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ESTABLISHMENT OF A PILOT DEMONSTRATION PLANT FOR THE PRODUCTION OF VACCINES FOR AFRICA

XA/RAF/88/666

CAMEROON

Technical report: Establishment of a pilot demonstration plant for the production of tetanus vaccines at Lanavet*

Prepared for the Government of Cameroon
by the United Nations Industrial Development Organization

Based on the work of J. Zsidai and L.Gy. Hegedüs

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Chemical Industries Branch

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* This document has not been edited.

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Their professional caliber and skill which provided the grounds for the outcome of this mission is hereby recognised.

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EXPLANATORY NOTES

1 USD = 310 CFA

APPROVAL - The certification that the batch under evaluation meets the required level of quality.

An approval is needed for proceeding to the subsequent manufacturing step /process approval/ or to release any batch for sale /final approval/.

BATCH - A specific quantity of biological produced during a defined cycle of manufacture. The main criterium of a manufacturing batch is its homogeneity.

CROSS CONTAMINATION - The introduction in a product, by any cause, of one or more components /regardless of amount/ which is not part of the actual formula of that product and it is not supposed to be part of its composition. The mixing up of different products amoung themselves.

G.M.P. - /Good Manufacturing Practices/ - The whole of all those rules, procedures and actions necessary to assure the highest degree of quality, purity and activity of a pharmaceutical product.

N.C.L. - /National Control Laboratory/ - An independent governmental laboratory for testing and release of imported or locally produced human vaccines.

STERILITY - The complete and total absence of living organism /e.g. in a pharmaceutical product/.

STERILIZATION- The complete destruction or removal of all living organisms, esp. microorganisms.

VALIDATION - The action of proving that any equipment, or piece of, process, procedure, etc., used during the manufacture or the control of a product will and/or does achieve the desired and intended results.

ABREVIATIONS

AU - Antitetanus Unit

DPT - Diphtheria-Pertussis-Tetanus vaccine, adsorbed

DT - Diphtheria-Tetanus vaccine, adsorbed

EP - European Pharmacopeia

EPI - Expanded Programme on Immunization

IOU - International Opacity Unit

IU - International Unit

LANAVET - Laboratoire National Vétérinaire

Lf - Limes flocculans

MOH - Ministry of Health

OCEAC - Organization for the Control of Epidemic Diseases in Central Africa

QC - Quality Control

TRS - Technical Report Series /Issued by WHO/

TT - Tetanus toxoid vaccine, adsorbed

SOP - Standard Operation Procedure

UDEAC - Union Douaniére de l'Etat de l'Afrique Centrale. /Cameroon, Central African Republic, Democratic Republic of Congo, Gabon, Tchad/

WHO - World Health Organization.

SUMMARY AND RECOMMENDATIONS

The purpose of the project is the establishment of a Pilot Production Plant for the production of human vaccines at the premises of LANAVET in Cameroon.

1. Based on the Cameroonian and Central African /UDEAC/ statistical data and the National Immunization Programme of Cameroon the domestic and export demand has been determined. DPT and Polio vaccines are proved to be the biggest items with a yearly demand of more than 4 million doses each. For the Tetanus toxoid vaccination of the present target population appr. 16-17 million doses are required.
   An estimated marketing programme has been worked out for the years 1990-94 with a marketing strategy proposal. The required capacity for the planned production units has been determined with additional filling capacity for veterinary vaccines and other injectables.
   Detailed costing estimates have been prepared for the products;
   TT vaccine CFA 111.37-148.50/20 dose vial
   DPT vaccine CFA 273.90-365.20/20 dose vial
   DT vaccine CFA 273.90-365.20/20 dose vial
   These prices were compared with the presently registered import prices in Cameroon and found much lower. /page ..../
   Sales revenue for a 5 year period /1990-94/ has been prepared together with the relevant production programme.
   Materials and inputs for the 1990 production programme have been calculated and specified included security stock.
   Manpower requirement has been analysed in detailes, /4 academics, 9 senior technicians, 12 technicians/ proposal for the duration and content of the training has been given.
   Recommendations:
   - A powerful sales force should be established in limited number of staff for the domestic and export marketing. The same unit could be responsible for the direct importation /shipping/ clearing of various materials which could save funds.
   - Domestic marketing strategy should trend to convince health authorities to base immunization programmes on the locally produced vaccines.
   - All efforts should be made to build up useful connections with potential export partners in the Central African /UDEAC/ subregion and other regions.

- Training of technical staff should be performed in the Institute providing technology.

2. Considering the present possibilities of LANAVET, establishment of a Tetanus toxoid production, formulation and filling unit has been proposed and designed. Based on the results of demand calculations, the capacity of the proposed Tetanus toxoid production unit is 14.4 million doses of Tetanus toxoid vaccine yearly. Capacity of the formulation unit is 1.4 million 20 dose vials and the filling unit is 2.3 million vials yearly.

Location of the units has been analyzed in detailes together with the optimal utilization of the local infrastructural facilities /water, steam; electricity, air control etc./

Detailed "Terms of reference" of contracting services for the remodelling has been prepared which could form a basis for detailed engineering layout.

List of required machinery with specifications has been compiled. /Total cost is appr. USD 750.000/.

Detailed technological prescriptions have been prepareo for the production of Tetanus toxoid vaccine and for the formulation of DPT and DT vaccines from imported concentrated Diphtheria toxoid and concentrated Pertussis suspension.

Specimen texts for printed components have been prepared in 2 languages.

Recommendations:
- A Tetanus toxoid production and DPT, DT and Tetanus toxoid vaccine formulation unit should be established within the existing facilities of LANAVET.
- A sterile Filling and Finishing unit should be established within the existing facilities of LANAVET.
- The Terms of Reference chapter of this report should serve as basis for the preparation of final plans and engineering layouts.
- Full technology transfer should be arranged for the production of Tetanus toxoid and formulation of DPT, DT and Tetanus toxoid vaccine.
- Equipments should be purchased according to the list presented in the report. Before placing final orders exact specification of machinery /systems/ should be negotiated with LANAVET, subcontractor, consultant, and/or Institute providing technology.

3. Detailed analyzis of the local implementation of Quality control has been prepared on the basis of WHO requirements.
   Recommendations:- A well organized, partially separated Quality control laboratory should be established within the existing facilities of LANAVET.

4. Prefeasibility study has been compiled for the expansion of vaccine production at LANAVET, analyzing techno-economical aspects, too.
   Recommendations:- As a follow up step of this project establishment of a new Bacterial vaccine production unit for Diphtheria toxoid and Pertussis suspension is recommended.
   - BCG vaccine production laboratories could be attached technically to this unit but economically it is not justified.
   - Establishment of Virus vaccine production units is not justified by the economical calculations but in case of positive governmental decision, the realization is technically possible.

5. Project implementation scheduling time programme has been drafted.

1. INTRODUCTION

The present 2 months consultantship is meant to assist Lanavet to establish a Pilot Demonstration Plant for the production of human vaccines. The work undertaken at Lanavet, Garoua, Cameroon was prescribed by UNIDO job descriptions XA/RAF/88/66/11-01-03.

It comprised:

1. Collect all relevant data for a market survey and establish production and product diversification programme.
2. Prepare a market survey for manufacture of vaccines from imported bulk materials and for basic manufacture of different EPI vaccines such as Tetanus and DPT vaccines.
3. Discuss the acceptance and price of Tetanus toxoid vaccine with concerned government officials.
4. Identify technological requirements for the establishment of a vaccine filling and packaging unit.
5. Develope a production programme to utilize the installed production capacity.
6. Prepare the final detailed engineering layout, design of remodelling/ reconstruction and changes required at the existing facilities of LANAVET.
7. Prepare the substantive terms of reference of contracting services for remodelling of LANAVET.
8. Develop a quality control programme to utilize the installed laboratory facilities for testing of vaccines.
9. Introduce the quality control of Tetanus toxoid vaccine.
10. Prepare a detailed layout of the quality control unit.
11. Give the specifications of equipements required.
12. Select the LANAVET senior staff for training.
13. Advise names and addresses of training institutions abroad.
14. Prepare a technical report on the mission jointly with the other international experts.

    The job discription set out above was supplemented by UNIDO at the briefing period to include:

15. Prepare a prefeasibility study for the production of all EPI vaccines with the estimate cost of construction and machinery investment.

The duties described in the job description of the mission and the subsequent orientations outlined in the time briefing period at the headquarters have been fulfilled.

The contract started on 4 September 1988 with travel and briefing in Vienna.

Work in Cameroon commenced on 6 September 1988. Within the 2 months term of the contract there were no public holidays. LANAVET was operating a 40 hour work week, Monday through Friday.

LANAVET is provided with reasonable manufacturing capacity in the areas of:

- Bacterial vaccine manufacture for veterinary use
- Viral vaccine manufacture for veterinary use
- Manufacture of diagnostics for veterinary infectious diseases

LANAVET is planning to establish manufacturing facilities for human vaccine production.

II. PROJECT BACKGROUND AND HISTORY

A. Vaccination in Cameroon

Vaccination services have been provided for many years by the Government and Private Sector Hospitals and Clinics, but acces to these services has been limited to about 20 % of the target population.
A National expanded programm on immunization, /EPI/ was launched in 1975 under the Direction of OCEAC /Organization for the Control of Epidemic Diseases in Central Africa/. By 1979, the EPI has been extended to three Administrative Departments and the Ministy of Public Health Assumed responsability for the programme.
The EPI has operated in 182 district fixed health centres, each supplied with cold-chain equipment.

Expanded programme of Immunization /EPI/ became one of the priority programmes in the Ministry of Public Health in 1982.

A goal has been set in 1985 to vaccinate 85 % of all children under five years of age by the year 1990, and to administer tetanus toxoid to all pregnant women /women between 15 and 49 year/.

The total population is just under 11 Million. 37 % of the total population lives in urban communities but this figure varies from 10 % to 81 % in different parts of the country.

Sample surveys show that only 30 % of the target group of children /over 1.600.000 children under five years of age/ has completed their immunization schedule in 1985, varying between 23 - 49 % in urban areas, and less than 5 - 23 % in rural areas.
In 1985, Cameroon joined other African countries in declaring 1986 African vaccination year.
By the end of 1985, the EPI network throughout the country included 500 fixed centres, one-third of which were operated by non Government organizations. Acces to vaccination services had been existed to about 70 % of the population. Due to Cameroon's national vaccination campaign of 1986 the above figure improved to 49.7 % in urban areas and 45.9 % in rural areas. /Results of the post-campaign coverage survey may 1987 Annex 1/.

A total of over 4 million doses of BCG, DPT, Polio, Measles and Tetanus Toxoid vaccines were administered during the three campaign days. This is about equal to the number of vaccines given during the whole of 1986 by the routine services.
The campaign costs approximately USD 3,724.000 of which USD 3.1 million were provided by the Government. The finantial cost of each vaccination was USD 0.40 compared with USD 0.11 in routine services. The campaign costed finantially USD 8.33 for each fully immunized child compared with the cost of USD 2.19 in routine services.

Infant mortality has slowly declined from about 160 deaths per 1000 live births in 1950 to about 92 in 1986. Even the most favourable projection of this trend however will result in a reduction to only about 67 deaths per thousand live births by the year 2000.

The principal causes of morbidity and mortality among the 1.600.000 Cameroon children under five years of age - of whom about 350.000 are under one year - are malaria, acuite respiratory illness, intestinal parasites, diarrhoeal diseases, measles, diphtheria, pertussis, polyomyelitis and neonatal tetanus.

The national EPI schedule of Cameroon is given in Annex 2.

Basic data for the population is given in Annex 3.

Data for the target population is given in Annex 4.

Comperativ table of immunization is given in Annex 5.

B. Project background

1977/78 First contact between UNIDO and the Government of Cameroon about UNIDO support for the establishment of a National Control Laboratory and vaccine production facilities in Yaounde.

1982/83 Five Cameroon scientists were trained in Hungary for production and QC of acterial vaccines for more than a year. Basic equipments required for the filling unit were delivered.
Due to non availability of the required laboratory facilities in Yaounde the trained scientists had to leave the project and the equipments are still staying unpacked for 5 to 6 years.

1983 The Government of Cameroon has started construction of a veterinary center in Garoua with bilateral technical assistance of the French Government. The center called Laboratoire National Vétérinaire /LANAVET/ was belonging to the Ministry of Livestock, Fisheries and Animal Industry

1985 Jan. It was agreed between the Government of Cameroon and UNIDO to establish a "Pilot Demonstration Plant for Production of Human Vaccines" in the facilities of LANAVET.

1985 April First UNIDO Mission
It was agreed that for establishment of the pilot scale production plant, for technology transfer tetanus would be taken as bacterial and measles as virus vaccine.

1985 Oct. Second UNIDO Mission took place for technical evaluation The Dutch consultant suggested to change from measles to rabies as virus vaccine.

1986 March The suggestion of changing from measles to rabies has been taken over by the advisory Panel and UNIDO. Further it was emphasized that the establishment of a National Control Laboratory should be given high priority.

1986 Aug. Third UNIDO Mission

Government of Cameroon confirmed its interest in the project. Although rabies vaccine was accepted as on example for virus vaccine production, the Ministry of Health expressed its preference for the measles vaccine which standpoint was finally taken over by the representatives of other Ministries.

Tetanus as bacterial vaccine was accepted.

Government of Cameroon was interested in the establishment of a National Control Laboratory in Yaounde.

At least one year of training period was requested at the facilities of the contractor.

Detailed lay-out of the changes for the establishment of the demonstration plant at LANAVET was requested.

Response to the above:

the consultants expressed that the establishment of measles vaccine production in the existing facilities of LANAVET is not feasible for various reasons. Disagreement on this point will delay considerably realization of the project.

Government of Cameroon should apply for support for establishment of NCL at UNIDO in Vienna. From the original budget in 1979/80 still about USD 80,000 was available for the delivery of the required equipments.

A training period of 6 months was accepted. It was promised that the basic lay-outs for the rebuilding of the existing facilities will be provided soon.

III. MARKET SURVEY AND ECONOMIC ASPECTS OF HUMAN VACCINE PRODUCTION

A. Domestic market

The size and composition of the present effective market demand can be determined relatively reliably from the available statistical data.

The total demand can be divided into 2 essential groups.

The first group shows the quantity required for the uncovered target population originated from the low vaccination coverage of the country. This single vaccination demand could be fulfilled in appr. 2-4 years by making available the required quantity of vaccines, increasing planning and organization and improving certain conditions /increasing number of vaccination centres, securing appropriate cold chain system, social mobilization, conveying clear and specific messages to the target families, etc./

The calculation was made from the available epidemiological information of the target population.

Estimated demand of EPI vaccines for the immunization of the present population in Cameroon

BCG

Target population 1987 /OCEAC/		
0-5 years	1 686 262	
mean coverage 65 %, uncovered		590 192
0-14 years	2 803 411	
5-14 years	1 117 149	1 117 149
		1 707 341
Booster /appr. 20 %/		341 468
Wastage /appr. 20 %/		341 468
	Total	2 390 277

DTP

Target population 1987 /OCEAC/		
0-5 years	1 686 262	
mean coverage 50 %, uncovered		843 131
DPT 1,2,3 and booster		3 372 524
Wastage /appr. 20 %/		674 505
	Total	4 047 029

DT

Target population 1987 /OCEAC/		
5-14 years	1 117 149	1 117 149
Booster		1 117 149
	Total	2 234 298

Polio

Target population 1987 /OCEAC/		
0-5 years	1 686 262	
mean coverage 49 %, unrovered		859 972
Polio 1,2,3 and booster		3 439 886
Wastage /appr. 20 %/		687 978
	Total	4 127 866

Measles

Target population 1987 /OCEAC/		
0-5 years	1 686 262	
mean coverage 41 %, uncovered		994 895
Wastage /appr. 20 %/		198 975
	Total	1 193 870

Based on empirical figures watage could reach 50 % in case of multidose freeze-dried vaccines.

Estimated demand of Tetanus toxoid vaccine for the complete immunization of the present population in Cameroon

Target population 1988 /MOH/		
Women, 15-49 years		
/22 % of the population/	2 419 268	
1st, 2nd, 3rd immunization		7 257 804
Wastage /appr. 20 %/		1 451 561
	Total	8 709 365

The second group of demand is presented by the repeated quantity required for the annualy increasing target population.

Yearly demand of EPI vaccines in Cameroon

Basic data for the calculation	
Population /1987/	10 539 140
Annual growth rate	3.1 %
Target population /0-12 months/	326 713
Wastage estimated	20 %
Number of doses required yearly	
BCG	400 000
DPT 1,	400 000
2,	400 000
3	400 000
booster	400 000
	1 600 000
Polio 1	400 000
2	400 000
3	400 000
booster	400 000
	1 600 000
Measles	400 000

The above calculation is based on a generally accepted vaccination strategy. The local determination of immunization policy is depending on the decision of the local public health system of the Government. The accuracy of the above figures is being confirmed by the quantities ordered by the MOH of Cameroon for 1987 and 1988 /Annex 6/.

The dynamically expanding Cameroon is attributing great importance to the development of the health services. This effort and the competent personnels of MOH are the guarantees that the vaccine requirements of the fast increasing population will always be fulfilled, especially if vaccines will be provided in good quality by a local manufacturer.

At present the purchase power of the private sector is not significant, but gradually it could develop to an important market potencial. For the time being size of the private market is being below 1 % but by the increasing number of doctors and pharmacy shops it could reach 5 % within few years.

Thoughts about the marketing activities will be further presented, but it is obvious that the whole production of the "Human Vaccine Department" of LANAVET - when the premises are fully used - can not be purchased by the Cameroonian government.

B. Export markets

1. Central Africa /UDEAC/

As export market, in the first place the Central African subregion /UDEAC/ can be selected for the first few years of production. Total population of the Central African /UDEAC/ countries is appr. equivalent to the population of Cameroon. The public health statistics are also similar /Annex 7/.
Anticipated the vaccine coverage and the vaccination trends to be similar to the Cameroonian figures, the Central African /UDEAC/ EPI vaccine demand is the following.

Yearly demand of EPI vaccines
in Central African subregion /UDEAC/

Basic data for the calculation	
Population /1987/	22 000 000
Annual growth rate	4 %
Target population /0-12 months/	880 000
Wastage estimated	20 %
Number of doses required yearly	
BCG	1 056 000
DTP 1	1 056 000
2	1 056 000
3	1 056 000
booster	1 056 000
	4 224 000
Polio 1	1 056 000
2	1 056 000
3	1 056 000
booster	1 056 000
	4 224 000
Measles	1 056 000

2. Other regions

In order to utilize its feasible working capacity LANAVET must pursue a determined course of export policy from the beginning of the production. There are large potential export markets in Africa fo example the neighbouring Nigeria with a population of 5 times bigger than the total population of Central Africa.

C. Marketing strategy

The aims and objectives of a government owned company in a competitive market could be defined as;

- Production of safe, efficacious and quality medicines in a way that will lead the country towards self sufficiency in essential drugs.
- Distribution and sale of products at prices that resonably be fair and affordable.

Since in this case the major buyer is the Government itself, close contact between the Marketing Dept. of LANAVET and the Purchasing Dept. of the MOH is very important.

The production period of vaccines is relatively long compared to other pharmaceutical products. Therefore the Government could facilitate the Production Planning by placing orders well in advance and on the whole giving forecasts.

Although the EPI vaccines are generic products the local and export private markets require strong marketing efforts and well trained marketing personnel.

Since at the beginning LANAVET as manufacturer of human pharmaceuticals will be completely unknown to the medical profession the need for samples and medical promotional materials will be remarkable.

The Senior Marketing Officer must train the salesman how to visit the Physician. How to present the company's products, how to describe their properties stressing their superiority without "talking bad" of competitive products, present medical literature of interest, draw attention to the side effects and precautions, etc.

When the budget has been fixed a detailed break-down of sales and marketing programmes must be provided for the marketing people.

They have to constantly improve their ability to make forecasts, considering their own and competitors influence on the market, customers reactions and preferences, likely development of public health sevices, etc.

D. Sales forecast and production programme

Based on the present purchases of Ministry of health and the demand calculation given before, the following sales forecast is provided for the years 1990-1994, followed by the break-down of the relevant production programme and antigen requirements.

Estimated marketing programme for the period of 1990-1994

Description of product	1990			1991		
		Export			Export	
	Cameroon	Centr. Afr.	Other regions	Cameroon	Centr. Afr.	Other regions
TT vacc. ads. 10 ml,20 dose	230000	110000	100000	230000	110000	200000
DPT vacc.ads. 10 ml,20 dose	80000	20000	20000	80000	40000	50000
DT vacc. ads. 10 ml,20 dose	60000	20000	20000	60000	20000	20000

Formulation and filling programme for the above marketing programme

TT vacc.ads.10 ml,20 dose	25 batches of 200 litres = =25x18000 vials=450000 vials	30 batches of 200 litres = =30x18000 vials=540000 vials
DPT vacc.ads.10 ml,20 dose	7 batches of 200 litres= =7x18000 vials=126000 vials	10 batches of 200 litres= =10x18000 vials=180000 vials
DT vacc.ads. 10 ml,20 dose	6 batches of 200 litres= =6x18000 vials=108000 vials	6 batches of 200 litres= =6x18000 vials=108000 vials

Fermentation, concentration and purification programme for the above formulation programme

Tetanus conc.toxoide	25 batches of TTx4 million Lf=100 million Lf	30 batches of TTx4million Lf=120 million Lf
	7 batches of DPTx2 million Lf=14 million Lf	10 batches of DPTx2million Lf= 20 million Lf
	6 batches of DTx4 million Lf=24 million Lf	6 batches of DTx4 million Lf=24 million Lf
	Total: 138 million Lf	Total: 164 million Lf
	Based on a yield of 4million Lf per fermentation run of 100 litr.=34.5 fermentation run /appr.35 weeks/	Based on a yield of 4 million Lf per fermentation run of 100 litres=41 fermentation runs /appr.41 weeks/

Diphtheria and Pertussis antigen requirement for the above formulation programme

Diphtheria conc.toxoid	7 batches of DPTx6million Lf=42 million Lf	10 batches DPTx6million Lf=60 million Lf
	6 batches of DTx12 million Lf=72 million Lf	6 batches of DTx12 million Lf=72 million Lf
	Total: 114 million Lf	Total: 132 million Lf
Pertussis conc.suspension	7 batches of DPTx6million IOU=42 million IOU	10 batches of DPTx6million IOU=60 million IOU

1992			1993			1994		
	Export			Export			Export	
Cameroon	Centr. Afr.	Other regions	Cameroon	Centr. Afr.	Other regions	Cameroon	Centr. Afr.	Other regions
18000	220000	240000	18000	18000	410000	18000	18000	410000
80000	80000	100000	80000	80000	120000	80000	80000	120000
10000	20000	20000	10000	10000	30000	10000	10000	30000

Formulation and fillling programme for the above marketing programme

27 batches of 200 litres= 27x18000 vials=486000 vials	25 batches of 200 litres= 25x18000 vials=450000 vials	25 batches of 200 litres= 25x18000 vials=450000 vials
15 batches of 200 litres= =15x18000 vials=270000 vials	16 batches of 200 litres= =16x18000 vials=288000 vials	16 batches of 200 litres= =16x18000 vials=288000 vials
3 batches of 200 litres= =3x18000 vials=54000 vials	3 batches of 200 litres= =3x18000 vials=54000 vials	3 batches of 200 litres= =3x18000vials=54000 vials

Fermentation, concentration and purification programme for the above formulation programme

27 batches of TTx4 million Lf= 108 million Lf	25 batches of TTx4 million Lf=100 million Lf	25 batches of TTx4 million Lf=100 million Lf
15 batches of DPTx2million Lf=30 million Lf	16 batches of DPTx2million Lf=32 million Lf	16 batches of DPTx2million Lf=32 million Lf
3 batches of DTx4 million Lf=12 million Lf	3 batches DTx4 million Lf=12 million Lf	3 batches DTx4 million Lf=12 million Lf
Total: 150 million Lf	Total: 144 million Lf	Total: 144 million Lf
Based on a yield of 4 million Lf per fermentation run of 100 litres=37.5 fermentation runs /appr.38 weeks/	Based on a yield of 4 million Lf per fermentation run of 100 litres=36 fermentation runs /appr. 36 weeks/	Based on a yield of 4 million Lf per fermentation run of 100 litres=36 fermentation runs /appr.36 weeks/

Diphtheria and Pertussis antigen requirement for the above formulation programme

15 batches DPTx6million Lf= =90 million Lf	16 batches DPTx6million Lf= =96 million Lf	16 batches DPTx6million Lf= =96 million Lf
3 batches of DTx12 million Lf=36 million Lf	3 batches of DTx12million Lf=36 million Lf	3 batches of DTx12million Lf=36 million Lf
Total : 126 million Lf	Total: 132 million Lf	Total: 132 million Lf
3 batches of DPTx6 million IOU=18 million IOU	3 batches of DPTx6 million IOU=18 million IOU	3 batches of DPTx6 million IOU=18 million IOU

Production programme for 1990

I.quarter	II.quarter	III.quarter	IV.quarter
Fermentation:	Fermentation:	Fermentation:	Fermentation:
Tetanus toxoid 6batches of 100 litre /6 weeks/	Tetanus toxoid 10 batches of 100 litre /10 weeks/	Tetanus toxoid 10 batches of 100 litre /10 weeks/	Tetanus toxoid 9 batches of 100 litre /9 weeks/
			3 batches of 100 litre for security stock /3 weeks/
Formulation and Filling:	Formulation and Filling:	Formulation and Filling:	Formulation and Filling:
Tetanus toxoid vacc. 10 ml/20 dose 3 batches of 200 litre=3x18000 vials /9 days formulation/ /6 days filling/	Tetanus toxoid vacc. 10 ml/20 dose 7 batches of 200 litre=7x18000 vials /21 days formulation/ /14 days filling/	Tetanus toxoid vacc. 10 ml/20 dose 7 batches of 200 litre=7x18000 vials /21 days formulation/ /14 days filling/	Tetanus toxoid vacc. 10 ml/20 dose 8 batches of 200 litre=7x18000 vials /24 days formulation/ /16 days filling/
	DPT vacc.10 ml/20 dose 2 batches of 200 litre=2x18000 vials /6 days formulation/ /4 days filling/	DPT vacc.10ml/20 dose 3 batches of 200 litre=3x18000 vials /9 days formulation/ /6 days filling/	DPT vacc.10ml/20 dose 2 batches of 200 litre=2x18000 vials /6 days formulation/ /4 days filling/
	DT vacc.10 ml/20 dose 2 batches of 200 litre=2x18000 vials /6 days formulation/ /4 days filling/	DT vacc.10 ml/20 dose 2 batches of 200litre=2x18000 vials /6 days formulation/ /4 days filling/	DT vacc.10 ml/20 dose 2 batches of 200 litre=2x18000 vials /6 days formulation/ /4 days filling/

E. Product pricing and estimate of annual sales revenue

1. Product costing card

Product: Tetanus toxoid vaccine adsorbed

Presentation: 10 ml/20 doses packed in boxes of 50 vials

1st phase: Production of purified and concentrated Tetanus toxoid /4 million Lf/

Batch size: 100 litre

Material and labour

The production process requires many kinds of chemicals and biological preparations and there are numerous phases of the production process.

Here we do not give detailes of the calculation. We use an average figure of USD 300/million Lf as direct production cost /material and labour/ which is internationaly experienced at this scale of production.

2nd phase: Formulation. Batch size: 200 litre		Unit price CFA	Total CFA
Material			
Tetanus toxoid concentrated	4 million Lf	93000	372 000
2% Aluminium phosphate gel	56 000 g	2.79	156 240
Sodium chloride /NaCl/	1279 g	1.548	1980
Thiomersal	20 g	58	1 160
Water for injection	140 lit.	7.33	1 027
Labour			
Academics	12 hours	1785.7	21 428.4
Senior technicians	24 hours	892.8	21 427.2
Technicians	24 hours	297.6	7 142.8
			582 405.4

3rd phase: Filling and closing of appr. 18 000 vials /5% overfill, 5% production wastage/ Batch size: 200 litre			
Material			
10 ml vial	18 367 pcs	9	165 303
Rubber stopper	18 367 pcs	6.03	110 753
Aluminium caps.	18 367 pcs	2.01	36 918
Labour			
Academics	16 hours	1785.7	28 571.2
Senior technicians	32 hours	892.8	28.569.6
Technicians	80 hours	297.6	23.808
			393 922.8

4th phase: Packaging of 360 boxes of 50 vials

Material			
Carton box/65 mm x 245 mm x 130 mm/	367 pcs	185	67 895
Direction for use /2 pcs for each box/	734 pcs	8	5 872
Vial label	18 500 pcs	2.0875	38 619
Carton label	380 pcs	6	2 280
Labour			
Academics	-	-	-
Senior technicians	8 hours	892.8	7 142.4
Technicians	16 hours	297.6	4 761.6
			126 570

5th phase: Quality control

Material			
Guinea pig	30 pcs	1240	37 200
Mouse	250 pcs	167.4	41 850
Labour			
Academics	6 hours	1785.7	10 714.2
Senior technicians	15 hours	892.8	13 392
Technicians	30 hours	297.6	8 928
			112 084.2

Direct production cost: CFA 1 214 982.4

Direct production cost for a 20 dose /10 ml/ vial:	CFA 67.5	CFA 67.5	CFA 67.5
Production and administration overhead cost:	50 %	70 %	100 %
	CFA 33.75	CFA 47.25	CFA 67.5
Profit/gross/ 10 %	CFA 10.12	CFA 11.48	CFA 13.5
Sales price /net/	CFA 111.37	CFA 126.23	CFA 148.5

Note: Overhead costs must be very carefully studied before choosing sales price.

2. Product costing card

Product: Diphtheria-Pertussis-Tetanus vaccine adsorbed

Presentation: 10 ml/20 doses packed in boxes of 50 vials

1st phase: Formulation. Batch size: 200 litre		Unit price	Total
Material		CFA	CFA
Concentrated Tetanus toxoid	2 million Lf	93 000	186 000
Concentrated Diphtheria toxoid	6 million Lf	141 670	850 020
Concentrated Pertussis suspension	6 million IOU	162 750	976 500
2% Aluminium phosphate gel	56 000 g	2.79	156 240
Sodium chloride /NaCl/	1 125 g	1.548	1 741.5
Thiomersal	20 g	58	1 160
Water for injection	125 lit.	7.33	916.25
Labour			
Academics	12 hours	1 785.7	21 428.4
Senior technicians	24 hours	892.8	21 427.2
Technicians	24 hours	297.6	7 142.8
			2 222 576.1

2nd phase: Filling and closing of appr. 18 000 vials /5% overfill, 5% production wastage/ Batch size: 200 litre			
Material			
10 ml vials	18 367 pcs	9	165 303
Rubber stopper	18 367 pcs	6.03	110 753
Aluminium caps.	18 367 pcs	2.01	36 918
Labour			
Academics	16 hours	1 785.7	28 571.2
Senior technicians	32 hours	892.8	28 569.6
Technicians	80 hours	297.6	23 808
			393 922.8

3rd phase: Packaging of 360 boxes of 50 vials			
Material			
Carton box/65mm x 245mm x 130 mm/	367 pcs	185	67 895
Direction for use /2 pcs for each box/:	734 pcs	8	5 872
Vial label	18 500 pcs	2.0875	38 619
Carton label	380 pcs	6	2 280

Labour			
Academics	-	-	-
Senior technicians	8 hours	892.8	7 142.4
Technicians	16 hours	297.6	4 761.6
			126 570

4th phase: Quality control

Material			
Guinea pig	97 pcs	1 240	120 280
Mouse	260 pcs	167.4	43 524
Labour			
Academics	18 hours	1 785.7	32 142.6
Senior technicians	25 hours	892.8	22 320
Technicians	90 hours	297.6	26 784
			245 050.6

Direct production cost:	CFA 2 988 119.5		
Direct production cost for a 20 dose /10 ml/ vial:	CFA 166	CFA 166	CFA 166
Production and administration overhead cost:	50 %	70 %	100 %
	CFA 83	CFA 116.2	CFA 166
Profit/gross / 10 %	CFA 24.9	CFA 28.2	CFA 33.2
Sales price /net/:	CFA 273.9	CFA 310.4	CFA 365.2

Note: Overhead costs must be very carefully studied before choosing sales price.

3. Product costing card

Product: Diphtheria-Tetanus vaccine adsorbed

Presentation: 10ml/20 doses packed in boxes of 50 vials

1st phase: Formulation. Batch size: 200 litre		Unit price CFA	Total CFA
Material			
Concentrated Tetanus toxoid 4 million Lf		93 000	372 000
Concentrated Diphtheria toxoid 12 million Lf		141 670	1 700 040
2 % Aluminium phosphate gel	56 000 g	2.79	156 240
Sodium chlorid /NaCl/	1 224 g	1.548	1 895
Thiomersal	20 g	58	1 160
Water for injection	136 lit.	7.33	997
Labour			
Academics	12 hours	1 785.7	21 428.4
Senior technicians	24 hours	892.8	21 427.2
Technicians	24 hours	297.6	7 142.8
			2 282 330.4

2nd phase: Filling and closing of appr. 18 000 vials /5% overfill, 5% production wastage/ Batch size: 200 litre			
Material			
10 ml vial	18 367 pcs	9	165 303
Rubber stopper	18 367 pcs	6.03	110 753
Aluminium caps.	18 367 pcs	2.01	36 918
Labour			
Academics	12 hours	1 785.7	28 571.2
Senior technicians	32 hours	892.8	28 569.6
Technicians	80 hours	297.6	23 808
			393 922.8

3 rd phase: Packaging of 360 boxes of 50 vials			
Material			
Carton box/65 mm x 245 mm x 130 mm/	367 pcs	185	67 895
Direction for use /2 pcs for each box/:	734 pcs	8	5 872
Vial label	18 500 pcs	2.0875	36 619
Carton label	380 pcs	6	2 280

Labour			
Academics	-	-	-
Senior technicians	8 hours	892.8	7.142.4
Technicians	16 hours	297.6	4 761.6
			126 570

4th phase: Quality control

Material			
Guinea pig	92 pcs	1 240	114 080
Mouse	80 pcs	167.4	13 392
Labour			
Academics	12 hours	1 785.7	21 428.4
Senior technicians	20 horus	892.8	17 856
Technicians	60 hours	297.6	17 856
			184 612.4

Direct production cost:	CFA 2 987 435.6		
Direct production cost for a 20 dose /10 ml/ vial:	CFA 166	CFA 166	CFA 166
Production and administration overhead cost:	50%	70%	100%
	CFA 83	CFA 116.2	CFA 166
Profit /gross/ 10%	CFA 24.9	CFA 28.2	CFA 33.2
Sales price /net/	CFA 273.9	CFA 310.4	CFA 365.2

Note: Overhead costs must be very carefully studied before choosing sales price.

The above prices are appr. half of the West African market prices even if they are calculated with the highest overhead cost rates.
Compairing them with the officially accepted Cameroonian import prices it is obvious that the locally produced vaccine prices are for below the import costs of the finished products.

Product	Sales price of the domestic product	Registered import prices
Tetnus toxoid	CFA 148.5o/20 dose	CFA 417.56/single dose!
DPT vaccine	CFA 365.20/20 dose	CFA 511.21/single dose!
DT vaccine	CFA 365.20/20 dose	not registered

It must be imperative that a new costing is compiled for every new batch of raw material supposed to be bought at a price, that differs more than slightly from the previous. If a corresponding increase in sales price can not be applied it must be very seriously considered if the raw material at this high cost should be bought or the item discontinued.
The costing officer must keep records/product costing cards/ of all items manufactured and new calculation made as soon as there has been a change in cost of material, machine time or labour, that is not quite insignificant.
Costing must under all circumstences be reviewed once in a year.
If for political reasons it is permissible to operate at a loss this should be clearly stated that subsidies clearly accounted for.

Estimate of sales revenues

Products	Unit price/CFA		Quantities to be sold/vials/			Sales revenues/CFA/		
Description	export	local	export	local	total	export	local	total
				Year 1				
TT vaccine /20 dose/	126.23	148.50	210 000	230 000	440 000	26 508 300	34 155 000	60 663 300
DPT vaccine/20 dose/	310.40	365.20	40 000	80 000	120 000	12 416 000	29 216 000	41 632 000
DT vaccine /20 dose/	310.40	365.20	30 000	60 000	90 000	9 312 000	21 912 000	31 224 000
Grand total						48 236 300	85 283 000	133 519 300
				Year 2				
			310 000	230 000	540 000	39 131 300	34 155 000	73 286 300
			90 000	80 000	170 000	27 936 000	29 216 000	57 152 000
			40 000	60 000	100 000	12 416 000	21 912 000	34 328 000
						79 483 300	85 283 000	164 766 300
				Year 3				
			460 000	18 000	478 000	58 065 800	2 673 000	60 738 800
			180 000	80 000	260 000	55 872 000	29 216 000	85 088 000
			40 000	10 000	50 000	12 416 000	3 652 000	16 068 000
						126 353 800	35 541 000	161 894 800
				Year 4				
			428 000	18 000	446 000	54 026 440	2 673 000	56 699 440
			200 000	80 000	280 000	62 080 000	29 216 000	91 296 000
			40 000	10 000	50 000	12 416 000	3 652 000	16 068 000
						128 522 440	35 541 000	164 063 440
				Year 5				
			428 000	18 000	446 000	54 026 440	2 673 000	56 699 440
			200 000	80 000	280 000	62 080 000	29 216 000	91 296 000
			40 000	10 000	50 000	12 416 000	3 652 000	16 068 000
						128 522 440	35 541 000	164 063 440

IV. MATERIALS AND INPUTS

A. Characteristics of materials

1. Material requirements for Tetanus toxoide vaccine adsorbed production

Raw materials	Quality requirement	Source of supply	Unit cost CFA
Ammonium sulphate	pharm.qual.	SCAE-Cameroon	2400/kg*
Aluminium phosphate gel 2 %	standard ADJU-PHOS	Superfos Biosector a/s Denmark	2790/kg
Biotin	pharm.qual.	Prolabo-France	2075/g
Ca panthotenate	pharm.qual.	Prolabo-France	471/g
Cystine	pharm.qual.	SCAE-Cameroon	91000/kg*
Ethanol	p.a.	Prodilab-France	5956/litre*
Hydrochloric acid 37 %	p.a.	Prodilab-France	3100/litre
Fe SO_4 /7 H_2O/	pharm.qual.	Prodilab-France	14600/kg*
Formaldehyde 36 %	pharm.qual.	SCAE-Cameroon	3560/litre*
Glucose	pharm.qual.	Prolabo-France	2871/kg*
KH_2PO_4	p.a.	Prodilab-France	5620/kg*
Mg SO_4/7 H_2O/	p.a.	SCAE-Cameroon	7451/kg*
Na OH	p.a.	Biochica-France	6000/kg*
Na_2HPO_4	p.a.	Prodilab-France	3534/kg*
NZ-case	standard	Sheffield farm-USA	14208/kg
Pyridoxin HCl	pharm.qual.	Prolabo-France	86/g
Riboflavin	pharm.qual.	Prolabo-France	10/g
Sodium chloride	pharm.qual.	Prodilab-France	304/kg
Sodium chloride	p.a.	SCAE-Cameroon	1548/kg*
Thiamin	pharm.qual.	Prolabo-France	100/g
Thioglycolate broth	standard	Oxoid-U.K.Difco-USA	29840/kg*
Thiomersal	pharm.qual.	Prolabo-France	58/g
Tyrosine	pharm.qual.	Prolabo-France	34000/kg
Uracil	pharm.qual.	Prolabo-France	94/g
Auxiliary materials			
Aluminium cap	Diameter 20 mm POHL-Art NR 1725--00-800-XX	Francz-Pohl-Germany	2010/1000
Carton box complete with partitioner	Height:65 mm Width:245 mm Depth:130 mm	Apim-France	185/pc

Carton label	200mmx100mm English and French	Cameroon	6.-/pc
Cartridge for the ultrafilter	Pending on the type of the equipment		
Direction for use	140mmx95mm,double	Cameroon,printing	8000/1000*
Guinea pig	standard	Lanavet-Cameroon	1240/pc*
Mouse	OF1 or NMRI	Lanavet-Cameroon	167.40/pc*
Pall filter cartridge	SLK 700 NRP	Pall	13000/pc
Rubber stopper	Diameter 13 mm 1030PH4104/40 grey	Pharma Gummi	6030/1000
Seitz filter EK	Ashestos free	Seitz-Germany	354/pc.
Seitz filter EKS	Asbestos free	Seitz-Germany	478/pc.
Silicon emulsion	standard		
Vial	10 ml,tube glass III hydrolitical class	Desjonqueres-France Metrimpex-Hungary	9000/1000
Vial label	40mmx22mm,self adhesive in rolls	Apim-France	2087.50/1000

2. Material requirement for Diphtheria Tetanus vaccine adsorbed production

In addition to the materials listed under point 1.:

Diphtheria concentrated toxoide	Meets WHO requirements Purity is not less than 1500 Lf/ /mg protein	Merieux-France Connaught-Canada Conpharma-Canada Human Inst.-Hungary Commonwealth Serum Labs.-Australia	141670/million Lf

3. Material requirement for Diphtheria Pertussis Tetanus vaccine adsorbed production

In addition to the materials listed under points 1 and 2.:

Pertussis concentrated suspension	Meets WHO requirements Number of germs is not less than 300×10^9/ml Potency:80 IU/ml	Merieux-France Connaught-Canada Conpharma-Canada Human Inst.-Hungary Commonwealth Serum Labs.-Australia	162750/million IOU

*Landing cost prices provided by Lanavet

Prices not marked are FOB European prices plus 50%

Addresses of the suppliers are given in Annex

B. Supply programme

At the preparation of the supply programme the following production scheduling is anticipated

- Fermentation trial runs of Tetanus toxoide will be started in July 1989
- Formulation trial runs of Tetanus toxoide will be started in November 1989
- Routine production of Tetanus toxoide vaccine adsorbed will be started in the first quarter of 1990.
- Routine formulation of DPT and DT will be started in the second quarter of 1990.
- For smooth running of the production 90-180 days security stock of raw- and packaging materials are kept.

Time schedule of supply programme for 1990

Description of material	Requested quantities									
	June 1989		Jan.1990		Apr.1990		July 1990		Oct.1990	
	Qty.	CFA	Qty.	CFA	Qty.	CFA	Qty.	CFA	Qty.	CFA
Raw materials										
Ammonium sulphate	150 kg	360000	-		-		-		-	
Alu.phosph.gel 2%	500 lit.	1395000	650 lit.	1813500	650 lit.	1813500	650 lit.	1813500	500 lit.	1395000
Biotin	0,2 kg	415000	-		-		-		-	
Ca panthotenate	0,5 kg	235500	-		-		-		-	
Cystine	1,5 kg	136500	-		-		-		-	
Ethanol	20 lit.	119120	-		-		-		-	
Hydrochloric acid 37%	24 lit.	74400	-		-		-		-	
Fe $SO_4/7H_2O/$	1 kg	14600	-		-		-		-	
Formaldehyde 36%	25 lit.	89000	-		-		-		-	
Glucose	50 kg	143550	-		-		-		-	
KH_2PO_4	1 kg	5620	-		-		-		-	
Mg SO_4 $/7H_2O/$	1 kg	7451	-		-		-		-	
NaOH	5 kg	30000	-		-		-		-	
Na_2HPO_4	7 kg	24738	-		-		-		-	
NZ-case	100 kg	1420800	-		-		-		-	
Pyridoxine HCl	0,5 kg	43000	-		-		-		-	
Riboflavin	0,5 kg	5000	-		-		-		-	

Sodium chloride p.a.	15 kg	23220	-		-		-		-	
Sodium chloride pharm.	100 kg	30400	-		-		-		-	
Thiamin	0,5 kg	50000	-		-		-		-	
Thioglycolate broth	2 kg	59680	-		-		-		-	
Thiomersal	2 kg	116000	-		-		-		-	
Tyrosine	3 kg	102000	-		-		-		-	
Uracil	1,5 kg	141000	-		-		-		-	
Diphtheria conc.tox.*	-		29m Lf	4108430	28m Lf	3966760	29mLf	4108430	28m Lf	3966760
Pertussis conc.susp.*	-		12m IOU	1953000	11m IOU	1790250	12m Lf	1953000	11m Lf	1790250
Auxiliary materials										
Aluminium cap	175000	351750	175000	351750	175000	351750	175000	351750	175000	[illegible]750
Carton box	3500	647500	3500	647500	3500	647500	3500	647500	3500	[illegible]00
Cart.ultrafilter										
Direction for use	7000	56000	7000	56000	7000	56000	7000	56000	7000	56000
Guinea pig*	150	186000	600	744000	600	744000	600	744000	600	744000
Mouse*	1250	209250	2500	418500	2500	418500	2500	418500	2500	418500
Pall cartridge	5 pc	65000	-		-		-		-	
Rubber stopper	175000	1055250	175000	1055250	175000	1055250	175000	1055250	175000	1055250
Seitz EK	1000	354000	-		-		-		-	
Seitz EKS	250	119500	-		-		-		-	
Silicon emulsion	2 lit		-		-		-		-	
Vial 10 ml	175000	1575000	175000	1575000	175000	1575000	175000	1575000	175000	1575000

Vial label										
TT	120000	250500	120000	250500	120000	250500	120000	250500	120000	250500
DPT	33000	68887	33000	68887	33000	68887	33000	68887	33000	68887
DT	28000	58450	28000	58450	28000	58450	28000	58450	28000	58450
Carton label										
TT	2500	15000	2500	15000	2500	15000	2500	15000	2500	15000
DPT	700	4200	700	4200	700	4200	700	4200	700	4200
DT	600	3600	600	3600	600	3600	600	3600	600	3600
T O T A L :	CFA	10.061.466	CFA	13.123.567	CFA	12.819.147	CFA	13.123.567	CFA	12.400.647

* No security stock is calculated

V. TECHNOLOGICAL REQUIREMENTS

A. Preparation of Tetanus toxoid

1. Definition

Tetanus Toxoid is a concentrated steril physiological solution of formalin detoxified and purificated toxin of Clostridium tetani

2. Composition

Purified tetanus toxoid is physiological saline solution.
pH: 7,4
Purity: not less than 1000 Lf/mg protein N.
Preservative: 0,01 % thiomersal

3. Production

3.1 Strain

The Harvard strain/No. 49205/ of Clostridium tetani is used. It should be stored at $4^{O}C$ in liophylized form.

3.2 Precultivation

The liophylized culture is transferred into tubes with thioglycolate culture medium and incubated at $35^{O}C$ for 24 hrs. 2 - 3 subcultivations are needed.

For precultivation 200-300 ml thioglycolate culture medium in 500 ml bottle is inoculated by appr. 10 ml or microscopically pure subculture and incubated at $35^{O}C$ for 20-24 hrs.

3.3 Production medium

For the tetanus toxin production in fermenter Müller-Miller culture medium is used.
Composition for one hundred litre.

Glucose	1.100 g
Na Cl /p.a./	250 g
$Na_2 HPO_4$ /p.a./	100 g
$KH_2 PO_4$ /p.a./	15 g
$Mg SO_4$ /$7H_2O$/ /p.a./	15 g
$Fe SO_4$ /$7H_2O$/ /1% sol. in distilled water/	4 g
Cystine - HCl /10%/	250 ml
Tyrosine - HCl /10%/	500 ml
Uracil - HCl /2,5%/	1.000 ml
Ca panthothenate in ethanol 25 %	100 mg
Thiamin in ethanol 25 %	25 mg
Pyridoxin HCl in ethanol 25 %	25 mg
Riboflavin in ethanol 25 %	25 mg
Biotin in ethanol 25 %	250 mg
Na OH 5n	400 ml
Beef heart infusion	5 lit.
NZ - case solution*	15-25 g/lit.
Destilled water	ad 100 lit.

*To determine the optimal concentration each new batch is tested for toxin production.
The pH is adjusted to pH : 7,3. Sterilization is performed at 120°C for 20 minutes.

3.4 Fermentation

The production medium is terily filtered into the fermenter and/ or sterilized in the fermenter. The most important parameters of the cultivation are as follows: temperature /35°C/, nitorgen air flow rate /from 2 lit/min. to 10 lit/min./, vibromixer amplitude /from 1.0 mm to appr. 2,0 mm/. When all the cells have lysed /normally 6-7 days/ the cultivation is stopped.

To separate the lysed cells from the fluid culture containing toxin prefiltration and steril filtration are performed where closed system is very important.

3.5 Detoxification

Immediately after filtration 0,5 v.v. of a 40% w/v formaldehyde solution is added into each container.
Adjusting of the pH is needed /appr. pH : 7,0/.
After four weeks detoxification at 35°C samples for sterility control, specific toxicity, Lf/ml value and total binding volume determination are taken. The containers awaiting release, are kept at 4°C.

3.6 Concentration and purification.

For the concentration of the crude toxoid ultrafiltration method is used. The cut-off limit of the ultrafilter should be about 10.000 mw. to prvent excessive losses. Before operation the equipment has to be sterilized by heat/steam at 120°C/ and rinsed with steril destilled water.

The maximum operating pressure should not exceed 25 p.s.i.
An acceptable ultrafiltration rate is 10-15 lit/hr.
The disired degree of the concentration is 10 to 15 times.

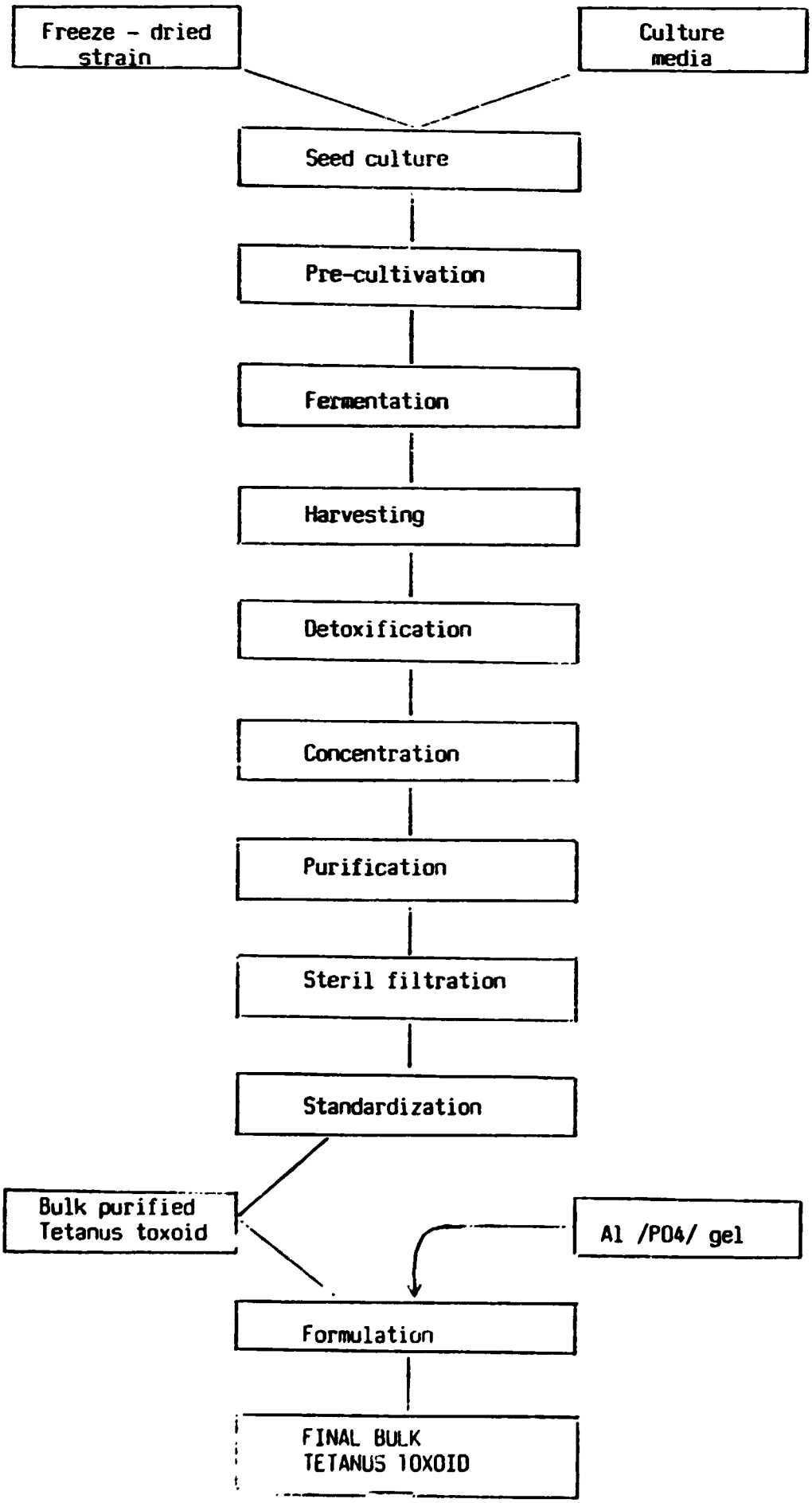
For the purification of the concentrated toxoid trichloroacetic acid and/or ammonium sulphate precipitation is used.
The ammonium sulphate precipitation is preferred.

To determine the optimal concentration of the ammonium sulphate a model experiment has to be performed.
To samples of 25 ml of toxoid increasing quantities of ammonium sulphate should be added /2.25, 2.75, 3.5, 4.25, 5.0 and 5.75 g/.
After one hour the suspensions are centrifuged,and the sediments are dissolved in saline.
The toxoid concentration of the samples is determined by Ramon - flocculation.

Having the calculated optimal ammonium sulphate concentration the purification of the concentrated toxoid could be performed. After dissolving the ammonium sulphate the toxoid is placed at room temperature for 24 hours. The supernatant is siphoned off and the suspension is centrifuged. /With the clear supernatant the process is repeated./ The precipitate is collected and dissolved in saline.

The residual ammonium sulphate is removed by gelfiltration. /Dialysis is also an acceptable method/.
The concentrated and purificated tetanus toxoid has to be sterily filtered. As preservative 0.01% thiomersal is added.
Complete quality control should be performed.

FLOW CHART OF THE PRODUCTION
OF TETANUS TOXOID FINAL BULK



B. Formulation of Tetanus toxoid vaccine adsorbed

Process for 200 litres:

Vaccine should be formulated to contain per ml:

20 Lf Tetanus toxoid
< 5.6 mg Al PO_4 /< 1.25 mg Al/
0.1 mg Thiomersal
9 mg Na Cl

Composition for 200 litres:

I.	Concentrated Tetanus toxoid		4 million Lf
II.	Aluminium phopsh. gel 2% /0,9% Na Cl content/		56 000 g
III.	2 n Na OH quantum satis		
IV.	Thiomersal		20 g
	Water for injection		200 ml
V.	Natrium chloride /Na Cl/		1 279 g
	Water for injection		130 l
VI.	Water for injection	to	200 litres

Preparation

1. Clean and prepare the 200 litre formulation tank together with fittings and sterilize by steam.

   Clean and prepare the 100 litre filling tanks together with fittings. Place 50 ml water in the tank. Sterilize by steaming for 30 minutes and autoclave for 90 minutes at 121^{o} - 125^{o}C.

2. Aluminium phosphate /II/

   a/ Prepare the 10 - litre bottles containing the correct amount of Al Po_4 suspension

   This is calculated as : 200 000 x 5.6 mg = 1 120 g
   The adjuphos gel contains 2 g per 100 ml /2%/

Therefore 56 000 ml should be run out into
6 sterile bottles and autoclaved

b/ Add the gel sterily to the 200 litre formulation tank, together with the Thiomersal solution /IV/

3. Tetanus toxoid

To determine how much to add the following calculation is performed:

$\frac{200\,000 \times 20}{T}$ where T is the Lf/ml of the concentrated Tetanus toxoid

e.g. If the Lf content is 2000/ml than 2000 ml would be required. The calculated volume should be dispensed sterily into a suitable container. /This can be accomplished by filtering the toxoid through a 0.22 micron filter into the bottle./

4. Formulation

a/ Add the calculated volume of Tetanus toxoid concentrate sterily to the formulation tank containing the Al PO_4. Adjust the pH to 6.0-6.2 if necessary with sterile 2 n Na OH solution /III/

b/ Allow the tank to stand with mixing at 100-200 r.p.m. for the minimum time of 4 hours.

c/ Add sufficient saline /V./ and bring the volume to 200 litres with Water for injection /VI./ /calculated either by volume or weight/.

5. Sample for sterility. Test the pH. It should be between 6.0 and 7.0

6. Transfer the bulk vaccine sterily into the filling tanks and store at $4^{o}C$ until filling.

PROCESS FLOW CHART

PRODUCTION OF TETANUS TOXOID VACCINE ADSORBED FROM THE ANTIGEN LEVEL

Transfer 56 lit.sterile 2% Al PO_4 gel containing 200 ml 10% Thiomersal into the mixing tank under sterile conditions and mix for 10 minutes.

Add under sterile conditions the calculated quantity of concentrated Tetanus toxoid.

Mix for 15 min.at 100-200 r.p.m.

Adjust pH with sterile 2n Na OH

Mix for 4 hours at 100-200 r.p.m.

Add the 0.9% Na Cl solution under sterile conditions.

Adjust the volume to 200 litre with Water for injection under sterile conditions.

Mixing, homogenisation

pH control /6.0-7.0/ Take sample for sterility test

Bulk

Filling into 10 ml vials, stoppering, capping

Visual control

Labeling, packaging

Identification
Sterility
Innocuity
Potency
Specific toxicity
Al contest
pH
Free formaldehyde
Thiomersal

Finished Tetanus toxoid vaccine adsorbed

C. Formulation of Diphtheria-Tetanus vaccine adsorbed
/For pediatric use/

Process for 200 litres

Vaccine should be formulated to contain per ml:

20 Lf Tetanus toxoid
60 Lf Diphtheria toxoid
< 5.6 mg $AlPO_4$ / < 1.25 mg Al/
0.1 mg Thiomersal
9 mg NaCl

Composition for 200 litres

I.	Concentrated Tetanus toxoid		4 million Lf
II.	Concentrated Diphtheria toxoid		12 million Lf
III.	Aluminium phosph. gel 2% /0.9 NaCl content/		56 000 g
IV.	2 n NaOH quantum satis		
V.	Thiomersal		20 g
	Water for injection		200 ml
VI.	Natrium chloride /NaCl/		1224 g
	Water for injection		120 lit.
VII.	Water for injection	to	200 lit.

Preparation

1. Clean and prepare the 200 litre formulation tank together with fittings and sterilize by steam. Clean and prepare the 100 litre filling tanks together with fittings. Place 50 ml water in the tank. Sterilize by steaming for 30 minutes and autoclave for 90 minutes at 121-125°C.

2. Aluminium phosphate /III./

   a. Prepare the 10-litre bottles containing the correct amount of $AlPO_4$ suspension.

This is calculated as:

200 000 x 5.6 mg = 1120 g

The "Adjuphos" gel contains 2 g per 100 ml /2%/. Therefore 56 000 ml should be run out into 6 sterile bottles /5 x 10 lit. and 1 x 6 lit./ and autoclaved.

b. Add 5 of the bottles /containing the 10 lit. gel/ sterily to the 200 litre formulation tank together with 180 ml sterile Thiomersal solution /V./. Add 20 ml of the sterile Thiomersal solution to the remaining bottle of $AlPO_4$.

3.a. Tetanus toxoid /I./

To determine how much to add, the following calculation is performed:

$\frac{200\,000 \times 20}{T}$ where T is the Lf/ml of the concentrated Tetanus toxoid

e.g. If the Lf content is 2000/ml than 2 litres will be required. The calculated volume should be dispensed sterily into a suitable container. This can be accomplished by filtering the toxoid through a 0.22 micron filter into the bottle.

b. Diphtheria toxoid /II./

To determine how much to add, the following calculation is performed:

$\frac{200\,000 \times 60}{D}$ where D is the Lf/ml of the concentrated Diphtheria toxoid

e.g. If the Lf content is 2000/ml then 6 litres would be required. The calculated volume should be dispensed sterily into a suitable container. This can be accomplished by filtering the toxoid through a 0.22 micron filter into the bottle.

4. Formulation

   a. Add the calculated volume of Diphtheria toxoid concentrate sterily to the formulation tank and gently stir at appr. 100-200 r.p.m. Adjust the pH to 6.0-6.2 if necessary with sterile 2 n NaOH /IV./ solution.

   b. Add the calculated volume of Tetanus toxoid concentrate to the bottle of $AlPO_4$. Adjust the pH to 6.0-6.2 if necessary.

   c. Allow both bottle and tank to stand with mixing/stirring for a minimum time of 4 hours. During this time the tank is stirred at 100-200 r.p.m. and the bottle gently shaken every 15 minutes.

   d. Add the bottle contents sterily to the tank, together with salin /VI./ and bring the volume to 200 litres with Water for injection /VII./ calculated by either volume or weight.

5. Sample for sterility. Test the pH. It should be between 6.0 and 7.0

6. Transfer the bulk vaccine sterily into the filling tanks and store at $4^{o}C$ until filling.

PROCESS FLOW CHART

Production of Diphtheria-Tetanus vacc. adsorbed from the antigen level

Diphtheria antigen

- 50 lit.2% Al PO_4 gel containing 160 ml of Thiomersal is transfered under sterile - conditions into the mixing tank.
- Add under sterile conditions the calculated quantity of Diphtheria conc.toxoide.
- Adjust pH to 6.0-6.2 with sterile 2n NaOH
- Mixing at 100-200 r.p.m.for 4 hours.

Tetanus antigen

- 6 lit.2% Al PO_4 gel containing 20 ml of 10% Thiomersal /in glass bottle/
- Add under sterile conditions the calculated quantity of conc. Tetanus tox.
- Adjust pH to 6.0-6.2 with sterile 2n NaOH
- Store for 4 hours. Shake the content of the bottle gently in every 15 minutes.
- Transfer to mixing tank under sterile conditions.

- Add the 0.9% NaCl solution under sterile conditions.
- Adjust the volume to 200 litre with Water for injection under sterile condition.
- Mixing, homogenistion

pH control /6.0-7.0/
Take sample for sterility test.

- Bulk
- Filling into 10 ml vials, stoppering, capping
- Visual control
- Labeling, packaging

Identification
Sterility
Innocuity
Potency
Specific toxicity
Al content
pH
Free formaldehyde
Thiomersal

- Finisched DT vacc.ads.

D. Formulation of Diphtheria-Pertussis-Tetanus vaccine adsorbed

Process for 200 litres

Vaccine should be formulated to contain per ml

10 Lf Tetanus toxoid
30 Lf Diphtheria toxoid
30 I.O.U. Pertussis suspension /8 I.U./
< 5.6 mg Al PO_4 /< 1.25 mg Al/
0.1 mg Thiomersal
9 mg Na Cl

Composition for 200 litres

I.	Concentrated Tetanus toxoid		2 million Lf
II.	Concentrated Diphtheria toxoid		6 million Lf
III.	Concentrated Pertussis suspension		6 million I.O.U.
IV.	Aluminium phosphate gel 2% /0.9% Na Cl content/		56 000 g
V.	2n Na OH quantum satis		
VI.	Thiomersal		20 g
	Water for injection		200 ml
VII.	Natrium chloride /Na Cl/		1.125 g
	Water for injection		115 lit
VIII.	Water for injection	to	200 lit

Preparation

1. Clean and prepare the 200 litre formulation tank together with fittings and sterilize by steam.

   Clean and prepare the 100 litre filling tanks together with fittings. Place 50 ml water in the tank. Sterilize by steaming for 30 minutes and autoclave for 90 minutes at 121 - 125°C.

2. Aluminium phosphate /IV./

   a/ Prepare the 10-litre bottles containing the correct amount of Al PO_4 suspension

This is calculated as :

200 000 x 5.6 mg = 1.120 g

The "Adjuphos" gel contains 2 g per 100 ml /2%/ therefore 56 000 ml should be run out into 7 sterile bottles /5 x 9 lit. and 2 x 5.5 lit./ and autoclaved.

b/ Add 5 of the bottles /containing the 9 lit. gel/ sterily to the 200 litre formulation tank together with 160 ml sterile Thiomersal solution /VI./ . Add 20-20 ml of the sterile Thiomersal solution to the remaining 2 bottles of Al PO_4.

3. a/ Pertussis suspension /III./

To determine how much to add the following calculation is performed:

$\frac{200\ 000 \times 30}{P}$ where P is the IOU/ml of the Pertussis concentrated suspension

e.g. If the I.O.U. content is 300/ml then 20 litres would be required. The calculated volume should be dispensed sterily into a suitable container.

b/ Tetanus toxoid /I./

To determine how much to add, the following calculation is performed

$\frac{200\ 000 \times 10}{T}$ where T is the Lf/ml of the concentrated Tetanus toxoid.

e.g. If the Lf content is 2000 Lf/ml then 1 litre would be required.

The calculated volume should be dispensed sterily into a suitable container. This can be accomplished by filtering the toxoid through a 0.22 micron filter into the bottle.

c/ Diphtheria toxoid /II./

To determine how much to add the following calculation is performed.

$\frac{200\,000 \times 30}{D}$ where D is the Lf/ml content of the concentated Diphtheria toxoid.

e.g. If the Lf content is 2000/ml then 3 litres would be required. The calculated volume should be dispensed sterily into a suitable container. This can be accomplished by filtering the toxoid through a 0.22 micron filter into the bottle.

4. Formulation

a/ Add the calculated volume of Pertussis suspension concentrate sterily to the formulation tank and gently stir at appr. 100-200 r.p.m.

b/ Add the calculated volume of Tetanus toxoide concentrate to one of the bottles of Al PO_4 adjust the pH to 6.0 - 6.2 with 2 n Na OH /V./ if necessary.

c/ Add the calculated volume of Diphtheria toxoid concentrate to the remaining bottle of Al PO_4. Adjust the pH to 6.0 - 6.2 with 2 n Na OH /V./ if necessary.

d/ Allow both of the bottles and the tank to stand with mixing/stirring for a minimum time of 4 hours. During this time the tank is stirred at 100-200 r.p.m., and the bottles gently shaken every 15 minutes.

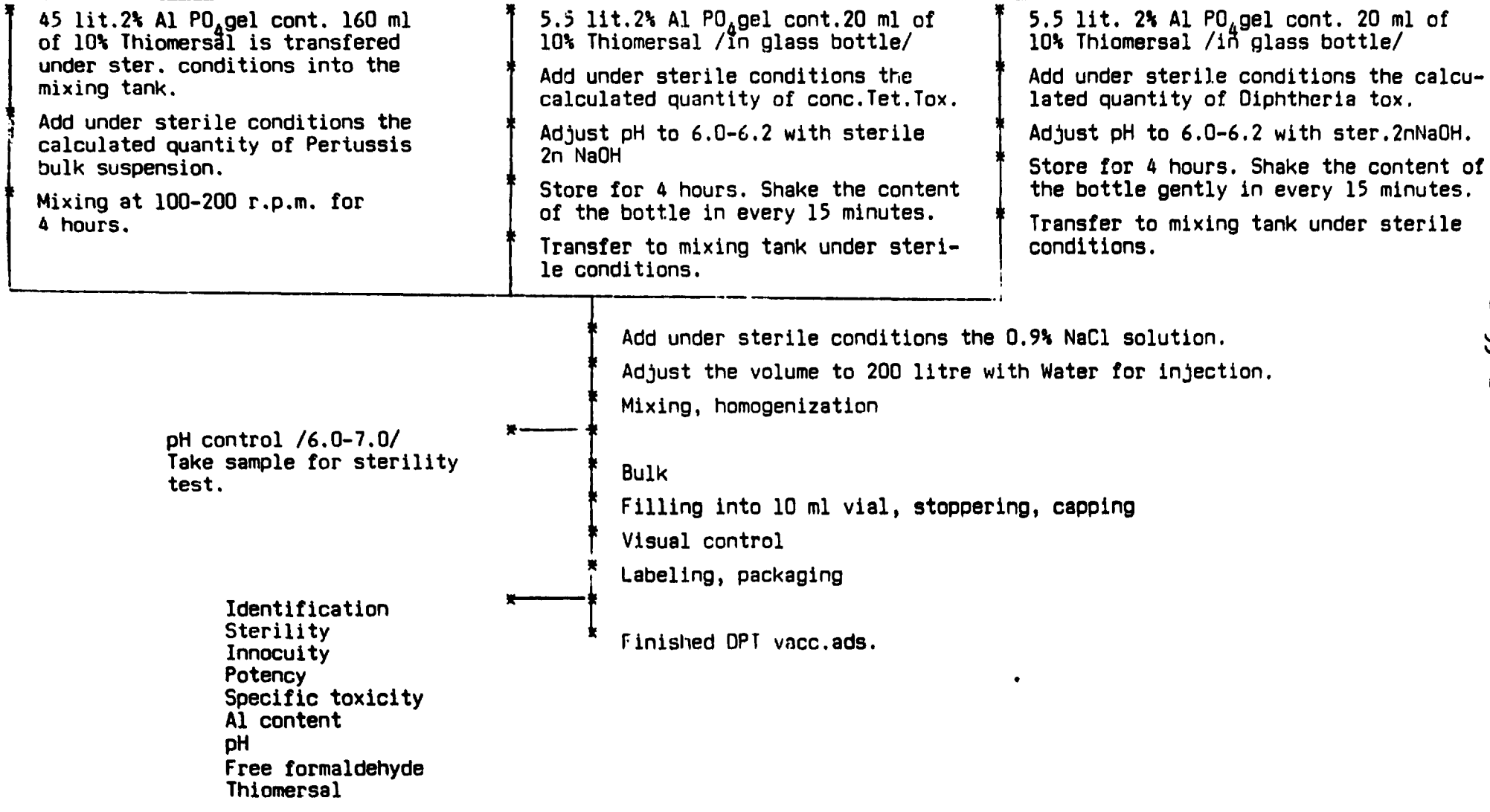
e/ Add the content of the bottles sterily to the tank together with sufficient saline /VII./ and bring the volume to 200 litres with Water for injection /VIII./ calculated by either volume or weight.

5. Sample for sterility. Test the pH. It should be between 6.0 and 7.0

6. Transfer the bulk vaccine sterily into the filling tanks and store at $4^{O}C$ until filling.

PROCESS FLOW CHART

Production of Diphtheria-Pertussis-Tetanus vacc.ads. from the antigen level



VI. SPECIMEN TEXTS FOR PACKAGING COMPONENTS

A. Specimen text for vial labels

10 ml
DIPHTHERIA-TETANUS-PERTUSSIS
VACCINE ADSORBED
Single dose. 0,5 ml I/M
Vaccine meets WHO requirements
Manufactured by
LANAVET-GAROUA
Batch No:
Exp:
at2°-8°

10 ml
TETANUS TOXOID VACCINE
ADSORBED
Single dose: 0,5 ml I/M
Vaccine meets WHO requirements
Manufactured by:
LANAVET-GAROUA
Batch No:
Exp:
at2°-8°

10 ml
DIPHTHERIA-TETANUS VACCINE
ADSORBED
Single dose: 0,5 ml I/M
Vaccine meets WHO requirements
Manufactured by:
LANAVET-GAROUA
Batch No:
Exp:
at2°-8°

B. Specimen text for carton label

TETANUS TOXOID
ADSORBED
50x20 Doses
0,5 ml Dose I/M
Meets W.H.O.
requirements
Manufactured by:

ANATOXINE TETANIQUE
ADSORBED
50x20 Doses
0,5 ml Dose I/M
Conforme aux
exigences de I'O.M.S.
Fabrique par:

LANAVET
Laboratoire National Veterinaire
de Bokle
Garoua-Republique du Cameroun

LANAVET
PRODUCTION

DIPHTHERIA-TETANUS-PERTUSSIS VACCINE ADSORBED

VACCIN ANTIDIPHTHERIQUE, ANTITETANIQUE ET ANTICOQUELUCHEUX
ADSORBEE

50x20 Doses
0,5 ml Dose I/M
Meets W.H.O.
requirements
Manufactured by:

50x20 Doses
0,5 ml Dose I/M
Conforme aux
exigences de I'O.M.S.
Fabrique par:

LANAVET
Laboratoire National Veterinaire
de Bokle
Garoua-Republique du Cameroun
Batch/Lote No:
Exp: at 2^{o}-8^{o}

LANAVET
PRODUCTION

DIPHTHERIA-TETANUS VACCINE ADSORBED
/Pediatric/

VACCIN ANTIDIPHTHÉRIQUE ET ANTITÉTANIQUE ADSORBÉE
/infantile: usage pédiatrique/

50x20 Doses
0,5 ml Dose I/M
Meets W.H.O.
requirements

50x20 Doses
0,5 ml Dose I/M
Conforme aux
exigences de l'O.M.S.

Manufactured by:

Fabrique par:

LANAVET
PRODUCTION

LANAVET
Laboratoire National Veterinaire
de Bokle
Garoua-Republique du Cameroun

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE
BOKLE - GAROUA
REPUBLIQUE DU CAMEROUN

TETANUS TOXOID VACCINE ADSORBED

DESCRIPTION

Tetanus toxoid adsorbed is prepared by detoxification of the sterile filtrate of broth cultures of Clostridium tetani with formalin and heat. The toxoid is purified by chemical methods and is adsorbed on to aluminium phosphate or aluminium hydroxide as adjuvant, corresponding to not more than 1.25 mg aluminium per single human dose. 0.01% Merthiolate is added as preservative. The vaccine has the appearance of a fine grayish-white suspension and does not contain any horse serum protein. Therefore it does not induce sensitization to sera of equine origin.

POTENCY

The vaccine meets the requirements of WHO and EP when tested by the methods outlined in WHO, TRS. /1979/, 638, /1981/, 658 /1982/, 673, /1984/, /1985/, 700, /1985/, 725 and in the European Pharmacopoeia. Each single dose contains 10 Lf Tetanus toxoid with not less than 40.I.U.

INDICATIONS

The vaccine is used for the prevention of tetanus in children and adults, especially those liable to be exposed to tetanus infection, particularly women of childbearing age and persons engaged in outdoor activites e.g. gardeners, farm workers and athletes.

APPLICATION AND DOSAGE

Vaccination is carried out with 2 doses of 0.5 ml each at 4-6 week intervals. To ensure long-lasting immunity a further 0.5 ml booster dose is recommanded 6 months to one year later. To maintain a high level of immunity further 0.5 ml booster doses are recommanded every 5-10 years.

METHOD OF INOCULATION

BEFORE USE THE VACCINE SHOULD BE WELL SHAKEN

Only sterile syringes and needles should be used. The vaccine should be given intramuscularly into the gluteal muscle or the M. deltoideus, according to the choice of the physician. Children younger than 2 years should be inoculated into the M. quadriceps femoris, between the upper and middle third, on the lateral side. Care should be taken not to inject into a blood vessel or the skin.
Open vials should not be preserved for later use.

VACCINATION OF INJURED PERSONS

For those subjects who have proof of either completing their course of primary immunizations containing tetanus toxoid or receiving a booster shot within the previous 5 years, no additional dose of tetanus toxoid is recommanded.
If more than 5 years have elapsed, and infection with tetanus because of injury of other cause is suspected, 0.5 ml of the adsorbed tetanus toxoid should be given immediately. Where the immunization history is inadequate, 1500 IU /3000 old AU/ tetanus antiserum and 0.5 ml toxoid should be injected, with separate syringes, to different body sites. /If available, 250 units of tetanus immune globulin /human origin/ can be substituted for the tetanus antiserum/. A seconc 0.5 ml dose of toxoid is recommanded after 2 weeks and a third dose after a further 1 month.

/A note of caution: if horse origin tetanus antiserum is used in prophylaxis, the patient should be tested for sensitivity to horse serum protein prior to its administration. It is desirable to have 1 ml of Epinephrine Hydrochloride Solution /1:1000/ immediately available and the normal precautions followed when injecting antitoxins/.

REACTIONS

Reactions are generally mild and confined to the site of injection. Some inflammation may occur together with transient fever, malaise and irritability. Occasionally a nodule may develop at the site of injection but this is rare. Infiltration can be palliated by putting on a cold compress.

CONTRAINDICATIONS AND WARNINGS

Individuals receiving corticosteroids, other immunosuppressive drugs or undergoing radio-therapy may not develop an optimal immune response. The vaccine should not be given in febrile states, acute infectious diseases, leukaemia, severe anaemia and other severe diseases of the blood system, severe impairment of the renal function, decompansated heart diseases, or known allergies to vaccine components. Occasionally an increased severity of reactions to vaccination is noted in subjects who have had many booster immunizations.

STORAGE OF THE VACCINE

The vaccine should be stored in a dry, dark place at a temperature between $2^{O}C$ and $8^{O}C$. Transportation should also be at 2^{O} - $8^{O}C$.
DO NOT FREEZE.
Once a vial has been opened, its contents should be used the same day.

SHELF LIFE

Thirty six months from the date of manufacture.

PRESENTATION

1 dose Ampoule	of	0,5 ml
10 dose Vial	of	5 ml
20 dose Vial	of	10 ml

Manufactured by

L A N A V E T
LABORATOIRE NATIONAL VETERINAIRE
DE BOKLE - GAROUA
REPUBLIQUE DU CAMEROUN

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE
DE BOKLE - GAROUA
REPUBLIQUE DU CAMEROUN

VACCIN ANTITÉTANIQUE /ANATOXINE TÉTANIQUE ADSORBÉE/

DESCRIPTION

Le vaccin antitétanique /anatoxine tétanique adsorbée/ est préparé par détoxification du filtrat stérile de bouillon de culture de Clostridium tetani avec formaline et chaleur. La toxine est purifiée par des méthodes chimiques et est adsorbé sur du phosphate d'aluminium comme adjuvant, correspondant à pas plus de 1,25 mg d'aluminium par dose humaine unique. 0,01% de merthiolate est ajouté comme agent de conservation.

Le vaccin a l'apparence d'une suspension fine de couleur blanc-grisâtre et ne contient pas de protéine de sérum de cheval. Il ne provoque donc pas de réaction immunologique aux sérums d'origine équine.

EFFICACITE

Le vaccin se conforme aux exigences de l'OMS et de la PE quand il est testé selon les méthodes indiquées dans les TRS /série de rapports techniques/ de l'OMS /1979/, 638, /1981/, 658, /1982/, 673 /1984/ /1985/, 725 et dans la Pharmacopée européenne. Chaque dose unique contient 10 Lf d'anatoxine tétanique avec pas moins de 40 I.U.

INDICATIONS

Le vaccin est utilisé dans la prévention du tétanos chez les enfants et les adultes, particulièrement ceux qui peuvent être exposés à l'infection tétanique, spécialement les femmes en âge d'avoir des enfants et les personnes ayant des activités à l'extérieur comme les jardiniers, les ouvriers agricoles et les athlètes.

APPLICATION ET POSOLOGIE

Le vaccin est administré avec deux doses de 0,5 ml chacune à intervalles de 4 à 6 semaines. Pour assurer une immunité à long terme une dose de rappel de 0,5 ml est recommandée de 6 à 12 mois plus tard. Pour maintenir un haut niveau d'immunité des doses de rappel de 0,5 ml supplémentaires sont recommandées tous les 5 à 10 ans.

METHODE D'INOCULATION

LE VACCIN DOIT ÊTRE BIEN SECOUE AVANT L'UTILISATION

Seules des seringues et des aiguilles stériles doivent être utilisées. Le vaccin devrait être administré par voie intramusculaire dans le muscle fessier ou le muscle deltoide, au choix du médecin. Les enfants de moins de deux ans devraient être inoculés dans le muscle quadriceps, entre les tiers supérieur et médian, sur la face latérale. Des précautions doivent être prises pour ne pas injecter le vaccin dans un vaisseau sanguin ou dans la peau. Les ampoules ouvertes ne peuvent pas être conservées pour utilisation ultérieure.

VACCINATION DES PERSONNES BLESSEES

Pour les sujets qui ont des preuves d'avoir terminé la série d'immunisations de base contenant l'anatoxine tétanique ou qui ont eu une dose de rappel dans les 5 dernières années, on ne recommande pas une dose supplémentaire d'anatoxine tétanique. Si plus de 5 ans ont passé, et qu'une infection tétanique soit possible à cause d'une blessure ou pour d'autres raisons, 0,5 ml l'anatoxine tétanique adsorbé devrait être administré immédiatement. Dans les cas où les antécédents d'immunisation sont suffisants on doit injecter 1500 I.U. /3000 anciennes AU/ d'antisérum tétanique et 0,5 ml d'anatoxine tétanique, avec deux séringues différentes et dans des parties différentes du corps. /On peut substituer à l'antisérum tétanique 250 units de globuline anti-tétanique /d'origine humaine/ si elle est disponible/. Une seconde dose de 0,5 ml d'anatoxine tétanique est recommandée après deux semaines et une troisième dose un mois après la seconde dose. /Avertissement: si un antisérum tétanique d'origin équine est utilisé en prophylaxie, le patient doit être testé pour sa sensibilité aux protéines de sérum de cheval avant l'administration de l'antisérum.

Il est recommandé d'avoir à sa disposition immédiate 1 ml de solution d'hydrochlorure d'épinéphrine /1:1000/ et de suivre les précautions habituelles quand on injecte des antitoxines./

RÉACTIONS

Les réactions sont généralement bénignes et se limitent à l'endroit de l'injection. Une inflammation peut avoir lieu ainsi qu'une fièvre passagère, un malaise ou de l'irritabilité. Parfois, un nodule peut se développer à l' endroit de l'injection, mais ceci est rare. L'infiltration peut être attenué en appliquant des compresses froides.

CONTRE-INDICATIONS ET AVERTISSEMENTS

Il est possible que les personnes recevant des corticosteroides, autres médicaments immonosuppressifs ou suivant une radio-thérapie ne développent pas une réponse immunitaire optimale. Le vaccin ne devrait pas être administré aux sujets en état fébrile et aux sujets ayant des maladies infectueuses aigues, la leucémie, une anémie grave ou autres maladies graves du système sanguin, une détérioration grave de la fonction rénale, des insuffisances cardiaques décomposées ou des allergies connues aux composantes du vaccin.
On remarque parfois des réactions plus sévères à la vaccination dans les sujets qui ont eu de nombreuses immunisations de rappel.

CONSERVATION DU VACCIN

Le vaccin doit être conservé dans un endroit sec et sombre à une température de 2^{o} à 8^{o}C. Le transport doit aussi être effectué une température de 2^{o} à 8^{o}C.

NE PAS CONGELER

Après l'ouverture d'une ampoule, son contenu doit être utilisé dans la journée.

DURÉE DE CONSERVATION

Trente-six mois à compter de la date de fabrication.

PRESENTATION

Ampoule d'une dose de 0,5 ml
Fiole de dix doses de 5 ml
Fiole de vingt doses de 10 ml
Fabriqué par:

L A N A V E T
LABORATOIRE NATIONAL VETERINAIRE DE BOKLE
GAROUA - REPUBLIQUE DE CAMEROUN -

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE
DE BOKLE
GAROUA-REPUBLIQUE DU CAMEROUN

DIPHTHERIA, TETANUS AND PERTUSSIS VACCINE ADSORBED

DESCRIPTION

Diphtheria, Tetanus and Pertussis Vaccine Adsorbed is prepared by combining purified diphtheria toxoid, purified tetanus toxoid and 15 x 10^9 killed Phase I Bordetella pertussis bacilli per dose. The antigens are adsorbed on to aluminium phosphate as adjuvant corresponding to not more than 1.25 mg aluminium per single human dose. 0.01% Merthiolate is added as preservative. The vaccine has the appearance of a greyish-white suspension and does not contain any horse serum protein. Therefore it does not induce sensitization to sera of equine origin.

POTENCY

The vaccine meets the requirements of WHO, EP and BP when tested by the methods outlined in WHO, TRS. /1979/, 638, /1981/, 658, /1982/, 673, /1984/ /1985/, 700, /1985/, 725, and in the European and British Pharmacopoeias. Each single 0.5 ml human dose contains 15 Lf and not less than 30 I.U. of diphtheria toxoid, 5 Lf and not less than 40 I.U. of tetanus toxoid /guinea pig assay/ /or 60 I.U. in a mouse assay/, and 15 OU pertussis containing not less than 4 P.U.

INDICATIONS

For the primary immunization of infants, above the age of two months, and of pre-school children against diphtheria, tetanus and whooping cough.

APPLICATION AND DOSAGE

For the purpose of primary immunization it is recommended that 3 doses of 0.5 ml should be inoculated on 3 separate occasions at 4 to 6 weeks intervals. The first dose should be given at approximately 3 months of age. Reinforcing injections of 0.5 ml should be given 12 months after primary immunization and also between the ages of 4 to 6 years.

METHOD OF INOCULATION

BEFORE USE THE VACCINE SHOULD BE WELL SHAKEN

Only sterile syringes and needles should be used. The vaccine should be given intramuscularly into the gluteal muscle or the M. deltoideus, according to the choice of the physician. Children younger than 2 years should be inoculated into the M. quadriceps femoris, between the upper and middle third, on the lateral side. Care should be taken not to inject into a blood vessel or the skin.
Open vials should not be preserved for later use.

REACTIONS

Mild, local reactions such as pain, tenderness, erythema, induration are common and may be associated with temperature elevation /38^{0} - 39^{0}C/ and an infiltration of 3 to 4 cm in diameter. Other reactions that may be observed include shills, irritability, persistent crying in infants and general malaise. most reactions last for 24 to 48 hours. In such cases the use of antipyretics and, in the case of local reaction, cold compresses should be considered. Occasionally a nodule may persist at the site of injection but this is without any harmful effects. More serious reactions such as fever above 40^{0}C, excessive screaming, and encephalopathic symptoms /e.g. convulsions/ may also be observed but are extremely rare. By strict observance of the contraindications listed below the number of such complications will be reduced to a minimum.

CONTRAINDICATIONS AND WARNINGS

Individuals receiving corticosteroids, other immunosuppressive drugs or undergoing radio-therapy may not develop an optimal immune response. The vaccine should not be given to infants or children with fever or other evidence of acute illness, or with a personal cr family history of central nervous system disease or convulsions. Leukaemia, severe anaemia, other severe diseases of the blood system, impairment of renal function, decompensated heart disease or allergy to any of the vaccine components are all contraindications to the use of the vaccine.
The development of "persistent screaming", shock, convulsions or encephalopathy following any injection of DPT Adsorbed is an ABSOLUTE CONTRAINDICATION to further doses of the vaccine being given to that particular individual. Non-pertussis containing vaccines should be substituted, such as DT.

DPT Vaccine adsorbed should not be given to children older than 6 years of age or to adults, due to possible reactions to the pertussis component.

STORAGE OF THE VACCINE

The vaccine should be stored in a dry, dark place at a temparature between $2^{o}C$ and $8^{o}C$. Transportation should also be at 2^{o} - $8^{o}C$. DO NOT FREEZE. Once a vial has been opened, its contents should be used the same day.

SHELF LIFE

Thirty months from date of manufacture.

PRESENTATION

1 dose	Ampoule	of	0,5 ml
10 dose	Vial	of	5 ml
20 dose	Vial	of	10 ml

Manufactured by

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LABORATOIRE NATIONAL VETERINAIRE
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DE BOKLE
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VACCIN ANTIDIPHTÉRIQUE, ANTITÉTANIQUE ET ANTICOQUELUCHEUX /DPT/ ADSORBÉE

DESCRIPTION

Le vaccin antidiphtérique, antitétanique et anticoquelucheux, /DPT/ adsorbée, est préparé en mélangeant une anatoxine diphtérique purifiée, une anatoxine tétanique purifiée et des Bordetella pertussis baicilli, 15 x 10^9 tués en Phase I par dose. Les antigenes sont adsorbés sur du phosphate d'aluminium comme adjuvant correspondant pas plus de 1,25 mg d'aluminium par dose humaine unique. 0,01 % de merthiolate est ajouté comme agent de conservation. Le vaccin a l'apparence d'une suspension de couleur blanc-grisâtre et ne contient pas de protéine de sérum de cheval. Il ne provoque donc pas de réaction immunolique aux sérums d'origine équine.

EFFICACITÉ

Le vaccin se conforme aux exigences de l'OMS, de la PE et de la PB quand il est testé selon les méthodes indiquées dans les TRS /Série de rapports techniques/ de l'OMS /1979/, 638, /1981/, 658, /1982/, 673, /1984//1985/, 700, /1985/, 725, et dans les Pharmacopées européenne et britannique. Chaque dose humaine unique de 0,5 ml contient 15 Lf et pas moins de 30 I.U. d'anatoxine diphtérique, 5 Lf et pas moins de 40 I.U. d'anatoxine tétanique /test effectué sur cobaye/ /ou 60 I.U. dans un test effectué sur souris/, et 15 OU de pertussis contenant pas mois de 4 I.U.

INDICATIONS

Pour l'immunisation de base des nourrissons, agés de plus de 2 mois, et pour les enfants d'age préscolaire contre la diphtérie, le tétanos et la coqueluche.

APPLICATION ET POSOLOGIE

Aux fins de l'immunisation de base, il est recommandé d'inoculer 2 à 3 doses de 0,5 ml à 3 différentes reprises à 4 à 6 semaines d'intervalles. La premiere dose devrait être administrée à environ 3 mois d'age. Des injections de rappel de 0,5 ml devraient être données 12 mois aprés l'immunisation de base et aussi entre l'age de 4 à 6 ans.

MÉTHODE D'INOCULATION

LE VACCIN DOIT ÊTRE BIEN SECOUÉ AVANT L'UTILISATION

Seules des seringues et des aiguilles stériles doivent être utilisées. Le vaccin devrait être administré par voie intramusculaire dans le muscle fessier ou le muscle deltoide, au choix du médecin. Les enfants de moins de 2 ans devraient être inoculés dans le muscle quadriceps, entre les tiers supérieur et médian, sur la face latérale.
Des précautions doivent être prises pour ne pas injecter le vaccin dans un vaisseau sanguin ou dans la peau.
Les ampoules ouvertes ne peuvent pas être conservées pour utilisation ultérieure.

Réactions

Des réactions bénignes et locales telles que douleur, sensibilité, érythème, induration, sont courantes et peuvent être associées à une élévation de la température /38^{0} - 39^{0}/ et une infiltration de 3 à 4 cm de diametre. D'autres réactions qui peuvent survenir sont des refroidissements, l'irritabilité, des pleurs persistants chez les nourrissons et un malaise général. La plupart des réactions durent de 24 à 48 heures. On peut considérer, dans de tels cas, l'usage d'antipyrétiques et, pour les réactions locales, des compresses froides. Un nodule peut parfois persister a l'endroit de l'injection, ceci est sans effets nuisibles. On peut aussi observer, dans des cas extremement rares, des réactions plus sévères telles qu'une fièvre au-dessus de 40^{0}C, des cris excessifs, et des symptomes d'encephalopathie /par exemple, des convulsions/. En se conformant strictement aux contre-indications énumérées cidessous, le nombre de ces complications peut être rèduit à un minimum.

CONTRE-INDICATIONS ET AVERTISSEMENTS

Il est possible que les personnes recevant des corticostéroides ou autres médicaments immunosuppressifs ou suivant une radiothérapie ne développent pas une réponse immunitaire optimale. Le vaccin ne devrait pas etre administré aux nourrissons ou aux enfants ayant une fièvre, ou d'autres signes d'une maladie aigue, ou avec des antécédents personnels ou familiaux de convulsions ou de maladies du système nerveux central. La leucémie, l'anémie grave, et autres maladies graves du système sanguin, une détérioration de la fonction rénale, une insuffisance cardiaque décompensée ou une allergie à l'une des composantes du vaccin, sont toutes des contre-indications à l'administration du vaccin. Le développement de < cris excessifs > , de choc, de convulsions ou d'encephalopathie à la suite de toute injection du vaccin DPT adsorbée constitue une CONTRE-INDICATION ABSOLUE à l'administration de doses supplémentaires du vaccin à cette personne. Il faut, dans ces cas, substituer au vaccin, des vaccins ne contenant pas de pertussis, el que le vaccin DT. Le vaccin DPT adsorbée ne doit pas être administré aux enfants de plus de 6 ans ou aux adultes, de à des réactions possibles au composant pertussis.

CONSERVATION DU VACCIN

Le vaccin doit être conservé dans l'obscurité a l'abri de l'humidité à une température de 2^{O} à 8^{O}C. Le transport doit aussi être effectué à une température de 2^{O} à 8^{O} C. NE PAS CONGELER. Apres l'ouverture d'une ampoule, son contenu doit être utilisé dans la journée.

DURÉE DE CONSERVATION

Trente mois à compter de la date de fabrication.

PRÉSENTATION

Ampoule	d'une dose	de	0,5 ml
Fiole	de dix doses	de	5 ml
Fiole	de vingt doses	de	10 ml

Fabriqué par:

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE

DE BOKLE

GAROUA-REPUBLIQUE DU CAMEROUN

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE
BOKLE - GAROUA
REPUBLIQUE DU CAMEROUN

DIPHTHERIA AND TETANUS VACCINE ADSORBED /Pediatric/

Diphtheria and Tetanus Toxoid Adsorbed is prepared by combining purified diphtheria toxoid and purified tetanus toxoid. The antigens are adsorbed onto aluminium phosphate as adjuvant corresponding to not more than 1.25 mg aluminium per single human dose. o.01 % Merthiolate is added as preservative.
The vaccine has the appearance of a greyish-white suspension and does not contain any horse serum protein. Therefore it does not induce sensitization to sera of equine origin.

POTENCY

The vaccine meets the requirements of WHO, EP and BP when tested by the metods outlined in WHO, TRS. /1979/, 638, /1981/, 658, /1982/, 673 /1984/ /1985/, 700, /1985/, 725, and in the European and British Pharmacopoeias. Each single 0.5 ml human dose contains 30 Lf of diphtheria toxoid with not less than 30 I.U. and 10 Lf of tetanus toxoid with not less than 40 I.U.

INDICATIONS

For the primary immunization and re-immunization of children up to 10 years of age and of infants above the age of two months is whom pertussis vaccination is contraindicated. Children older than 10 years are immunized with a special diphtheria and tetanus vaccine containing a reduced amount of diphtheria.

APPLICATION AND DOSAGE

For the purpose of primary immunization it is recommended that 2 or 3 doses of 0.5 ml should be inoculated at intervals of 4 to 6 weeks. For

infants the first dose may be given at approximately 3 months of age.
A reinforcing injection of 0.5 ml should be given one year later.

METHOD OF INOCULATION

BEFORE USE THE VACCINE SHOULD BE WELL SHAKEN

Only sterile syringes and needles should be used. The vaccine should be injected intramuscularly into the gluteal muscle or the M. deltoideus, according to the choice of the physician. Children younger than 2 years should be inoculated into the M. quadriceps femoris, between the upper and middle third, on the lateral side. Care should be taken not to inject into a blood vessel or the skin.
Open vials should not be preserved for later use.

REACTIONS

Reactions are generally mild and confined to the site of injection. Some inflammation may occur together with transient fever, malaise and irritability. occasionally a nodule may develop at the site of injection but this is rare. Infiltration can be palliated by putting on a cold compress. In older children the local and general reactions may be more severe due to sensitivity to the diptheria protein.

CONTRAINDICATIONS AND WARNINGS

Individuals receiving corticosteroids, other immunosuppressive drugs or undergoing radio-therapy may not develop an optimal immune response. The vaccine should not be given in febrile states, acute infectious diseases, leukaemia, severe anaemia and other severe diseases of the blood system, severe impairment of the renal function, decompensated heart diseases, or known allergies to vaccine components. Ocassionally an increased severity of reactions to vaccination is noted in subject who are sensitive to diphtheria protein and in these individuals the special preparation containing the lower amount of diphtheria should be used. DO NOT USE AS RECALL IMMUNIZING AGENT FOR COMPLETELY IMMUNIZED PERSONS.

PRESENTATION

1 dose Ampoule	of	0,5 ml
10 dose Vial	of	5 ml
20 dose Vial	of	10 ml

Manufactured by

L A N A V E T
LABORATOIRE NATIONAL VETERINAIRE
DE BOKLE
GAROUA-REPUBLIQUE DU CAMEROUN

L A N A V E T

LABORATOIRE NATIONAL VETERINAIRE
DE BOKLE
GAROUA-REPUBLIQUE DU CAMEROUN

VACCIN ANTIDIPHTÉRIQUE ET ANTITÉTANIQUE ADSORBÉE
/Infantile-Usage Pédiatrique/

DESCRIPTION

Les anatoxines diphtérique et tétanique adsorbée sont préparées en mélangeant une anatoxine diphtérique purifiée et une anatoxine tétanique purifiée. Les antigenes sont adsorbés sur du phosphate d'aluminium comme adjuvant, correspondant a pas plus de 1,25 mg d'aluminium par dose humaine unique. 0,01 % de merthiolate est ajouté comme agent de conservation. Le vaccin a l'apparence d'une suspension de couleur blanc-grisâtre et ne contient pas de protéine de sérum de cheval. Il ne provoque donc pas de réaction immunologique aux sérums d'origine équine.

EFFICACITÉ

Le vaccin se conforme aux exigences de l'OMS, de la PE et de la PB quand il est testé selon les méthodes indiquées dans les TRS /Série de rapports techniques/ de l'OMS /1979/, 638, /1981/, 658, /1982/, 673, /1984/ /1985/ 700, /1985/, 725, et dans les Pharmacopées européenne et britannique. Chaque dose unique humaine de 0,5 ml contient 30 Lf d'anatoxine diphtérique avec pas moins de 30 I.U. et 10 Lf d'anatoxine tétanique avec pas moins de 40 I.U.

INDICATIONS

Pour l'immunisation de base et l'immunisation de rappel des enfants de moins de 10 ans et pour les nourrissons, de plus de deux mois pour qui la vaccination contre la coqueluche est contre-indiquée.Les enfants agés de plus de dix ans sont immunisés avec un vaccin antidiphtérique et antitétanique spécial qui contient une plus petite quantité de diphtérie.

APPLICATION ET POSOLOGIE

Aux fins de l'immunisation de base il est recommandé d'inoculer 2 à 3 doses de 0,5 ml à intervalles de 4 à 6 semaines. Pour les nourrissons la premiere dose peut être administré à environ trois mois d'age. Une injection de rappel de 0,5 ml devrait être donnée un an plus tard.

MÉTHODE D'INOCULATION

LE VACCIN DOIT ÊTRE BEIN SECOUÉ AVANT L'UTILISATION

Seules des seringues et des aiguilles stériles doivent être utilisées. Le vaccin devrait être administré par voie intramusculaire dans le muscle fessier ou le muscle deltoide, au choix du médecin. Les enfants de moins de deux ans devraient être inoculés dans le muscle quadriceps, entre les tiers supériaur et médian, sur la face latérale. Les ampoules ouvertes ne peuvent pas être conservées pour utilisation ultérieure.

RÉACTIONS

Les réactions sont généralement bénignes et se limitent a l'endroit de l'injection. Une inflammation peut avoir lieu, ainsi qu'une fievre passagere, un malaise ou de l'irritabilité. Parfois, un nodule peut se développer à l'endroit de l'injection, mais ceci est rare. L'infiltration peut etre atténuée en appliquant des compresses froides. Chez les enfants plus agés les réactions locales et générales peuvent etre plus sévères du à une sensibilité à la protéine diphtérique.

CONTRE-INDICATIONS ET AVERTISSEMENTS

Il est possible que les personnes recevant des corticosteroides ou autres médicaments immunosuppressifs ou suivant une radio-thérapie ne développent pas une réponse immunitaire optimale. Le vaccin ne devrait pas être administré aux sujets en état fébrile et aux sujets ayant des maladies infectueuses aigues, la leucémie, une anémie grave ou autres maladies graves du système sanguin, une détérioration grave de la fonction rénale, des insuffisances cardiaques décompensées ou des allergies connues aux composants du vaccin. On remarque parfois des réactions plus sévères à la vaccination dans les sujets qui ont une sensibilité à la protéine

diphtérique et pour ces sejuts on devrait utiliser la préparation spéciale contenant la quantité moindre de diphtérie.

NE PAS UTILISER COMME IMMUNISATION DE RAPPEL POUR LES PERSONNES COMPLETEMENT IMMUNISÉES.

CONSERVATION DU VACCIN

Le vaccin doit être conservé dans l'obscurité, l'abri de l'humidité à une tepérature de 2^{O} à 8^{O}C. Le transport doit aussi être effectué a une température de 2^{O} à 8^{O}C. NE PAS CONGELER.
Après l'ouverture d'une ampoule, son contenue doit être utilisé dans la journée.

DURÉE DE CONSERVATION

Trente-six mois à compter de la date de fabrication.

PRÉSÉNTATION

Ampoule	d'une dose	de	0,5 ml
Fiole	de dix doses	de	5 ml
Fiole	de vinght doses	de	10 ml

Fabriqué par:

L A N A V E I
LABORATOIRE NATIONAL VETERINAIRE DE BOKLE
GAROUA - RAPUBLIQUE DU CAMEROUN

VII. QUALITY CONTROL

This section of the Report will be published at a later date.

VIII. LIST OF REQUIRED MACHINERY

A. Crude Tetanus toxoid production unit

1. Kitchen

2 pcs. Autoclave steam heated

1 pc. 100 lit. and 1 pc. 200 lit. volume vertical with single door.

Supplier:

Lequeux-France
Fedegari-Italy
VEW-Austria

1 pc. Hot air sterilizer
appr. 0.75 m^3 single door
Supplier:
See the above item

1 pc. Technical balace 1000 g

Supplier:
Prolabo-France
Laprovet-France

2. Seed culture, precultivation

1 pc. Aseptic laminar-flow bench vertical

Height: 750 mm
Width : 872 mm
Depth: 570 mm
or the nearest standard size

Supplier:
ADS-France
SIBM-France
Gelman-Italy

1 pc. Small freeze dryer laboratory type

Supplier:
Usifroid-France
Edwards-U.K.

1 pc. Refrigerator 180 lit.
1 pc. Freezer 60 lit.
1 pc. Light microscope
1 pc. Table centrifuge with accessories
1 pc. Ramon water-bath
1 pc. Laboratory thermostat 35 C^{o}
1 pc. pH meter with accessories

Supplier:
Bioblock-France
Laprovet-France
Radiometer-Denmark

3. Fermentation

1 pc. Biofermentor specified for tetanus toxin production with 100 lit.working capacity of use equipped with incinerator for desinfection of the gas from the Biofermentor. Depending on the model Vibromixer might be also needed.

Supplier:

SGI - France
Contact-Flow-Netherlands /Tetonapaljas/
Biolafit-France
Pls.note that fermentor can be purchased from such supplier only who will provide fermentation technology for tetanus toxin.

1 pc. Control unit for Biofermentor
1 pc. Seitz filter frame 40cmx40cm with 12 plates
2 pc. Peristaltic pump and silicon tubing

Supplier:
Laprovet-France

4. Detoxification

1 pc. Laminar-flow bench vertical
Height: 750 mm
Wi 1482 mm
Depth: 570 mm

or the nearest standard size
Supplier: see above

1 pc. Walk-in thermostate room 35 C^{o}
External dimension. Height: 250 cm
Width: 220 cm
Depth: 270 cm

Supplier:
Cameroonian supplier - Garoua

1 pc. Walk-in cold room 4 C^{o}

External dimension: Height: 250 cm
Width: 120 cm
Depth. 270 cm

Supplier:
Cameroonian suppl.:r - Garoua

B. Purification, Concentration, Formulation

1. Concentration, Purification

1 pc. Ultrafilter
Ultrafiltration rate: 10-15 lit.per hour
cut-off: about 10 000 mw
maximum operating pressure: 25 psi
sterilisation by autoclaving
equiped with pressure vessel
Supplier:
SFEC - France
Amicon - USA
Contact Flow - Netherland

1 pc. Seitz filter frame 20cmx20cm with 12 plates

1 pc. Ramon water-bath
1 pc. Analitical balance 100 g
1 pc. Laboratory thermostat 35 C^{o}
1 pc. pH meter
1 pc. Magnetic stearer
1 pc. Table centrifuge
1 pc. Refrigerator 180 lit
1 pc. Freezer 60 lit.

Supplier:
Laprovet - France
Biobloc - France
Radiometer - Denmark

1 pc. Aseptic laminar-flow bench vertical

Height: 750 mm
Width: 1482 mm
Depth: 570 mm

or the nearest standard size

Supplier: see above

2. Kitchen

1 pc. Autoclave steam heated
200 lit. volume
vertical with single door

Supplier:
Lequeux - France
Fedegari - Italy
VEW - Austira

1 pc. Balance. Capacity 10 kg
1 pc. Balance. Capacity 1000 g
Supplier: see above

1 pc. Medium preparation vessel. Jacketed.
120 lit. volume
Supplier:
SGI - France
SEITZ - West Germany
Contact-Flow, - Netherland

1 pc. Walk-in cold room $4^{O}C$

External dimensions:

Height: 250 cm

Widht: 200 cm

Dept: 270 cm

Supplier: see above

3. Formulation

1 pc. Jacketed mixing vessel

200 lit. working capacity of use

3 inlets

1 outlet

vision panel

sampling valve

1 ventillation valve

Suoplier:

SGI - France

SEITZ - West Germany

Contact-Flow, - Netherland

2 pc. Filling tank

100 lit. working capacity of use

with magnetic stearer

Supplier: see the above item

1 pc. PALL filter house complete

4. Water treatment system

1 pc. Ion Exchanger with 500 lit. capacity

reserve tank and pump

1 pc. Water Distiller of 100 lit. per hour

capacity with 500 lit. capacity reserve tank

Recirculation system on $80^{O}C$ is required

Supplier:
Millipore - USA
DIESSEL - West Germany
FINN-AQUA - Finnland

5. Filling and finishing

1 pc. Washing machine for rubber stoppers and alu.caps.
Capacity per wash appr. 10 000 Pcs of 13 mm item

Supplier:

Pascal Schubert - Denmark
Strunck - Germany

1 pc. Automatic vial washing machine
Vial size: 5 ml, 10 ml and 20 ml
Capacity: 3000 /hour

Supplier:

Bausch and Stroebel - West Germany
Strunck - West Germany
Bonapace - Italy

1 pc. Hot air sterilizer
Internal dimensions:
Height: 150 cm
Widht: 80 cm
Dept: 60 cm
Double door type equiped with racking system and boxes which can take 5 ml and 10 ml vials

Supplier: see above

1 pc. Fully automatic machine for filling and closing of vials
Filling range : 1 - 10 ml
Object diameter: 20 mm, 25 mm and 32 mm
Output per hour: up to 3000
Power: three-phase current, 380 V, 50 Hz
Compressed air: 6 bar available

Supplier:

Strunck - West Germany
ROTA - West Germany

1 pc. Machine for visual inspection
of 5 ml and 10 ml vials

Supplier:
BREVETTI - Italy
STRUNCK - Germany

For the above major equipments recommended SPARE PARTS for 2 years are required. Training for maintenance should be included in the price for filling and washing machine.

The following equipments are needed from LANAVET's existing machinery on time sharing basis:

1. Refrigerated centrifuge
2. Hot air sterilizer
3. Autoclave
4. Vertical laminar air flow /for filling/
5. Labeling machine
6. Cold room /for the storage of finished product/

IX. PLANT SITE AND LOCAL CONDITIONS

Garoua is situated appr. 600 km north of the capital Yaounde. Lanavet has been built in Bokle, 14 km south of Garoua in a nice native environments. The buildings of 13 000 m^2 are lying on 1200 hectare. The only communication between Garoua and Bokle is a good quality motor road. Garoua has got an international airport facility. Lanavet has been established in 1984 for the production of veterinary vaccines. diagnostics and other biological preparations. The facility has been designed and built according to modern principles. Materials of the highest quality, mostly imported have been used for the construction. The laboratories are well organised and equipped with modern facilities for the production and control of viral and bacterial veterinary vaccines.

The airconditioning equipment and the ventillation chanels are located at the technical floor above the laboratories, the pipework for general utilities /water, steam, electricity, etc./ is arranged in the basement of the building very well established and can easily be reached for maintenance and required reconstructions.

Water supply

Lanavet is supplied with water from its own bore-water system. The water is pumped into 2 large reservior tanks /350 m^3 each/ and passed through an iron purification system and 2 sand filters before consumption. Samples of tap water and distilled water were analised by RIVM experts at the end of 1985 and found acceptable. The ample supply of water ensures free capacity for further consumption.

Electricity supply

The electricity is provided by the National Electric Power Agency /SONEL/ through 30 KV high cables from Garoua. After the transformer units at Lanavet 440 KW /380 V, 50 Hz/ is secured for the consumption of the laboratories. /appr.half of this capacity is free for further consumption./

The facility has its own electricity generator system /700 KVA/ which is activated automatically in case of power failure.

Steam supply

A steam supply from a central generating plant /1000kg/hour, 10 bar/ provides steam in all areas where needed. The present consumption is appr. 500 kg/hour.

The steam is not filtered centrally. Terminal filtration has to be built in if necessary /e.g. for the fermentors which can be sterilised on the spot/.

Compressed air supply

Compressed air is supplied by 2 compressors 8 bar capacity each. Before consumption a 5 bar reductor is built in. Room for further consumption is available.

Air conditioning

Air conditioning designed to cope with extreme climatic conditions /45-48^{o}C, 100 % humidity/ is provided in alll areas where needed. Air filtered through absolute filters is equipped in the sterile areas with provisions to over pressure.

Airsupply to the human vaccine production unit has to be investigated and redesigned if necessary carefully because it could be a critical factor for the succes of the operation.

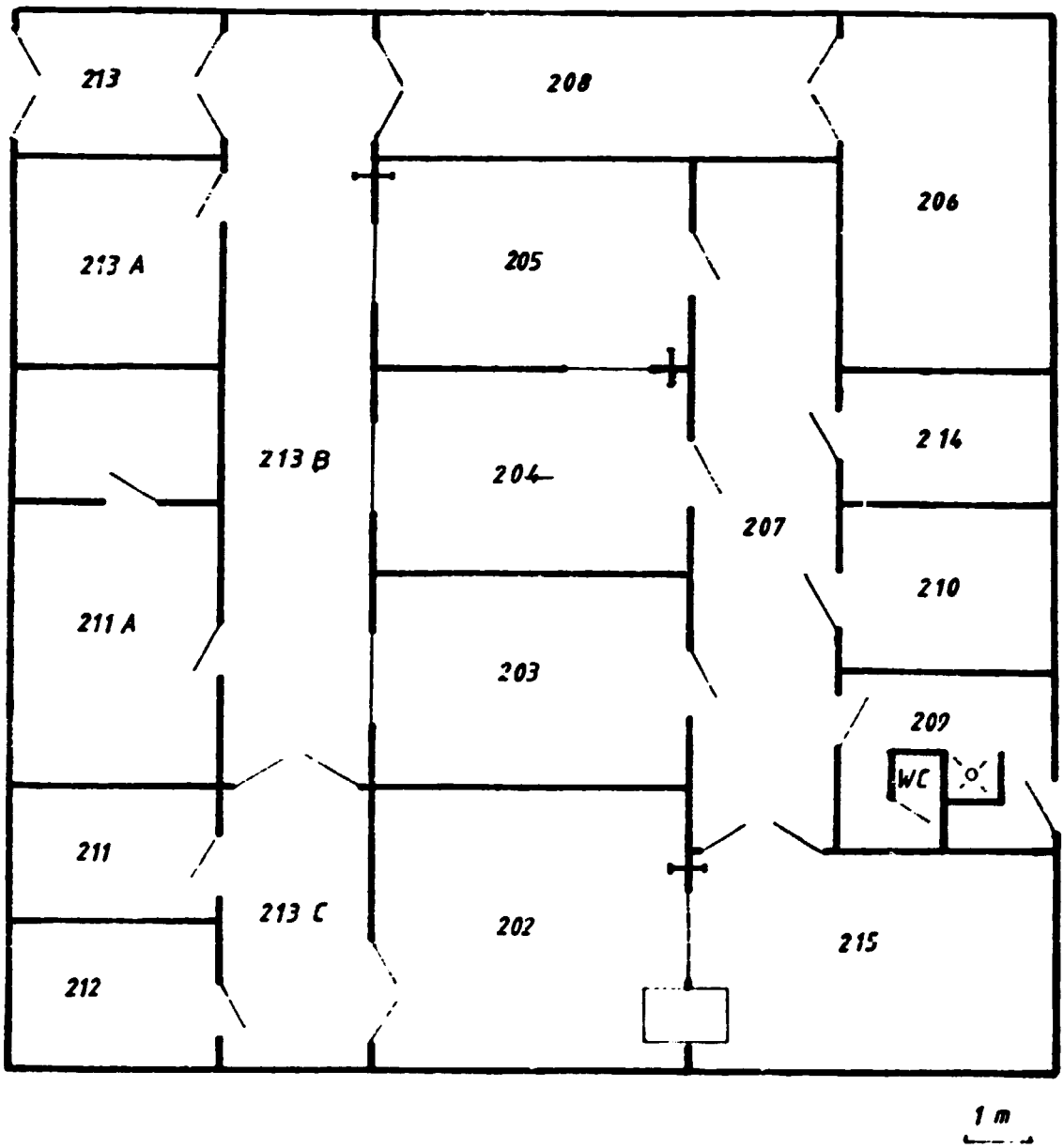
Site for the project.

The management of Lanavet secured 2 sites for the following purposes;

- Full production of Tetanus toxoid concentrated bulk.
- Formulation of Tetanus toxoide final bulk vaccine and other vaccines.
- Sterile filling of Tetanus toxoide vaccine adsorbed and other injectable preparations.

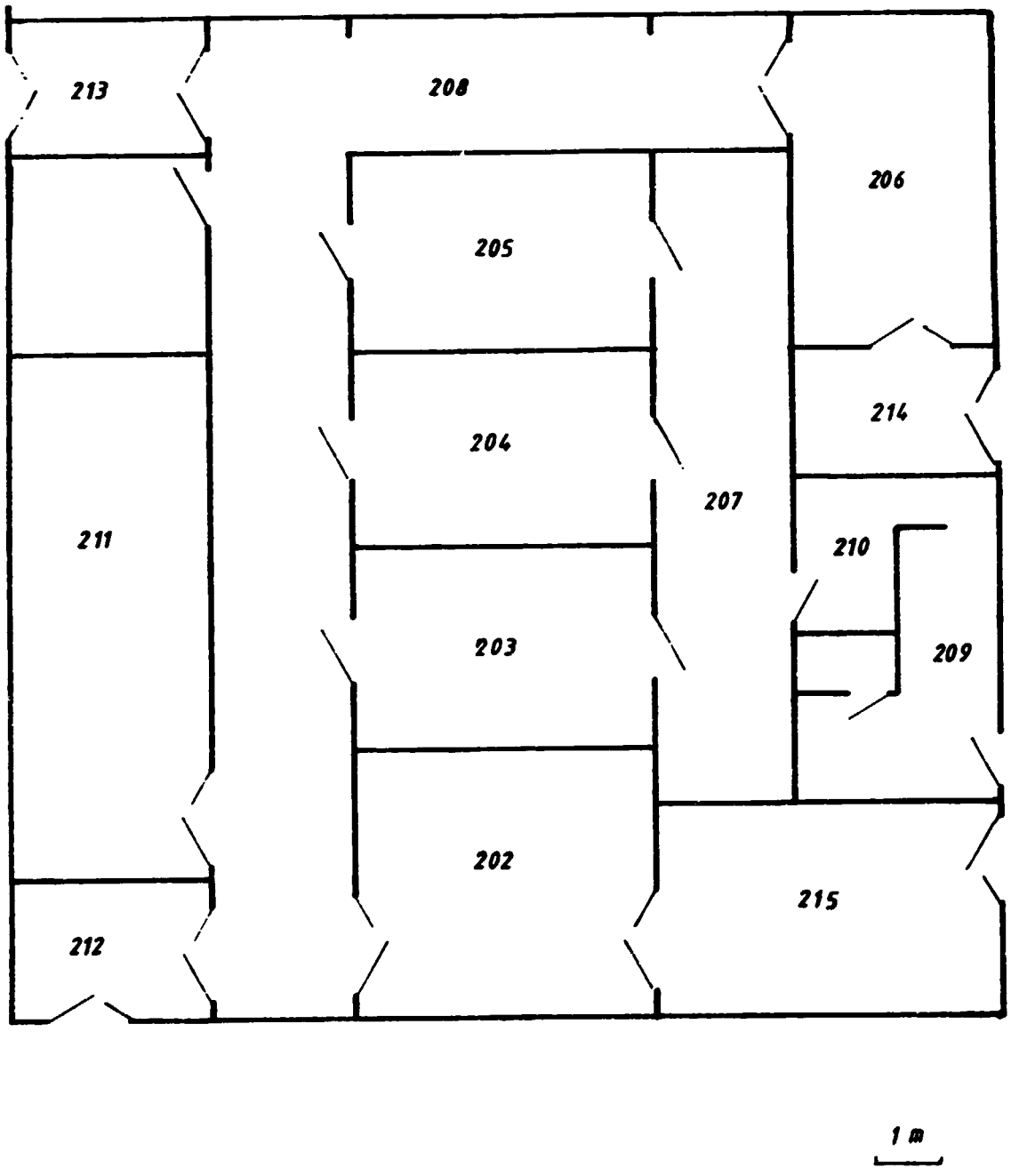
Both sites are parts of the main building-complex and access to the general infrastructural facilities can be built up relatively easily.

LABORATORIES FOR TETANUS TOXOID FERMENTATION, DETOXIFICATION, CONCENTRATION, PURIFICATION AND FORMULATION



Rooms No. 203, 204, 205, 206 and 207 are equipped with steril air. The parts marked with red show the places where reconstruction is required.

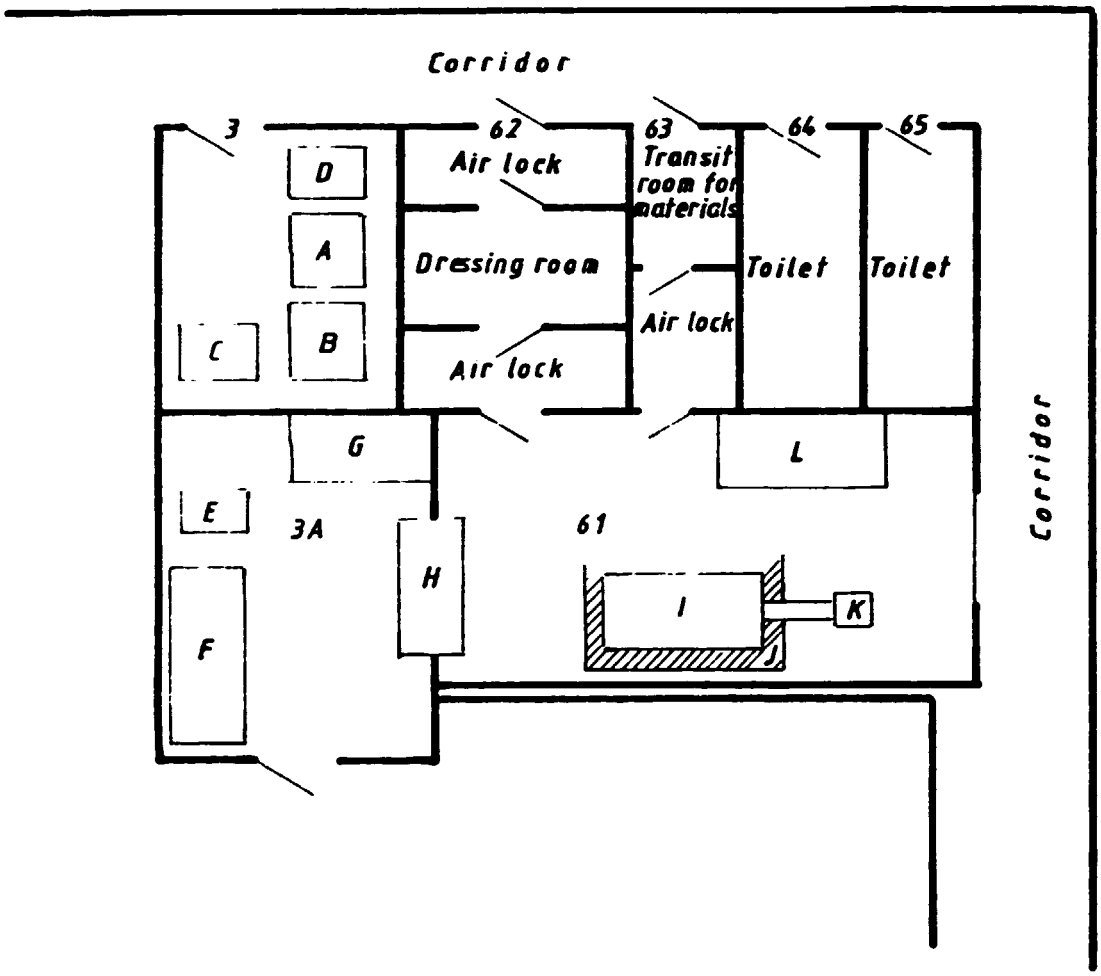
EXISTING BUILDING FACILITIES



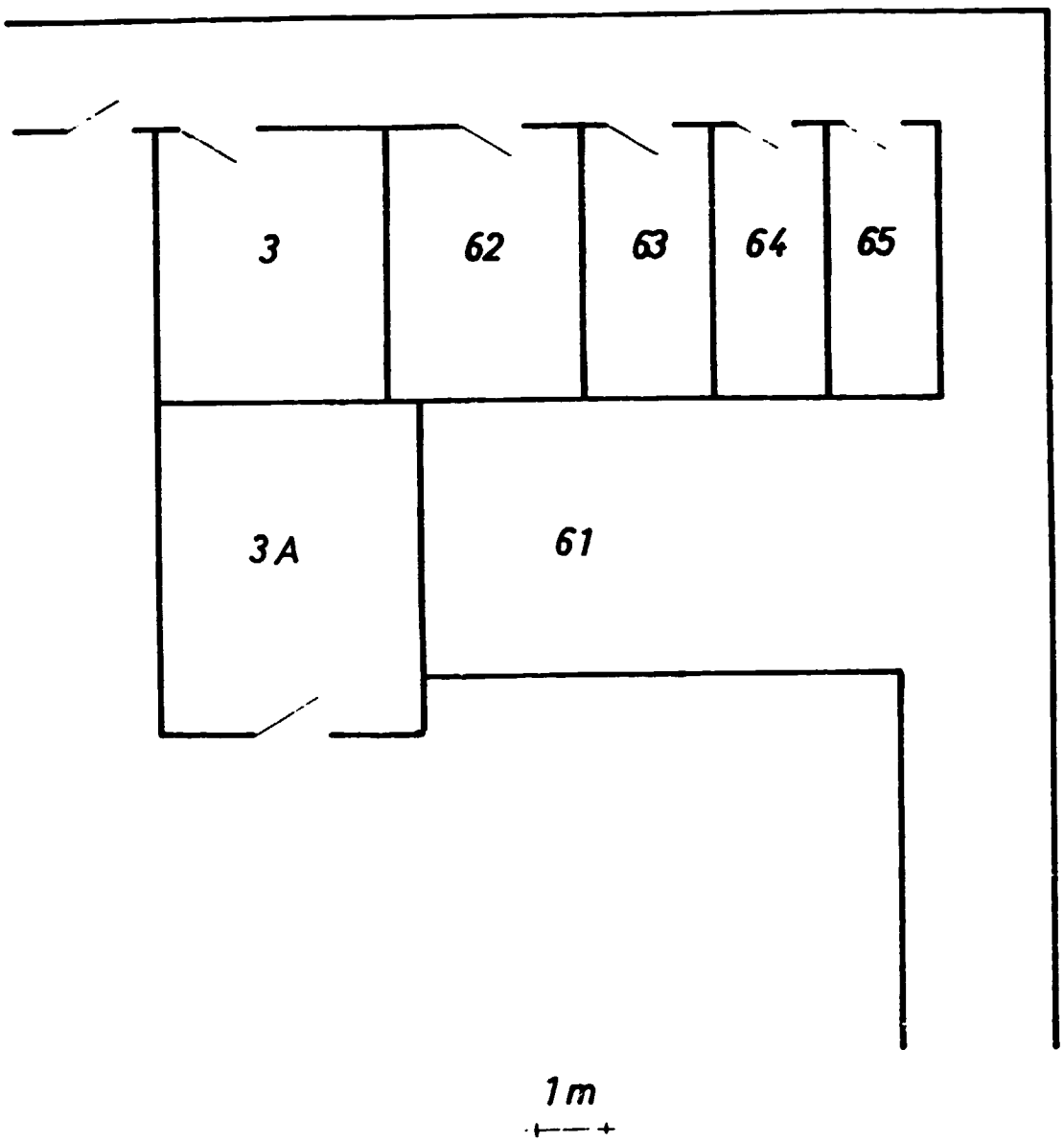
Room No.	Activity	Description of large equipments
203	Freeze-drying of the strain	Freeze-dryer, small LAF-cabinet
	Seed culture	Refrigerator Freezer
	Pre-cultivation	Table centrifuge Microscope
	Control	Ramon bath Incubator, small pH-meter Extinctiometer
205	Fermentation	Bioreactor specified for Tetanus toxin production /100 litre working
	Harvesting	capacity of use/
	Filtration	Control unit for bioreactor Incinerator for the desinfection of the gas from the bioreactor Seitz filter
204	Detoxification	LAF-cabinet
	Control	
210	Detoxification	Walk-in incubator
214	Storage	Walk-in cold room
209	Dressing room Shower, WC	
207	Air lock	
215	Kitchen	Autoclaves 2 pcs Hot air sterilizer
	Sterilization	Balance
	Cleaning	Wash-basin double
	Washing	
202	Kitchen	Autoclave Hot air sterilizer
	Culture media prod. Sterilization	Seitz filter Medium wessel /jacketed, 120 lit./ Balances
	Cleaning, washing 0,9 % saline production	Electric mincer Wash-basin double
213A	Concentration	Ultrafilter Pressure vessel
	Purification Steril filtration	Cooled centrifuge Seitz filter Sephadex G 50 /gelfiltration/ Magnetic stirrer Membran filter

211A	Laboratory	Incubator LAF-cabinet
	Control $AlPO_4$gel distribution	Ramon-bath pH-meter Table centrifuge Balance, analitical Refrigerator Freezer
211	Storage	Walk-in cold room
212	Office	
213	Air lock	
208	Air lock	
206	Formulation	Mixing vessel, jacketed, 250 lit. Control unit Filling tank 100 lit. 2 pcs.

BUILDING FACILITIES FOR WATER TREATMENT, WASHING, FILLING AND VISUAL CONTROL



EXISTING BUILDING FACILITIES



Room No.	Activity	Description of large equipments
3	Water treatment	"A" Ion exchanger
		"B" Water distiller
	Demineralization	"C" Reserve tank for demin.water
	Distillation	"D" Reserve tank for distilled water
	Water storage	
3/A	Washing	"E" Washing machine for closers
		"F" Vial washing machine
	Sterilization	"G" Wash-basin double
		"H" Hot air sterilizer
61	Vial filling	"I" Automatic vial filling and closing machine
		"J" Vertical laminar air flow cabinet
	Vial closing	"K" Visual control unit
	Visual control	"L" Laboratory table

C. Plant capacity

Feasible normal capacity of the proposed Tetanus production unit

Method of production:	Fermentation
Fermenter:	Bioreactor
Working capacity of use:	100 litres
Cultivation cycle:	7 days
Number of cultivation in a week.	1
Toxin concentration at the harvest:	60 Lf/ml
Recovery efficiency:	70 %
Tetanus toxin produced in a fermentation run:	$4x10^6$ Lf
in a year /40 weeks/:	$16x10^7$ Lf
Doses /10 Lf/ of Tetanus toxoid in a year:	14 400 000 /10 % filling loss is included/

Feasible normal capacity of the proposed Formulation unit

Machinery:	Mixing/formulation tank
Working capacity of use: /maximum batch size/	200 litres
Production cycle:	2.5-3 days pending on the number of the staff
Number of formulation run in a week:	1 or 2
Capacity per 200 lit. batch expressed in 20 dose /10 ml/:	20 000
Losses at filling:-5% overfill	1 000
-5% filling wastage	1 000
	18 000/batch
Maximum capacity per year /40 weeks/:	80 batches of 200 litres
expressed in 20 doses /10 ml/	1 440 000 vials

Feasible normal capacity of the proposed Filling unit

Vial washing machine nominal maximum capacity:	3 000 vial/hour
feasible normal capacity /70%/:	2 100 vial/hour

capacity per shift
/5.5 hours continuous
operation/: 11 500 vial

capacity per year
/200 days/ : 2 300 000 vial

Rubber stopper and alu.cap
washing machine

nominal maximum capacity:
/20 mm item/ 5 000 pcs/wash/hour
feasible normal capacity: 5 000 pcs/wash/hour

Hot air steriliser

nominal maximum capacity:
/10 ml vial/ 10 000 pcs/cycle/3 hours
feasible normal capacity: 10 000 pcs/cycle/3 hours

Vial filling and closing
machine

nominal maximum capacity: 3 000 vial/hour
feasible normal capacity
/70 %/: 2 100 vial/hour
capacity per shift /5.5
hours continous operation/: 11 550 vials

capacity per year
/200 days/: 2 300 000 vials

X. TERMS OF REFERENCE OF CONTRACTING SERVICES FOR THE REMODELLING

A. General remarks

- Premises should provide sufficient space to suit the operations to be carried out, allow an efficient flow of work and permit effective communication and supervision.
- The processing of materials for non medical use should be appropriately segregated from the processing of medicinal products.
- Cloakrooms should be separated from or partionated from processing areas. Toilets should be well ventillated and not open directly to manufacturing areas.
- Premises in which medicinal products are manufactured or stored should be made secure, with acces restricted to authorized personnel. Additional security arrangements necessary in specific areas for specific product /e.g. Tetanus toxin production/.
- Floors in processing areas should be made of impervious materials, laid to an even surface. They should be free from cracs and joints and should allow prompt and efficient removal of any spillages. Walls should be sound and finished with a smooth, impervious and washable surface. Ceilings should be so constracted and finished that they can be maintained in clean conditions. All surfaces must be formed to prevent erosion by water and desinfection agents. The coving of junctions between walls, floors and ceiling in critical areas is recommended. The doors and frames should be formed from silver anodised aluminium.
- Pipework, light fittings, ventillation points and other services in manufacturing areas should be sited to avoid creating uncleanable recesses. Services should preferably run outside tho processing areas. They should be sealed into any walls and partitions through which they pass.
- Drains should be of adequate size and should have trapped gullies and proper ventillation. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and desinfection.
- Buildings should be effectively lit and ventillated, with air control facilities /including temperature, humidity and filtration/, appropriate both to the operations undertaken within them and to external enviroment.

- Air intakes and exhaust and associated pipework and trunking should be sited to avoid product contamination hazards.
- Animal houses should be well isolated from manufacturing areas.

B. General services

Electricity

Sufficient spare capacity is secured for appr. 100 kw further consumption. The power outlets should be distributed so that when all laboratory equipments are operating, sufficient spare capacity should remain for the cleaning equipments and monitoring devices. All electrical fittings should be moisture proof.

Gas

Some production areas require gas point for Bunsen burners. Propan/butan gas is available in different size containers at LANAVET. For the Tetanus toxin production laboratory nitrogen supply is required.

Air conditioning

The whole building complex of LANAVET is air conditioned. /Temperature $18^{O}C$ - $20^{O}C$, relative humidity 35%-65//. For the steril rooms of the Tetanus toxoid production and the filling room steril airsupply is needed with overpressure. Aire pressure recorders are required. For these rooms air class 10 000 - 1 000 is necessary. If an activity requires greater purity /air class 100/ LAF cabinet should be used.

Steam supply

Two steam generators of 1 000 kg/hour capacity are installed at LANAVET. Appr. 50 % of this capacity is free at present. Dry steam is required to operate the autoclaves and for the in situ sterilization of the fermenter tank. /2.5 - 3.0 bar/

Water

Well organized distribution network for potable water is available at LANAVET. No central or terminal ionexchanger is installed. Distillation is performed in 2 small capacity units. Pure water is required for the preparation of culture media and for the rinsing of vials and other glasswares and

equipments. Distilled water is required for the formulation of final bulk and for the various steps of the manufacturing process. Installment of a new water treatment system is required according to GMP requirements /central tanks for storage, recirculation system at 80°C, final steril filtration etc./

Compressed air and vacuum

Compressed air and/or vacuum is required in the production areas. The compressed air is supplied by 2 central compressors. The vacuum could be locally produced by vacuum pumps /outside the working area/.

C. Detailed description of the changes required.

1. Tetanus toxoid production and formulation unit.

Room no.	Basic services required	Description of changes required
202	Electricity 220 V, 4 sockets Steam supply Compressed air Vacuum Tap water supply Propan butan gas	Air lock chambre to be constructed in between 202 and 215 /appr. 1 m^2 equipped with ultraviolet light/ Visual panel to room 215 Stainless steel pipe connection with room 215 More effective lighting Drainage for wash basin.
203	Electricity 220 V, 6 sockets Steril air supply with positive pressure Compressed air Vacuum Tap water supply Propan butan gas supply	Door to non sterile corridor to be changed to fixed window /vision panel/ More effective lighting Drainage for wash-basin
204	Electricity 220V, 4 sockets Steril air supply with positive pressure Compressed air	Door to non sterile corridor to be changed to fixed window /vision panel/ More effective lighting Drainage for wash-basin

	Tap water supply	Vision panel to be installed between rooms 204 and 205 close to sterile corridor
	Vacuum	
	Propan butan gas supply	Sterilizable /steam/ stainless steel pipe connection through the wall under the vision panel between rooms 204 and 205
205	Electricity 220 V, 4 sockets /depending on the type of fermenter 380 V might be needed/	Door to non sterile corridor to be changed to fixed window /vision panel/
		More effective lighting
	Steril air supply with positive pressure	Outside nitrogen supply from the non sterile corridor /valve and manometer should be inside the room/
	Compressed air	
	Tap water supply	
	Vacuum	Drainage for wash-basin
	Exhaust to outside	
	Steam supply	
	Propan butan gas supply	
206	Electricity 220 V, 4 sockets /motor for mixing tank might require 380 V/	Door to room 214 to be walled up
		More effective lighting
	Sterile air supply with positive pressure	Drainage for wash-basin
	Compressed air	
	Vacuum	
	Tap water supply	
	Steam supply	
	Propan butan gas supply	
207	Electricity	More effective lighting
		Double door to room 215
208	Electricity	Double door to room 213B
		More effective lighting
209	Electricity	New changing room with WC and shower /"normal" and "clean" sides/
	Tap water supply	
		Wall to separate room 209 and 210

210 Electricity		Walk-in incubator Door to corridor 207
211	Electricity	Walk-in cold room Wall to separate from room 211A
211A	Electricity 220V, 6 sockets Tap water supply Compressed air Vacuum Propan butan gas	Wall to separate electrical switch panels already installed with a small door More effective lighting Door to corridor 213B Drainage for wash basin
212	Electricity 220V, 2 sockets	Door to yard to be changed to window
213A	Electricity 220V, 4 sockets Tap water supply Compressed air Vacuum Propan butan gas	More effective lighting Drainage for wash basin
213B	Electricity	Double door to 213C more effective lighting
213C	Electricity	More effective lighting
214	Electricity	Walk-in cold room Door to corridor 207 Door to 206 to be walled up Door to yard to be walled up
215	Electricity 220V, 4 sockets /Hot air sterilizer might require 380 V/ Tap water supply Steam supply Compressed air Vacuum Propan butan gas supply	Door to yard to be walled up Drainage for wash basin

Walking path to be constructed around the building.

2. Filling and finishing unit

Room no.	Basic services required	Description of changes required
3	Electricity 220 V, 3 sockets /distiller might need 380 V/	Stainless steel pipe connection to room 3A
	Tap water	Drainage
3A	Electricity 220 V and 380 V	Double door hot air sterilizer in the wall between 3A and 61
	Tap water supply	Drainage for wash basin double
	Demineralized water supply	More effective lighting
	Distilled water supply	Valve for draining distilled Water
	Compressed air	
61	Electricity 220 V /Filling machine might require 380 V/	2 new walls facing the corridor and the yard
		Vision panel from the corridor
	Steril air supply with positive pressure or effective germicide lamps as last solution	Sterile air inlets
63	Electricity	Transit room and airlock to be constructed /airlock with sterile air supply or germicide lamps/
		More effective lighting
62	Electricity	Changing room with shower
	Tap water supply	Airlock with sterile air supply or germicide lamps
		More effective lighting

XI. MANPOWER

A. Personnel requirements

1. Tetanus toxin fermentation and detoxification

Biotechnologist /bacteriology/	1	/to be trained abroad/
Senior technician	2	/to be trained abroad/
Technician	2	

2. Concentration, purification, formulation

Chemist or pharmacinst	1	/to be trained abroad/
Senior technician	3	/2 to be trained abroad/
Technician	3	

3. Filling and finishing

Pharmacist	1	/to be trained abroad/
Senior technician	2	
Technician	5	

4. Quality control

B. Training

Both professional and labour staff should be highly motivated disciplined because only this behaviour can assure that during the rutine work, the aseptic and sterile conditions will as far as possible be kept. The importance of the above can not be overemphasized since vaccine production at any stage based on aseptic and sterile work. Familiarizing with aseptic and sterile work needs a long term training aimed not only to teach the technics themselves but to promote the personal and environmental hygenic conditions and to abandon the unhygenic practices.

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

The number of personnel and qualifications required for production and quality control are given in paragraph "A".
The aim of the training is to get the participants acquainted with the general sterile technics, detailed production and quality control of Tetanus toxoid formulation, filling and quality control of DPT, Dt and Tetanus toxoid vaccines.
It is recommended that the persons from the production and quality control go simultaneously in teams. They will go together through the production and control process of a number of vaccine batches during the training and will be able to replicate the whole production and controll process after returning.

Proposed teams

1st team

Personnel	Qualification	Purpose of training	Duration of training
Head of fermentation	Biotechnologist	Theoretical background Production technics Production planning	3 months
2 Senior technicians for fermentation	Technician	Production processes Laboratory technincs	3 months
Head of conc.pur. and formulation	Chemist or pharmacist	Theoretical background Production technics Production planning	3 months
2 Senior technicians for conc.pur. and formulation	Technician	Production processes Laboratory technics	3 months

2nd team

Head of filling and finishig	Pharmacist	Theoretical background Production technics Production planning	3 months
Head of QC	Medical doctor or pharmacist	Theoretical background Control technics	3 months
1 Senior technician for QC	Technician	Control technics	3 months

The consultants strongly recommend that the present head of the Bacteriological Dept.of Lanavet be the overall superviser to the proposed Tetanus production unit. Dr. J.J.Tulasne is a French specialist who has gained some experience in Tetanus toxoid production years ago. We propose a short term training /minimum 4 weeks/ for him in the Institute providing technology.

XII. PROJECT IMPLEMENTATION SCHEDULE

In this chapter a schedule is drawn up for the various stages of the project. The schedule lays down a time-programme that combines the various stages into a consistent pattern of activities that dovetail into one another. This comprehensive schedule covers the entire project from the planning stage to the start of production.
The efficient implementation of the project may depend considerably on an efficient implementation management team. Such team should be established with the participation of the following organizations.

LANAVET

Ministry of Livestock, Fisheries and Animal Industries
Ministry of Plan and Territorial Development
Ministry of Health

UNIDO

An adequate period should be provided for various activities. There is normally a considerable lapse of time between the invitations for machinery quotations and the placing of orders. The time elapsing before equipment is delivered may range from 3 to 6 months.
The sequence of civil work and construction activities, in terms of construction time and building requirements, needs to be carefully defined in relation to infrastructure requirements, availability and the arrival and installation schedule of different equipments.
The recruitment and training of staff and labour has also to be appropriately scheduled, so that trained personnel is available as and when required.
The preparation of the sales market should start early enough that the output can really be sold as scheduled.

Implementation scheduling time-programme

Timing	Remodelling/Reconstruction	Machinery/Materials	Training	Production and QC	Marketing
Nov.1988	Final engineering layout should be prepared by international experts in coordination with national counterpart. Necessary materials to be ordered and despatched by the subcontractor.	Invitation for machinery quotation from different suppliers. Final specification to agreed between supplier, national counterpart and licensor /consultants/	Selection of Lanavet senior staff for the training by Government counterpart and UNIDO		Relevant Government Authorities should be informed about the project and the expected inplementatic scheduling
Dec.1988	Governmental approval	Orders should be placed for machinery for May arrival at latest.	Recruitment of additional staff for the training if necessary.		
Jan.1989	Govermental approval				Progress report to the Purchasing Depth.of MOH
Feor.1989	Selection of a local company for the execution of the job.	Quotations should be requested for raw and packaging materials by Lanavet.	Training of the first team should be started.		
March.1989		Orders should be placed for raw and packaging materials for Juna arrival by Lanavet.			

Timing	Remodelling/Reconstruction	Machinery/Materials	Training	Production and QC	Marketing
Apr.1989	Start up of the reconstruction/remodelling. Performance should be supervised by experts.	Orders for the general laboratory instruments should be placed by Lanavet /Annex 8/ for June arrival.	Training for the first team is finished		Progress report and offer with firm prices for 1990 to be given to MOH.
May.1989		Deadline for the arrival of the machinery. Installation.	Training for the second team should be started.		
June 1989	Completion of the construction work.	Installation of the machinery.			Purchase orders should be obtained from MOH for 1990 /based on Lanavet's offer/
July 1989		Validation and trial runs with the participation of the consultants.	Training for the second group is finished.	Production programme should be prepared for 1990.	Well drafted Memorandum should be sent to potential export partners about the production unit, forecasting capacity figures.
Aug.1989		Trial runs and preparation of SOP-s with the participation of the consultants.		Trial Tetanus toxoid production with complete QC floow up.	

Timing	Remodelling/Reconstruction	Machinery/Materials	Training	Production and QC	Marketing
Sept.1989		Orders should be placed for raw and packaging materials for January arrival.			
Oct.1989					
Nov.1989				Trial Formulation of Tetanus toxoid vaccine with complete QC follow up.	Opening ceremony with the participation of potential big purchase partners.
Dec.1989		Orders should be placed for raw and packaging materials for April arrival.			
Jan.1990				Routine production of Tetanus toxoid vaccine and trial formulation of DPT and DT vaccines with the participation of the consultants.	Offer to be given to potential export partners and proper follow up.
Febr.1990					

Timing	Remodelling/Reconstruction	Machinery/Materials	Training	Production and QC	Marketing
March 1990		Orders should be placed for raw and packaging materials for July arrival.			
Apr.1990				Routine formulation of DPT and DT vaccines.	
May 1990					
June 1990					

XIII. PREFEASIBILITY STUDY FOR THE EXPANSION OF HUMAN VACCINE PRODUCTION

In the present project titled "Establishment of a pilot demonstration plant for the production of vaccines for Africa" a proposal was made for the implementation of a complet Tetanus toxoid vaccine production unit within the existing facilities of LANAVET.

In this unit parallelly with the formulation of Tetanus toxoid vaccine production of DPT and DT vaccine could also be realized from imported concentrated bulk Diphtheria toxoid and Pertussis suspension.

As a further step, it seems to be logical to establish a new vaccine production unit for the preparation of concentrated Diphtheria toxoid and concentrated Pertussis suspension. In this case full production of the DPT and DT vaccines could be carried out at LANAVET and the Cameroonian and Central African demand could be fulfilled with completely locally produced vaccines. The estimated construction cost of this unit is appr. 65-80 million CFA excluding machinery.

An additional separated wing could also be attached to this new "Bacterial Vaccine" unit for the production of BCG vaccine. In this case production of all bacterial EPI vaccines could be realized. Estimated cost of this increased unit is appr. 100-125 million CFA excluding machinery. It is obvious that by adding the BCG unit costs will substantially be increased. Before taking this decision economical and strategical aspects have to be considered.

For the production of the virus vaccines of the EPI two production units are required /inactivated and live virus production units/. Estimated constraction cost of the live measles production unit is appr. 90-110 million CFA excluding machinery. Licencing arrangement for the technology is required. Capacity of this unit is far more than the domestic demand.

Estimated construction cost of the inactivated poliomyelitis production unit is appr. 110-140 million CFA excluding machinery. The quality requirements for the product are very rigorous. The production process includes quite difficult biotechnological and immunochemical steps. Capacity of this unit is far more than the domestic demand.

Although in the domestic vaccination practice DPT polio vaccine has already been introduced, majority of the polio vaccination is done by oral poliomyelitis vaccine /OPV/. If this trend will not change in the future, production of this live type polio vaccine

might be considered.
Estimated value of the required machinery, lay-out of the laboratories, flow charts, technological aspects and staff questions are discussed in detailes in the following part of the report.
Three very important factors are stressed here in advance.

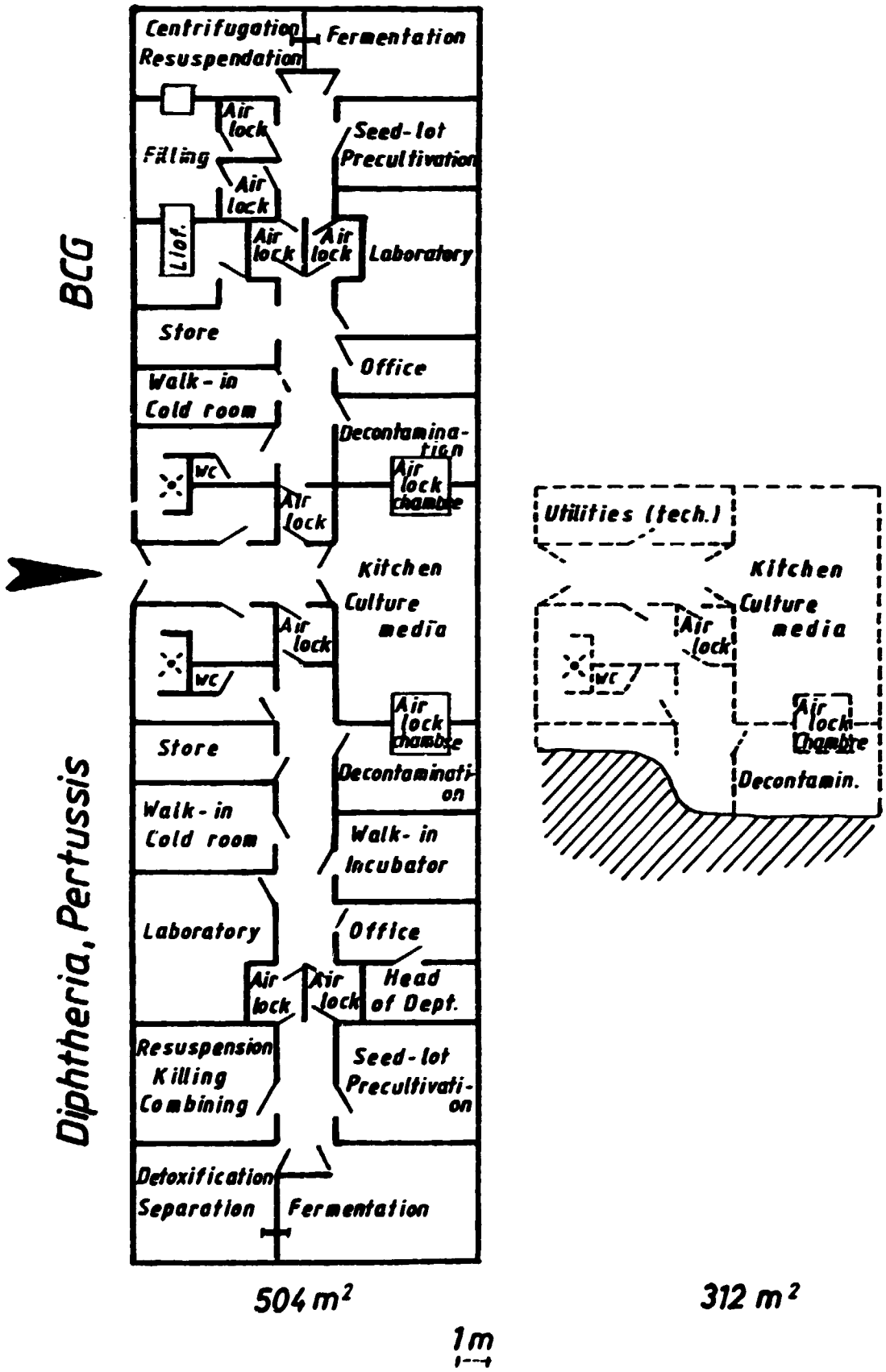
- Full technology transfer is essential for the products.
- Strong and from the production independent Quality Control labs. must be established.
- Development and maintenance of stabil and well trained staff is absolutely necessary.

A. Production Unit for Bacterial Vaccines

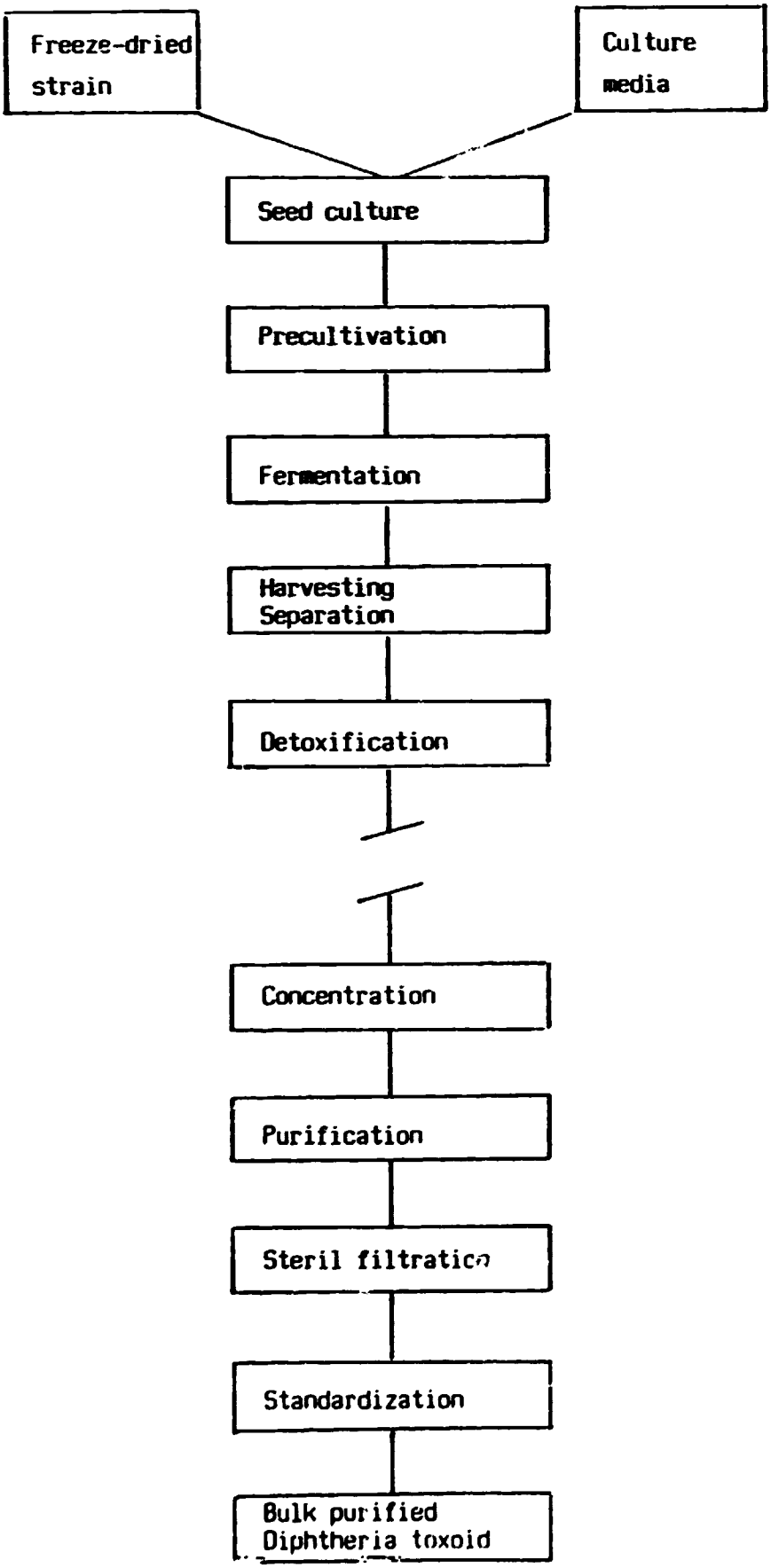
- In this unit production of concentrated Pertussis bulk suspension, detoxified Diphtheria toxoid and separately BCG vaccine can be produced. /Technology transfer is necessary/.
- The concentration and purification of the detoxified Diphtheria toxoid is performed in the proposed Tetanus Unit.
- Formulation of DPT final bulk from components /concentrated Pertussis bulk suspension, concentrated and purified Diphtheria toxoid and concentrated and purified Tetanus toxoid/ is carried out according to the given prescriptions in the proposed Tetanus Unit.
- In the Production Unit for Bacterial Vaccines some other vaccines /Typhoid, Cholera etc./ could be produced. /Technology transfer is necessary/.
- The estimated capacity of the BCG vaccine production part of the Unit is appr. 600-800 000 doses per cultivation /using a fermenter of 10 litre/.
  Using a fermenter of 100 litre for the production of Diphtheria toxin and Pertussis bulk suspension the estimated capacity is 4.9×10^6 Lf /appr. 300 000 doses for DPT vaccine/ or 1.8×10^6 IOU B.pertussis bacteria /appr. 110 000 doses for DPT vaccine/ per week.
- The estimated cost for this building is appr. 200-250 000 CFA per m^2. /Without equipments/. The essential services must be done according to WHO and GMP requirements.
- Machinery and equipments are similar to those of installed at LANAVET. Their estimated cost is 500-700 000 USD. The most important units are: bioreactors, filling machine, freeze-drying appratus, separator, walk-in cold room and incubator, freezer /-70°C/ etc.
- Staff.3 academics, 5 senior technicians, 5 technicians are recommended. Their continuous training is necessary.
- In process and final quality control have to be established.
- For the biological control of these products a separated animal house is necessary, which meets the WHO requirements.
- If the BCG vaccine production is not preferred, the Production Unit for Bacterial Vaccines /Diphtheria, Pertussis etc./ could be established on appr. 300 m^2. In this case the estimated cost of the necessary equipments is appr. 300-400 000 USD.
- The liofilized BCG vaccine can also be performed in static culture /on the surface of culture medium/, without fermentation. /Technology transfer is necessary/.

- The lay-out, flow chart, estimates and requirements of the BCG vaccine production are based on the WHO and UNIDO Model Programme for the Production of Vaccines in Developing Countries.

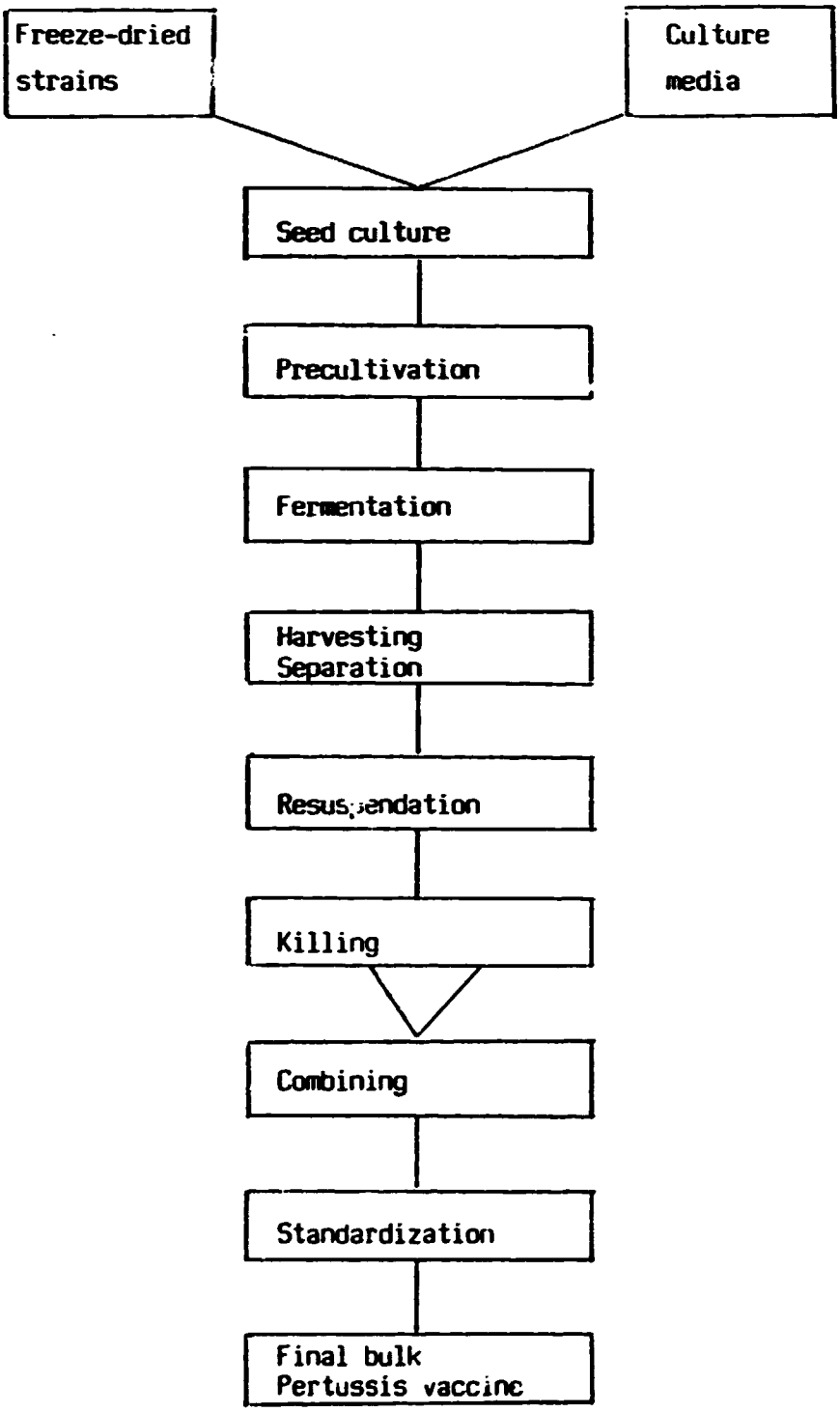
PRODUCTION UNIT FOR THE BACTERIAL VACCINES
(BCG, Diphtheria, Pertussis)



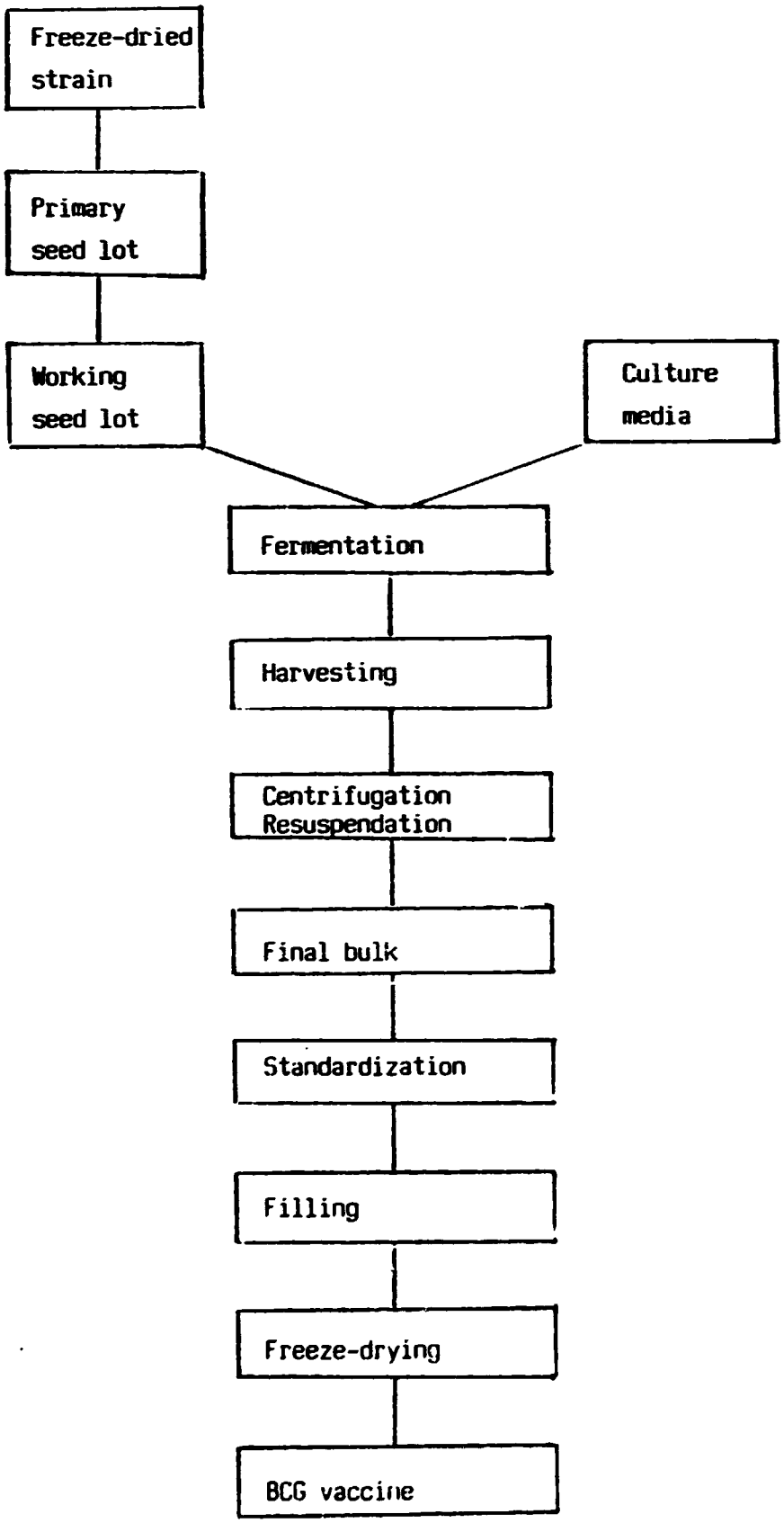
Flow chart of Diphtheria toxoid production



Flow chart of Pertussis vaccine production



Flow chart of freeze-dried BCG vaccine

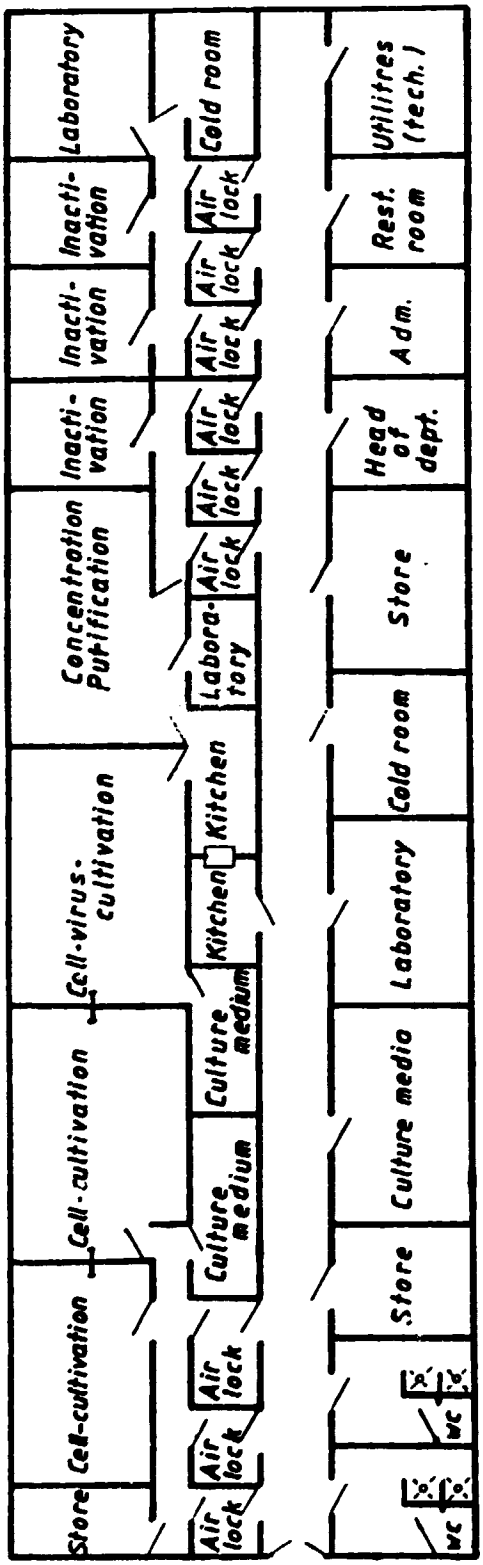


B. Production units for inactivated virus vaccines /poliomyelitis/ and for live virus vaccines /measles/

- The two units have to be established separately
- A critical point of the production of virus vaccines is the cell substrate used for the virus cultivation.
  HDCS /human diploid cells/ or a non tumorigenic, well characterized cell line /VERO/ is proposed.
  VERO-cells can be obtained from the American Type Culture Collection /ATCC/
  For the production of measles vaccine chick embrio fibroblast cells can be used.
- For small scale production the cells can be cultivated in standard monolayer cultures in Roux bottles, but for large scale production microcarrier culture system is used. /Bioreactors of 10,50, 150 lit. or bigger, continuous perfusion system, etc./
- For the concentration and purification of the inactivated virus vaccines gel filtration on Sepharose 6B /the volume of column is appr.25 litres/ and DEAE-Sephadex column chomotography is necessary. The level of cellular DNA is suggested to be between 10 and 100 pg per dose!
- The seed viruses in case of poliomyelitis /type 1,2 and 3/ can be obtained from the WHO Reference Center.The attenuated measles virus strains are not freely available.
- For the freeze-drying of measles vaccine an appropriate stabilizer is necessary. This is also not freely available.
- Technology transfer for the production of inactivated and live virus vaccines are absolutely essential.
- The space required for the two production units is appr. 500-500 m^2. The estimated cost of the buildings is appr. 200-250 000 CFA/m^2. The essential services must be done according to WHO and GMP requirements.
- The estimated capacity of the two production units would be more than sufficient for the immunization programme of Cameroon and Central African Subregion.
  In the new units some other virus vaccines could be produced.
  In this case technology transfers are necessary.

- The machinery and equipments are similar to those of installed at Lanavet except the microcarrier culture system adopted to the bioreactors. Their estimated cost is appr. 1 million and 500 000 USD respectively.
- Staff. Academics /2/, senior technicians /2/, technicians /2/ and other personnel /3/ for both units are recommended. Their continous training is necessary.
- In process control and final quality control must be established.
- Production of DPT polio vaccine from imported bulk of the inactivated poliomyelitis vaccine could be carried out in the formulation part of the proposed Tetanus unit /technology transfer is necessary/, but in the official National Immunization Programme of Cameroon oral polio vaccine /OPV/ is used.
- The lay-outs, flow charts, requirements and estimations are based on the WHO and UNIDO Model Programme for the production of Vaccines in Developing Countries.

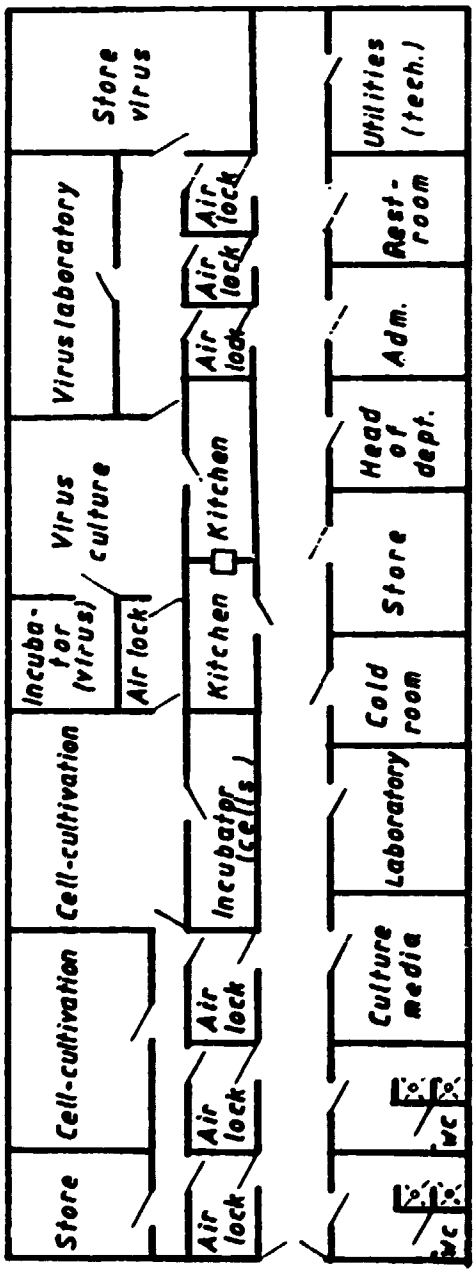
PRODUCTION UNIT FOR THE INACTIVATED VIRUS VACCINES



546 m²

1m

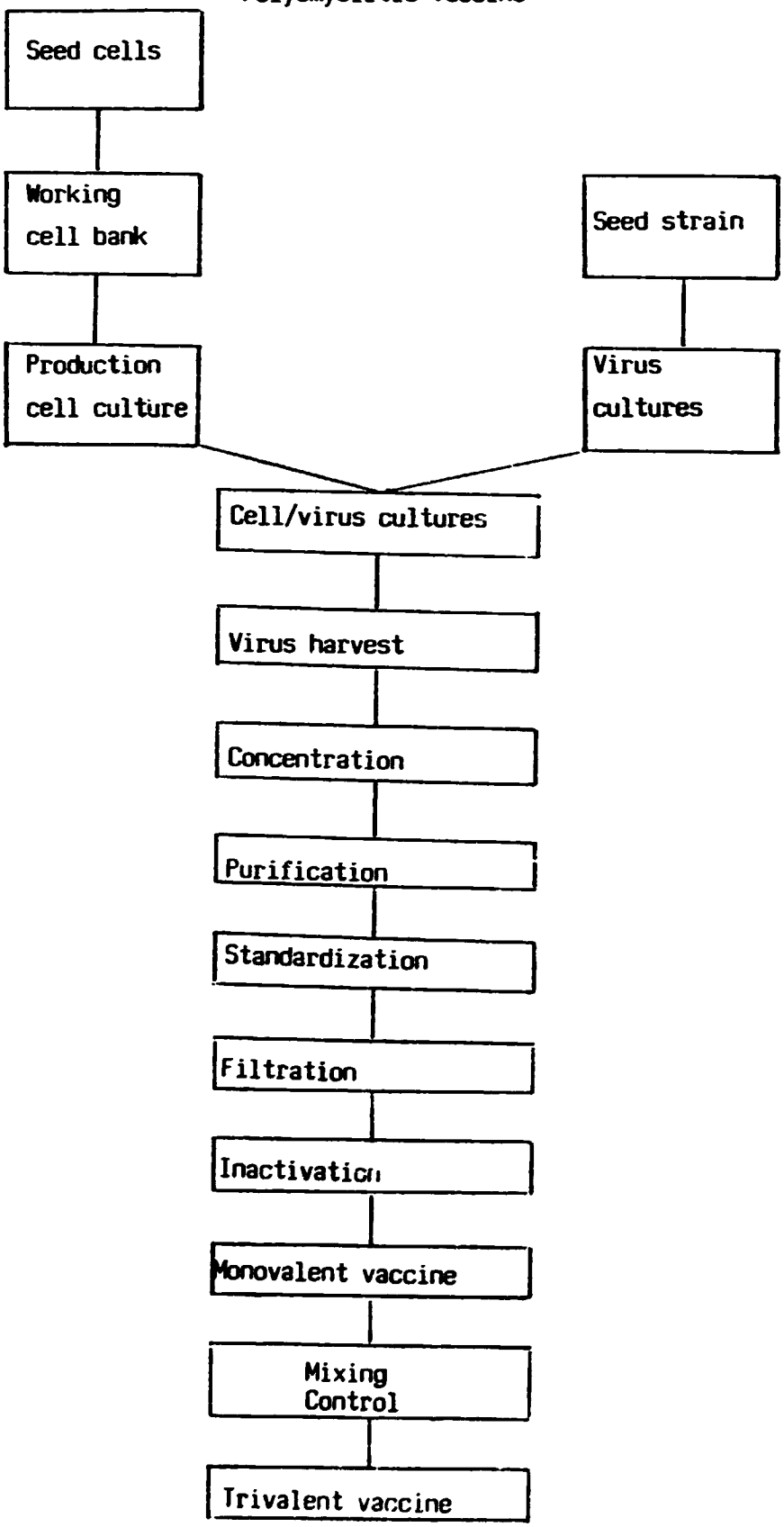
PRODUCTION UNIT FOR THE VIRUS VACCINES



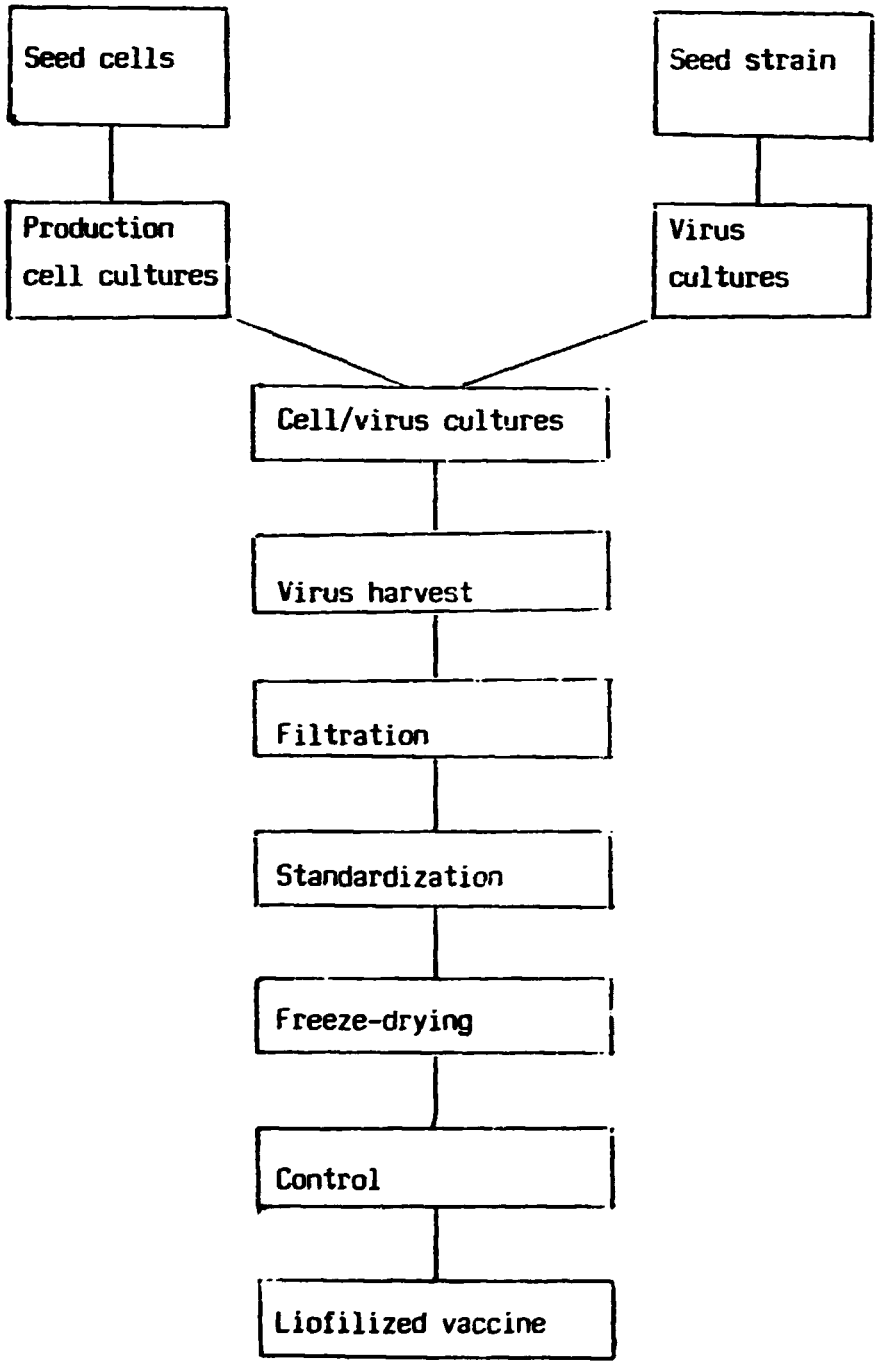
442 m²

1m

Flow chart of the production of inactivated Polyomyelitis vaccine



Flow chart of the production of live
Measles vaccine



ANNEX 1

Results of the post-campaign coverage survey May 1987

vaccine	urban	rural
	%	%
B C G	89.2	81
D P T 1	76.9	86.7
D P T 2	70.1	69.5
D P T 3	65.2	57
POLIO 1	76.9	78.5
POLIO 2	69.5	69.1
POLIO 3	63.7	55.5
MEASLES	58.4	64.1
Competely vaccinated after the campaign	49.7 $\pm$ 6.01	45.9 $\pm$ 7.7
Completely vaccinated before the campaign	36.25 $\pm$ 6.7	15.07 $\pm$ 5.5

Reference: Rapid assesment: Cameroon's National Vaccination Campaign of 1986

ANNEX 2

The national EPI schedule
of Cameroon

Birth	B C G	and	Polio /oral/
2 nd month	D P T	and	Polio /oral/
3 rd month	D P T	and	Polio /oral/
9 th month	Measles	and	Yellow fever
18 th month	D P T	and	Polio /oral/

Pregnant women should receive one dose of TT vaccine at the 4 th month of pregnancy, and one dose 1 month later
The 3 rd immunization should be given 1 yaer after first immunization.

Practically all women being in the child-bearing age should receive three doses of tetanus toxoid.

Reference: data provided by Min. of Health. Dept. of Preventive Medicine.

ANNEX 3

Basic data

Populetion	in 1983	8.965.700
	in 1986	10.446.400
	in 1991	11.876.908 /estimated value/

Annual population growth rate	:	3.1 %
Crude birth rate	:	4.54 %
Crude death rate	:	1.49 %

Mortality rate age	0 - 1 yrs	:	9,2 %
	1 - 4 yrs	:	1,6 %
	0 -14 yrs	:	4,3 %

Life expectancy at birth /in years/	males	:	51
	females	:	54

Reference: Rapid assesment Cameroon's National Vaccination Campaign of 1986

ANNEX 4

Target population

/from the: "Programme élargi de vaccination du Cameroun"/

Children	%	1986	1987	1988*	1989*	1990*
0-11 month	3.47	362.490	311.519	381.585	391.506	401.685
1-3 years	6.53	682.150	619.886	718.083	736.753	711.908
3-5 years	7.1	741.694	760.978	780.764	801.064	821.891
under 5 years	17.1	1.786.334	1.832.778	1.880.432	1.929.322	1.979.485
Total population		10.446.400	10.718.006	10.996.674	11.282.587	11.575.934
Women 15-49 years	22	2.298.208	2.357.961	2.419.268	2.482.169	2.546.705

* Estimated values

Reference: data provided by Min. of Health. Dept. of Preventive Medicine
"Programme élargi de vaccination du Cameroun"

ANNEX 5

Comparative table on vaccine coverage

	Rural				Urban			
	1988	1988	1988	1987	1988	1988	1988	1987
	0-11 months	12-23 months	24-35 months	17-28 months	0-11 months	12-23 months	24-35 months	17-28 months
BCG								
DPT 1	48 %	61 %	62 %	79 %	56 %	72 %	76 %	77 %
DPT 2	31 %	49 %	57 %	70 %	43 %	65 %	70 %	70 %
DPT 3	17 %	32 %	51 %	57 %	32 %	57 %	63 %	65 %
DPT booster		8 %	20 %			8 %	35 %	
Polio 1	46 %	59 %	62 %	79 %	55 %	72 %	76 %	77 %
Polio 2	26 %	47 %	57 %	69 %	40 %	65 %	70 %	70 %
Polio 3	14 %	30 %	50 %	64 %	30 %	55 %	63 %	58 %
Polio booster		8 %	20 %			8 %	35 %	
Measles	9 %	45 %	56 %	64 %	18 %	53 %	67 %	58 %
Completed vaccination	3 %	27 %	45 %	46 %	15 %	44 %	58 %	50 %

Reference: Rapport préliminaire sur les enquêtes de couverture vaccinale en zones rurales et urbaines du Cameroun /mai 88/
OCEAC.

ANNEX 6

Vaccine requirement by
Government of Cameroon

Vaccine	Volume in doses 1988	Provided by		Projected volume in doses 1989
BCG	866.500	UNICEF Inst.Merieux	862.000 4.500	860.000
D T P	1.887.000	UNICEF		1.600.000
Measles	379.000	USAID UNICEF Save the Children Inst.Merieux	255.000 100.000 20.000 4.500	700.000
Polio	1.822.000	UNICEF SMITH Kline	1.722.000 100.000	2.000.000
T T	304.000	UNICEF Inst.Merieux	299.000 5.000	600.000
Yellow fever	550.000	UNICEF Min.Santé	500.000 50.000	700.000
Meningococcus A + C	900.000	UNICEF Min.Santé	600.000 300.000	300.000
Tetravaccine	4.600	Inst.Merieux		20.000
Rabies	14.000	Min.Santé		14.000
Rabies Serum	1.000 amp.	Min.Santé		3.000 amp.

Reference: data provided by Min. of Health, Dept. of Preventive Medicine

ANNEX 7

Comparative statistical data of the
Central African subregion /UDEAC/

		Population	Population under 5 yrs in percent	BCG	DPT	TT	POLIO	Measles
Cameroon	1986	10 282 089	16 %	228 422	429 027	172 926	397 664	221 792
	1987	10 539 140	16 %	111 241	260 227	121 435	256 102	92 456
Central African	1985	2 457 600	16.5 %	100 248	123 069	132 069	113 517	155 612
Republic	1986	2 511 667	16.5 %	57 110	62 801	66 432	54 926	52 450
Democratic Republic	1986	1 912429	18.5 %	76 410	80 444	109 828	80 444	80 934
of Congo	1987	1 952 590	18.5 %	35 318	39 819	62 777	39 819	26 270
Gabon	1986	1 270 141	13.5 %	90 665	45 742	213 439	45 742	37 699
	1987	1 270 141	13.5 %	20 963	14 599	51 272	14 599	11 002
Tchad	1986	5 145 000		77 057	30 720	13 837	27 811	79 857
	1987	5 145 000		35 188	16 055	33 845	15 236	25 724

Reference: Le bulletin de liaison et de documentation No. 83
Janvier-Fevrier-Mars 1988. OCEAC

ANNEX 8

List of general laboratory instruments and materials

Glassware		
glass container 10 litre /PYREX/		appr. 80 pcs
glass container 15 litre /PYREX/		appr. 15 pcs
Erlenmeyer flasks		
and volume flasks	3 litre	appr. 30 pcs
	1 litre	appr. 100 pcs
	0.5 litre	appr. 100 pcs
	0.25 litre	appr. 100 pcs
Flocculation tubes		appr. 400 pcs
Test tube and containers with cap, for sterility sampling		appr. 400 pcs
Pipets with security ball pump	0.5 ml	appr. 100 pcs
	1.0 ml	appr. 100 pcs
	2.0 ml	appr. 100 pcs
	5.0 ml	appr. 50 pcs
	10.0 ml	appr. 50 pcs
	25.0 ml	appr. 25 pcs
	100.0 ml	appr. 25 pcs
Connection pipes		
Funels and buchner funels		
Measuring cylinders		
Glass mixing rods		
Ceramic mortar with stirrer		
Ceramic or glass containers for infected pipets		
Microscop slides		
Rubber/plasticware		
Petri dishes		appr. 500 pcs
Rubber stoppers		
Disposable syringes and needles		

Materials, chemicals		
Prefilter, sterile filter sheets, filter paper		
Paper for autoclaving, Hyphlo filter aid		
Reagents, staines, desinfectants, cotton plugs		
Silicon tubing/in different diameters/	appr. 50-100	m each
Others		
Artery forceps, parallel clamps	appr. 50- 50	pcs
Pincers, loops	appr. 10- 10	pcs
Stainless steel analytical spoon	appr. 5	pcs
Trolley	appr. 3	pcs
Closed containers for the sterilization of infectious waste materials	appr. 6	pcs