badly in need of a repaint. Wooden entry doors are showing signs of being affected by the weather and the tiled sink in the equipment preparation area is badly cracked and with tiles missing. There is no hot water available for equipment washing and distilled water for rinsing and medium preparation must be transported from the still house about 100 metres away. The two autoclaves used for equipment and medium sterilization are old and badly rusted. Neither has a chart for keeping a record of the temperature during the sterilizing cycle. No laminar flow cabinets are available for sterile work and there is direct access from outside, into the culture area. The building falls far short of the standard required by WHO (WHO Technical Report Series No 323, 1966). GPO has recognized the deficiencies and plans to construct a new building of 240 square metres.

Production is carried out in 25 litre volumes in stainless steel jars and a total of 100 litres of medium is inoculated twice weekly. The medium used contains Tryptone T and meat infusion as the source of nitrogen. Toxin levels are usually in the range of 30 to 40 Lf/mL. Toxoiding, concentration and purification is carried out by conventional means. The culture filtrate is toxoided in the presence of 0.45% v/v formalin and is concentrated by ultrafiltration using a Millipore Pellicon cassette system. Purification of the toxoid concentrate is by ammonium sulphate fractionation, with ammonium sulphate removal by dialysis. The purified toxoid is finally sterilized by filtration through a Seitz EK asbestos filter pad followed by membrane filtration to remove the risk of asbestos particles contaminating the final product.

The final purified toxoid concentrate is recovered in a volume of half to one litre with a toxoid content of 1,500 - 2,000 Lf/mL and a purity of about 750 Lf/mg protein nitrogen. Recovery is about 50 per cent of the original harvested culture. The low purity is probably a reflection of the low toxin level in the culture; a purity twice the level should be obtained.

7.4.3.2 Production Requirement

The quantities of vaccines required are calculated in Section 7.2.

DPT Vaccine	4.05×10^6 doses (1/2 mL)
DT Vaccine	2.7×10^6 doses (1/2 mL)
T Vaccine	2.7×10^6 doses (1/2 mL)

Each vaccine contains 20 Lf purified tetanus toxoid per mL.

Total 1/2 mL dose requirement = 9.45×10^6
Total Lf requirement = $9.45 \times 10^6 \times 10$
= 94.5×10^6 Lf purified tetanus toxoid

It is worth noting that the use of 10 Lf of toxoid per dose is unusually high and probably could be halved if the purity of the toxoid could be raised. The WHO limit is 1000 Lf per mg protein nitrogen but most manufacturers achieve nearer 2000 Lf per mg protein nitrogen.

7.4.3.3 Capacity

The department is currently producing 144×10^6 Lf of purified tetanus toxoid by static culture. This is sufficient to meet requirements but is of below standard purity.

In planning the proposed new tetanus facility, production of the culture would be more efficiently carried out in a fermentor. To meet the estimated yearly requirement for the year 2000 of 94.5×10^6 Lf units of toxoid would require a fermentor with a working capacity of 200 litres. A list of equipment needed for the new tetanus facilities is appended (Appendix 10). A suggested layout of the proposed facility is appended (Appendix 11). The facility should be supplied with separate air-conditioning systems for the culture area and other areas. The culture area should be at a negative pressure with respect to the other areas and the area where the sterilizing filtration of the purified toxoid concentrate is carried out should be at the highest positive pressure relative to the other areas. The facility should be supplied with steam at 200 kPa sufficient for operation of the autoclave, medium preparation vessel and fermentor sterilization all concurrently. Oil-free compressed air at 150 kPa and 200 litre/min is required and ideally should be distributed to each of the units within the facility. It is preferable that a supply of distilled water is available piped directly to the facility.

I am aware that planning of the new layout has already commenced and I recommend most strongly that actual construction should not start until the proposed plan is reviewed and approved by an expert in this field.

The staff of the Tetanus Department seemed to be well trained in the carrying out of their duties. The OIC, Mr Jamnu Chantorn, a graduate in Pharmacy, impressed as having a good understanding of his particular field. He is of course restricted by the inadequate facility that he has to contend with. He seems to have the ability and a sufficient understanding of English to warrant training in the application of fermentor culture for manufacture of tetanus toxoid.

7.4.4 BCG Vaccine

Although the policy is said to be for the GPO to produce BCG vaccine there has been no action to implement. Because the Queen Saovabha Memorial Institute has invested to a large extent to upgrade its BCG manufacture (Section 7.5), it should be a low priority item at the GPO.

As a lower priority item, the GPO should provide a new separate building for BCG vaccine production (proposed floor plan at Appendix 12) which would be equipped under this UNIDO project. A member of the GPO staff could be trained in vaccine production and testing. Training in testing would also be available from the Department of Medical Sciences of the MOPH.

Equipment required by the GPO is at Appendix 13.

7.4.5 Measles and Poliomyelitis Vaccines

Thailand purchases freeze dried Measles Vaccine and Live (Oral) Poliomyelitis Vaccine from overseas. The Department of Communicable Disease Control told me that the current policy is not to manufacture locally, but the GPO indicated that is believes that it should start to move in that direction. The Department of Medical Services is able to carry out all of the necessary testing and the Virus Research Institute believes that it could actively participate and collaborate with the GPO on the transfer of the required technology.

I do not believe that Thailand should undertake the development of a manufacturing capacity because:

(a) The population is not sufficient to enable manufacture on a large enough scale so that vaccines could be produced at prices competitive with world prices.

(b) The total investment required would probably exceed the amount (5 to 6,000,000 US$) estimated for Indonesia because the GPO would have a greater requirement for new support services ie. steam, distilled water, power etc.

(c) Thailand is not as technically prepared for this step as is Indonesia.

(d) The arguments for and against LPV compared to the inactivated vaccine are well documented. I believe that the best vaccine for Thailand at this time is the LPV because of its ease of administration, capacity to spread to unimmunized contacts and low cost. Its heat labile nature is recognized as a problem which must be addressed by maintaining an effective cold chain. For the future, there may well be a trend towards extensive use of inactivated poliomyelitis vaccine, possibly combined with bacterial vaccines. At this stage I think it is too early for Thailand to consider manufacture or the type of vaccine to be manufactured.

(e) Importing of concentrates for dilution, dispensing and testing requires almost as much expertise and most of the equipment needed for full scale production. Measles vaccine is unstable in the wet form and must be freeze dried. Handling of concentrates would cause problems.

(f) The GPO, as stated in other sections of this report needs to make many improvement to its production processes for bacterial vaccines. I refer to the provision of such items as:

(i) a new tetanus vaccine laboratory
(ii) a new equipment preparation area
(iii) a new vaccine formulation area
(iv) a new dispensing, packaging line
(v) reticulated distilled water
(vi) modification of many areas including the provision of HEPA filtered air conditioning to comply with GMP.

I believe that investment in these projects and pursuing them through to satisfactory completion should take priority over LPV and Measles Vaccine production.

7.4.6 Tank Washing and Equipment Preparation

The present area is most unsatisfactory. It has two old autoclaves which are in poor condition and do not have recording equipment. The area is open to dust and flies from the outside, there is no air conditioning nor hot water supply. Distilled water is transported from the still house almost 50 metres away. Vials for final products are washed in this department which is unsuitable and lacks the proper equipment.

It is recommended that this space be utilized to provide facilities for tank washing and equipment preparation. A proposed plan is at Appendix 14 and an equipment list is at Appendix 16. A properly designed area is needed to enable the large number of portable tanks to be efficiently cleaned, fitted and autoclaved. Cleaning, fitting and sterilization of bottles, filters and other laboratory equipment would also be done in this area which has the advantage of very close proximity to the diphtheria, pertussis, typhoid, cholera and new media making departments.

The building should be supplied with hot, cold and distilled water and adequate air conditioning. The distilled water could be supplied by transferring the still from the boiler house to the top of the Typhoid/Cholera building from which it could also supply the Tank Washing and Equipment Preparation area and also the Diphtheria and pertussis Departments.

7.4.7 Vaccine Formulation

The present system of formulating small batches (maximum about 45 l) of final product is very inefficient and larger batch sizes are needed. This would enable quality control requirements to be met by reducing the total number of batches to be tested and would ensure longer, more efficient dispensing runs.

Suggested batch sizes and number of batches to meet estimated annual requirements for the year 2000 are:

DPT Vaccine	150 litres	14 batches
DT Vaccine	150 litres	9 batches
T Vaccine	150 litres	9 batches

The number of portable 150 l stainless steel tanks required has been estimated on the assumption that:

(i) each batch is dispensed within 4 weeks of formulation;
(ii) batches are dispensed at an even rate through the year;
(iii) diluent is formulated in one tank and then filtered into another;
(iv) diluent is stored for up to 3 weeks to complete testing; and
(v) adjuvant is sterilized in tanks before antigens are added.

On this basis the number of tanks needed is 12. Up to 10 of these tanks could be in use at one time for vaccine, diluent and adjuvant.

It is considered that one properly designed formulation area would be sufficient for these vaccines. The present DPT formulation area is unsuitable for the large batch sizes envisaged because of lack of space and suitable access for tanks. To at least allow a sterility test to be completed before dispensing a batch, a larger capacity cold room is required, capable of holding at least 10 tanks, and antigen concentrates.

It is desirable that a male of good mechanical aptitude be given a period of training in all aspects of cleaning, fitting up and operating mixing tanks as well as product formulation and sampling.

If the recommendation (Section 7.4.9) that vaccines be dispensed in the Pharmaceuticals Division is accepted, the area on the third floor of the Typhoid-Cholera building could be re-designed as a formulation area. A proposed floor plan is given at Appendix 15 and an equipment list is at Appendix 16.

7.4.8 Final Container Dispensing

The present relatively new facility for dispensing and packing of multi-dose final container vials provides for up to four filling rooms where vials are filled semi-automatically and stoppered manually. Vials and stoppers are washed in an old building (see section 7.4.6) which is quite unsuitable for this task, being open to the dust and flies and not having a supply of hot water for washing and distilled water must be transported from the still house for rinsing. All washing and rinsing is a manual operation. The equipment available for sterilization of vials and stoppers is not completely satisfactory as recorders are not fitted to indicate that the required sterilizing conditions have been met.[6] With the expanding biological production leading to about 1.0×10^6 multidose vials being filled annually by the year 2000 even the present facility is inadequate.

In contrast to the multidose filling area, single dose ampoules of DPT are filled under ideal conditions in the Injections Section of the Pharmaceuticals Division. This area is extremely well set up for sterile dispensing. Ampoules are washed in a high speed automatic machine that is supplied with pyrogen free distilled water for final rinsing. Ampoules and stoppers are sterilized into the filling room via a double-ended autoclave and oven.

The filling room is supplied with HEPA filtered air and filling is carried out by automatic machine under a laminar flow hood. These are the conditions needed for vial preparation and filling of multidose Biological Division products.

As the filling of sterile parenteral products is an exacting and expensive process, the GPO should consider rationalizing its resources so that the organization's total requirement for sterile filling is carried out by the one group within the organization. The Injections Section of the Pharmaceutical Division already carries out a limited amount of manual vial filling and it is logical that it should do the dispensing of all biological products. They are experienced in the operation of high speed washing and filling machines and have a mechanic on the staff able to adjust and service the machines. There appears to be ample space in the equipment preparation area if an automatic vial washing machine is required, although the present ampoule washing machine is also capable of washing vials. Some additional capacity may be required for vial sterilization but the GPO has plans for the installation of a high capacity sterilizing tunnel. Vial filling is at present a manual operation in a room measuring 6 m x 5 m. This room would be of a suitable size for a high speed vial filling machine such as a Bausch and Strobel KSF 1020 with a maximum output of 3000 units per hour. This machine has the capacity to meet the filling requirements of the Biological Division in 6 months, leaving the remainder of the year for the filling of other products. The high speed automatic filling machine has the advantage of dispensing the proposed large batch size of 150 litres in 1 to 2 days with minimal risk of contamination. The vial filling room also adjoins a labelling and packing room, where vials could be conveyed from the filling machine for immediate labelling and if required, packing. Dispensed product could be returned to the Biological Division for cold storage until testing is complete and product is required for issue.

If the above proposal is not acceptable to the GPO then an area in the Biological Division is required, fitted out to the same standard as the Injections Section washing and filling area. Appendix 17 lists the equipment required for dispensing.

7.4.9 Engineering Services

The GPO has an Engineering Division to provide general maintenance and the backup support services necessary for the continued day-to-day operation of plant and equipment. In addition some divisions have a mechanic on their staff trained in the service and adjustment of key items of plant. The services of outside agencies are also called on. This applies particularly for the service of laminar flow equipment, some laboratory equipment and some refrigeration plant.

There does not appear to be a good preventative maintenance program, and this is particularly exemplified in the area of steam generation and distribution. A boiler, of 3000 kg/hour capacity, that is only 4 years old, now supplies all of the present steam requirements and is operating at half its capacity. Although there is a purification unit for treating the boiler feed water this is not used and as a result there is already apparently a build up of scale in the boiler. Maintenance of the steam distribution system also is not good. Large sections of pipe are unlagged and steam leaks were evident.

A reliable supply of good quality steam is a primary requirement in the manufacture of biologicals. The expansion of facilities in the Biological Division will place an even greater importance on the maintenance of the steam generation and distribution system. The feed water treatment unit should be brought into operation and the resins regenerated on a regular basis. The boiler water should be regularly checked for chemical content. The steam distribution system should be regularly checked, particularly the steam traps. It would be of benefit for an engineer from GPO to have some training in the operation and maintenance of steam generation and distribution plant. Training in the servicing of autoclaves and distilled water generating plant could also be included, as there appears to be some neglect in this area also.

Because of the climatic conditions in Bangkok, reliable air-conditioning is most important. The amount of air-conditioning and refrigeration plant at the GPO is already quite extensive and with the rebuilding program there will be an even greater demand for service in this area in the near future. There may need to be an increase in the number of refrigeration mechanics and further training may be needed particularly in the service of low temperature freezers and freeze drying plant.

7.5 Science Division, Queen Saovabha Memorial Institute (QSMI)

The Science Division was established in 1917 when the activities of the Pasteur Institute were transferred to the Thai Red Cross Society. The QSMI was established on its present site as headquarters of the Science Division in 1922. The Institute produces and tests a number of parenteral solutions, antivenoms and BCG vaccine.

I visited the QSMI on 18th April and discussions took place with Dr Praphan Phanuphak, Deputy Director Science Division and senior officers of the BCG department.

As far as I can establish from discussions with the Department of Communicable Diseases, the Department of Medical Sciences and the GPO, Thai policy is for vaccine production to be at the GPO for all EPI vaccines which are not obtained from overseas. The QSMI does not appear to share this view and is currently investing a considerable amount of money to upgrade its BCG production facility.

7.5.1 BCG Vaccine

This vaccine is produced in a separate two storey building which is about 30 years old. Culture work, harvesting, dispensing and quality control are done on the top floor. This area consists of three rooms which are air-conditioned with the temperature controlled to about 20°C. There is an entry lock and service corridor. The lower floor contains the freeze dryer and equipment washing and sterilizing facilities.

The QSMI has recognized the deficiencies of the old system of dispensing and freeze-drying and are currently upgrading the entire area.

Under the old system dispensing was done at an open bench by a semi-automatic process delivering 0.5 mL volumes (10 doses) into vials. Stoppers were inserted under a laminar flow cabinet. The stoppered vials were placed in sterile covered trays and transported through a hatch and down a lift to the floor below where they were placed on shelves which were then loaded into a Usifroid freeze dryer. This unit is very old and was not performing efficiently. It is housed in a room which has no entry lock or air-conditioning. The lowest temperature it was attaining was - 45°C, whereas originally - 60°C was reached regularly. I was unable to ascertain the level of vacuum achieved. The vials were held at - 45°C for 24 hours and then dried for 24 hours. After drying, the vials were removed to another unit in which they were again evacuated and the stoppers were pushed in to seal the vials. They were then capped manually.

Approximately 10% of the vials from each batch were discarded because of poor vacuum. The viable cell recovery rate and heat stability were very unsatisfactory no doubt due to inadequate drying.

The QSMI is refurbishing the area by the provision of new laminex bench tops, re-lining the walls and installing new ceilings about 2400 mm height below the old 3000 mm high ceilings. A new laminex flow cabinet has been installed and a new EF/10 freeze dryer is to be installed on the same level. Some aspects of the area could have been designed better and to bring it up to GMP standard, it would need:

(1) The air conditioning should be terminally HEPA filtered at the room ceilings.

(2) The new freeze dryer should be installed opening into the dispensing area. The media making should be transferred outside to the area set aside for the freeze dryer.

(3) The new autoclave should have been a pass through type from the media area to the production area. This is not a major problem as an excellent UV pass through cabinet has been provided.

(4) The building needs reticulated hot water and distilled water.

I recommend that UNIDO assist by providing a still which could be installed on the roof of the building, a hot water service and a washing machine for washing vials and rubber stoppers. An equipment list is at Appendix 18.

The QSMI has very satisfactory and relatively new animal housing for test animals and staff appear well qualified to carry out all the necessary testing, both in vivo and in vitro. Two members of the staff have been trained at the State Serum Institute, Copenhagen.

It is very evident that the QSMI has no engineering back up to ensure that refrigeration, vacuum equipment, autoclaves and other equipment are properly maintained, the end result being a slow deterioration in performance. This must be rectified by appropriate staffing.

In the long term, it is considered that the QSMI is not a viable institute as far as the production of vaccines is concerned. The very large investment in buildings, equipment and in the establishment of an Engineering Section to produce only BCG vaccine and comply with WHO requirements cannot be justified in view of the fact that the GPO has already got suitable buildings (completed or started) for most of this work, is better organized, is better equipped technically and has better engineering backup.

In the shorter term, say the next 10 years, it appears that the GPO will probably not be producing BCG vaccine and therefore the QSMI should receive support to ensure that satisfactory BCG vaccine is produced in Thailand during this period.

8. THE PHILIPPINES

8.1 Bureau of Research and Laboratories: Ministry of Health

Discussion was held with the Director: Dr V Basaca-Sevilla.

The Bureau is responsible for:

(a) the provision of quality vaccines for the EPI
(b) laboratory investigations on reported disease outbreaks
(c) registration and standardization of diagnostic laboratories and blood banks throughout the country.

The Director's office and the main diagnostic laboratories are in Manila. Vaccine production takes place at the Serum and Vaccine Laboratory which is situated at Alabang; approximately 25 kilometers from Manila.

The Ministry of Health decides the dose regimes for the vaccines and sets targets for the number of doses of each vaccine to be administered each year. At present, the target for DPT vaccine is only about 40% of the new borns and for TVA it is about 60% of the pregnant women. The plan is to provide full cover with all of the EPI vaccines by 1990.

The planned dose schedule is:

DPT Vaccine	3 doses
Tetanus Vaccine	2 doses (pregnant women)
BCG Vaccine	2 doses (3 months and at school age)
Measles Vaccine	1 dose
Poliomyelitis Vaccine	3 doses

It is worth noting that there is no requirement for DT Vaccine. I was assured that this is correct although it was agreed that it is most unusual. It would be worthwhile arranging for a qualified epidemiologist to discuss this point with the Ministry of Health.

The current birth rate is 2.4% and is expected to remain constant. The population will increase from the present 52×10^6 to 60×10^6 by 1990. The number of new borns in 1990 will be 1,440,000.

To give 100% cover in 1990, it will be necessary to administer the following numbers of doses:

DPT Vaccine	4.32×10^6
T Vaccine	2.88×10^6
BCG Vaccine	2.88×10^6
Measles Vaccine	1.44×10^6
LPV Vaccine	4.32×10^6

The cost of vaccine produced at Alabang was said to be:
BCG Vaccine 0.02 US$ per dose
T Vaccine 0.016 US$ per dose

These figures are much lower than those given for other countries however I discovered later that they do not include labour costs. All of the other vaccines are donated by UNICEF and Rotary International.

There is no national quality control of vaccines. Vaccines produced at Alabang are tested there to WHO standards while imported vaccines must be provided with a WHO protocol. The national cold chain has been tested and is considered to be satisfactory.

8.2 Quantities of Vaccines Needed in 1990

The numbers of doses to be administered are given in Section 8.1. Calculation of quantities required for this program is based on allowance for 20% losses during formulation, dispensing and testing and a further 25% (50% for BCG) for wastage and breakage during administration. For the virus vaccines, allowance is only made for administration losses as these vaccines will not be manufactured in the Philippines.

Requirements for 1990 are:

DPT Vaccine	$4.32 \times 10^6 \times 1.2 \times 1.25$	$= 6.48 \times 10^6$ doses
T Vaccine	$2.88 \times 10^6 \times 1.2 \times 1.25$	$= 4.32 \times 10^6$ doses
BCG Vaccine	$2.88 \times 10^6 \times 1.2 \times 1.5$	$= 5.18 \times 10^6$ doses
Measles Vaccine	$1.44 \times 10^6 \times 1.25$	$= 1.8 \times 10^6$ doses
LPV	$4.32 \times 10^6 \times 1.25$	$= 5.4 \times 10^6$ doses

8.3 Serum and Vaccine Laboratory: Alabang

Discussion took place with:

Dr O'Campo	Production Manager
Mrs B Ann	Head, Quality Control
Miss M Redimano	Head, Pertussis Laboratory
Mr S Banan	Head, Diphtheria Laboratory
Mrs P Lojo	Head, Tetanus Laboratory
Mr Savio	Head, BCG Laboratory
Mr San Juan	Mechanical Engineer.

This institute was established some time prior to 1940 under the Department of Science. In 1946 it was transferred to its present administration under the Ministry of Health. It produces a number of vaccines including Rabies Vaccine in addition to antisera and diagnostic reagents. Full quality control testing is carried out in a Section which is not responsible to the Production Manager but is responsible to the Director.

The institute is responsible for obtaining supplies of vaccine from overseas. It must ensure that they are correctly stored in cold rooms at Alabang and then distributes them throughout the country as required.

The Director, Dr Basaca-Sevilla informed me that she is due to retire towards the end of this year and the Ministry of Health is considering separating the activities of the Serum and Vaccine Laboratory from the other activities of the Bureau of Research and laboratories. If this happens, there would be a full time Director stationed at Alabang. I see this as a great improvement over the current arrangement as the current management system needs strengthening.

There has been a continuing policy to provide overseas training for staff whenever possible. All of the staff listed at the start of this Section have received the benefit of this scheme, in some cases more than once. Knowledge of and compliance with GMP is minimal, although they have recently received a copy of the Australian Code of GMP and there appears to be some intention to try to understand and begin implementing this.

8.4 BCG Vaccine

8.4.1 Production Method

The production strain is received each year as a seed lot from the State Serum Institute, Copenhagen. Production and harvesting is in accord with the widely used Copenhagen process. Harvests are suspended in 1.5% sodium glutamate and freeze dried in a Vertis Freeze Dryer in amber coloured ampoules which are sealed under vacuum in two Japanese ampoule sealing machines.

The viable count is about 0.4×10^6 colonies per dose. The vaccine containes about 2% moisture and is said to easily comply with the WHO heat stability best (recovery is about 40% after 1 month at 37°C compared to WHO requirement: 20%)

Full WHO testing is carried out and a Japanese consultant visits once per year to advise. Batch samples are regularly sent to Copenhagen for confirmatory testing.

8.4.2 Production Requirements

The quantity of vaccine needed in 1990 is calculated in Section 8.2.

Quantity of BCG Vaccine required = 5.18×10^6 doses.

8.4.3 Capacity

The Vertis freeze dryer can dry 7000 x 20 doses ampoules per batch. The number of batches required per year is $\frac{5,130,000}{140,000} = 37$

The contamination rate is less than 2%, so that the current capacity is more than adequate to meet the 1990 demand.

8.4.4 GMP

I was unable to enter the culture area for inspection. The building constructed in 1949 is a solid building but is in need of maintenance and rooms need to have a better finish. It was noted that there is water damage to the ceiling of the freeze dryer room caused by leakage of rain water. The department has its own steam operated still for making a small amount of distilled water, it has satisfactory gowning up entry areas and the flow of the culture work through the department, while not ideal, is acceptable. The department needs reticulated hot water and distilled water.

Horizontal rather than vertical laminar flow is used. Room air conditioners are installed in the wall of each room and are switched on when the rooms are in use. This is most unsatisfactory as the air is not filtered and must be a hazard to aseptic operations. The reasons given for its use instead of ducted HEPA filtered air conditioning were cheaper installation and cheaper to use.

I recommend that ducted air conditioning with terminal HEPA filtration should be provided. A complete list of equipment required and cost estimates are at Appendix 18.

8.5 Tetanus Vaccine

8.5.1 Production of Toxoid

This is produced by static culture using Mueller's beef heart medium yielding about 100 Lf/mL. Harvests are filtered through a Seitz filter press, formalin is added and then they are incubated until testing shows that toxoiding is complete.

Infected material must be transferred to another building for decontamination in an autoclave which is old, excessively corroded and in need of replacement.

The toxoid is transferred to another building for concentration via collodion coated candles and fractionation by ammonium sulphate precipitation. The ammonium sulphate is dialysed out via cellophane sacs and the purified toxoid is sterilized by Seitz filtration. The ultrafiltration and dialysis steps would be more efficiently performed with a membrane system eg. Hollow fibre filtration.

8.5.2 Production of Vaccine

The toxoid is adsorbed onto aluminium phosphate in another building. There is an autoclave for sterilizing the adjuvant and mixing takes place under laminar flow cover. There is a steam powered still for the production of a small amount of distilled water and a room air conditioner installed in the wall. There are no proper entry locks for staff and equipment.

8.5.3 Production Requirements

The quantities of vaccines needed in 1990 are calculated in Section 8.2.

DPT Vaccine 6.48×10^6 doses ($^1/_2$ mL)

T Vaccine 4.32×10^6 doses ($^1/_2$ mL)

DPT Vaccine contains 20 Lf tetanus toxoid per mL

T Vaccine contains 30 Lf tetanus toxoid per mL

DPT Vaccine requires $6.48 \times 10^6 \times 10$ Lf = 64.8×10^6 Lf tetanus toxoid

T Vaccine requires $4.32 \times 10^6 \times 15$ Lf = 64.8×10^6 Lf tetanus toxoid

Total requirement = 129.6×10^6 Lf purified tetanus toxoid.

8.5.4 Capacity

At present there are about 20 production batches per year by static culture of 50 litres of medium. The annual yield is about 50×10^6 Lf of purified toxoid. Clearly this is not nearly enough to meet the 1990 demand. This was recognized as far back as 1975 when a project began to upgrade the production system to the use of fermentor technology. The proposed fermentor technology and GMP are discussed in Section 8.7.

The required fermentor capacity can be calculated as follows:

Assuming 50% recovery of purified toxoid from toxin harvests, then require $2 \times 129.6 \times 10^6$ Lf toxin.

Assume 25 successful ferments per year, then each ferment must produce $\frac{2 \times 129.6}{25} \times 10^6$ Lf

$= 10.368 \times 10^6$ Lf toxin.

Assuming that tryptic digest of casein is used as the medium and the average yield of toxin is 50 Lf/mL, then:

Harvest volume required $\frac{10.368 \times 10^6}{50}$ mL

= 207,360 mL (208 litres)

There will be 10% processing loss of volume:

Harvest volume required = 208 litres x 1.1
= 228.8 litres

A fermentor needs to have a 250 litre capacity in order to meet the 1990 demand.

8.6 Diphtheria and Pertussis Antigens

8.6.1 Production

These are not produced at Alabang at present. It is proposed that future production will be done in fermentors. All required DPT vaccine is provided from overseas.

8.6.2 Production Requirement

The quantity of DPT vaccine required is calculated in Section 8.2.

DPT Vaccine 6.48×10^6 doses ($^1/_2$ mL)

The formulation contains 50 Lf diphtheria toxoid per mL and 40 opacity units ie. 40×10^9 pertussis organisms per mL.

Purified diphtheria toxoid required = $6.48 \times 10^6 \times 25$ Lf.
= 162×10^8 Lf

Pertussis required = 3240 litres at 40×10^9 organisms per mL.

8.6.3 Capacity

The capacity required for the proposed fermentor production can be calculated as follows:

(a) Diphtheria

Assuming 50% recovery of purified toxoid from toxin harvests, then require $2 \times 162 \times 10^6$ Lf toxin.

Assume 25 successful ferments per year, then each ferment must produce $\frac{2 \times 162}{25} \times 10^6$ Lf

= 12.96×10^6 Lf toxin

Assume harvest yield = 120 Lf/mL
∴ Harvest volume = $\frac{12960}{120}$ litres

= 108 litres recovered.

There will be a 10% processing loss of volume
∴ Harvest volume required = 108 x 1.1 litres
= 120 litres.

(b) Pertussis

Assume 85% recovery from ferment.
∴ Must harvest 3240 x 1.15 litres at 40 x 10^9 organisms/mL.
= 3726 litres.
Assume harvests are at 50 x 10^9 organisms/mL.
∴ Require $\frac{3726 \times 40}{50}$ litres of harvest

= 2981 litres
Assume 25 successful ferments per year, then each ferment must have a volume of $\frac{2981}{25}$ litres

≈ 120 litres.

8.7 Fermentors for Tetanus, Diphtheria and Pertussis

An overseas expert visited the Alabang Laboratories in 1975 and recommended that the technology should be modernized. In 1977 in line with the expert's recommendations, renovation of the Bacterial Vaccine Building for diphtheria and pertussis was commenced and a new Tetanus Laboratory was started. Due to lack of funds and other problems, this work was not completed until 1982.

Under this project new fermentors were provided as follows:

For tetanus: 1 x Tetano-Paljas: Capacity 1 x 140 litres
For diphtheria: 1 x Novo-Paljas: Capacity 2 x 40 litres
For pertussis: 1 x Novo-Paljas: Capacity 2 x 40 litres

(a) Capacity

Tetanus: The required capacity (Section 8.5.4) is 250 litres. To meet the 1990 program, another Tetano-Paljas fermentor with 140 litres capacity is needed.
Diphtheria: The required capacity (Section 8.6.3) is 120 litres.
Pertussis: The required capacity (Section 8.6.3) is 120 litres.

More fermentor capacity is needed to meet the program for diphtheria and pertussis and this could be adequately met by the provision of 1 x Novo-Paljas with 2 x 70 litre capacity. Fermentors will be in one room and could be used for either diphtheria or pertussis, ensuring sufficient capacity for both antigens.

(b) Problems Experienced with the Fermentors

None of the fermentors are currently operative for many reasons. After installation by Contact-flow, only the Pertussis fermentor has functioned at all. Problems have occurred because of constant break-downs which have resulted in spare parts being used up. The vibromixer on the tetanus fermentor is said to require a new assembly and electronic parts are said to be corroded. Automatic temperature recorders and pH adjustments do not function, nor does the oxygen controller. The Meta-filter for the filtration of diphtheria culture harvests does not function properly due possibly to the use of the incorrect grade of filter aid. The heat inactivator for pertussis is not working.

It will serve no purpose to chronicle these problems further here bearing in mind that construction of the new laboratories commenced in 1977 and installation of equipment took place around 1984. After a visit by a WHO consultant to commission the fermentors in early 1985, only one fermentor (Pertussis) was operative. I am unable to discuss the reasons for this but I suspect that poor quality services, eg. wet steam and air supply and fluctuating voltages may have contributed to the constant break-downs which occurred.

The Heads of each department have been overseas a number of times for fermentor training mainly at Bilthoven. They are confident that they can operate the machines providing all of the control systems function properly. Maintenance personnel are unable to give any assurance that they can repair the fermentors in the event of break-down even if there is a supply of spare parts.

It was noted that there was no autoclave in or near the culture room, so that infected material has to be transported elsewhere for decontamination. As with all other areas there is no proper entry facility for gowning up or for introducing large pieces of equipment such as portable tanks.

8.8 Measles and Poliomyelitis Vaccines

These are not produced in the Philippines but are provided by donation from UNICEF and Rotary International. WHO protocols are required with each batch and no quality control is carried out prior to distribution.

The Alabang laboratories have many problems at the moment with services, buildings and production of bacterial vaccines so that the feasibility of production of the virus vaccines or the dilution and dispensing of concentrates is not even being considered. I support this view wholeheartedly and believe it will be well into the future before such action can be contemplated. During the intervening period, the type of vaccine, particularly the poliomyelitis vaccine, may change and the population will increase to a level which could justify production from the economical point of view.

8.9 Dispensing Vaccines

BCG vaccine is dispensed and packed by hand into packs of 5 ampoules with diluents in the BCG laboratory.

An area has been renovated on the first floor of the Bacterial Vaccine Building for the purpose of formulating vaccines, dispensing, capping, labelling and packing. It has adequate cold room storage although neither room had temperature gauges or recorders. There is not proper staff entry for changing into sterile clothing nor is there appropriate provision for handling portable tanks. The dispensing room has a Bausch and Strobel machine under laminar flow cover. Staff did not appear to know how to operate this machine.

The quantities of vaccines required in 1990 (Section 8.2) are:

DPT vaccine	6.48×10^6 doses
T vaccine	4.32×10^6 doses

Assuming vaccines are formulated in 150 litre batch sizes, Alabang will need to make 22 batches of DPT and 15 batches of T vaccine per year.

Assuming that vaccine batches are sterility tested before dispensing, Alabang would required 5 portable tanks for formulation and 4 tanks for the preparation of aluminium phosphate adjuvant and diluent.

The Bausch and Strobel Machine will quite easily dispense 150 litres into 5 mL (10 dose) vials in 2 days, so that the machine has more than adequate capacity for the work although an accumulating table is needed to feed vials into the machine.

There is a Newman Labeller installed in the next room. It is new but is said not to work.

It was noted that the renovated area does not have an autoclave, a tank washing area nor an area for washing and sterilizing vials and stoppers. A hot air sterilizer and a number of appropriately sized stainless steel trays are needed. Similarly, the need to store packaging materials has been overlooked and there is no proper air conditioning with HEPA filtered air, nor is there reticulated hot water and distilled water.

Equipment which is required for a new facility for dispensing and packaging is at Appendix 19 and a floor plan for a tank washing area is at Appendix 14.

8.10 Quality Control

Vaccines can be tested to WHO requirements at Alabang. The Head of the department, Mrs B Ann is very competent and well trained. She has gained quality control experience both at the National Biological Standards Laboratories and at the Commonwealth Serum Laboratories in Australia. The work at Alabang is conducted in the old smallpox vaccine building which is isolated from all others and fairly delapidated. Equipment and small animal housing appears adequate. Several years ago, it was decided to build a new Quality Control building. Construction commenced and concrete slabs were poured at ground and first floor level. The work was then abandoned due to lack of finance and has subsequently begun to decay.

8.11 Engineering Department

This Department is badly run down and has not got any proper buildings for its staff. It lacks equipment, funding and expertise as a result of which the provision of all of the various services required by biological manufacturing laboratories is unsatisfactory.

Some comments on the services are:

Electricity: The supply from the Manila Authority is subject to voltage fluctuations and regular break-downs requiring the use of a stand-by generator.

Steam: Capacity is only about $3^1/_2$ tones which is probably not enough if the laboratories become fully operational to GMP standards. Steam lines are not insulated, leaks were evident, pressure fluctuates and the steam is not dry.

Air: Compressed air is too wet and requires dehumidification in-line.

Water: Ground water is used and the current pump is inadequate and in need of either repair or replacement. For most purposes, the water should be sand filtered and treated with resins to remove anions and cations before use. This is not done.

Hot Water: Should be reticulated throughout the laboratories, but is not.

Distilled Water: A few small steam heated stills are in use. Supply is very inadequate and should be reticulated throughout the laboratories.

Air Conditioning: Wall units providing unfiltered cool air are installed in production areas. These are contrary to GMP and should be replaced by ducted air conditioning with terminal HEPA filtration.

8.12 The Future of the Alabang Laboratories

The whole operation at Alabang has been allowed to deteriorate to a stage where is appears to be only barely viable. I do not propose to attempt to apportion blame for this, but I will try to comment on what I see as the essential requirements needed to revive this institution and to make it into a manufacturing facility which can produce bacterial EPI vaccines in compliance with GMP and to WHO standards.

The Bacterial Vaccine Building and BCG Laboratory appear to be sound structures but require re-designing inside, refurbishing and some repair. An engineer with building expertise needs to be consulted on this matter. All other production buildings on the site should be replaced. This proposal would require a massive injection of funds and could only occur with the complete commitment of the Government of the Philippines to wanting to ensure the future of Alabang and to actively participating in planning and funding that is essential.

Strong management would be needed on site and the role of Director should be separated from the Bureau of Research and Laboratories and should be stationed at Alabang.

The new construction program and the service problems (Section 8.7) which must be addressed, will need the expertise of a professionally qualified engineer. Such a person should be appointed as Chief Engineer.

Management, with help from outside experts, should plan a program of construction and renovations, estimate costs and establish priorities. It seems to me that the first priority would be to upgrade the Engineering Section and to take all of the necessary steps to ensure that it can supply satisfactory services.

A new Tetanus Building is needed and a proposed plan of a facility which would house production up to the completion of toxoid purification is given at Appendix 11 and a list of equipment required is at Appendix 20.

The renovation of the Bacterial Vaccine building should provide a portable tank washing and equipment preparation and sterilization area. A proposed floor plan is at Appendix 14 and an equipment list for vaccine formulation and tank washing is at Appendix 19.

The diphtheria-pertussis area should be re-designed and furnished with a pass through autoclave, entry locks for staff and ducted HEPA filtered air conditioning. Additional equipment required is at Appendix 21. The new design of this building needs to be carefully planned. It is possible that there is not sufficient area to house both diphtheria-pertussis production and equipment preparation along with dispensing and packaging. Once this area is re-designed, and all of the engineering services have been rendered satisfactory, arrangements should be made for an expert from Contact-flow, Holland to visit Alabang to supervise the repair and installation of two existing Novo-Paljas fermentors. An estimate of costs has not been made but it appears certain that any involvement by Contact-flow at this stage will be charged for by them. This will also be required for the Tetano-Paljas fermentor in the new Tetanus Building. The new Chief Engineer should actively participate in this work and also visit Contact-flow for a period of training. He must be able to maintain and repair this equipment if necessary and should ensure that there is an adequate supply of spare parts for the purpose. I am assuming that current staff will then be able to operate this equipment satisfactorily, but if this is not so the first preference is to send an expert from Bilthoven to give further training on site.

Finally, when all of the equipment is operational the additional fermentors (Section 8.7a) should be obtained and installed.

The dispensing, packaging area must be re-designed and provided with equipment as listed at Appendix 19. The vaccine formulation area adjacent to this also needs re-designing with provision of proper entries for portable tanks and a sterile gowning lock.

As a lower priority, Quality Control needs new premises. The first priority for this department is for it to be trained in all aspects of GMP so that it can participate in staff training and carry out regular quality audits to ensure compliance with the Code throughout the Laboratories. They have recently received a copy of the Australian Code of GMP which will be used to begin staff training.

Equipment for Diphtheria Department - Bio Farma

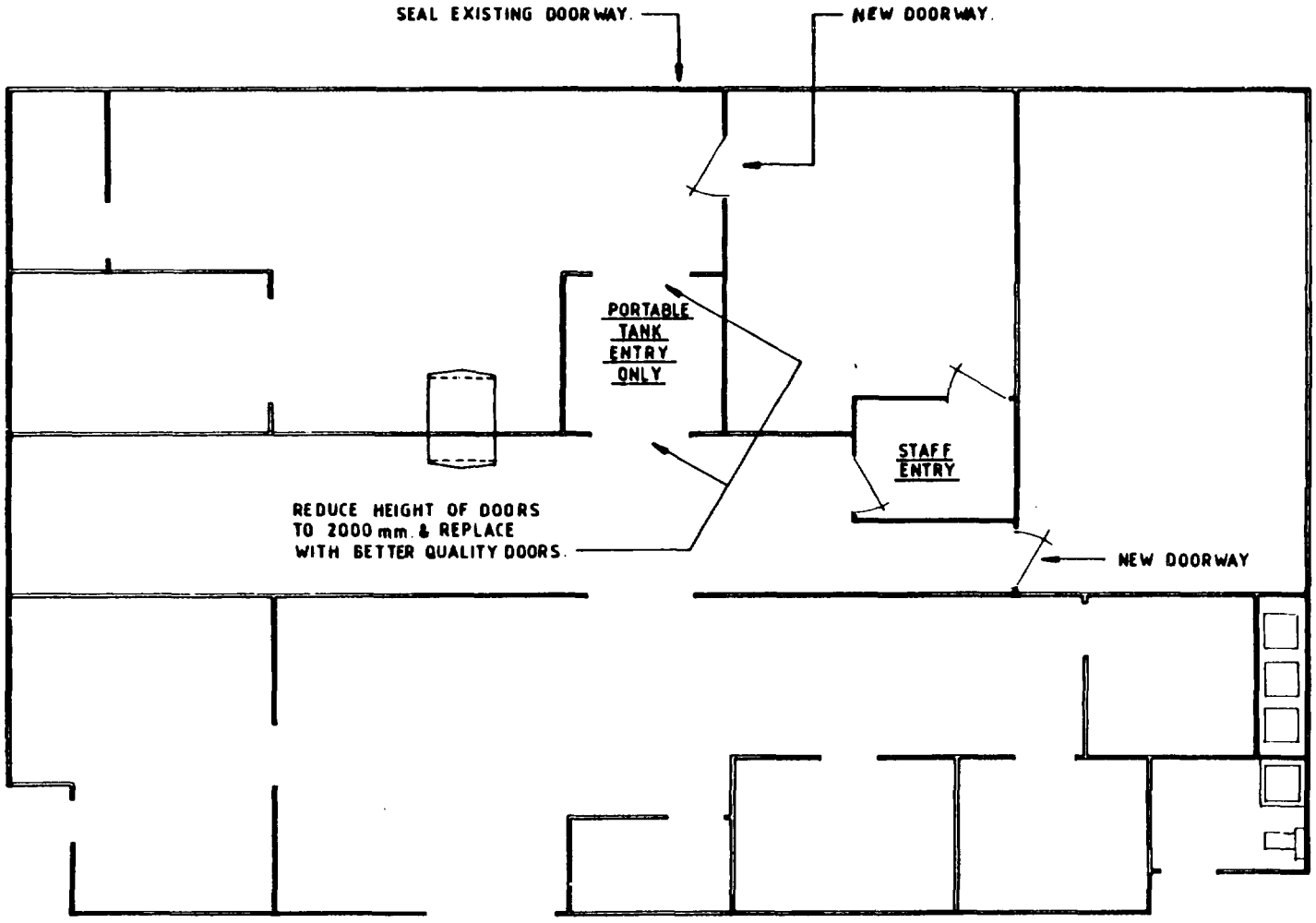
Item	Quantity	Cost (US$)
Vertical Laminar Flow Cabinet 1.8 M	1	7,000
Autoclave (pass through/jacketed, fitted with vacuum system and automatic manual control.	1	80,000
Air conditioning plant with terminal HEPA filtered air.	1	65,000
		152,000

Equipment for Pertussis Department - Bio Farma

Item	Quantity	Cost (US$)
Vertical Laminar Flow Cabinet 1.8 M	1	7,000
Autoclave (pass through/jacketed, fitted with vacuum system and automatic manual control.	1	80,000
Air conditioning plant with terminal HEPA filtered air.	1	90,000
		177,000

Equipment for Tetanus Departmert - Bio Farma

Item	Quantity	Cost (US$)
Vertical Laminar Flow Cabinet 1.8 M	1	7,000
Incubator	1	3,500
Air conditioning plant with terminal HEPA filtered air.	1	45,000
		55,500



TETANUS LABORATORY MODIFICATIONS.

(Bio – Farma : Bandung.)

SCALE 1:100

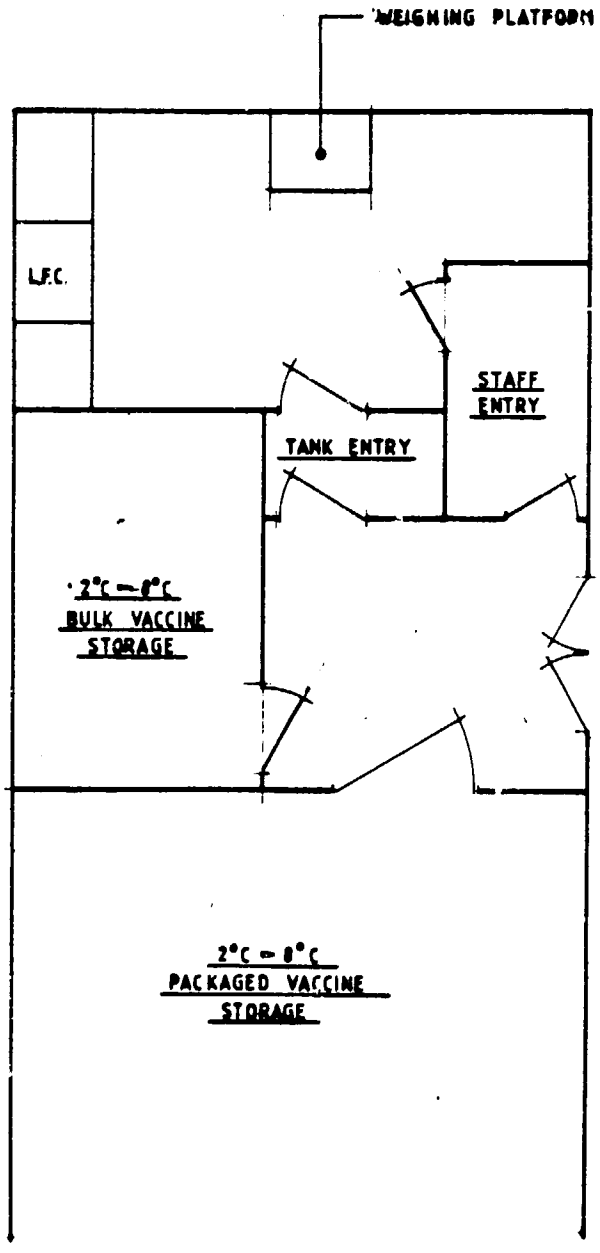
Equipment for Vaccine Formulation - Bio Farma

Item	Cost (US$)
Vertical Laminar Flow Cabinet 1.8 M	7,000
Weighing platforom 500 kg capacity	5,000
Prefabricated cold rooms	35,000
Air conditioning plant with terminal HEPA filtered air	8,000
	53,000

Equipment for Dispensing - Bio Farma

Item	Cost (US$)
Still for distilled water 200 litres/hour	40,000
Sand filter and demineralizer	17,000
	57,000

APPENDIX 4.



PROPOSED FLOOR PLAN
(Vaccine Formulation Bio-Farma.)

Scale 1:100

PRODUCTION OF MEASLES VACCINE AND POLIO VACCINE IN INDONESIA

A FEASIBILITY STUDY BY A JOINT WHO/UNICEF/USAID CONSULTING TEAM

INTRODUCTION

- Under the auspices of WHO, UNICEF and USAID a team of international experts was gathered to undertake a "Feasibility Study regarding the Production in Indonesia of Polio Vaccine and Measles Vaccine".

- The Team visited Jakarta and Bandung from September 10 to 20, 1984.

- This Report gives the Team's findings and recommendations

EXECUTIVE SUMMARY

We studied the technical and economic feasibility of Biofarma producing Measles and Polio Vaccines in Indonesia.

We recommend a step-wise approach to basic production of these two vaccines, as follows:

1) Increase the processing of Polio Vaccine from imported bulk concentrates from the current 30% of the amount used to 100%;

2) Process Measles Vaccine from imported bulk concentrate;

3) Introduce basic production of Measles Vaccine; and

4) Move to basic production of Polio Vaccine.

This step-wise approach allows for gradual transfer and assimilation of production skills, moving from less to more difficult types of vaccine technologies. It also allows for re-appraisal of the recommended programme on actual performance.

We estimate that the total capital investment to achieve basic production of both vaccines would be approximately $5.3 million, excluding the cost of technology transfer.

Our estimate of the cost per dose is $0.12 for Measles Vaccine and $0.04 for Polio Vaccine. These estimated domestic production costs appear to be of the same order as those of vaccines imported into Indonesia.

Concurrent with the development of production capabilities at Biofarma, the capability of the national control laboratory must be strengthened to assure that vaccines will meet WHO specifications.

Subject to the acquisition of production technology from an outside source, coupled with the provision of new facilities and considering the present level of expertise at Biofarma, we are confident that the basic production of Measles Vaccine and Polio Vaccine in Indonesia has an excellent chance of success.

TERMS OF REFERENCE FOR THE STUDY

- The Team spent approximately five days acquainting itself with the prevailing local conditions and obtaining definitions of the Terms of Reference for the Study.

- Following discussion with the Secretary - General of the Kementerian Kesehatan, the Director - General of Communicable Disease Control and other memebers of the Ministry of Health the following parameters were established:

  . the products to be considered are:
  Measles Vaccine (Live) and
  Poliomyelitis Vaccine (Oral);

  . the maximum annual production capacities are to be:
  Measles Vaccine - 7 million doses
  Polio Vaccine - 20 million doses.

  . the options available to Indonesia are to be indicated;

  . general recommendations are to be made concerning the choice of options, methodologies and technologies to be employed;

  . estimates are to be prepared of the approximate costings of the various options (wherever practical) broken down into individual components (such as buildings, equipment, etc);

  . approximate production costings/dose are to be calculated;

  . estimated manpower requirements are to be indicated.

ASSESSMENT OF CURRENT SITUATION

1. Demographics of Indonesia

- Estimated total population: 160,000,000
- Birth-rate: 3.3 to 3.5%
- Number of New Borns Annually: 5.2 to 5.6 million infants.

2. Major Causes of Infant Deaths

- Diarrheal diseases
- Acute respiratory infections
- Tetanus

3. Estimated Immunization Coverage

- For diphtheria, tetanus and whooping cough - using DPT Vaccine 40%

- For tuberculosis-using BCG Vaccine 80%

- For poliomyelitis-using Polio Vaccine less than 10%

- For Measles-using
  Measles Vaccine — less than 10%

4. Vaccine Demand

- Current demand for vaccines is determined largely by Government purchases; the private market demand is small.

- REPELITA IV, the Indonesian five-year plan that began in 1984/85 states as one of its aim a minimum of 65% overall immunization coverage.

- Eventually the Government intends to achieve 95% average.

5. Infra-Structure for Vaccine Distribution

- Biofarma - Bandung is responsible for all imports and production of biologicals, both for Government and private market use.

- Biofarma distributes to the Propinsis, which in turn send it to the Kabupatens from which it goes to the Kecamatans.

- Actual immunization is effected through the Puskesmas (Community Health Center).

6. Biofarma - Bandung

- Biofarma is the organization in Indonesia manufacturing and importing biologicals.

- Biofarma is a Government entity, responsible directly to the Minister of Health. However it operates as a private concern and pays taxes applicable to a private Indonesian concern.

- Currently Biofarma manufactures the following:
  - Cholera Vaccine
  - Typhoid Vaccine
  - TAB Vaccine
  - Cholera - TAB Vacine
  - Pertussis Vaccine
  - Plague Vaccine
  - Polyvalent Staphylococcal Vaccine
  - Polyvalent Streptococcal Vaccine
  - BCG Vaccine
  - Diphtheria Toxoid
  - Tetanus Toxoid
  - DT Toxoid
  - DPT Vaccine
  - DP Vaccine
  - Rabies Vaccine
  - Oral Polio Vaccine (from imported concentrates)

- Diphtheria Antitoxin
- Tetanus Antitoxin
- Rabies Antitoxin
- Infusion Fluids (6)
- Diagnostics (8)

- The Team visited Biofarma and was extremely impressed with the level of expertise, facilities and housekeeping as applied to products currently being manufactured.

- Biofarma has essentially no expertise nor facilities for the large-scale production of Measles and Polio Vaccines and limited expertise and facilities for the control of these two products.

STUDY ASSUMPTIONS

The following major assumptions have been made:

- Biofarma will continue to be the sole source in Indonesia of all human vaccines.

- Technology for basic production of Measles and Polio Vaccines will have to be obtained in one form or another from source(s) outside Indonesia.

- The annual consumption of Polio Vaccine will eventually reach 20,000,000 doses and that of Measles Vaccine 7,000,000 doses.

- **The Polio Vaccine required will be the Oral Live Vaccine type rather than the Injectable Killed Vaccine type.**

- **Production and quality control (Q.C.) facilities will conform to the pertinent WHO specifications. The final products will also conform to the appropriate WHO product specifications.**

- **Indonesia will have a adequate supply of cynomolgus monkeys.**

- **All estimates have been made on maximum capacity of 20 million doses Polio Vaccine and 7 million doses Measles Vaccine.**

- All figures stated in this Report are estimates only, based on 1984 price. Before proceeding with implementation of any of the options, a detailed, up-to date costing should be undertaken.
- The price of technology transfer has not been included in the Report as the possible configurations and components of technology transfer arrangements are highly variable. This cost will have to be determined by negotiations between Biofarma and potential sources it such technology.
- It is noted that in order to comply with the requirements of WHO the establishment of a comprehensive, independent national control facility must precede the manufacture of biological products. It is therefore assumed that if a decision is taken to initiate the production of Measles and/or Polio Vaccines in Indonesia, the Q.C. capability of the Food and Drug Directorate will be increased appropriately.
- As instructed by the Director - General of CDC the cost of money has not been included.

MAJOR OPTIONS

Summary of Option

Option I - Import Polio Vaccine bulk concentrate and import Measles Vaccine in final containers.

Option II - Import both Polio and Measles Vaccine bulk concentrates

Option III - Import Polio Vaccine bulk concentrate and basic production of Measles Vaccine

Option IV - Basic production of both Measles and Polio Vaccines sequentially

Option V - Basic production of both Measles and Polio Vaccine simultaneously

- All of these Options can be pursued and with the exception of Option V none are exclusive of one another.

- In arriving at our final recommendation we considered a large number of factors such as cost, technical expertise, chances for success (or failure) and the often stated objective of almost all of the Indonesian officials to make Indonesia independent of outside sources to Polio and Measles Vaccines.

- Our analyses, although only estimates, indicate that the cost of Vaccine produced in Indonesia could be competitive with currently purchased vaccine once facilities and technologies are in place.

- On the other hand opportunities may exist for reductions in the purchase price of vaccines from outside sources.

RECOMMENDATIONS CONCERNING THE OPTIONS

Step 1:

- Currently Biofarma purchases 30% of Polio Vaccine as bulk concentrate for dilution and filling and 70% as final filled containers.

- As the initial step we recommend that all Polio Vaccine be purchased as bulk concentrate for finishing at Biofarma (Option I).

- We also recommend that improvements in long-range planning coupled with increased purchase volumes might be used as factors in negotiating lower prices for both vaccines.

Step 2:

- Measles Vaccine currently is purchased in final containers.

- It is recommended that Measles Vaccine be bought as bulk concentrate for filling, freeze-drying and finishing (Option II).

- Although this may not be any savings, this would provide Biofarma with valuable additional technical experience in freeze-drying and final container Q,C.

- Financial outlay for processing of Measles Vaccine bulk concentrate represents a very significant portion of the total outlay required for basic production, so that the additional outlay required for Step 3 is greatly reduced.

Step 3

- We recommend that Biofarma introduce the basic production of Measles Vaccine while continuing to finish Polio Vaccine from bulk concentrates. (Option III).

- Having already introduced the processing of Measles Vaccine from bulk concentrate in Step 2, the major outlays for equipment and facilities will have already been made.

- Basic production of Measles Vaccine requires simpler production and control methods than that of Polio Vaccine, and thus would lead to greater possibility of initial success.

Step 4

- Once the Measles Vaccine basic production programme has been successfully completed, Polio Vaccine basic production should be introduced. (Option IV).

- We strongly recommend that Measles and Polio Vaccines basic production not be undertaken simultaneously (Option V). The resources and facilities at Biofarma or likely to be available to Biofarma are in our view, inadequate to handle both vaccine programmes simultaneously.

- Step 1 could be initiated immediately only requiring additional filling equipment.

- Initiation of Step 2 will need the provision of suitable space and services, and purchase and installation of filling and freeze-drying equipment for Measles Vaccine.

- We caution Biofarma to obtain outside expertise preferably from the transferor of Measles Vaccine technology prior to purchase and installation of the equipment.

- It is important to assure the compatibility of the equipment with the final facility design and production process.
- A proposed time-table for Steps 3 and 4 can be found later in this Report.

RECOMMENDED PRODUCTION TECHNOLOGY

Introduction

- It should be emphasized that the undermentioned recommendations are those of the Team but that final choice of technology has to be made by Biofarma and the transferor of technology.

- It is anticipated that the technology adopted will be similar or identical to that used in many major production laboratories. The technology will have been proven in past experience and it is anticipated that this technology will not be displaced by an improved technology in the forseeable future.

- Stress is laid on the absolute need for the transferor of technology to supply Biofarma not only with expertise (see "Recommended Methodology of Project Execution") but also most importantly, with seed strains, cell substrates and continuing technical support.

Measles Vaccine Technology

- Chick embryo fibroblasts should to be used to grow a strain of measles approved by WHO.

Oral Polio Vaccine Technology

- Primary monkey kidney cells should be used, with the Sabin seed strains approved by WHO.

RECOMMENDED METHODOLOGY OF PROJECT EXECUTION

- It is essential for Biopharma to first make arrangements with a current, large volume producer of Measles Vaccine for the transfer of the necessary technology and know-how, and for Polio Vaccine at some later date.

- For technical reasons and as a matter of practicality the purchase of technology should go hand in hand with the purchase of bulk concentrates from the same source. This is essential as production technology of one manufacturer may not be appropriate to process bulk concentrates from another producer.

- Transfer of technology to Biofarma should as a minimum, cover the undermentioned major items. It is of course understood that for all of these the transferor of technology will work in close collaboration with Biofarma.

a. General Consulting.

. scheduling of all major tasks and the monitoring thereof;
. lay-out design of the facilities and collaboration with local architect/contractor;
. regular inspection of the building of the facilities;

- selection of the required equipment and production components and potential sources thereof;
  purchase of the equipment and pre-shipment inspection thereof (if so desired);
- shipment and insurance of equipment and production components (if so desired);
- supervision of the installation of all static equipment;
- validation of buildings and equipment;
- trial production runs;
- monitoring of the manufacture of the "consistency" production runs;
- supply of all essential manuals;
- assistance in obtaining product "registration" from the appropriate local authorities;
- "trouble-shooting".

b) Training

- training of selected Biofarma personnel in premises of the transferor of technology in all required aspects of production, Q.C., maintenance, record-keeping etc;
- assistance in the training of other Biofarma personnel in Bandung.

c) Duplicate Q.C.

- Duplicate testing by the transferor of technology during certain stages of production until both parties are satisfied that production and Q.C. are running satisfactorily.

MAJOR REQUIREMENTS AND ESTIMATED COSTS FOR PROJECT EXECUTION

1. Site

- Sufficient ground is available at Biofarma to accommodate buildings for production and quality control of Measles Vaccine and Polio Vaccine and related requirements.

- No cost for land has been included in the calculations.

2. Buildings

- For production and quality control it is proposed that one building be erected consisting of the following:

  . quality control facilities for both Measles Vaccine and Oral Polio Vaccine (Space A);

  . production facility for Measles Vaccine (Space B);

  . central facility for washing and sterilizing, media preparation, water distillation, inspection, packaging, warehousing which can serve both Measles and Polio (Space C);

  . production facility for Oral Polio Vaccine (Space D).

- Such a building can be erected in two stages: Space A, B and C first with Space D later.
- In addition, before Polio Vaccine production can be commenced a separate Animal Holding Facility will have to be erected (Space E).

- The undermentioned figures for area and approximate building costs are approximations only and must be refined jointly by Biofarma and the transferor of technology.

Designated Space	Area in Sq. Meters	Cost/ Sq. M* (Rp.000's)	Estimated Total Total cost (Rp.000's)
A	230	250	57,500.0
B	450	250	112,500.0
C.	550	250	137,500.0
Sub total I	1.230		307,500.0
D	550	250	137,500.0
E	550	200	110,000.0
Sub total II	1.100		247,500.0
Grand Total	2,330		555,000

* The cost/sqm was estimated by Dr. Nasution of Biofarma and does not include airconditioning/ purification

3. Services

- No provisions have to be made for the generation of either steam or electricity as Biofarma have sufficient spare capacity.

- Water is also in abundance apparently, but provision will have to be made for deionization and distillation facilities.

- Gas will have to be purchased in bottles (LPG) and compressors will have to be installed for compressed air.

4. Estimated Equipment Costs

(includes airconditioning/purification)

4.1 Q.C, Measles production and Services	Rps. 000's	US$ 000's
Space A (Q.C. Facilities)		105.0
Space B and C (Measles Production and Central Services		1,600.0
Freight and Insurance		170.5
Duty, Sales Tax, VAT	600,160.0	
Installation and Validation		85.0
Sub Total I	600,160.0	1,960.5

4.2 Polio Vaccine

Space D (Polio Production)		1,300.0
Freight and Insurance		130.0
Space E (Animal House)		120.0
Freight and Insurance		12.0
Duty, Sales Tax and VAT	449,840.0	
Space E (Animal House locally made equipment)	30,000.0	
Installation and validation		71.0
Sub Total II	529,840.0	1,633.0
	(Rps.000's)	(US$000's)

4.3 Grand Totals	Rps.1,130,000.0	$3,593.5

5. Animals

- In this case "animals" refer only to the monkeys required for Polio Vaccine production and quality control.

- Other animal requirements are small and can be serviced by Biofarma's existing animal facilities.

- For full Polio Vaccine production/quality control it is estimated that the following number of monkeys will be required annually:
  - production: 140 "clean" monkeys
  - quality control: 430 monkeys (not necessarily "clean")

  (The quantity for production may be over-stated)

- Assuming a 50% rejection rate of incoming monkeys the total estimated annual requirements are:

. production	280 animals
. quality control	430 animals
	710 animals

- It has been assumed that monkeys will be purchased from local sources at a laid-down price in Bandung of Rps. 30,000 each.

- Hence, total annual costs (in Rps. 000's):

  710 x Rp. 30 = Rps 21,300.0.

  (It has been taken that this figure will allow for feeding etc of the animals as well)

6. Production Components

- These comprise all chemicals, fetal calf serum, filters etc required for production and quality control.

- Estimated costs.

	Rps. 000's	US$000's
Measles Production		225.0
Quality control		50.0
Duty, Sales Tax, VAT	27,500.0	
Sub total I	27,500.0	275.0
Polio Production		225.0
Duty, Sales Tax, VAT	22,500.0	
Sub total II	22,500.0	225.0

7. Vials

7.1 Measles Vaccine

- It has been assumed that locally made vials will be used for the diluent and imported ones for the vaccine itself.

- It has further been assumed that approximately 15% breakage and discards will be experienced.

- Estimated costs:

	Rps.000's	US$000's
Diluent vials		
805,000 x Rps.49	39,445.0	
Vaccine vials		
805,000 x US$0.12		96.6
Duty, sales tax, VAT	20,500	
Total	59,945	96.6

7.2 Polio Vaccine

- It has been assumed that locally made vials will be used.

- Breakage and discards to be the same as for Measles Vaccine.

- Estimated costs	Rps.000's
2,300,000 x Rp. 32	73,600.0

8. Seals

- Locally made ones will be used

- Estimated cost -	Rps.000's	US$000's
Measles diluent		
805,000 pieces	3,220.0	-
Measles Vaccine -		
805,000 pieces	3,220.0	-
VAT	161.0	
Sub Total I	6,601.0	-
	=======	
Polio Vaccine - 2,300,000	9,200.0	-
VAT	230.0	
	9,430.0	
	=======	

9. Stoppers

- Imported stoppers will be employed

- Estimated costs	Rps.000's	US$000's
Measles Diluent 805,000		4.8
Measles Vaccine 805,000		4.8
Duty, Sales Tax, VAT	2,040.0	
Sub Total Measles	2,040.0	9.6
	=======	====

Polio Vaccine 2,300,000		13.8
Duty, Sales Tax, VAT	2,932.5	
Sub Total Polio	2,932.5	13.8

10. Dropper/Stoppers for Polio Vaccine

- Imported Dropper/Stoppers will be used, as is the case currently.

- Estimated costs	Rps.000's	US$000's
2,100,000 stoppers		42.0
Duty, Sales Tax, VAT	8,925.0	
	8,925.0	42.0

PERSONNEL

- It is considered that the following minimum staffing is required:

	Sr. Scientist	Engineer	Sr. Technician	Technician	Attendant
Quality Control*	1		1	5	1
Maintenance		1			
Measles production	1		5	14	3
Sub Total I	2	1	6	19	4
Polio production	1	-	5	14	3
Animal House	1		1	4	2
Sub Total II	2	-	6	18	5
Grand Totals	4	1	12	37	9

* For Polio Vaccine Q.C. a consultant histopathologist and two technicians will be required over and above the abovementioned staffing.

- Annual salary costs have been taken at the undermentioned figures which were supplied by Dr Nasution of Biopharma and are expressed in Rps. 000's:

  . Sr. Scientist 6,000.0 + 40% fringe = 8,400.0

  . Engineer (est) 4,000.0 + 40% fringe = 5,600.0

  . Sr. Technician 3,000.0 + 40% fringe = 4,200.0

  . Technician 2,100.0 + 40% fringe = 2,940.0

  . Attendant 1,800.0 + 40% fringe = 2,520.0

- Consequently the estimated annual salary costs calculate out as follows (in Rps. 000's):

  . Measles production and Q.C Rps. 113,540.0

  . Polio production and Animal house Rps. 107,520.0

FINANCIAL PROFILE

Notes:

- All figures stated are estimates only and must be refined jointly by Biofarma and the transferor of technology prior to proceeding with project execution.

- Estimated 1984 cost served as a basis.

- No allowance has been made for inflation.

- Cost of money has not been taken into account

- Direct production costs only have been calculated. None of Biofarma's overhead charges have been included.

- Depreciation has been calculated straight line 10 years for equipment and 50 years for buildings (as requested by Dr Nasution of Biofarma).

- Cost of technology transfer has not been included (see "Assumptions").

Estimated Direct Production Cost Measles Vaccine

	Rps.000's	US$000's
Depreciation Buildings	6,150.0	-
Depreciation Equipment	60,016.0	196.0
Production Components	27,500.0	275.0
Vials	59,945.0	96.6
Seals	6,601.0	-
Stoppers	2,040.0	9.6
Salaries	113,540.0	-
	275,792.0	577.2

No. of Doses produced: 7,000,000

Cost per Dose	Rps.39.40	US$0.0825

Total cost/dose

(1 US$=Rps.1000) Rps.121.00

Estimated Direct Production Costs - Oral Polio Vaccine

	Rps.000's	US$000's
Depreciation Buildings	4,950.0	-
Depreciation Equipment	52,984.0	163.3
Monkey Supply	21,300.0	-
Production Components	22,500.0	225.0
Vials	73,600.0	-
Seals	9,430.0	-
Stoppers	2,932.5	13.8
Droppers	8,925.0	42.0
Salaries	107,520.0	-
	424,841.5	444.1
No. of Doses produced: 20,000,000		
Cost per Dose	Rps.15.21	US$0.0222
Total cost/dose	Rps.37.41	
(1 US$=Rps.1000)	=========	

ANTICIPATED TIME FRAMES

Note:

- The undermentioned Time Table assumes that Option III will be executed with Option IV commencing in Year 4.

- Again it has to be stressed that Biofarma should redefine this Time Table with the transferor of technology.

Year 1

- Planning of Buildings for Measles Vaccine and Q.C;
- Erection of Buildings for Measles Vaccine and Q.C;
- Selection and Ordering of Equipment for Measles Vaccine and Q.C;
- Overseas training of Biofarma's Senior staff in "Intermediate" production and quality control of Measles Vaccine.

Year 2

- Training of staff in Bandung in "intermediate" production and final container quality control of Measles Vaccine;
- Installation and Validation of equipment;
- Validation of buildings;
- Production of Measles Vaccine from imported concentrates;
- Overseas training of Biofarma's senior staff in basic production and quality control of Measles Vaccine.

Year 3

- Training of staff in Bandung in basic production and quality control of Measles Vaccine;
- Production of Measles Vaccine from imported concentrate until basic production is running satisfactorily.

Year 4

- Planning of buildings for Oral Polio Vaccine;
- Erection of buildings for Oral Polio Vaccine;
- Selection and ordering of equipment for Polio Vaccine;
- Overseas training of Biofarma's senior staff in basic production : Oral Polio Vaccine;
- Basic production of Measles Vaccine continues.

Year 5

- Training of staff in Bandung in basic production and quality control of Oral Polio Vaccine;
- Installation and Validation of equipment;
- Validation of buildings;
- Biofarma's production of Oral Polio Vaccine from imported concentrates is moved from current facility to new building and continues until basic production of Oral Polio Vaccine runs smoothly;
- Basic production of Measles Vaccine continues.

Year 6

- End of Prcject.

SUMMARY OF ESTIMATED CAPITAL COSTS BY YEAR

Year	Details	Rps000's	US$000's
1.	Building for Measles Production and quality control	307,500.0	
	Downpayment for Measles/Q.C. Equipment (33%)		568.0
		307,500.0	568.0
2.	Remaining Measles/Q.C Equipment Costs		1,137.0
	Freight/Insurance Equipment		170.5
	Duty, Sales Tax, VAT on Equipment	600,160.0	
	Installation and Validation Equipment		85.0
		600,160.0	1,392.5

4. Buildings for Oral Polio Vaccine Production	247,500.0	
Downpayment for Equipment for Oral Polio Vaccine Production and for Animal House		473.0
	247,500.0	473.0
5. Remaining Polio/Animal House Equipment Costs	30,000.0	947.0
Freight/Insurance Equipment		142.0
Duty, Sales Tax, VAT on Equipment	499,840.0	
Installation and Validation Equipment		71.0
	529,840.0	1,160.0
1 - 5 GRAND TOTAL	1,685,000.0	3,593.5

NAMES OF TEAM MEMBERS

Name	Country	Agency
Dr. Miroslav Beck (Chairman)	Yugoslavia	WHO
Mr. Robert E. Binnerts	Canada	USAID
Dr. Murray S. Cooper	U.S.	USAID
Dr. Alan Gray	U.S.	USAID
Dr. Stephen J. Lerman	U.S.	UNICEF
Dr. David Magrath	Britain	WHO

LIST OF PERSONS MET BY THE TEAM

1. Ministry of Health

- Dr. Soekaryo	-	Secretary General
- Dr. Brotowasisto	-	Head, Planning Bureau
- Prof. Dr. Loedin	-	Director, Research & Development.
- Dr. Median Siraid	-	Director General, Food and Drugs.
- Mr. Charles Siregar	-	Head Technical Implementation Unit, Food & Drugs
- Dr. M Adhyatma	-	Director General, CDC.
- Dr. Gandung Hartono	-	Secretary to Director-General
- Dr. Gunawan	-	Head Epidemiology and Immunization
- Dr. Karyadi	-	Chief, Epidemiology and Surveillance
- Dr. Titi Indijati Soewarso	-	Medical Officer, Epidemiology and Surveillance
- Dr. Guno Wiseso	-	Chief, Immunization
- Dr. Sorta Toruan	-	Medical Officer, Immunization

2 Perusahaan Umum Bio Farma

- Dr. M.S. Nasution	-	Director
- Mrs. S. Soeharto	-	Commercial Director
- Dr. Sutaryo	-	Production Director
- Dr. Ina Madiapura	-	Head, Virus Vaccine Production

3. Resident Agencies

- Dr. David H. Calder	-	Chief, Office of Population and Health, USAID
- Mr. Warren Jones	-	Administrative Officer, USAID
- Dr. Richard S. Arnold	-	Medical Epidemiologist, USAID
- Mr. Daniel J. Brooks	-	Representative to Indonesia UNICEF
- Mr. Rodney Hatfield	-	EPI Project Officer, UNICEF

AN INTRODUCTION TO CONNAUGHT LABORATORIES' TECHNOLOGY TRANSFER ACTIVITIES

Connaught Laboratories, Toronto, Canada has a long history in the transfer of technology for production and quality control of biological products.

This, coupled with Connaught being one of the world's major vaccine producers, caused the World Health Organization/Pan American Health Organization to appoint Connaught as its Consultant for Smallpox Vaccine by Latin American Governments.

A considerable amount of additional experience was gained through the technology transfer by Connaught to its joint ventures in Mexico and Brazil.

During the past three years, Connaught has acted as Consultant to the Government of Pakistan for the establishment in Islamabad of an Oral Polio Vaccine processing plant. This project, which was financed jointly by the Government of Pakistan and the Canadian International Development Agency was executed on time and under budget. Since then Connaught's services have been retained for this project in a "continuing support services" role.

In January 1983 Connaught won an international UNICEF tender to act as Consultants to the Pakistan Government for the setting up of a Measles Vaccine production unit. This project currently is being executed.

Negotiations with other foreign Governments for operations to manufacture Injectable Polio Vaccine, Rabies Vaccine (Human Diploid Cell origin), Measles Vaccine etc. are in advanced stages.

Connaught's philosophy of technology transfer is one of total commitment. It is for this reason that, in 1981, Connaught established a separate Division involved solely with technology transfer. To the best of our knowledge, Connaught is the only commercial biological producer to have such an entity.

Connaught's production of a broad range of biologicals, coupled with its extensive research and development as well as its expertise in systematic technology transfer, enables Connaught to assist its clients in very many difference aspects of production and quality control.

In addition, Connaught always is interested in considering acquisition of incoming technology as well, thus potentially creating two-way technology transfer.

Last but not least, Connaught is acutely aware that its reputation is at stake in each and every project it undertakes. Consequently it tries to ensure at all times that commitments, time-frames, costings, etc. are strictly observed.

TECHNOLOGY TRANSFER FOR BIOLOGICAL PRODUCTION

Introduction

For the implementation of their "Expanded Programme on Immunization", Governments may wish to consider undertaking local production of certain biological products. To assist in the rapid establishment of such local production, Connaught Laboratories have formulated a Technology Transfer Plan which already has been implemented successfully in Pakistan. These projects are as follows:

"Intermediate" production of oral polio vaccine;
"Basic" production of measles vaccine; and
Production of human diphoid cell rabies vaccine.

Connaught can offer technology transfer for manufacture of the following products:

Diphtheria Toxoid
Pertussis Vaccine --------and combinations
Tetanus Toxoid
Injectable Poliomyelitis Vaccine (Salk;and combinations)
Oral Polio Vaccine (Sabin)
Measles Vaccine (Live, Attenuated)
Rabies Vaccine (Human Diploid Cell)
Human Plasma Fractions
(e.g. Normal Serum Albumin, Immune Serum Globulin)
Meningococcal Vaccine (A,C, W-135, Y)
Intravenous Infusion Fluids

The Main characteristics of the Connaught Technology Transfer Plan

This plan as devised by Connaught consists of two distinct phases:
"Intermediate" Production (manufacture of ready-for-use preparations from imported bulk components)
"Basic" Production

The implementation of the Technology Transfer Plan comprises four separate stages:

The Project Proposal

The Project Plan

The Execution of the Project Plan

The Continuing Support Services

Details of the Connaught Technology Transfer Plan

The Project Proposal broadly outlines the following topics:

Products and quantities to be produced;

Requirements for manufacturing and quality control, buildings, utilities and equipment;

Production materials;

Personnel;

Connaught's services to be provided;

Approximate costs of the project.

The Project Plan consists of the following:

Design of the physical facilities;

Engineering drawings for air-conditioning/purification and all other services;

Detailed specifications for equipment and production materials and their potential sources;

Personnel training schedules (in-situ and in Canada/USA);

Project schedules, including Connaught's activities;

Detailed costing for total project.

The Execution of the Project will comprise the following services by Connaught:

Supervision of construction of building(s) for production and quality control (Note: In selected instances, arrangements can be made with a process engineering company in Toronto to undertake the erection of the physical facilities and the installation of air conditioning purification and all other services)

Procurement of equipment, etc. (if required);

Training of personnel at Connaught in all aspects of production and quality control;

Provision of Connaught staff to supervise the commissioning of the buildings and equipment, the preparation of the first lots of the products in the new facilities and the quality control thereof;
Performance of parallel quality control tests by Connaught, on each lot of product until each party is functioning properly;
Provision of all necessary manuals and other documentation as well as assistance in the registration of all products with the local regulatory authorities.

The Continuing Support Services Plan

This plan should be prepared at the same time as the project, and should be put into action at the termination of the Execution stage.
It can comprise all or any of the following services on a yearly or two-yearly contractual basis:

GMP Audit
Spare Part Procurement
Procurement of Consumables
Assistance in solving such production and quality control problems as may arise from time to time (trouble shooting service)
Performance of parallel quality control tests
Training of new senior staff
Implementation of new WHO requirements
Raw material testing

Keys to the success of technology transfer

During the execution of the project and the continuing support services particular attention should be paid to the following problems.

Staff of the technology holder should be at the project site along the whole period of construction.

System of professional promotion should be incorporated into the project through training programmes

Training in maintenance of equipment should be organized at project site and in the premises of equipment manufacturers.

Lower level personnel should be trained at project site and operation manuals should be provided in local language.

Equipment should be shipped if possible only by air. The supplier should be responsible for installation and trial runs.

Training in quality assurance, quality control and record keeping should be carried out.

TERMS OF REFERENCE
LIVE ATTENUATED ORAL POLIOMYELITIS- AND MEASLES VACCINE PRODUCTION

I. BACKGROUND AND SUPPORTING INFORMATION

1. Justification of the project

1.1. WHO initiated the Expanded Programme on Immunization in 1974 and it has become an essential element of the strategy to achieve "health for all by the year 2000" (WHO Resolution no. 30.53, adopted in May 1977) with the goal of reducing morbidity and mortality from diphtheria, pertussis, tetanus, measles, polio and tuberculosis by providing immunization against these diseases for every child in the world by the year 1990.

While the reported numbers of cases and death may underestimate the extend of the consequence of those 6 disease, they are thought to cause some 5 million deaths among children under 5 years, while an additional 5 million are permanently desabled worldwide (6th Report on the World Health Situation, part I: 1980). The importance of EPI as an essential component of maternal and child health and primary health was emphasized at various forums.

The demand for vaccines in Indonesia is expected to increase sharply because the present coverage of the target population will increase to 100% at the end of the Fourth Five-year Development Plan (Repelita IV).

It is therefore essential to increase the production of vaccines required in the Expanded Programme on Immunization accordingly.

1.2. This project proposal is submitted with the objective of improving the health services by the provision of viral vaccines, particularly live attenuated oral poliomyelitis and measles vaccines in sufficient amounts and at a reasonable price to be within financial reach of the people.

One of the targets of the 4th Five Years Development Plan (REPELITA IV) is to strengthen the general public health status of the population through prevention of communicable diseases by immunization. By improving the health services, it is expected that the mortality rate of the population which stands now at 11.9 per 1.000 will drop to 10.3 per 1.000 at the end of 1989, the infant mortality rate

from 90.1 to 70 per 1.000 live births and the mortality rate for children younger than 5 years (the so-called "Balita" group) from 17.8 to 14 per 1.000.

Many childhood diseases, in this particular case poliomyelitis and measles could be prevented by active immunization only.

Poliomyelitis, a viral and communicable disease is recognized as a disease entity with epidemic potentials, occurring throughout the year in tropical regions.

A great majority of cases occur in the younger age group; over 90% in infants under 5 years of age, almost 80% under 2 years, and about 50% in children younger than 1 year.

1.3. In Indonesia during polio outbreaks in several regencies in 1976 - 1977, attack rates in the 0 - 4 year age group was 90 per 100.000 population with estimated paralytic poliomyelitis incidence rates between 4 - 7 per 10.000 in the 0 - 14 year age group.

During that period, surveys by house to house visits revealed that 80% were paralytic at the age of 3 years and 50% after receiving either therapeutic or preventive injections.

All three types of poliomyelitis viruses have been encountered in the outbreaks. Cases among adults were also detected and clinically diagnosed either as polyneuritis and/or encephalitis; the youngest was 17 years old and the oldest over 60 years of age, also accompanied by paralysis.

This means that the disease is highly endemic.

1.4. Measles is an acute and highly contagious viral disease in childhood, and in developing countries half the children become infected during their first year of life with mortality rates reaching as high as 60%.

Measles is usually contracted during childhood with bronchopneumonia, encephalitis and otitis media as its chief complications, with some of these complications resulting in lifelong handicaps and sequellae.

Secondary bacterial and viral complications are mainly responsible for the high fatality rates of measles in certain developing countries.

Besides, a direct correlation was also found between mortality and malnutrition which alters the host response to the virus.

Socio-economic and public health factors play also an important role in the outcome of the disease.

1.5. Measles is endemic throughout most countries of the world, having a characteristic tendency to become epidemic every 2 - 3 years. The highest incidence is usually in the 1 - 5 years age group, and by the age of 20 years about 90% of persons have had an infection with measles virus.

1.6. Serious outbreaks of measles with significantly high mortality rates have been reported in some developing countries.
In Chile for instance, measles was responsible for 2 to 3.5% of all deaths in the country and for 50% of all deaths due to acute communicable diseases.
In West Africa, measles was one of the leading causes of death and disability in children with an overall mortality rate of 5 - 10%.

A large outbreak of measles occurred on the islands of Lombok in 1977 affecting 12.500 children with a case fatality rate of 2 - 9%.
In 1983 - 1984, outbreaks of measles also occurred in West Java with case fatality rates between 15% and 24%.
Smaller outbreaks have subsequently occurred in several regions of the country with case fatality rates ranging between 2.9 to 25 %.
It was also evident that during these outbreaks most of the victims were at age 1 to 4 years, and that nutritional status plays an important role on the outcome of the disease as proved by the fatal cases. Secondary bacteriological and viral complications are most probable responsible for the relativey high case fatality rates.

1.7. Hospital surveys carried out in Indonesia during 1969 - 1971 proved that the case fatality rates for measles was still as high as 8,8%. Although data concerning complications of measles in Indonesia are not available yet, but as can be seen from the figures in the German Democratic Republic, complications occur in 6 - 7% of all measles cases. After introduction of mass immunization, only sporadic cases were recorded in that country during the following years.

1.8. The excistance of well-organized immunization programmes and public health services in developed countries reduced the complications due to measles to 0.2 - 1.0 per 1.000 cases.

1.9. After the eradication of smallpox globally, and knowing the achievement reached by developed countries in controlling infectious diseases, WHO has launched an Expanded Programme on Immunization in 1974 and it has become an essential element of the strategy to achieve "health for all by the year 2.000" (WHO resolution no. 30.53 adapted in May 1977) with the goal of reducing morbidity and mortality from diphtheria, pertussis, tetanus, tuberculosis, poliomyelitis and measles for every child in the world by the year 1990.

1.10. Indonesia also commits to this Expanded Programme on Immunizarion and is active conducting it; therefore the demand of poliomyelitis and measles vaccines in Indonesia is expected to increase sharply because the present coverage of the target population will increase to about 100% at the end of the Fourth Five-year Development Plan.
Hence, it is therefore essential to increase the production of poliomyelitis- and measles vaccines required for the Expanded Programme on Immunization.

1.11. In order to protect these susceptible children, preventing measures by active immunization as has been carried out in developed countries should be initiated.

1.12. In the frame of efforts to be self-reliant on the production and supply of poliomyelitis- and measles vaccines needed for the immunization programme, strengthening of Perum Bio Farma as a state enterprise assigned by the Government to produce vaccines, in this case poliomyelitis- and measles vaccines in essential.
When the vaccines are produced locally, a large amount of foreign currency could be saved annually, while the price of the vaccines could be expected lower and within the financial reach of a larger part of the population.

1.13. Tis project proposal is submitted with the objective of improving the health services by the provision of live attenuated poliomyelitis- and measles vaccines in sufficient amounts and at a reasonable price to be within financial reach of the population.
One of the targets of the 4th Five-year Development Plan (REPELITA IV) is to strengthen the general public health status of the population through prevention of communicable diseases by immunization.

By improving the health services, it is expected that the mortality rate of the population which stands now at 11.9 per 1.000 will drop to 10.3 per 1.000 at the end of 1989, the infant mortality rate from 90.1 to 70 per 1.000 live births and the mortality rate for children younger than 5 years (the so-called "Balita" group) from 17.8 to 14 per 1.000.

Many childhood diseases, in this particular case measles, could be prevented by active immunization only.

2. Name of the project and its activities

2.1. Name of the project: Live attenuated oral Poliomyelitis and Measles Vaccine production.

2.2 Purpose and significance of the project:

a. Criteria have been used by countries to determine whether poliomyelitis is a health problem requiring regular immunization such as, if paralytic cases in the age group of --1 years are higher than 10 per 100.000, and also if the number of new poliomyelitis cases is at least 1 per 100.000 per year.

b. In Indonesia poliomyelitis is endemic and occurs throughout the year, occasionally in epidemics.
Although the infection may be inapparent or subclinical, paralysis may result for which the patient may be handicapped for life.

c. Considering the data accumulated during poliomyelitis outbreaks, the above mentioned criteria have been fulfilled, even exceeded such as for instance in North Sulawesi and on the island of Bali. Paralysis prevalence rates were respectively 34 and 37 per 10.000 during 1977 and 1987 and in Palembang it was 21 per 10.000 in 1977.

d. As far as measles is concerned, this pedriatic diseases has been previously always considered as a mild disease with occasionally secondary bacterial infection of the lungs as a complication. However, since 1976-1977, outbreaks have ocurred particularly in the age group of 1-4 years, with a case fatality rate ranging between 2.9% to 25%, a majority of these patients suffering also from malnutrition.

In 1983-1984, outbreaks of measles also occurred in West Java with case fatality rates between 15% and 24%.
Encephalitis as a complication of this disease have been detected during these outbreaks, leaving permanent sequellae on its victims.

e. Since measles mainly encounter children, prevention should be conducted of which immunization is the only way reduce morbidity, mortality and consequences of complication among these youngsters.

f. Immunization are usually given as basic immunization in the first year of life.

g. Since poliomyelitis and measles mainly encounter children, prevention should be conducted of which immunization is the only way to reduce morbidity, mortality and consequences of complications among these youngsters.

h. Immunizations are usually given as basic immunization in the first year of life.

3. Institutional framework

3.1. Similar to the production of other bacterial and viral vaccines in Indonesia, Perum Bio Farma will be the only institute responsible for the production of poliomyelitis-and measles vaccines.

3.2. Perum Bio Farma is a state enterprise under the auspices of the Ministry of Health and was assigned by the Government to produce vaccines and sera.
Perum Bio Farma is responsible for the production of biologicals especially vaccines, antisera, diagnostics etc. which are urgently needed for the improvement of the Social Health Services as outlined by the 4th Five Years Development Plant (REPELITA IV).

3.3. By submitting this project Perum Bio Farma intends to develop its production to provide for live attenuated oral poliomyelitis-and measles vaccines for the country.

3.4. Besides Perum Bio Farma's intention to develop its production capacity, this project will also strengthen the capabilities of the National Control Authority, resulting in the development and production of vaccines of high quality.

4. Government follow up

4.1. Whenever this project is completed, the need for poliomyelitis may be fulfilled since this project will be able to produce 2.000.000 vials @ 10 doses of live attenuated oral poliomyelitis vaccine per annum at a reasonable price to conduct the Expanded Programme on Immunization of the Government.
The need for measles live vaccine may also be fulfilled since this project will be able to produce 700.000 vials @ 10 doses of measles live vaccine per annum.

4.2. As a further development at the completion of this project, the production of poliomyelitis-and measles vaccines may be increased continually, while improving its quality in compliance with the development of the latest technology and increasing its capacity in accordance with the increasing needs in the future.

4.3. Through this project, Perum Bio Farma will gain technical knowhow about the manufacturing process and quality control of poliomyelitis- and measles live vaccines.

II. OBJECTIVES OF THE PROJECT

As its immediate objective, whenever this project has been completed, the provision of poliomyelitis- and measles vaccines will be fulfilled in accordance with Government's program for the supply of biologicals as outlined by the 4th Five Year Development Plan (REPELITA IV).
The long term objective of this project is to continually improve the products quality as well as its quantity and to manufacture with the latest technology of production so that it may become more commonly available and within the financial reach of the people.

III. PLAN OF OPERATION

This project is to be carried out in three years as follows :
A. Designing of buildings, approval of design, and erection of buildings.
B. Purchasing, procurement, installation and testing of equipment.

C. Training of Bio Farma personnel.

D. Production starts after finishing of building and installation of equipment.

IV. EXTERNAL AND BIO FARMA INPUTS

1. External Inputs :

1.1. Equipment for the production and quality control of live attenuated poliomyelitis-and measles vaccine.

1.2. Transfer of technology for poliomyelitis-and measles vaccine.

1.3. Expert Services

Expert on production and quality controle and expert for installation, testrun and troubleshooting of equipment.

1.4. Training of Bio Farma personnel;

trainees for production manager, production processing, production control, animal care and for quality control;

training of technicians and machine operator.

1.5. Other expenses.

2. Bio Farma Inputs :

2.1. Building for production and quality control of poliomyelitis-and measles vaccine including warehouse, restrooms, shower rooms etc.

2.2. Building space for above buildings.

2.3. Services

Consisting of installation of electricity, piping for gas, pressured air, vacuum, distilled water, household water etc., including installation of complete air conditioning system.

V. ESTIMATED COST OF THE PROJECT

A. External Inputs :

1. Equipment for :

1.1. Animal house	US $	150.000,-
1.2. Polio Production Laboratory	US $	350.000,-
1.3. Measles Production Laboratory . . .	US $	350.000,-
1.4. Sterile Filling	US $	275.000,-
1.5. Sterile Filling and freeze-drying Measles vaccine	US $	425.000,-

1.6. Packaging Department	US $	225.000,-
1.7. Sterile Zone	US $	600.000,-
1.8. Medium Preparation	US $	75.000,-
1.9. Bulk Storage of Polio and Measles vaccines	US $	50.000,-
1.10. Controle Laboratory	US $	350.000,-
1.11. In Vitro Controle Laboratory . . .	US $	80.000,-
1.12. Histology Laboratory	US $	40.000,-
1.13. Warehouse: storage of finished products	US $	160.000,-
	US $	3.130.000,-

- Costs for packaging, freight and insurance of equipment :
  15% x US $ 3.130.000,- = US $ 469.500,-
- Incidental expenses :
  10% x US $ 3.130.000,- = US $ 313.000,-

. . . . .	US $	782.500,-
T o t a l	US $	3.912.500,-

2. Transfer of Technology fee for Poliomyelitis- and Measles vaccines . . US $ 500.000,-

3. Expert Services :
   For Poliomyelitis vaccine
   3.1. 1 expert for production (10 weeks)
   3.2. 2 experts for quality control (2 months each)
   3.3. 1 expert for installation, testrun and troubleshooting of equipment (6 weeks)
   3.4. Travel expenses
   3.5. Hotel and meals for experts during 32 m. weeks

   Estimated expenses ..... US $ 150.000,-

   For Measles Vaccine
   3.6. 1 expert for production (10 weeks)
   3.7. 1 expert for quality control (10 weeks)
   3.8. 1 expert for installation, testrun and troubleshooting of equipment (6 weeks)

3.9. Travel expenses

3.10. Hotel and meals for experts during 26 m. weeks

Estimated expenses ..... US $ 125.000,-

4. Training of Bio Farma Personnel :

For Poliomyelitis Vaccine

4.1. 1 production manager (1 month)

4.2. 1 for production processing (3 months)

4.3. 2 for production controle (3 months each)

4.4. 2 for neurovirulence testing (12 months each)

4.5. 1 for animal care

4.6. 2 technicians (3 months each)

4.7. 2 for quality control (1½ months each)

4.8. Travel expenses

4.9. Lodging and meals for trainees during 46 m. months

Estimated expenses ..... US $ 200.000,-

For Measles Vaccine

4.10. 1 production manager (1 month)

4.11. 1 production processing (3 months)

4.12. 1 for animal care (3 months)

4.13. 1 for production control (3 months)

4.14. 2 technicians (3 months each)

4.15. 2 for quality control (1½ months each)

4.16. 1 machine operator (1 month)

4.17. Travel expenses

4.18. Lodging, meals and other expenses during 20 m. months

Estimated expenses ..... US $ 125.000,-

5. Other expenses ..... US $ 300.000,-

6. Total :

6.1. Equipment, including packaging, freight, insurance and incidental espenses ..... US $ 3.912.500,-

6.2. Transfer of technology fee for Poliomyelitis and Measles vaccines ..... US $ 500.000,-

6.3. Expert Services :		
for Poliomyelitis and Measles vaccines	US $	275.000,-
6.4. Training of Bio Farma Personnel,		
for Poliomyelitis and Measles vaccines	US $	325.000,-
6.5. Other expenses	US $	300.000,-
	US $	5.312.500,-

B. Bio Farma Inputs :

1. Buildings

1.1. Shared facilities for Poliomyelitis and Measles vaccines

- medium preparation room	36	sqm
- storage room	46	sqm
- toilets	12	sqm
- freezer rooms for storage of bulk vaccine and finished products	144	sqm
- washing and sterilizing rooms	124	sqm
- corridors	20	sqm
	382	sqm

1.2. Building for Poliomyelitis vaccine

- production facilities	170	sqm
- quality control facilities	170	sqm
- laboratory for virulent polio-virus strains . . .	36	sqm
- laboratorium for neurovirulence test	36	sqm
- filling and dispensing room	70	sqm
- offices, meeting rooms, rooms for personnel . . .	55	sqm
- corridors	110	sqm
- animal room	285	sqm
	932	sqm

1.3. Building for Measles vaccine

- production facilities	169	sqm
- quality control facilities	169	sqm
- laboratory/reading room	36	sqm
- offices, meeting rooms, rooms for personnel . .	55	sqm

- toilets	36	sqm
- filling and dispensing room	70	sqm
- freeze drying room	32	sqm
- corridors	110	sqm
	677	sqm

Estimated cost : 2.000 sqm x Rp. 400.000,- = Rp. 800.000.000,-

2. Building space

   1.200 sqm x Rp. 175.000,- . . . . . Rp. 210.000.000,-

3. Services, consisting of :

   3.1. Installation of electricity wiring

   3.2. Installation of piping for gas, pressured air, vacuum, distilled and household water, etc.

   3.3. Air conditioning . . . . . Rp. 350.000.000,-

   Rp.1.360.000.000,-

Grand total :

- External Inputs : US $ 5.312.500,-
- Bio Farma Inputs : US $ 1.360.000.000,-

(Project Aid Proposal) Code Number :

1. Project Title : Live attenuated oral poliomyelitis and measles vaccine production.

2. Location : Perum Bio Farma, 28 Jalan Pasteur, Bandung, West-Java, Indonesia.

3. Executing Agency : Directorate General of Food and Drug Administration, Ministry of Health.

4. Objectives : To improve the Health Services by the provision of viral vaccines, particularly live attenuated oral poliomyelitis and measles vaccines in sufficient amounts and at a reasonable price to be within financial reach of the people.

5. Project Description : The project is planned to build a complete manufacturing plant for live attenuated oral poliomyelitis and measles vaccines.
The plant will consist of facilities for production, quality control, washing, and for animal holding.
When finished, the plant will be able to produce 20 million doses of live attenuated oral poliomyelitis vaccine and 7 million doses of measles vaccine per annum.
The scope of work consists of :
- Construction of a completely new production facility.
- Provision of production- and laboratory equipment including its spare parts.
- Provision of equipment for quality control-, washing-, and animal holding facilities.

6. Implementation time	: 3 (three) years after approval of the proposal.		
7. Project Cost	: Total cost	: US $ 5.312.500,- and Rp. 1.360.000.000,-	
	Local cost	: Rp. 1.360.000.000,-	
	Foreign Exchange Cost	: US $ 5.312.500,-	
8. Amount Proposed for Commitment	: US $ 5.312.500,-		
9. Related to Technical Assistance	:		
10. Stage of Project Preparation	: - A feasibility study by a joint with WHO/Unicef/Usaid consulting team has been carried out on September 1984. - Building space available at this moment.		

(Technical Assistance Proposal) Code Number :

1. Project Title : Live attenuated oral poliomyelitis and measles vaccines production.

2. Location : Perum Bio Farma,
28, Jalan Pasteur,
Bandung, West-Java, Indonesia.

3. Executing Agency : Directorate General of Food and Drug Administration, Ministry of Health.

4. Objective : To improve the Health Services by the provision of viral vaccines, particularly live attenuated oral poliomyelitis and measles vaccines in sufficient amounts and at a reasonable price to be within financial reach of the people.

5. Project Description : To provide expert services, fellowships and transfer of technology for a complete manufacturing plant for live attenuated oral poliomyelitis and measles vaccines.
The plant will consist of facilities of production, quality control, washing, and for animal holding.
When finished the plant will be able to produce 20 million doses of poliomyelitis and 7 million doses of measles vaccines per annum

6. Scope of assistance required :

6.1. Equipment including packaging, freight, insurance and incidental expenses	US $	3.912.500,-
6.2. Transfer of technology fee	US $	500.000,-
6.3. Expert Services	US $	275.000,-
6.4. Training of Bio Farma personnel	US $	325.000,-
6.5. Other expenses	US $	300.000,-
T o t a l	US $	5.312.500,-

7. Related to Project Aid :

Strengthening of the production of diphtheria, tetanus and pertussis vaccine (DTP) - by Government Pharmaceutical Organization (GPO) Bangkok, Thailand

Developmental objective

To strengthen Biology Division of GPO, to enable it to produce DTP vaccine required for EPI in support of primary health care in Thailand.

Immediate objective

1. To strengthen technical and managerial competence to produce DTP vaccines of assured quality in the required quantities for EPI.

2. To assist in the production of pertussis and diphtheria vaccine in fermenters.

3. To provide consultants and fellowships to nationals for training in fermentation techniques.

4. To advise on the remodelling of the production area to make it suitable for vaccine production with the use of fermenters.

5. To provide some equipment to enable GPO to achieve the above objectives.

6. To provide training to nationals to strengthen laboratory animal breeding programme.

Background information

GPO has a long experience in the production of DTP vaccine. The scientists have been trained in the production and quality control of vaccines in India, UK, Yugoslavia and Canada. The staff is adequately qualified and has developed sufficient experience in vaccine production.

The present premises are not quite suitable for vaccine production. The place is crowded and it is difficult to introduce GMP. The place also is not suitable for lay-out with modular basis or an inner box with outer shell as recommended by WHO. It is not possible to increase vaccine production in the present premises unless some alterations are made. Since the space was not originally designed for vaccine production, even if modifications are made some of the activities such as final mixing, filling and packaging would have to be carried out in other parts of the building.

Tetanus toxoid is produced in a separate block which is quite adequate.

The Institute is producing at present 1.5 million doses of DPT, 2.1 million doses of diphtheria toxoid and 6 million doses of tetanus toxoid annually.

Major constraints in increasing the production under the existing circumstances are heavy losses during production of pertussis particularly due to contamination; inadequate incubator space, inadequate equipment, and unsatisfactory and limited production space and therefore inadequate GMP.

Although production can be increased with existing technology, the GPO has decided to go in for a fermentation technology to increase its production of these vaccines to meet the demands of EPI in Thailand.

Project output

1. Fermentation technology will be introduced in vaccine production.

2. Vaccine production after the completion of the project will be sufficient to meet the requirement of EPI.

3. Nationals will be trained in fermentation technology.

4. One national will be trained in GMP and management for vaccine production.

5. Animal house facilities will be strengthened.

Project activities

1. Remodelling of the existing premises to make them suitable for production of vaccines by use of fermenters (suggested plan for modification taking into account utilisation of existing space etc., is attached*).

2. Provide all services including air-conditioning, steam, power, etc.

3. To assign consultants to advise on remodelling of premises, obtaining appropriate fermenters and back up equipment.

4. To assign consultants for introducing fermentation technology and training of nationals.

* This plan was not provided to us.

5. To train nationals in fermentation techniques, GMP, management and laboratory animal breeding techniques.

Input by GPO

Remodelling of the premises provision of all services including water, gas, air-conditioning, etc., and some pieces of equipment.

UNICEF will provide $300,000 for purchase of equipment required for successful completion of the project.Funds will have to be provided for assigning a consultant initially for 2 weeks to advise architects and engineers of GPO. After installation of equipment, consultant will have to be assigned for 8 weeks to introduce new technology and initiate production of pertussis and diphtheria vaccines. Two nationals will require training - each for 3 months in production of pertussis and diphtheria in fermenters. They should return to their home laboratory when STC arrives for initiating production in the fermenters installed in the new premises. Two more nationals will have to be trained again in subsequent year abroad. Chief of the Division will need a visit to the Institutes where fermenters are installed to study CMP and management practices. A veterinarian will need training for 6 weeks in the laboratory animal technology.

GPO has satisfactory animal house facilities. These are also being upgraded. While as supply of mice is adequate, supply of guinea pig has to be improved.

GPO has in-process quality control exercised by independent quality control department. Besides, every batch of vaccine is tested by national quality control before it is released for use by EPI.

Activities and work plan *

		Begins	Ends
1.	Remodelling of laboratory	Oct-Nov '83	May '84
2.	Provision of services	Apr '84	May '84
3.	Assignment of STC - 2 weeks	Oct '83	Nov '83
4.	Preparation of detailed specification of equipment	Oct '83	Nov '83
5.	Ordering of equipment	Nov '83	-
6.	Receipt of equipment and its installation	Mar '84	Sep '84

* Schedule will be updated if the proposal is approved.

Activities and work plan (cont)

		Begins	Ends
7.	Training of nationals in fermenter technology 2 x 3m	Mar '84	Jun '84
8.	Training of national in GMP and management - 1 x 1m	Jul '84	Aug '84
9.	Training of veterinarian 1 x 6w	Jun '84	Jul '84
10.	Training of engineers in maintenance and repairs 2 x 2w	Feb - Mar'84	
11.	Assignment of consultant starting production and training 2 x 3mm	Jun '84	Aug '84
		Jun '85	Aug '85

Fermenters

Taking into account the existing situation, state of repairs and maintenance services, etc., it has been decided to buy two fermenters for pertussis and diphtheria, each of 75 litres capacity. Specifications for fermenters have been annexed. Some back-up equipment will be required which has been listed.

Tetanus production is adequate and can be stepped up to 10 million doses with addition of two pieces of equipment.

Existing staffing pattern in DPT section

Diphtheria section	-	Microbiologist	- 1
		Scientist	- 1
		Laboratory Assistants	- 3
Pertussis section	-	Microbiologist	- 1
		Scientists	- 2 (one post vacant)
		Laboratory Assistants	- 4
Tetanus section	-	Microbiologist	- 1
		Scientist	- 1 (vacant)
		Laboratory Assistants	- 3

APPENDIX 9

GPO: Equipment for Diphtheria - Pertussis

Item	Quantity	Cost (US$)
Binocular microscope	2	7,000
Fermentors (75 litre)	2	130,000
Ekwip filter assembly	2	7,000
S.S. Portable tanks (150 litre)	6	27,500
Industrial continuous flow centrifuge	1	80,000
Ultrafiltration unit (Amicon)	1	10,000
Metafiltration unit	1	8,500
pH meter	1	2,000
Autoclaves, jacketed, fitted with vacuum system and automatic/manual control. Chamber 0.9 m x 1.45 m x 1.54 m	2	112,000
	Total	384,000

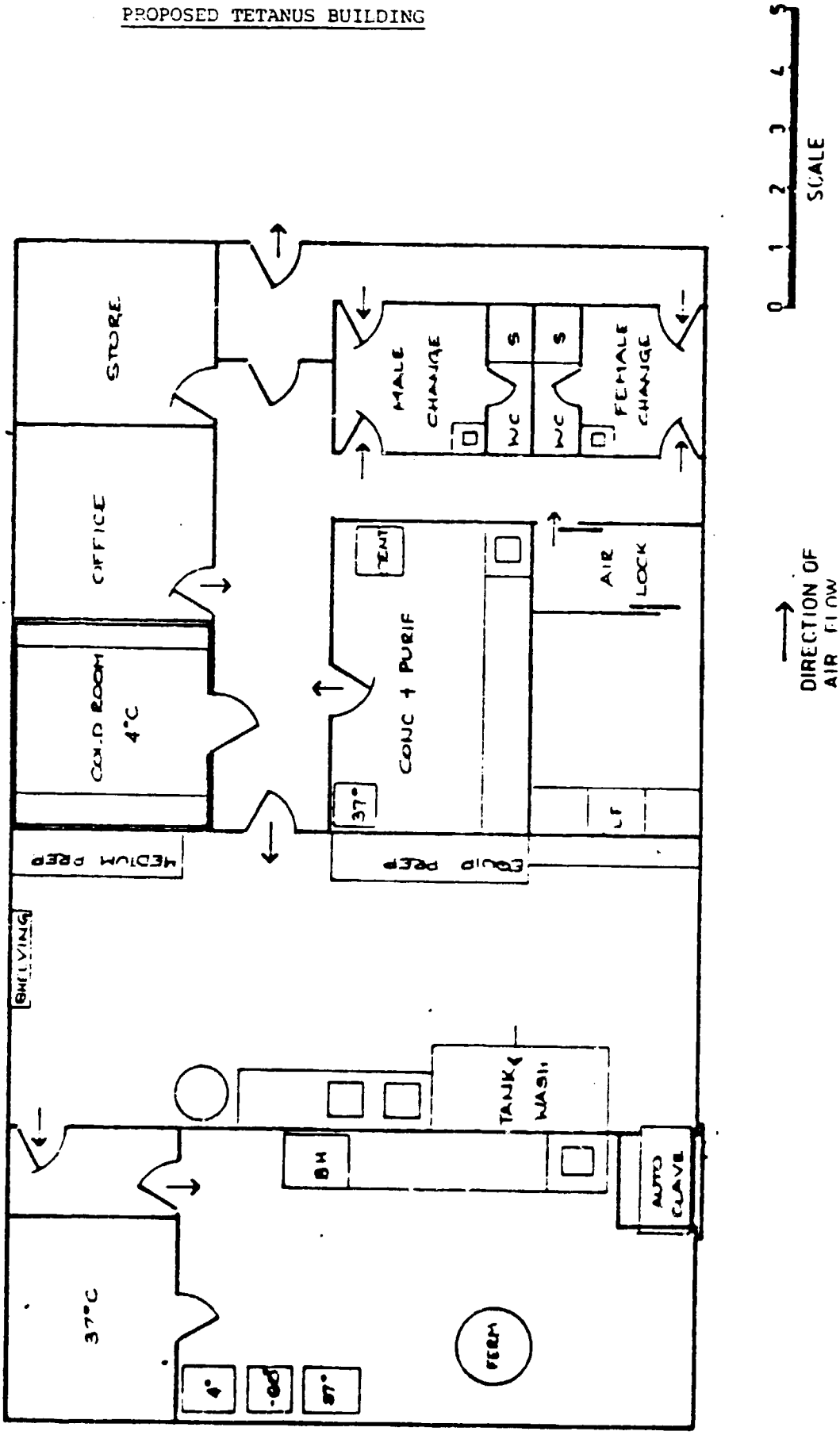
Note: The funding available through UNICEF is 300,000 US$. Additional funding required from UNIDO is approximately 84,000 US$.

APPENDIX 10

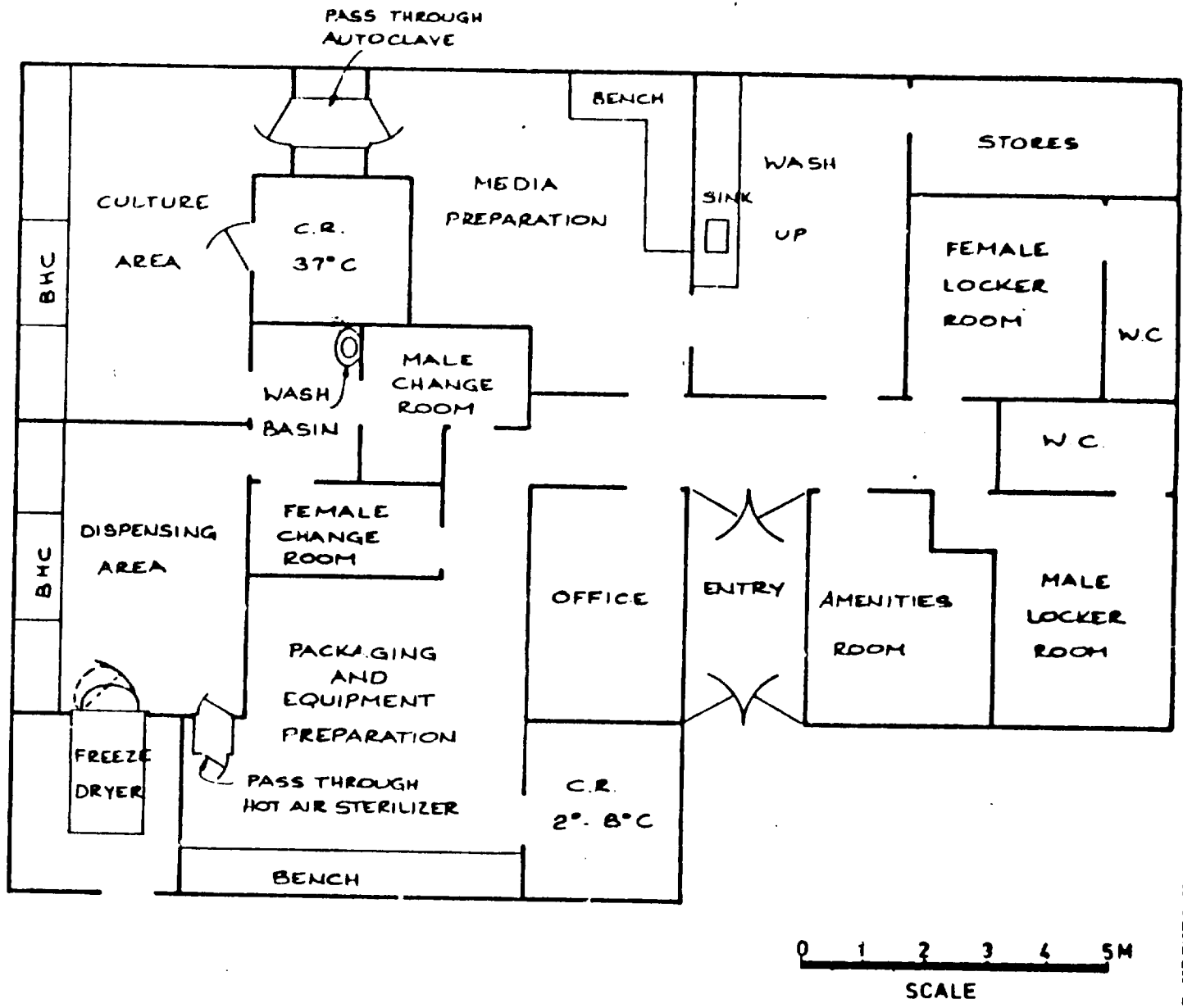
GPO: Tetanus Department - Equipment required

Item	Quantity	Cost (US$)
Fermentor 200 litre working volume 300 litre total volume	1	80,000
Inactivation tanks, 200 litre capacity	4	22,000
Autoclave (1.2 m long x 0.7 m high x 0.75 m wide)	1	5[illegible],000
Ultrafiltration unit (Amicon DC30)	1	10,000
Jacketed medium preparation vessel 100 litre wp 200 kPa	1	8,500
Biohazard cabinet, 4 foot	1	4,500
Crossflow laminar flow cabinet 6' x 4'	1	5,000
Balance 100 g, sensitivity 0.05 mg	1	1,000
Balance 1000 g, sensitivity 0.1 mg	1	1,000
Balance 10 kg, sensitivity 5 g	1	2,000
Millipore filter holder, 142 mm	1	1,000
Filter press, 20 cm + 20 cm, 20 plates	1	13,000
Air-compressor, oil-free, 150 kPa 200 litre/min	1	8,500
Peristaltic pump, Watson Marlow HRD	1	4,000
Magnetic stirrer	1	800
Mixer Lightning 1/3 HP variable speed equivalent	1	1,000
Hot water service, steam heated, with hot water holding tank of 100 litre capacity and necessary piping	1	14,000
Prefabricated cold room, complete 3.5 m x 3.5 m x 3 m external	1	25,000
Prefabricated warm room, complete with heater, fan and controls.	1	8,000
Air-conditioning plant	1	65,000
	Total	329,300

PROPOSED TETANUS BUILDING



PROPOSED BCG LABORATORY FLOOR PLAN

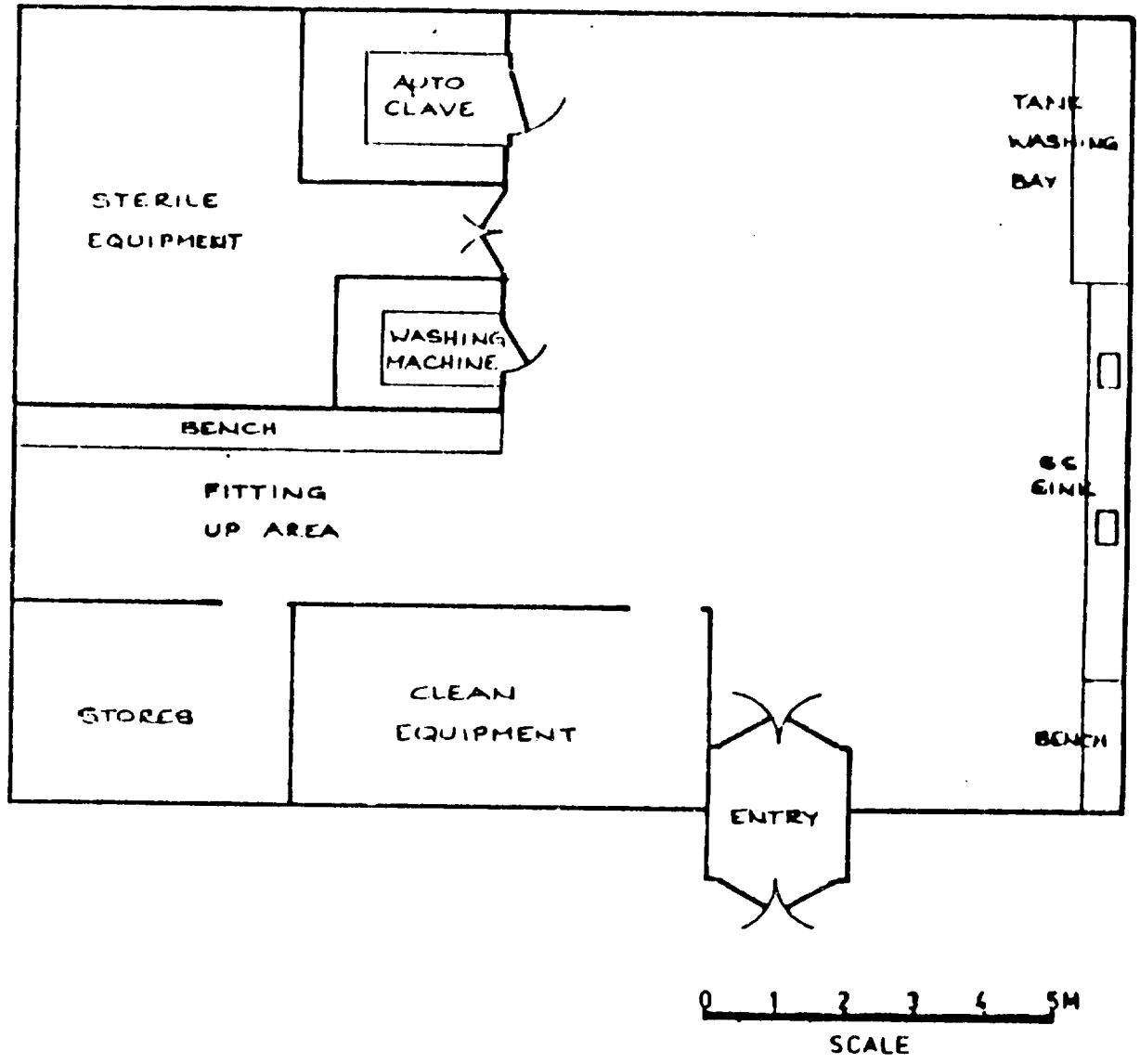


APPENDIX 13

Equipment Required for BCG Laboratory - GPO

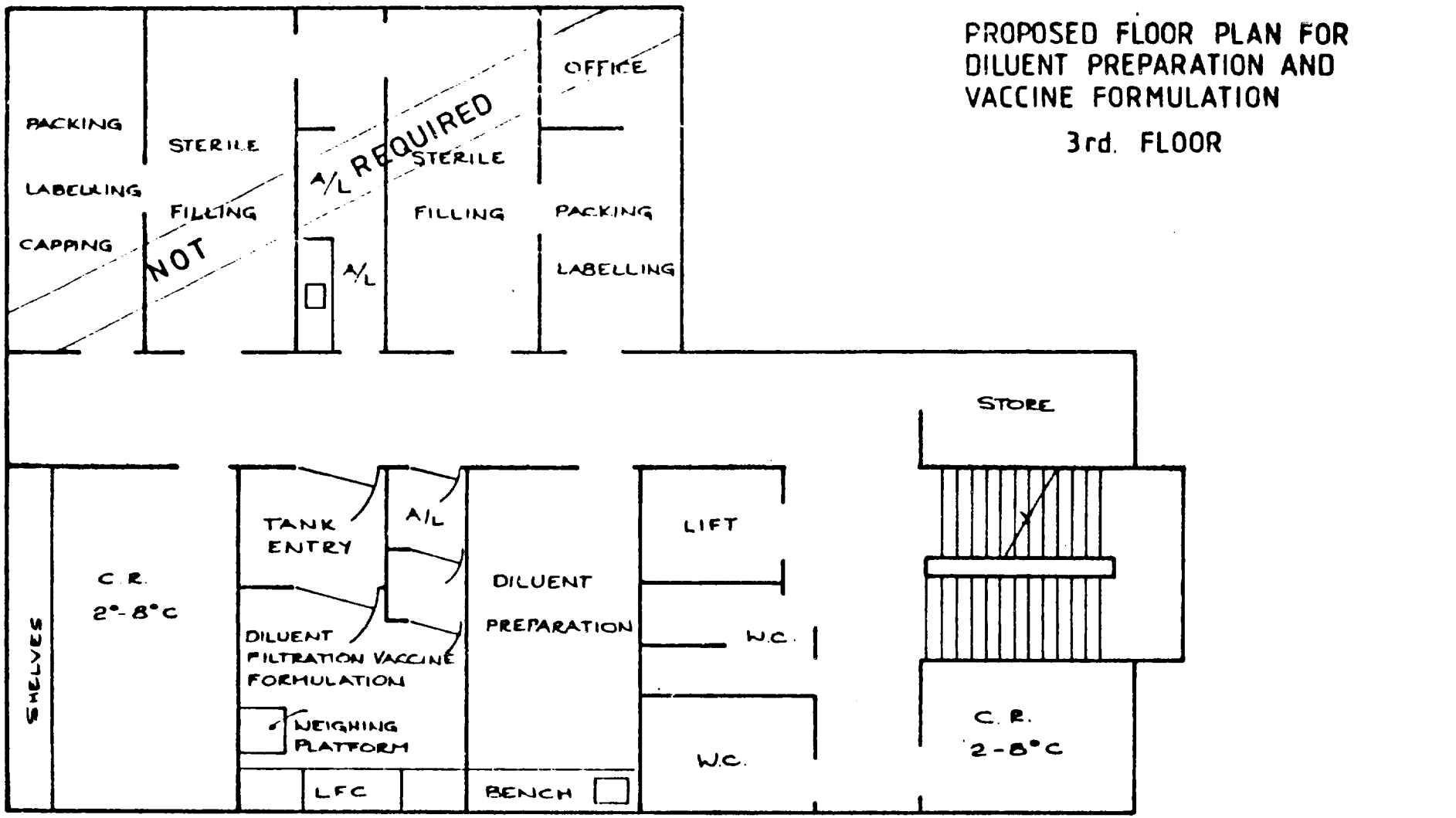
Item	Quantity	Cost (US$)
Autoclave (0.6 m wide x 0.75 m high x 1.0 m long)	1	56,000
Membrane filter holder (142 mm)	1	1,000
Weighing balance 1000 g, 1 mg sensitivity	1	1,200
Laminar Flow Safety Cabinets (1.8 m)	2	13,000
Hot air sterilizer	1	21,000
Refrigerator (300 litre)	1	850
Brewer Pipetting Machine	3	6,500
Capping Machine	1	1,500
Nephelometer	1	1,500
Birkhaug filters	5	1,200
Edwards (EF10) Freeze Dryer	1	42,000
Equipment Washing Machine	1	5,000
Hot water service (steam heated) with holding tank of 100 litre capacity with necessary piping and lagging for reticulation	1	14,000
Water still	1	40,000
Prefabricated cold room, complete 2.5 m x 2.5 m x 3 m external	1	20,000
Prefabricated warm room, complete with heater, fan and controls 2.5 m x 2.5 m x 3 m external	1	14,000
Air-conditioning plant	1	65,000
Air compressor, oil free, with air receiver and pressure piping for reticulation	1	13,000
Pressure reducing sets (0 to 70 kPa)	4	2,000
	Total	318,750

PROPOSED FLOOR PLAN
FOR TANK EQUIPMENT
PREPARATION AREA



PROPOSED FLOOR PLAN FOR DILUENT PREPARATION AND VACCINE FORMULATION

3rd. FLOOR



APPENDIX 16

GPO: Vaccine Formulation and Tank Washing - Equipment Required

Item	Quantity	Cost (US$)
Tank, portable, stainless steel 150 litre	6	27,500
Laminar flow cabinet, 6' x 4'	1	5,000
Vibromix, Model E2	3	5,000
Balance, 10 kg capacity sensitivity 1 g	1	2,000
Weighing platform, 500 kg capacity	1	5,000
Prefabricated cold room (2° to 8°C) (6 m x 4 m x 3 m high)	1	20,000
Air-compressor, oil-free, 100 kPa suitable for pressurising tanks	1	8,500
Autoclave, jacketed, fitted with vacuum system, and automatic/manual control. Chamber (900 mm x 1450 mm x 1540 mm)	1	56,000
Hoist for lifting tanks	1	5,000
Washing machine for test tubes and small bottles	1	3,500
Hot water service (steam heated) for tank washing and equipment preparation area, 200 litre storage tank and reticulation piping.	1	15,000
	Total	152,500

APPENDIX 17

GPO - Final Container Dispensing - Equipment Required

Item	Quantity	Cost (US$)
Filling machine, equipped with change parts for 5, 20 and 50 mL vials, capacity 300 x 5 mL vials per hour.	1	55,000
Laminar flow hood for filling machine	1	8,500
Stainless steel trays (lidded) 450 mm x 250 mm x 65 mm high	200	8,500
Stopper washing machine capacity 30,000 x 13 mm stoppers per day	1	19,000
Prefabricated cold room (6 m x 4 m x 3 m high, 2° to 8°C)	1	20,000
Labelling machine capacity 15,000 containers per day	1	28,000
Vial washing machine, equipped with change parts for 5, 20 and 50 mL vials, capacity 3000 x 5 mL vials per hour	1	40,000
	Total	179,000

APPENDIX 18

Equipment Required for BCG Laboratory - QSMI

Item	Quantity	Cost (US$)
Water still	1	40,000
Hot water service, steam heated with a hot water holding tank of 100 litre capacity.	1	14,000
Vial washing machine	1	20,000
	Total	74,000

Equipment Required for BCG Laboratory - Alabang

Item	Quantity	Cost (US$)
Water still	1	40,000
Hot water service, steam heated with a hot water holding tank of 100 litre capacity.	1	14,000
Vial washing machine	1	20,000
Air-conditioning plant	1	65,000
Equipment washing machine	1	5,000
	Total	144,000

APPENDIX 19

Alabang - Vaccine Dispensing - Equipment Preparation

Equipment List

Item	Quantity	Cost (US$)
Stainless steel trays (lidded) 450 mm x 250 mm x 65 mm high	200	8,500
Hot air sterilizer	1	30,000
Tanks portable stainless steel 150 litre	9	40,000
Laminar flow cabinet 1800 mm	1	5,000
Accumulating table	1	7,000
Hoist for lifting tanks	1	5,000
Vibromix, Model E2	3	5,000
Balance, 10 kg capacity	1	2,000
Weighing platform, 500 kg capacity	1	5,000
Autoclave, jacketed, fitted with vacuum system and automatic/manual control. Chamber 900 mm x 1450 mm x 1540 mm	1	56,000
Vial washing machine	1	40,000
Stopper washing machine	1	19,000
	Total	222,500

NOTE: Hot water and distilled water should be reticulated to this building

APPENDIX 20

Alabang: Tetanus Department - Equipment Required

Item	Quantity	Cost (US$)
Fermentor Tetano-Paljas	1	70,000
Inactivation tanks, 200 litre capacity	4	22,000
Autoclave (1.2 m long x 0.75 m high x 0.75 m wide)	1	55,000
Jacketed medium preparation vessel 100 l. w.p. 200 kPa	1	8,500
Cross flow laminar flow cabinet 6' x 4'	1	5,000
Balance 1000 g sensitivity 0.1 mg	1	1,000
Balance 10 kg, sensitivity 5 g	1	2,000
Millipore filter holder, 142 mm	1	1,000
Filter press, 20 cm + 20 cm, 20 plates	1	13,000
Hot water service, steam heated, with hot water holding tank of 100 litre capacity and necessary piping	1	14,000
Prefabricated cold room, complete 3.5 m x 3.5 m x 3 m external	1	25,000
Prefabricated warm room, complete with heater, fan and controls.	1	8,000
Air-conditioning plant	1	65,000
	Total	289,500

APPENDIX 21

Alabang: Pertussis-Diphtheria - Equipment Required

Item	Quantity	Cost (US$)
Fermentor: Novo-Paljas (2 x 70 litre)	1	70,000
Autoclave, jacketed, fitted with vacuum system and automatic/manual control. Chamber 0.9 m x 1.45 m x 1.54 m.	1	56,000
	Total	126,000

NOTE: Hot water and distilled water should be reticulated to this building.

Questionnaire

1. Name of Country ..... Indonesia .....

2. Number of Inhabitants ..... 160,000,000 .....

3. Birth rate ..... 2,5 - 3,0% .....

4. Give the names and addresses of institutions manufacturing vaccines for human use:

Perum Bio Farma
Jl. Pasteur 28
P.O. Box 47
Bandung
Indonesia

5. Indicate which of the following (EPI) human vaccines are produced by each manufacturer:

DPT Vaccine ..... Perum Bio Farma .....

BCG Vaccine ..... Perum Bio Farma .....

Polio Vaccine .....

Measles Vaccine .....

BACTERIAL VACCINES

6. Diphtheria Antigen

6.1 Is a seed lot system used for the production strain. Give brief details:

The production of diphtheria toxin is based on a seed lot system. A new lyophilized ampoule strain NW 2000 is used for every new batch which should have the same characteristics as cultures of the strains from which the parent seed lot was derived.

6.2 Indicate whether a fermenter or other culture vessel is used for production. Give brief details:

A Novo Pal jas and a New Brunswick IF 25 are used for the diphtheria toxin production.

6.3 Indicate the culture batch size:

a. Volume of Novo fermentor 90 L. Culture volume is 2 x 70 L.
b. Volume of New Brunswick IF 25, 250 L, culture volume is 150 L.

6.4 Indicate the yield of toxin per batch:

a. 2 x 60 litres at 120 Lf/mL.
b. 120 litres at 120 Lf/mL.

6.5 Indicate the yield of purified toxoid per batch:

4.25 litres at 4000 Lf/mL.

6.6 Indicate the purity of the toxoid:

1800 Lf/mg protein nitrogen.

6.7 Indicate the annual production of purified toxoid:

500 M Lf.

7. Tetanus Antigen

7.1 Indicate whether the production building is separate from all other buildings:

The tetanus laboratory is separated from the other building.

7.2 Is a seed lot system used for the production strain. Give brief details:

A seed lot system is used. Every new batch a new lyophilized ampoule is prepared (Massach. A_1) which should have the same characteristics as the culture of the strain from which the parent seed lot was derived.

7.3 Indicate whether a fermenter or other culture vessel is used for production. Give brief details:

Static and fermentor system are used for production of tetanus toxin.

7.4 Indicate the culture batch size:

Fermentor has a culture volume of 800 L and Static (200 L) divided in stainless steel beakers of 20 L volume.

7.5 Indicate the yield of toxin per batch:

fermentor 730 litres at ...40... Lf/mL.
static 170 litres at 30 Lf/mL.

7.6 Indicate the yield of purified toxoid per batch:

....10.. litres at .2000... Lf/mL.

7.7 Indicate the purity of the toxoid:

....1200.-.2000..... Lf/mg protein nitrogen.

7.8 Indicate the annual production of purified toxoid:

.....480.....MLf.

8. Pertussis Antigen

8.1 Is a seed lot system used for the production strain. Give brief details:

The production of pertussis vaccine is based on a seed lot system. Each new batch a new lyophilized ampoule strain (Pelita III) is used, which should have the same characteristics as the strain from which the parent seed was derived.

8.2 Indicate whether a fermenter or other culture vessel is used for production. Give brief details:

A Bilthoven Unit system (R.I.V. - HOLLAND) is used for pertussis production. These include the Super and the Novo Pal jas fermentors.

8.3 Indicate the culture batch size:

Super Pal jas 70 L culture volume
Novo Pal jas 3 x 70 L culture volume

8.4 Indicate the number of B.pertussis organisms in a harvest:

15 - 25 billion organisms per mL.

8.5 Describe briefly how the harvest in inactivated:

After centrifuging the harvest the sediment is resuspended in physiological saline and inactivated by heat at 56°C for 20 minutes in the B10 flasks.

8.6 Indicate the yield of inactivated B.pertussis per batch:
60 L of 48 billion/mL per 70 L culture

8.7 Indicate the annual production of inactivated B.pertussis:
2300 L of 48 billion/mL

9. DPT Vaccine

9.1 Give the formulation that you use:

Diphtheria toxoid	40	Lf/mL
Tetanus toxoid	15	Lf/mL
B.pertussis organisms	24 billion/organisms	mL
Aluminium carrier	3 mg Al PO4/mL	mL

9.2 Indicate the normal batch size:
100 litres.

9.3 Indicate the normal dose size:
1/2 mL.

9.4 How many doses are dispensed in each final container:
10 doses

9.5 Indicate the annual output of dispensed final containers:
1,400,000

9.6 Indicate the name of the dispensing machine and the number of containers it can dispense per day:
Cozoli
20.000/day

9.7 Indicate the target population to be vaccinated each year:
5.000.000

9.8 Indicate the number of doses required per year to meet the program:
15.000.000

9.9 In addition to the information given in 9.8, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:
20%

10. DT Vaccine

10.1 Give the formulation that you use:

Diphtheria toxoid ..... 40 ..... Lf/mL

Tetanus toxoid ..... 15 ..... Lf/mL

Aluminium carrier ..... 3 mg Al PO4/mL ..... mL.

10.2 Indicate the normal batch size:

..... 150 ..... litres.

10.3 Indicate the normal dose size:

..... 1/2 ..... mL.

10.4 How many doses are dispensed in each final container:

..... 50 doses .....

10.5 Indicate the annual output of dispensed final containers:

..... 250,000 @ 25 mL .....

10.6 Indicate the target population to be vaccinated each year:

..... 9.000.000 .....

.....

.....

.....

.....

10.7 Indicate the number of doses required per year to meet the program:

..... 10.000.000 - 12.500.000 .....

10.8 In addition to the information given in 10.8, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

..... 20 - 30% .....

.....

11. Monovalent Vaccines

11.1 Do you make and use a diphtheria vaccine and/or a tetanus vaccine. Give details of formulations:

Tetanus toxoid adsorbed is produced.....

It contains in one mL, 20 Lf toxoid, 3 mg Al PO4 and.....

0.1 mg merthiolate.....

.....

.....

11.2 Indicate the normal batch size:

.....100..... litres.

11.3 Indicate the normal dose size:

.....1/2..... mL.

11.4 How many doses are dispensed in each final container:

.....10 doses.....

11.5 Indicate the annual output of dispensed final containers:

.....2.400.000 vials @ 5 mL.....

11.6 Indicate the target population to be vaccinated each year:

.....20 - 25 million.....

.....

.....

.....

.....

11.7 Indicate the number of doses required per year to meet the program:

.....14 million doses.....

11.8 In addition to the information given in 11.7, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

.....20%.....

.....

12. Quality Control of DPT Vaccine

Indicate whether full testing for compliance with WHO requirements is carried out for each vaccine antigen and for the final vaccine. If not, briefly describe the variations which occur.

12.1 Diphtheria Antigen:

.....

Potency test on Diphtheria vaccine is done using guinea pigs -.

Determination of antitoxin unit.

All other tests in compliance with WHO requirements.

.....

.....

.....

.....

12.2 Tetanus Antigen:

.....

.....Yes.....

.....

.....

.....

.....

.....

.....

12.3 Pertussis Antigen:

.....

.....Yes.....

.....

.....

.....

.....

.....

.....

12.4 DPT Vaccine:

.....

Potency of Diphtheria component is done using guinea pigs -.....

Determination of antitoxin.....

.....

All other tests in compliance with WHO requirements.....

.....

.....

.....

12.5 DT Vaccines:

.....

Potency of Diphtheria component is done using guinea pigs -.....

Determination of antitoxin.....

All other tests in compliance with WHO requirements.....

.....

.....

.....

.....

13 BCG Vaccine

13.1 Indicate whether the production building is separate from all other buildings:

The production building is separated from the other building...

13.2 Is a seed lot system used for the production strain. Give brief details:

The BCG vaccine production is based on a seed lot system.....
The secondary seed lot from Institute Pasteur Strain 1173 P2...
is used. Not more than 8 passage should be used.....

13.3 Indicate whether production is by the Copenhagen process or in a fermenter:

The production is by the Copenhagen process.....
Using a surface culture of BCG on the liquid souton medium.....

13.4 Indicate whether the vaccine is liquid or freeze-dried:

Freeze dried vaccine.....

13.5 What is the normal dose size:

0.075 mgr per 0.1 mL for normal human dose.....

13.6 Indicate the number of doses produced per batch:

240.000 doses per batch.....

13.7 Indicate the number of doses dispensed per final container:

20 doses per final containers.....

13.8 Indicate the number of dispensed final containers produced per year:

550.000 ampoule per year.....

13.9 Indicate the name of the dispensing machine and the number of containers it can dispense per day:

We used the STRUERS FILLING MACHINE 6000 ampoule.....

13.10 Indicate the target population to be vaccinated each year:

5.000.000 - 6.000.000.....

13.11 Indicate the number of doses required per year to meet the program:

.....11.000.000 doses.....

13.12 In addition to the information given in 13.11, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

.....50%.....

.....

VIRAL VACCINES

14. Polio Vaccines

14.1 Is a seed lot system used for each virus strain. Give brief details including the identity of each strain:

.....

.....

.....

.....

.....

.....

14.2 Indicate whether the virus seed lots are tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

14.3 Indicate what cell line is used:

.....

14.4 Is the cell line maintained as a seed lot system:

.....

14.5 Is the cell line seed lot tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

14.6 Indicate whether there are separate production facilities:

.....

.....

.....

.....

.....

14.7 Indicate whether the vaccine is living or inactivated:

.....

14.8 Is the vaccine freeze-dried or liquid:

.....

.....

14.9 Indicate the type of vessel used for cell culture:

.....

.....

14.10 Virus Assay

What is the titre of harvest: .....

What is the titre of final vaccine:

.....

.....

14.11 Indicate the volume of vaccine per batch:

.....

14.12 Is each batch fully tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

14.13 Indicate the total quantity of vaccine produced per year:

.....

14.14 Indicate the normal dose size:

..... mL.

14.15 How many doses are dispensed in each final container:

.....

14.16 Indicate the annual output of dispensed final containers:

.....

14.17 Indicate the name of the dispensing machine and the number of containers it can dispense per day:

.....

.....

14.18 Indicate the target population to be vaccinated each year:

.....

.....

.....

.....

.....

14.19 Indicate the number of doses required per year to meet the program:

.....

14.20 In addition to the information given in 14.19, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

.....

.....

15. Measles Vaccine

15.1 Is a seed lot system used for each virus strain. Give brief details including the identity of each strain:

.....

.....

.....

.....

.....

.....

15.2 Indicate whether the virus seed lots are tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

15.3 Indicate what cell line is used:

.....

15.4 Is the cell line maintained as a seed lot system:

.....

15.5 Is the cell line seed lot tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

15.6 Indicate whether there are separate production facilities:

.....

.....

.....

.....

.....

15.7 Indicate whether the vaccine is living or inactivated:

.....

15.8 Is the vaccine freeze-dried or liquid:

.....

.....

15.9 Indicate the type of vessel used for cell culture:

.....

.....

15.10 Virus Assay

What is the titre of harvest:

.....

What is the titre of final vaccine:

.....

.....

15.11 Indicate the volume of vaccine per batch:

.....

15.12 Is each batch fully tested to WHO Requirements. Give brief details:

.....

.....

.....

.....

.....

.....

15.13 Indicate the total quantity of vaccine produced per year:

.....

15.14 Indicate the normal dose size:

..... mL.

15.15 How many doses are dispensed in each final container:

.....

15.16 Indicate the annual output of dispensed final containers:

.....

15.17 Indicate the name of the dispensing machine and the number of containers it can dispense per day:

.....

.....

15.18 Indicate the target population to be vaccinated each year:

.....

.....

.....

.....

.....

15.19 Indicate the number of doses required per year to meet the program:

.....

15.20 In addition to the information given in 15.19, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

.....

.....

Questionnaire

1. **Name of Country** .....THAILAND.....

2. **Number of Inhabitants** .....50 million.....

3. **Birth rate** .....1.8%.....

4. **Give the names and addresses of institutions manufacturing vaccines for human use:**

.....

4.1 Thai Red Cross, Rama IV Road, Pratumwan, Bangkok, THAILAND

.....

4.2 The Government Pharmaceutical Organization, Rama VI Road, Phya Thai, Bangkok, THAILAND

.....

.....

5. **Indicate which of the following (EPI) human vaccines are produced by each manufacturer:**

DPT Vaccine The Government Pharmaceutical Organization (G.P.O.)

BCG Vaccine The Thai Red Cross

Polio Vaccine .....-.....

Measles Vaccine .....-.....

BACTERIAL VACCINES

6. Diphtheria Antigen

6.1 **Is a seed lot system used for the production strain. Give brief details:**

....Yes... The lyophilized C. diphtheriae PW8-strain is opened into Trypsin or Papain Digested Medium after 48 hrs... The seed tubes are checked for purity... After 4-5 passage daily subculture, these seed tubes are used for the production seed.....

.....

6.2 **Indicate whether a fermenter or other culture vessel is used for production. Give brief details:**

Stationary culture in Trypsin or Papain Digested Medium is used.

Production by fermentor method will be effective in 1987 with the assistance of UNICEF.

6.3 **Indicate the culture batch size:**

300 litres

6.4 **Indicate the yield of toxin per batch:**

200 litres at 80 Lf/mL.

6.5 **Indicate the yield of purified toxoid per batch:**

5 litres at 1,500 Lf/mL.

6.6 **Indicate the purity of the toxoid:**

800 Lf/mg protein nitrogen.

6.7 **Indicate the annual production of purified toxoid:**

90 million Lf.

7. **Tetanus Antigen**

7.1 **Indicate whether the production building is separate from all other buildings:**

Separated

7.2 **Is a seed lot system used for the production strain. Give brief details:**

Yes. The lyophilized Cl. tetani (Harward strain from Boston Massachusette) is opened into Fluid thioglycollate medium by incubating at 35°C for 24 hrs. The seed tubes are checked for purity. After 4-5 passages, the culture is used for toxin production.

7.3 **Indicate whether a fermenter or other culture vessel is used for production. Give brief details:**

Stationary culture in Mueller & Miller Media with Cl. tetani (Massachusette) is used. The working seed culture were maintained by daily subculture in thioglycollate medium until the culture shows a fall in toxin production. The daily subculture are grown in an anaerobic jar.

7.4 **Indicate the culture batch size:**

100 litres

7.5 Indicate the yield of toxin per batch:

...100... litres at ...30... Lf/mL.

7.6 Indicate the yield of purified toxoid per batch:

.....2.. litres at .1,500.. Lf/mL.

7.7 Indicate the purity of the toxoid:

.....800..... Lf/mg protein nitrogen.

7.8 Indicate the annual production of purified toxoid:

.....144 million..... Lf.

8. Pertussis Antigen

8.1 Is a seed lot system used for the production strain. Give brief details:

.....Yes...The lyophilized seed is opened on to B.G. plate, incubate at 35°C for 72 hrs., check the purity and then inoculate into Cohen & Wheeler liquid medium. Shake at 200 rpm. in incubator for 24 hrs. Do the purity check and use for the production seed.

.....

8.2 Indicate whether a fermenter or other culture vessel is used for production. Give brief details:

.....Culture in solid medium by stationary method is used along with culture in Cohen & Wheeler liquid medium by rolling machine. Production by fermentor method will be effective in 1987 with the assistance of UNICEF.

.....

8.3 Indicate the culture batch size:

.....30 litres.....

8.4 Indicate the number of B.pertussis organisms in a harvest:

.....30 O.U/ml.....

8.5 Describe briefly how the harvest in inactivated:

.....

.....The harvest is inactivated with 0.1% formalin, kept in refrigerator for 3 days.....

.....

.....

.....

8.6 Indicate the yield of inactivated B. pertussis per batch

9 litres of 30 O.U/ml

8.7 Indicate the annual production of inactivated B. pertussis:

300 litres of 40 O.U/ml

9. DPT Vaccine

9.1 Give the formulation that you use:

Diphtheria toxoid	60 Lf/mL
Tetanus toxoid	20 Lf/mL
B. pertussis organisms	40 /ml
Aluminium carrier	2.5 mg/mL

9.2 Indicate the normal batch size:

100 litres

9.3 Indicate the normal dose size:

0.5 mL.

9.4 How many doses are dispensed in each final container:

1 dose and 10 doses

9.5 Indicate the annual output of dispensed final containers:

200,000 vials of 10 doses

9.6 Indicate the name of the dispensing machine and the number of containers it can dispense per day:

King Technofill Model KT320/320L (England)

7,500 vials/day

9.7 Indicate the target population to be vaccinated each year:

1986 - 930,000

1987 - 894,000 80 coverage of children under 1 year

1988 - 862,000

1989 - 932,000 90% coverage of children under 1 year

1990 - 887,000

9.8 Indicate the number of doses required per year to meet the program:

1986 - * 4,947,000; 1987 - 4,776,000; 1988 - 4,583,000; 1989 - 4,958,000; 1990 - 4,718,000

* should be 2.70×10^6

9.9 In addition to the information given in 9.8, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

1986 = 1,836,750; 1987 = 1,189,000, 1988 = 1,146,250; 1989 = 1,239,500; 1990 = 1,179,500 25 %

10. DT Vaccine

10.1 Give the formulation that you use:

Diphtheria toxoid 4 Lf/mL

Tetanus toxoid 20 Lf/mL

Aluminium carrier 2.5 mg/ mL

10.2 Indicate the normal batch size:

litres.

10.3 Indicate the normal dose size:

0.5 mL.

10.4 How many doses are dispensed in each final container:

10 doses

10.5 Indicate the annual output of dispensed final containers:

110,000 vials of 10 doses

10.6 Indicate the target population to be vaccinated each year:

1986 - 1,698,000 - 80% coverage

1987 - 1,745,000

1988 - 1,778,000

90% coverage for primary school entrants

1989 - 1,799,000

1990 - 1,826,000

10.7 Indicate the number of doses required per year to meet the program:

1986 - 304,500; 1987 - 580,000; 1988 - 589,000; 1989 - 598,250; 1990 - 607,000 doses 25%

10.8 In addition to the information given in 10.7, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

1986 - 564,500 - 1987 - 580,000; [illegible] 589,000; 1989 - 598,250; 1990 - 607,000 doses 25 %

11. Monovalent Vaccines

11.1 Do you make and use a diphtheria vaccine and/or a tetanus vaccine. Give brief details of formulations:

We made adsorbed Tetanus toxoid which compose of purified Tetanus toxoid 10 Lf per dose and adsorbed with Aluminium hydroxide Gel 1.25 mg. per dose

11.2 Indicate the normal batch size:

300 litres.

11.3 Indicate the normal dose size:

0.5mL.

11.4 How many doses are dispensed in each final container:

10 doses

11.5 Indicate the annual output of dispensed final containers:

330,000 vials of 10 doses

11.6 Indicate the target population to be vaccinated each year:

1,5 million doses

11.7 Indicate the number of doses required per year to meet the program:

2.0 million doses

11.8 In addition to the information given in 11.7, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

25 %

12. Quality Control of DPT Vaccine

Indicate whether full testing for compliance with WHO requirements is carried out for each vaccine antigen and for the final vaccine. If not, briefly describe the variations which occur.

12.1 Diphtheria Antigen:

Full testing in process of Diphtheria antigen by G.P.O. and dt, DPT final vaccine by The National Quality Control Laboratories follow by WHO requirements is carried out.

12.2 Tetanus Antigen

Full testing in process and in final product

12.3 Pertussis Antigen:

Full testing in process is carried out but most of the Pertussis antigen was not met the WHO requirements in potency test. In order to supply DPT vaccine to meet demand of the country. Pertussis component was imported

12.4 DPT Vaccine:

Full testing by G.P.O. and The National Quality Control Laboratories of Biological Products is carried out

12.5 DT Vaccines:

Full testing by both G.P.O. and The National Quality Control Laboratories of Biological Products is carried out

13. BCG Vaccine

13.1 Indicate whether the production building is separate from all other buildings:

Separated

13.2 Is a seed lot system used for the production strain. Give brief details:

Yes

13.3 Indicate whether production is by the Copenhagen process or in a fermenter

By the Copenhagen Process

13.4 Indicate whether the vaccine is liquid or freeze dried:

Freeze-dried

13.5 What is the normal dose size:

0.1 ml

13.6 Indicate the number of doses produced per batch:

5,000 x 10 doses/batch

13.7 Indicate the number of doses dispensed per final container:

10 doses

13.8 Indicate the number of dispensed final containers produced per year:

5,000 x 4 x 12 vials = 240,000 vials

13.9 Indicate the name of the dispensing machine and the number of containers it can dispense per day:

Brewer (U.S.A.)

1,425 - 2,850 vials/hr.

13.10 Indicate the target population to be vaccinated each year:

	children < 1 year	1 school entrant
1986 - 930,000	1,698,000	
1987 - 894,000	1,746,000	
1988 - 862,000	1,772,000	
1989 - 932,000	1,789,000	
1990 - 887,000	1,881,000	

13.11 Indicate the number of doses required per year to meet the program: (including wastage)

1986 - 5,251,000; 1987 - 5,278,000; 1988 - 5,268,000; 1989 - 5,412,000; 1990 - 5,486,000 doses

13.12 In addition to the information given in 13.11, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

1986 - 1,314,000; 1987 - 1,319,500; 1988 - 1,317,000; 1989 - 1,368,000; 1990 - 1,356,500 doses

VIRAL VACCINES

14. Polio Vaccines- It is not yet produced, it was imported

14.1 Indicate the target population to be vaccinated each year:

1986 - 930,000	
1987 - 894,000	80 % coverage
1988 - 862,000	
1989 - 932,000	90% coverage of children undere 1 year
1990 - 887,000	

14.2 Indicate the number of doses required per year to meet the program:

1986 - 4,947,000; 1987 - 4,780,000; 1988 - 4,858,000; 1989 - 4,958,000; 1990 - 4,718,500 doses -

14.3 In addition to the information given in 9.8, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

1986 - 1,236,750; 1987 - 1,189,000; 1988 - 1,146,250; 1989 - 1,239,500; 1990 - 1,179,500 doses 25 %

15. Measles Vaccine

It is not yet produced. It was imported.

15.1 Indicate the target population to e vaccinated each year:

1986 - 930,000

1987 - 894,000 80 % coverage for children under 1 year

1988 - 862,000

1989 - 932,000 90% coverage of children under 1 year

1990 - 887,000

15.2 Indicate the number of doses required per year to meet the program:

1986 - 1,236,000; 1987 - 1,189,000; 1988 - 1,146,000; 1989 - 1,239,000; 1990 - 1,179,000 doses -

15.3 In addition to the information given in 15.2, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

1986 - 309,000 ; 1987 - 897,250; 1988 - 286,500; 1989 - 307,750; 1990 - 294,750 doses

Questionnaire

1. Name of the country: Republic of the Philippines
2. Number of Inhabitants: 52 million
3. Birth rate: According to EPI/GEN/83/in 1982, it was 214% i.e. 1,250,000
4. Give the names and addresses of institutions manufacturing vaccines for human use:

   Bureau of Research and Laboratories
   Ministry of Health
   Manila
5. Indicate which of the following (EPI) human vaccines are produced by each manufacturer:

   DPT Vaccine: X under experimentation on the Fermentor System.
   BCG Vaccine: X
   Polio Vaccine:
   Measles Vaccine:

BACTERIAL VACCINE

6. Diphtheria Antigen

6.1 Is a seed lot system used for the production strain. Give brief details:
Yes, Seed lot system is used. A freeze-dried C. diphtheria P & W # 8 strain (obtained from Connaught Laboratories, Canada) is inoculated on Loeffler's agar plate or slopes and from which the seed cultures in Erlenmeyer flasks are inoculated after 24-36 hours growth at 35-36°C.

6.2 Indicate whether a fermentor or other culture vessel is used for production. Give brief details:
A static flask production is used. As soon as sufficient growth is already obtained in the erlenmeyer flask, eventually these are inoculated to roux flasks and incubated at 35-36°C for six to seven days. We have a fermentor machine but it cannot be fully utilized in the fermentor medium as influenced by locally available materials. Some reagents and apparatus are not available in the laboratory to analyze such medium

6.3 Indicate the culture batch size:
40 liters per Batch (500 ml of the medium is dispensed into each each of 80 Roux flasks)

6.4 Indicate the yield of toxin per batch:
30 litres at 80-90 Lf/mL.

6.5 Indicate the yield of purified toxoid per batch:
600 ml litres at 3,000 Lf/mL.

6.6 Indicate the purify of the toxoid:
2,000 Lf/mg protein nitrogen.

6.7 Indicate the annual production of purified toxoid:
18,000,000 Lf.

7. Tetanus Antigen

7.1 Indicate whether the production building is separate from all other buildings:
A separate building is used exclusively for tetanus toxin production.

7.2 Is a seed lot system used for the production strain. Give brief details:
Yes, Seed lot system is used in production. Our seed culture originated form a lyophilized Harvard Strain # 49205 of Clostridium tetani obtained from the Institute of Laboratories, Boston. New batch of lyophilized strain are made after 2 transfers in fluid thioglyocollate medium.

7.3 Indicate whether a fermentor or other culture vessel is used for production. Give brief details:
Fermentor vessel is not used presently because of the problem encountered during the trial operation such as insufficient vibroximixing; defective air filters clogged exhaust valve to release condensate etc. The culture vessel used is a pyrex cylindrical jar with handle (25 litres capacity), equipped with cover made up of layers of cotton sandwiched between layrs of gauze, with outfits for inoculation and withdrawal of culture.

7.4 Indicate the culture batch size:
Each batch of culture is 50 liters medium dispensed in 4 jars with 12.5 liters medium per jar.

7.5 Indicate the yield of toxin per batch:
42 litres at 80 - 100 Lf/mL.

7.6 Indicate the yield of purified toxoid per batch:
1000 ml litres at 2,800 Lf/mL.

7.7 Indicate the purity of the toxoid:
2,000 - 2,500 Lf/mg protein nitrogen

7.8 Indicate the annual production of purified toxoid:
50,400,000 Lf.

8. Pertussis Antigen

8.1 Is a seed lot system used for the production strain. Give brief details:
No. For every batch of production a new lyophile is used. Presently two strains namely; 509 and 134 are individually used per culture batch and pooled together after detoxification to comprise a lot of vaccine. B pertussis strain 509 was obtained from the culture collection of the National Institute of Public Health, Bilthoven, The Netherlands and B. pertussis strain 134 obtained from Dr. Pellemer, Lederle.

8.2 Indicate whether a fermenter or other culture vessel is used for production. Give brief details:
Presently the fermentor system is used in the experimental production of pertussis. After the seed culture has grown in another medium which is the Verwey medium it is inoculated into the B_2 medium in the fermentor, and cultivated for about 60 hours after which it is further processed by centrifugation, decanting, pooling, resuspension and dilution of a minimum of 200 capacity units per ml.

8.3 Indicate the culture batch size:
Each culture is 40 liters in a 50-liter capacity vessel.

8.4 Indicate the number of B. pertussis organisms in a harvest:
A harvest may contain approximately from 40-50 million organisms per ml.

8.5 Describe briefly how the harvest is inactivated:
After cultivation the culture fluid is dispensed and centrifuged. After taking off the supernatant, the bacterial sediments are resuspended in buffered saline. After peeling and homogenization of the suspension the bacterial concentration is diluted to 200 capacity unit per ml. Suspension are brought in a special bottle for heating at 56°C during 10 minutes for inactivation.

8.6 Indicate the yield of inactivated B. pertussis per batch:
The yield per batch of inactivated B. pertussis is approximately 70,000 doses

8.7 Indicate the annual production of inactivated B. pertussis:
The annual production of inactivated B. pertussis is approximately 1,680,000 doses at the rate of 2 batches per month of 70,000 doses per batch.

9. DPT Vaccine

9.1 Give the formulation that you use:

Diphtheria toxoid	30	Lf/mL
Tetanus toxoid	20	Lf/mL
B. pertussis organisms	32 Opacity Unit	/mL
Aluminium carrier	1.32 mg/	/mL

9.2 Indicate the normal batch size:
2,500 ml (Experimental presently being undertaken). Normally each batch should consist of 35 liters equivalent to 70,000 doses.

9.3 Indicate the normal dose size:
0.5 ml/dose. The pertussis production is supported by manual production of diphtheria and tetanus toxoid.

9.4 How many doses are dispensed in each final container:
20 doses

9.5 Indicate the annual output of dispensed final containers:
The annual output of dispensed final containers is approximately 84,000 vials. This will only be when 5 consecutive lots of DPT have passed external quality control test.

9.6 Indicate the name of the dispensing machine and the number of containers it can dispense per day:
Bausch and Strobel, Western Germany Type UFVK 1001; No. 4231
The machine is not in use at present because we do not know how to sterilize it. The number of containers it can dispense per day has not yet been determined

9.7 Indicate the target population to be vaccinated each year:
The target populatiion which can be vaccinated with the estimated number of vials (84,000) to be produced is 560,000 by applying the 3-dose immunization scheme.

9.8 Indicate the number of doses required per year to meet the programme:

The number of doses required per year to meet the program is approximately 1.680,000 doses.

9.9 In addition to the information given in 9.8, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

21 - 25 %

10. Monovalent Vaccines

10.1 Do you make and use a diphtheria vaccine and/or a tetanus vaccine. Give brief details of formulations:

No diphtheria monovalent vaccine is produced. It is used in the Production of DPT vaccine. We make and use the monovalent tetanus vaccines at 30 Lf/ml adsorbed with Aluminium phosphate suspension.

10.2 Indicate the normal batch size:

16 litres.

10.3 Indicate the normal dose size:

0.5mL.

10.4 How many doses are dispensed in each final container:

20 doses

10.5 Indicate the annual output of dispensed final containers:

150,000 vials

10.6 Indicate the target population to be vaccinated each year:

Only 60 % will be dosed 2,500,000

10.7 Indicate the number of doses required per year to meet the program:

3,000,000 doses

10.8 In addition to the information given in 10.7, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:

25 % wastage on number of doses required per year.

12. Quality Control of DPT Vaccine

Indicate whether full testing for compliance with WHO requirements is carried out for each vaccine antigen and for the final vaccine. If not, briefly describe the variations which occur.

12.1 Diphtheria Antigen:

Full testing in accordance with WHO requirements is carried out in the final bulk and/or final lot.

12.2 Tetanus Antigen:

Full testing in accordance with WHO requirements is carried out in the final bulk and/or final lot.

12.3 Pertussis Antigen:

Full testing in accordance with WHO requirements is carried out in the final bulk and/or final lot.

12.4 DPT Vaccine

Experimental lots are scheduled for the current year. One lot it undergoing quality control testing in accordance with WHO requirements.

12.5 DT Vaccine

Full testing in accordance with WHO requirements is carried out in the final bulk and/or final lot.

13. BCG Vaccine

13.1 Indicate whether the production building is separate from all other buildings:

The BCG building is separate from other buildings

13.2 Is a seed lot system used for the production strain. Give brief details:

Seed Lot system is used for production. French Strain 1173 P_2 is used which is supplied by Statens Serum Institute, Copenhagen Denmark.

13.3 Indicate whether production is by the Copenhagen process or in a fermenter

By the Copenhagen process

13.4 Indicate whether the vaccine is liquid or freeze dried:

Freeze-dried

13.5 What is the normal dose size:

0.1 ml

13.6 Indicate the number of doses produced per batch:

One batch consists of 7,000 ampoules, 20 dose/ampoule equivalent to 140,000

13.7 Indicate the number of doses dispensed per final container:
20 doses per ampoule

13.8 Indicate the number of dispensed final containers produced per year:
The number of dispensed final containers is about 250,000 ampoules per year equivalent to 5,000,000 doses

13.9 Indicate the name of the dispensing machine and the number of containers it can dispense per day:
The number of dispensing machines (Brewer Automatic Pipetting Machine) used for 3 hours to dispense 7,000 - 7,500 ampoules per batch.

13.10 Indicate the target population to be vaccinated per batch.
Target population is about 4,500,000 a year

13.11 Indicate the number of doses required per year to meet the program:
Number of doses required per year is 4,500,000 doses

13.12 In addition to the information given in 13.12, indicate the number of doses which will be wasted during administration of the vaccine from multi-dose containers:
Wastage during the administration of the vaccine is 15-20% of the number of doses required per year

VIRAL VACCINES - Not manufactured