Pharmadule

Document name				
QUALIFICATION MASTER PLAN (QMP) **BIOLOGICAL PRODUCTION SERVICES** **VACCINE PRODUCTION PLANT** **DOH, PHILIPPINES**				
Doc. No	Prepared by	Date	Revision	Page
PH885-QMP-001	A. Cardelús Gassiot / RS	2000-12-12	00	2 (23)

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1. INTRODUCTION

The Qualification Master Plan (QMP) is a document for structuring the qualification activities within the project PH885, Vaccine Production Plant DOH, Biological Production Services (BPS). The QMP covers Pharmadule's part of the qualification according to the contract.

The QMP describes the purpose and scope and defines the responsibilities of the qualification exercise as well as the approach to be adopted.

The purchaser of the plant is Biological Production Services (BPS). The supplier is Pharmadule AB, Nacka, Sweden.

2. PURPOSE

The purpose of the QMP is to demonstrate that the qualification process will be performed in a methodical and continuos manner in compliance with WHO GMP.

The QMP will thus:

- Describe the general approach to qualification.
- Define areas of responsibility.
- Serve as a guide to those administering and performing qualification activities.
- Define management and retention of documents created for and during the qualification process.
- Identify the items that require qualification.
- Outline the programme for carrying out these activities.

3. APPROVAL OF THE QMP

The QMP will be prepared in the following principal steps:

- Pharmadule prepares a draft of the QMP.
- The draft is circulated for review to the Biological Production Services (BPS) and Pharmadule. The draft edition will be identified by adding Draft No. to the revision number (e.g. 00/Draft 1.)
- Comments from the reviewers will be evaluated.
- A new draft is circulated for review if applicable.
- The final version for signing and approval (see page 1) will be issued. Note that the Draft No. added to the revision number is deleted on the official edition.

The review and approval of the QMP is intended to ensure that the content of the QMP is accurate and that it covers relevant issues to ensure that the production facility will be qualified in compliance with the contract and WHO GMP.

4. REVISIONS OF THE QMP

All information included in this QMP is current as of the approval date. If changes are made, that significantly affect the qualification as defined in the QMP, a revision shall be made with reason(s) for the change(s) explained in the new revision (see 4.1).

4.1 Revision details

Table 1. Revision of the QMP

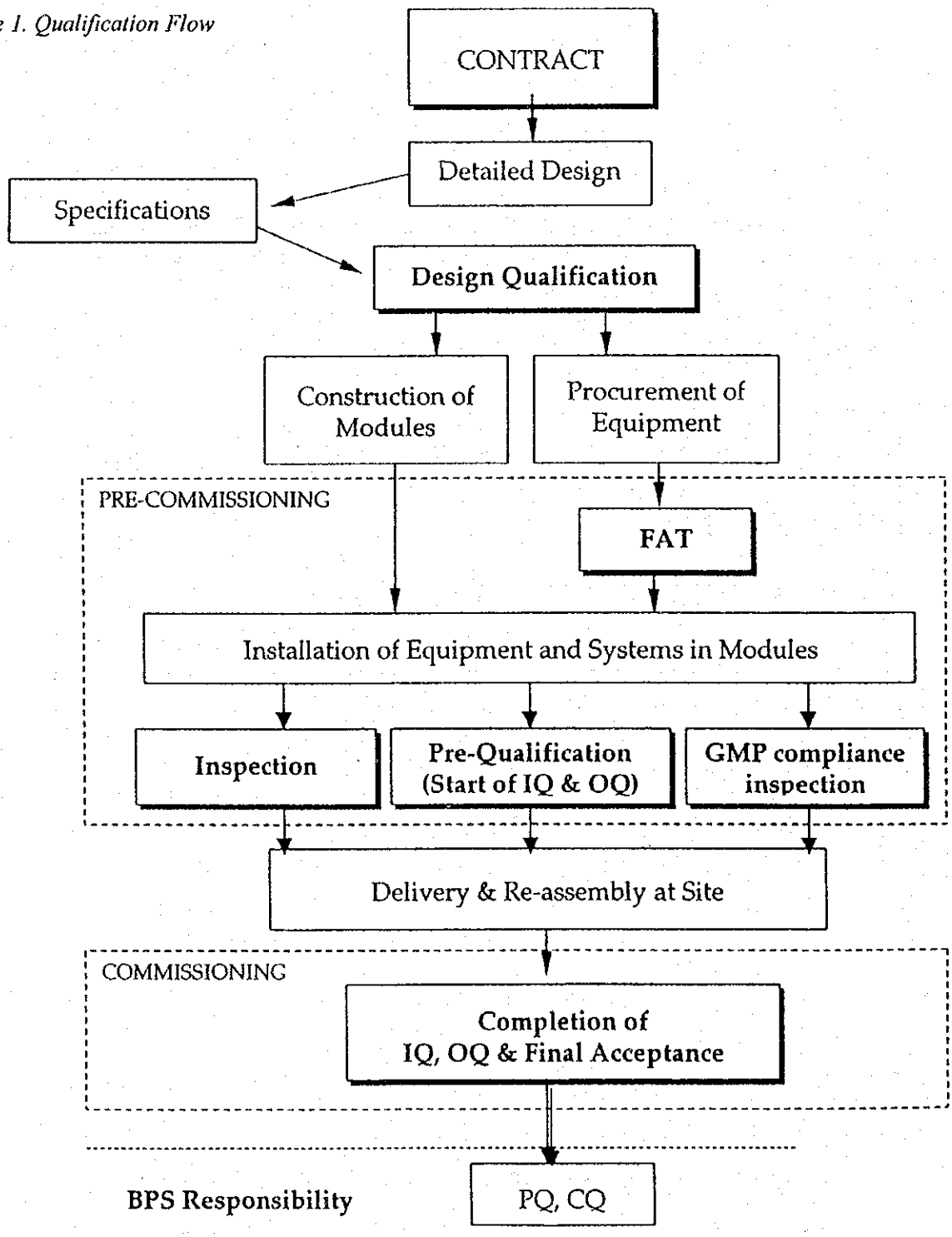
Revision No.	Date	Reason for changes
00	2000-12-12	New

5. APPROACH TO QUALIFICATION

The reason to qualify is to ensure that the premises, equipment and manufacturing processes are capable of routinely producing a product of specified quality. The qualification also provides a comprehensive knowledge of premises and equipment.

The qualification steps are incorporated in the main steps of the project that is described on the next page. The general approach is first described followed by an explanation of each step in the following subsections.

Figure 1. Qualification Flow



5.1 General Approach

The general approach to the qualification is to perform as much documented testing as early as possible in the project. Tests, which have been performed once, shall not be repeated during the next qualification step/steps, where this can be done without interfering with GMP or the demand to ensure the quality, function or capacity.

5.2 Contract

The contract is the legal document regulating the relation between Biological Production Services and Pharmadule in the project. This document states the overall design requirement of the production facility.

5.3 Detailed Design

Pharmadule performs the detailed design of the plant, process and equipment based on the user requirement specifications in the contract.

5.4 Specifications

Specifications are written requirements for the plant and its specific equipment and systems. The specifications form the basis for the acceptance criteria in the qualification documents. There are some different types of specifications where the main types are:

5.4.1 User requirement specifications

The user requirement specification is the Biological Production Services requirements on quality, types of products and output that the Plant, process, system and equipment should fulfil. This requirement specification is included in the contract.

5.4.2 Detailed design specifications

At the detailed design different types of specifications are produced. These are purchase specifications for major equipment, room specifications for the modular facility and P&ID's for process and utility systems. The contract and the detailed design are the basis for the specifications.

5.4.3 Supplier documentation

The supplier of equipment supplies a documentation package together with the equipment. This package contains documents like P&ID and wiring diagrams and operating and maintenance instructions. This also includes documentation from Pharmadule.

5.5 Design Qualification

The design qualification (DQ) proceeds during the whole detailed design phase and is documented as approved specifications, approved drawings and/or minutes of meetings.

5.6 Procurement of Equipment

Pharmadule procures equipment in accordance with the contract, detailed design and purchase specifications.

5.7 Construction of Modules

The modules are constructed at Emtunga AB's workshop in Sweden. The construction is made in accordance with the contract and the detailed design.

The Emtunga Company is certified according to ISO 9001. This quality system is used during the whole construction and inspection of the modules to ensure that the specified quality is fulfilled.

5.8 Pre-commissioning

The pre-commissioning consists of:

5.8.1 FAT

A Factory Acceptance Test (FAT) is performed for equipment and systems at the sub-supplier's workshop in order to verify that all the specifications are met before delivery to the supplier's workshop. FAT's are only made for selected critical equipment/systems, which shall be installed in the modules.

5.8.2 Inspection

Inspection is executed at the Emtunga AB's workshop in Sweden. That means, inspection of the modular structure and non-critical equipment to ensure:
-the proper erection, installation and function of the modular structure
-that components/equipment have been supplied and function properly according to technical specifications.

5.8.3 Pre-Qualification (Start of IQ & OQ)

The pre-qualification is the start of installation and operational qualifications (IQ & OQ) of the equipment, processes and systems. The execution of the qualification is started at the Emtunga site prior to shipment and is finalised at the local site. For more information refer to the below

5.8.4 GMP Compliance Inspection

The Plant shall be inspected by the Swedish Drug Inspection within the Medical Products Agency. Upon the satisfactory completion of this inspection a written statement shall be made verifying the compliance with the GMP regulations.

5.9 Delivery & Re-assembly at Site

When the modules have been completed they are shipped to the final site. On the site the modules are erected on a foundation and connected to the local utility systems. Biological Production Services prepares all local work in accordance with the contract and the detailed design.

5.10 Commissioning

The commissioning consists of the IQ and OQ, i.e. finalising the work remaining from the pre-commissioning and inspection of non critical systems.

5.10.1 Installation Qualification (IQ)

Installation Qualification (IQ) is the process of ensuring, and providing documentary evidence, that all critical equipment, systems and premises have been delivered and installed correctly. This also includes a verification of the supplied documentation and calibration of critical instruments. Those parts of a system that are disassembled prior to shipping should be verified again after re-assembly at the site.

5.10.2 Operational Qualification (OQ)

Operational Qualification (OQ) is the process of ensuring, and providing documentary evidence, that all critical equipment, systems and premises operate correctly.

5.11 Purchaser Qualification

In addition to the Pharmadule scope of qualification additional qualification activities must be performed before the plant can be taken in operation. These activities are under the responsibility of Biological Production Services (BPS) and therefore not included in this QMP.

6. PLANT DESCRIPTION

This plant, for the production of BCG vaccine and purification of Anti-venin, is intended to be docked to a corridor connected to a warehouse and administration building, supplied by the Purchaser.

The Plant will include facilities for:

- biotechnological production of BCG vaccine bulk active substance
- aseptic filling and freeze drying of BCG vaccine and filling of normal saline solution
- preparation of saline solution.
- purification and filling of Anti-venin
- microbiological quality control
- supporting utility services

The plant will be delivered and set up in the Muntinlupa area, south of Manila in the Philippines.

7. PROCESS DESCRIPTION

7.1 BCG Production

The current production process consists of the following steps.

7.1.1 Media Preparation

The Sauton Potato, the Bile Potato, the Sauton 1 and Sauton 2 media are prepared in room 1.
All medias are filtered through 0.5µm Cellulose Pre-filter.
Sauton Potato, 20 ml, is filled in tubes.
Bile Potato, 10 ml, is filled in tubes.
250 ml of Sauton 1 is filled in 24 pcs 1 liter Erlenmeyer flasks.
600 ml of Sauton 2 is filled in 18 pcs 2 liter Hafkins flasks.
The filled tubes and flasks are sterilized at 121°C.

Sodium Glutamate is filtered through a 0.5µm Cellulose pre-filter to the batch tank in room 1. The batch tank is sterilized.

7.1.2 Opening of strain

Sauton Potato media tubes are inoculated with Mycobacteria.
Mycobacteria is grown on the surface for three weeks at temperature 37 °C.
The growth is further inoculated.

7.1.3 Maintenance of BCG strain

The growth is inoculated in Bile Potato media in tubes.
The tubes are incubated for two weeks at 37°C.

The surface growth is put in glass tubes filled with 20 ml Sauton Potato media.
The tubes are incubated for two weeks at 37°C.

Growth from the liquid portion is transferred to 24 pcs 1 liter E-flasks filled with 250 ml Sauton 1 media.
The flasks are incubated for one week at 37°C.

Sauton 2 media in 2 liter Hafkins flasks is inoculated with virulent Mycobacteria. This is done by taking a small portion of surface growth from the E-flasks.
The flasks are put in the incubator at 37°C for six days

7.1.4 Vaccine Preparation

The surface growth in the Hafkins flasks is filtered through a sterile Birkhaug filter. The filter masses are collected and weighed. Transfer seven to eight grams to a steel ball mill and homogenize.

Sodium Glutamate is added to the steel ball mill and the solution is siphoned to 1 liter flasks. Samples for sterility and oxygen consumption tests are taken. During testing the flasks are kept refrigerated.
The flasks are pooled and the solution is diluted with Sodium Glutamate solution until the total volume is 11 liters/batch. The vaccine is immediately taken to filling.

7.1.5 Final Bulk filling

The batch is transferred to the filling area. The batch tank is kept cool during filling. The solution is also kept in motion to prevent sedimentation of bacteria.
The vaccine is filled in 2 ml vials with a volume of 0.5 ml ±0.5 % in each vial. The vials are partly stoppered and put on trays with a loose frame.
The vials are put in the freeze dryer with the frames around them.

7.1.6 Freeze Drying

The vials are loaded on to the cold 2-6 °C shelves in the freeze dryer. When the dryer is full, 22 000 vials, the batch is frozen for one hour.
After that the freeze-drying phase is set for 20 hours.
After 20 hours the vacuum is broken with nitrogen. When the pressure has reached the preset value the shelves are compressed and stoppers are fully inserted and the vials are closed. The shelves are kept at 2-6°C until all trays have been unloaded.

7.1.7 Capping

The trays with vials are brought from the freeze dryer to the filling machine one tray at the time where they are capped and again put on to trays. The trays are put back in the freeze dryer. After capping the entire batch the trays are unloaded from the freeze dryer to a trolley.

7.1.8 Inspection and labeling

The finished product is put in the quarantine cold storage 2-6°C until all tests have been run and the batch is released for labeling. The trays with the vials are brought to the inspection and labeling area in the local building. The final product is stored cold 2-6°C.

7.2 Anti-Venin Production

7.2.1 Purification & Concentration

The plasma is pooled up to 9 litres for 1 lot. After the second precipitation, the plasma solution is left to stand for 2 hours and then passed through a Whatman grade 50 filter.

7.2.2 Dialysis

The lot is passed through a HPLC column. The fraction is collected. The pooled fraction from the HPLC is dialysed. The resulting volume is 2000 ml of dialysate.

7.2.3 Final Filtration

The final bulk is added with normal saline solution and merthiolate solution. The solution is then passed through membrane filtration system to remove pyrogen contamination and dispense into 10 ml size ampoules. Each lot is subjected to potency, sterility, safety and pyrogen test including chemical analysis. Only lots passing 800 mouse units are released.

8. ADMINISTRATION OF THE QUALIFICATION

8.1 Qualification Protocols and Reports

8.1.1 Protocols and reports

Qualification protocols, e.g. IQ and OQ are written documents containing the necessary tests to qualify a defined equipment or system. All tests should have pre-determined acceptance criteria, and when the protocol has been filled in it should be clear if a test has passed or failed. Any items in non-compliance should be listed, see also Change Control below.

8.1.2 Numbering system

Each protocol shall have a unique number attached to it. The numbering system is built up according to the following principle: PH885-IQP-001, where "PH885" is the project number, "IQP" refers to the type of document and "001" is a unique number for each equipment or system.

8.1.3 Approval of protocols and reports

The protocols are written either by Pharmadule or by Pharmadule's suppliers. Pharmadule and/ or the supplier execute the tests. The completed protocol will serve as the qualification report. The protocol and reports are approved according to the table below.

Table 2. Approval of Documents

Document		BPS	Pharmadule
FAT	Protocol		✓
	Report		✓
INSPECTION	Report		✓
IQ	Protocol	✓	✓
	Report	✓	✓
OQ	Protocol	✓	✓
	Report	✓	✓

8.2 Document Control

A structured filing system for all qualification documentation will be applied. All completed and in process qualification documents will be logged and filed in the qualification file.

The location of supporting documentation, not included in the qualification file, will be appropriately referenced to, to allow retrieval as needed. All original qualification documents will be maintained in the qualification file. Upon completion, the entire qualification file will be relocated to a permanent storage location at the site.

Pharmadule will be responsible for filing of original protocols.

8.2.1 Tracking sheet of qualification protocols

Pharmadule will list all qualification protocols in a separate Tracking sheet to facilitate the tracing of the protocols.

8.3 Change Control

A change control procedure is implemented as part of the qualification to ensure that changes of process equipment and systems remain under control. The change control procedures start as soon as the execution of the qualification tests begins.

8.3.1 Change control procedure

The change control procedure will ensure that changes are approved and that the consequences to the associated equipment have been fully evaluated.

During the execution of the qualification, deviations from test methods and acceptance criteria may be found. Each change will be evaluated and a decision is made by Pharmadule or by Pharmadule´s suppliers whether the change can be handled within the protocols or has to be submitted to a separate investigation and evaluation. All those investigated changes shall be documented in a change control form. Executed change control forms will be included in the specific protocol prior to protocol approval.

9. PROJECT TEAM AND RESPONSIBILITIES

9.1 Project Team

The project team manages the qualification activities; i.e. it also functions as the qualification team. The team consists of key members from Biological Production Services and Pharmadule.

Table 3. Project/Qualification Team Members

Company	Name	Function
BPS	Remigio Olveda	Project Manager
	TBD	Project Engineer
	TBD	Quality Assurance
Pharmadule AB	Bruno Henriksson	Project Manager
	Rolf Strömgren	Quality Assurance
	Alberto Cardelús Gassiot	Validation Engineer
	Boel Angermund	Project Engineer
	Jan-Erik Finné	Project Engineer
	Raine Gustavsson	Project Engineer
	Bernt Selling	Project Engineer

9.2 Responsibilities for the project team members

The project team members have different functions in the qualification work. The responsibilities of the team members are detailed below. If a team member is exchanged during the project the new member takes the responsibilities of the corresponding function.

Note that in this section the responsibilities of the members refer to the qualification activities. Other responsibilities can thus apply in other areas.

Project Manager (Pharmadule)

- Leads the overall qualification activities.
- Reviews the QMP.
- Delegates responsibility for carrying out qualification activities to team members.
- Appoints, if required, new members to the team.
- Approves all qualification protocols and reports.

Validation Engineer (Pharmadule)

- Prepares the QMP.
- Prepares and co-ordinates the Qualification Protocols and related documents.
- Distributes the completed protocols for review and approval of the appropriate staff.
- Monitors and control progress of the qualification activities according to this QMP.
- Participates in FAT, IQ and OQ.
- Reviews qualification protocols written by other persons.
- Manage document retention

Project Engineer (Pharmadule)

- Participates in FAT, IQ and OQ.
- Prepares protocols and related documents.
- Reviews all qualification protocols within his/her area of responsibility.

Quality Assurance/Quality Control (Pharmadule)

- Approves the QMP

Quality Assurance/Quality Control (Biological Production Services)

- Reviews all qualification protocols and records

Project Engineer (Biological Production Services)

- Reviews all qualification protocols within his/her area of responsibility

Project Manager (Biological Production Services)

- Approves the QMP
- Purchases of material for the qualification
- Make local arrangements in accordance with the contract
- Locates resources for qualification activities
- Approves all qualification protocols and reports.

10. SCOPE OF QUALIFICATION

10.1 Criteria for determining qualification requirements

The determination of the extent of the qualification is based on a thorough review of the production facility. Whether or not a specific equipment or system requires qualification is dependent on its application. Each equipment and system must be categorised as either critical or non-critical. The criticality may be ascertained by considerations of its impact, based on the following:

- Whether or not it directly contacts the materials used in the process.
- Whether or not it monitors or generates labels where GMP regulations apply.
- Whether or not it is used to control and/or monitor a parameter of a system, process or piece of equipment which is inherently critical to environmental or process quality.

- Whether or not it stores primary data used for process and product evaluation or product release.
- Whether or not it stores or generates master and/or batch records.
- Whether or not it affects the quality or purity of the end product.
- Whether or not it is an inherently critical part of the classified area construction.
- Whether or not it is a part of the HVAC system inherently critical to environmental quality in classified areas.
- Whether or not it has impact on any GMP control activity

Support utilities, such as heat transfer fluids (e.g., cooling water, and steam), instrument air or electric power are not critical and need not be qualified. The parameters of a system that they affect, such as temperature, may be critical depending on their use. If so, the critical parameters would be incorporated in the qualification.

10.2 Qualification Protocols

To manage the qualification activities, protocols will be written for each system or group of systems. In the table below all the qualification protocols are detailed.

Each system is first categorised as critical or non-critical (also see above). A "✓" then indicates if a protocol is required for FAT, Inspection, IQ, and OQ.

Table 4. Qualification Protocols

Room No.	ITEMS	Critical or not (C/NC)	FAT	Insp.	IQ	OQ
1	Decontamination autoclave	C	v		v	v
	Component autoclave	C	v		v	v
	Dry Cabinet	NC		v		
	Laboratory washing machine	NC		v		
3	LAF bench, 1200x800 mm	C			v	v
	Refrigerators (2 pieces)	C			v	v
	* Incubators (2 pieces)	C				

Room No.	ITEMS	Critical or not (C/NC)	FAT	Insp.	IQ	OQ
7	Freezer	C			v	v
	Incubators (3x720 l)	C			v	v
	Incubator (1x50 l)	C			v	v
	Refrigerator/Freezer	C			v	v
	Refrigerators (2 pieces)	C			v	v
	Biosafety hoods, vertical (2 pieces)	C			v	v
	Holding tanks 20 l (2 pieces)	C			v	v
	Preparation tank 50 l	C			v	v
	pH-meter	C			v	v
	Steel ball mill	C			v	v
8	Freeze Dryer	C	v		v	v
9	Filling Machine	C	v		v	v
	Balance with printer	C			v	v
	Holding tank 50 l	C			v	v
	LAF unit vertical, 2400x3000 mm.	C			v	v
12	Refrigerator	C			v	v
	HPLC	C			v	v
13	LAF bench, 1200x800 mm	C			v	v
14	LAF unit vertical, 1800x900 mm	C			v	v

Room No.	ITEMS	Critical or not (C/NC)	FAT	Insp.	IQ	OQ
19	Product autoclave	C	v		v	v
	Dry Heat Steriliser	C	v		v	v
	Vial Washing Machine	C	v		v	v
	Component autoclave	C	v		v	v
101	WFI tank	C	v		v	v
	Pure Steam Generator	C	v		v	v
	Water Pre-treatment	C	v		v	v
	WFI Still	C	v		v	v
102	HVAC control system	C			v	v
	HVAC	C			v	v
Y	Labelling machine for vials	C	v		v	v
General	WFI distribution system	C			v	v
	Pure steam distribution system	C			v	v
	Nitrogen distribution system	C			v	v
	Classified areas	C			v	v
	Air Particle Counter	C			v	
	Filter Integrity test	C			v	v
	Compressor	NC		v		
	Compressed air distribution system	NC		v		

Room No.	ITEMS	Critical or not (C/NC)	FAT	Insp.	IQ	OQ
	Chiller	NC		v		
	Chilled water distribution system	NC		v		
	Potable water distribution system	NC		v		
	* Steam generator	NC				
	Steam distribution system	NC		v		
	* Emergency generator	NC				
	* Electrical supply transformer	NC				
	Electrical distribution system	NC		v		
	* Waste water piping system outside (below) the modules	NC				

* *Responsibility of BPS*

11. QUALIFICATION TESTS

The purpose of this section is to give information of what will be included in the qualification protocols.

11.1 Factory Acceptance Test

The FAT includes tests included in a typical IQ and OQ, therefore refer to those sections below.

11.1.1 Baseline

The baseline for the FAT is the purchase specification together with delivered documentation from the sub-supplier, such as installation and layout drawings, P&I diagrams, data sheets and technical documentation for components etc.

11.2 Installation Qualification

11.2.1 General

Installation qualification may be started at the Pharmadule/Emtunga's workshop for some equipment and/or systems but most of the IQ will be performed and finalised at the purchaser's site. When appropriate test results from the FAT will be referenced in the final IQ.

11.2.2 Baseline

The baseline for the IQ is the specifications and drawings from the detailed design and parts of the documentation package delivered from the supplier, e.g. P&ID's, technical documentation for the equipment, system or component.

11.2.3 Installation Verification

Verify the following:

- That equipment is undamaged
- That delivery is complete
- Brand, type or model of components
- Material of construction for product contact parts.
- Characteristic data (volume, capacity, power etc.)
- Piping routes and dimensions
- Utility connections
- Electrical connections
- Piping insulation
- Piping and component marking
- Documentation package

For piping system in product contact, e.g. WFI and clean steam system, also verify:

- Dead legs
- Piping slopes, drainability
- Distance from outlet pipes to drain

Acceptance Criteria:
The equipment and systems should be undamaged and installed as specified in the baseline documentation.

11.2.4 Calibration

It shall be examined that critical instruments/sensors have valid calibration certificates.

Acceptance Criteria:

Each critical instrument/sensor should have been calibrated against a national standard or reference and be accompanied with a valid calibration certificate.

11.3 Operational Qualification

11.3.1 General

Operational qualification will be performed at the purchaser's site.

Baseline
The baseline for the OQ is the specifications and drawings from the detailed design and parts of the documentation package delivered from the supplier.

11.3.2 Operation Verification

The functions and operating parameters described in the baseline documentation should be tested.

Acceptance Criteria:
Each function shall fulfil the criteria set in the baseline documentation.

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTÉ

REGIONAL OFFICE FOR THE WESTERN PACIFIC
BUREAU RÉGIONAL DU PACIFIQUE OCCIDENTAL

MISSION REPORT

Subject	:	Vaccine manufacture and quality control
Place visited	:	Philippines
Dates of mission	:	8 - 17 May 1995
Authors and designation	:	Dr Isao Arita, Dr F. Chino, Dr G. Smith. Dr T. Hashimoto, Dr D. W. Stainer. Dr N. R. Ackland and Mr P. Humphreys WHO Consultants
Title of project	:	Expanded Programme on Immunization
Participating agencies	:	Government of the Philippines World Health Organization
Source of funds	:	Regular Budget

Key words

Immunization / Vaccines - standard / Philippines

ICP/EPI/001

22 December 1995

RS/95/0282

English only

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

EXECUTIVE SUMMARY OF A MISSION REPORT

Dr Isao Arita, Dr F. Chino, Dr G. Smith.
Dr T. Hashimoto, Dr D. W. Stainer.
Dr N. R. Ackland and Mr P. Humphreys
Author

Philippines Place visited		8-17 May 1995 Dates of mission
RS/95/0282 Report series number	ICP EPI 001 RB Project identifier	01.190.STC.01 - 05 Activity code

Objectives of mission:

The terms of reference for the team were to provide the Government with information on options for vaccine self-sufficiency by:

(1) reviewing vaccine production facilities and the plans for proposed new production facilities to be built at Los Baños, Laguna, Philippines, and by making recommendations based upon this review;

(2) reviewing the vaccine production procedures, including quality control and quality assurance procedures, staff management structure and training, and the types of vaccine currently produced in the Philippines, and by making recommendations for changes if required.

Summary of activities, findings, conclusions and recommendations:

BCG and tetanus toxoid vaccines have been produced locally for many years. However, local production is now being reviewed in light of the need to move the facilities of the Biologicals Production Service (BPS) from Alabang to Los Baños, and of changes in Good Manufacturing Practice standards for vaccines which must be introduced. The mission reviewed the situation of current and planned vaccine production activities in the Philippines in order to provide the best information possible to the Government for a decision on whether or not to continue local production. It is clear that the continued production of vaccines meeting the minimum standards of quality, safety and efficacy will require a massive commitment, in financial, technical and management terms, from the Government of the Philippines. In the light of the findings of this mission, the Government should consider again the available options for vaccine self-sufficiency. Essentially these options are:

(1) the cessation of local manufacture and procurement of all vaccines from outside sources; and

(2) continued local production of some vaccines in a sustainable way.

The main recommendations are:

(1) The Department of Health should accept revised site and individual building plans for the possible new vaccine production facility at Los Baños.

(2) If it is decided to continue vaccine production, consideration should not be given to the production of other vaccines until such time as the successful and ongoing manufacture of tetanus toxoid and BCG has been demonstrated.

(3) To enable the Government to make informed decisions about the future of local vaccine manufacture and to ensure cost-effective production, a detailed technical review of manufacturing processes should be immediately commissioned, and the total production cost of vaccine production should be determined by the end of the third quarter of 1995.

(4) Legislation covering therapeutic goods (drug products) should be amended to include biological products and to formally establish BFAD as the National Control Authority (NCA) for biological products, including vaccines.

Key Words: Immunization / Vaccines - standard / Philippines

CONTENTS

1. PURPOSE OF MISSION

The team visited the Philippines from 8 to 17 May 1995 with the following terms of reference: to provide the Government with information on options for vaccine self-sufficiency by:

(1) reviewing the vaccine production facilities and the plans for proposed new production facilities, and making recommendations on options for vaccine self-suffiency; and

(2) reviewing the vaccine production procedures, including quality control and quality assurance procedures, staff management structure and training, and the types of vaccine currently produced in the Philippines, and making recommendations for changes if required.

2. BACKGROUND

The expanded programme on immunization (EPI) is a strong and successful programme which has, over the past few years, built on high routine immunization coverage to tackle disease control initiatives such as poliomyelitis eradication and neonatal tetanus elimination. The strong Government commitment to the EPI is evident in an annual allocation of approximately US$ 11 million for the purchase of EPI vaccines. Bacillus Calmette-Guérin (BCG) and tetanus toxoid vaccines have been produced locally by the Biologicals Production Service (BPS) for many years. There have been previous visits to the Philippines by missions and by individual experts to examine issues relating to local vaccine manufacture and quality.

A mission from the Children's Vaccine Initiative (CVI) Task Force on Situational Analysis in June 1993 recommended that production of BCG and tetanus toxoid continue in the Philippines, subject to high level Government support, adequate funding, the construction of new facilities, and the purchase or repair of equipment to produce safe and potent vaccines. The need for an independent national control authority was also identified.

In April 1994, the Agency for Cooperation in International Health (ACIH) prepared a report entitled "Vaccine Self-Sufficiency: Improving Local Production and Quality Control". A number of proposed activities relating to vaccine manufacture and quality were listed in the report, including the planning and construction of new laboratory facilities; the purchase and validation of new equipment; the adaptation of processes to new facilities; the appointment of a technical production manager; the establishment of a quality assurance unit; the training of staff in good manufacturing practice (GMP); the strengthening of the national control authority by legislative changes, and the appointment of biological experts and the provision of testing laboratory support.

The BPS site in Alabang has recently been acquired by the FILINVEST Development Corporation, under a Memorandum of Agreement with the Department of Health. As part of the agreement, FILINVEST are to construct replacement facilities at the new site at Los Baños, Laguna, to the value of 65 million pesos, the estimated worth of the existing facilities. This provides a unique opportunity to reconsider the options for future vaccine supply in the Philippines. These options are: (1) the cessation of local manufacture and the procurement of all vaccines from outside

sources; and (2) the continued local production of some vaccines in a sustainable way. If the latter course of action is adopted, then the transfer of BPS to Los Baños would allow the deficiencies at the existing site to be addressed in the design of the new facilities. Since demolition work has started at the Alabang location and some initial site development work has commenced at Los Baños, there is a need for this issue to be addressed promptly and for a final decision to be made regarding the continuation of vaccine production in the Philippines.

Accordingly, this mission was undertaken to review the existing and proposed vaccine manufacturing facilities and production methods and to provide advice on options for vaccine self-sufficiency in the Philippines. The team consisted of nine experts in vaccine production, quality control and regulation, GMP and management.

3. ACTIVITIES AND FINDINGS

3.1 Buildings and construction

3.1.1 Review of plans for a new vaccine production facility

The plans for the new facility, which had been drawn up by the FILINVEST architects, RSD Gutierrez, in consultation with the Department of Health Committee on Vaccine Production, were reviewed. Although the planners had attempted to incorporate the advice of previous missions and individual consultants, it was apparent that the proposed distribution of the buildings across the new site would be highly inefficient and expensive given the cost of reticulating the specialized services such as clean steam, pyrogen-free water, etc., over the long distances involved. It was also apparent that many of the buildings were conceived as totally independent stand-alone facilities. Consequently, there was duplication of areas such as wash-up, sterilization, filling and packaging. The other important factor which had an impact on cost was the provision of the necessary levels of air quality throughout the facility, particularly for the areas to be used for critical processes, such as aseptic filling. These require specialized air handling equipment and the use of HEPA (high efficiency particle arresting) filters, and are essential in order to meet basic standards for GMP. It was evident that the air handling that had been proposed for the new facilities was based on a series of individual wall or window-mounted air-conditioning units, which would not provide the levels of air quality required to meet basic GMP standards. The current local costs of constructing a facility of this nature were estimated to be approximately 20 000 pesos per square metre for normal laboratory areas and up to 90 000 pesos per square metre for the areas requiring the specialized air handling facilities.

3.1.2 Revision of proposed plans

The following approaches were used in revising the plans. Firstly, individual buildings were moved much closer together on the site, in order to reduce the cost of distributing essential services; secondly, where possible, common purpose areas were combined in order to reduce duplication and costs, and to increase the efficiency of manufacturing operations; finally, allowance was made for increased manufacturing capacity and for future expansion to manufacture other products at minimal additional costs. BCG and tetanus toxin producing facilities were kept essentially separate from other areas because of the particular hazards these products pose during manufacture. In the case of BCG, this means stand-alone manufacture up to and including filling and freeze drying. In the case of tetanus toxoid manufacture, the toxin part of the process needs to be segregated from the toxoid

which, once produced, may be dispensed in a central filling area. There is also a requirement for specialized treatment of waste coming from these facilities.

Through a series of productive discussions with the representatives of RSD Gutierrez and their consulting engineers, Department of Health officials and BPS personnel, proposals for new site and individual plans were developed. Factors that were taken into consideration during this process included: the particular areas required for each product; the class of the air quality required for each area; the essential service requirements; material access and flow; personnel access and flow; cleaning and sterilization of equipment; and allowing for increasing manufacturing capacity by equipment rather than construction. The plans as they stand at the time of writing this report are presented as Annex 1.

A key feature of the revised design is a central services building, which incorporates the features discussed above and an extension designated to accommodate a future expansion of manufacturing activities. Within the central services building are two filling suites. It is envisaged that one would be fitted out and used initially for tetanus toxoid but would also be used for dispensing other vaccines if produced in the future. The second allows for further expansion of manufacturing activities, e.g. to dispense bulk viral vaccines. Space in the site plan was also reserved for the possible future construction of additional buildings to produce viral vaccines or recombinant products. A major feature of the modified designs is the incorporation of specialized air-handling systems which are essential in meeting the minimum requirements of vaccine quality, safety and efficacy.

3.1.3 Costing of new facilities

A summary of the costing for construction of the proposed complex of buildings is given in Annex 2 of the report; detailed costings are presented in Annex 3. A sum of approximately 331 million pesos will be required for the construction and related capital equipment, e.g. power plant, steam generation. An additional sum of 28 million pesos is required for engineering and architectural costs and for the commissioning, start-up and validation. A further 66.1 million pesos has been flagged for contingency purposes.

3.1.4 EPI vaccine storage

Regardless of whether local vaccine production continues, appropriate cold-room facilities will be needed for the storage of EPI vaccines, as the current facilities will be demolished along with the BPS site.

3.1.5 BPS horses

The mission was advised that the number of horses (for anti-venin production) to be accommodated on the site may be increased. It is very important that adequate space be set aside for these animals in any plans for the new facility.

3.1.6 Los Baños Site

Three of the team members (Dr Ackland, Dr Stainer and Dr Smith) were able to visit the proposed construction site at Los Baños and were satisfied with the suitability of the area for the new complex, although the precise location is still to be settled. Consideration should be given to the provision of adequate amenities for BPS staff at the new location.

3.2 Equipment

A list of proposed equipment purchases for the new facilities was reviewed and a revised equipment list including approximate costs was prepared (Annex 5). Approximately 115 million Pesos will be required for equipment other than that already included in the construction costs. When purchasing temperature controlled equipment such as incubators or refrigerators, if possible, the equipment should have the same temperature monitor/recorder types for the purposes of standardization.

3.3 Manufacturing issues

3.3.1 Review of processes

Given the limited time available to the mission, and the fact that some aspects had been examined previously by other missions and individual consultants, it was not feasible to conduct an in depth review of all processes, tests and methods currently employed by the BPS in the manufacture of biologicals at Alabang. Similarly, it was not possible to define explicitly the nature of the process changes that need to be implemented at the new Los Baños facilities. However, particular areas were identified where process changes would seriously need to be considered and these are described below.

3.3.2 Validation of facilities/processes

As part of the process of making the new BPS complex operational for manufacture, proper validation of the facilities and equipment needs to be undertaken. The WHO requirements for validation should be addressed during equipment and facilities commissioning and initial manufacture at Los Baños.

3.3.3 BCG vaccine

The filling of BCG vaccine into ampoules must continue but certain development projects should be undertaken. Firstly, given concerns about the cost of the ampoules used, the suitability of ampoules from alternative suppliers for the filling of BCG vaccine should be examined. Secondly, the use of vials for filling BCG should be investigated, particularly with regard to the preservation of vaccine stability. This could be carried out in collaboration with a group such as the Research Institute of Tropical Medicine or the University of the Philippines.

The mission had serious concerns regarding the strain currently used for the production of BCG vaccine. There are several suitable alternatives including the Moreau, Sofia and Japanese strains and the BPS should immediately explore the options for obtaining a new strain for the preparation of master seed lots. Clinical data would have to be generated following the introduction of a new strain.

3.3.4 Tetanus toxoid

Given current regulatory concerns regarding the inclusion of materials of animal or human origin in vaccines and other biologicals, the removal of meat protein from the media for tetanus production should be strongly considered. The removal of cell material and of low molecular weight media components prior to the addition of formalin in the process is also likely to lead to improvements in purity and potency of tetanus toxoid manufacture.

3.3.5 In-process/quality control testing

Much in-process testing at BPS is currently performed by the production personnel. The same types of test are also carried out on finished product by the Quality Control Department. In order to avoid duplication and to ensure consistency of test performance, all such testing should be carried out by the QC Department. All testing should be the subject of standard operating procedures which should be based at least on WHO minimum requirements.

3.4 Personnel, training and management issues

3.4.1 Project Manager

The complex process of designing, constructing, fitting out and operating a new vaccine manufacturing facility is a major exercise involving a diverse range of professions and technical specialties. In order to ensure that the objectives of this project are achieved in a timely and cost-effective way, it is important that an individual be responsible for the management and coordination of the activities listed in the proposed timelines. This individual should have experience in large project management involving multidisciplinary teams, and ideally some technical qualifications or experience in a relevant field. Experience in the manufacture of vaccines or biological would be an advantage.

3.4.2 Expertise of BPS staff

Given the specialized nature of the equipment and processes that are likely to be used at the proposed facilities at Los Baños, there will be a need for additional knowledge and expertise in order to manufacture vaccines meeting at least the basic requirements for GMP. While some of this need may be met by training (discussed below), it is likely than new staff with particular skills will need to be recruited. A review of salary scales may be necessary in order for good staff to be attracted to join or remain with BPS.

3.4.3 BPS senior management and structure

Additional senior personnel will be needed to provide further support to the Director of BPS in the management of the organization. In keeping with current concepts of quality management, one of these senior managers should be responsible for a new quality assurance department or division which would have traditional quality control functions but also a function in creating, authorizing and auditing quality systems and procedures. Given the range of specialized equipment and services required for the proposed new facilities, there will be an increased emphasis on the installation, operation and maintenance of such services and equipment. A new senior manager should be given responsibility for all such engineering related matters. Although the BPS is part of the Department of Health, this relationship may change such that the BPS may become a Government owned company, or perhaps even eventually an independent commercial enterprise (see also section 3.5.2). Managing the activities of the BPS should be equated to that of managing a business. A senior manager should be appointed with responsibility for the business side of BPS operations. As any vaccine manufacture at BPS will be carried out using new facilities and equipment involving new or improved procedures, a new senior manager with appropriate qualifications and experience should take responsibility for all manufacturing activities.

The manufacture of vaccines to at least the minimum requirements for GMP will result from the coordinated interaction of the manufacturing, quality assurance and engineering divisions of BPS. In order to better equip the senior management team for their individual and

collective responsibilities, it is important that they receive specific training in their own discipline, as well as those of the other disciplines.

3.4.4 BPS skills audit/training plan

As mentioned above, the specialized nature of the new facilities and equipment will require staff to develop new skills. If a detailed technical review of the manufacturing processes is carried out, the senior management should then examine closely the duties, responsibilities and skills of all existing BPS staff as well as the staffing requirements in the new facilities. Training and/or recruitment of staff should then proceed as necessary. Any training undertaken should form part of a comprehensive plan for the whole of BPS. Staff should not carry out procedures for which they have not been adequately trained.

3.4.5 GMP training

In the course of reviewing batch manufacturing information, QC records and standard operating procedures at BPS, it became apparent that a there were a number of areas that could be improved. The GMP specialist on the team (Mr Humphreys) gave an introductory seminar to BPS staff on the concepts of traceability, accountability, record keeping and standard operating procedures. However, it was evident that there was a real need for a formal programme of basic GMP training and technical support for all BPS staff.

3.5 Vaccine manufacture policy issues

3.5.1 Economics of vaccine manufacture

The estimated costs for construction and equipment in the new facility are substantially more than had been originally estimated by the Department of Health, and have not been appropriately budgeted for. Given the nature of the specialized services that would be employed in the new facilities at least some of the operational costs, e.g. for electricity use, are likely to be greater than they are at the current site. While there may be some economic advantages by virtue of increased manufacturing capacity and the associated economies of scale, it is likely that the local cost of production will be greater, at least initially, than the cost of procurement. To enable the Government to make informed decisions about the future of local vaccine manufacture and to ensure cost-effective production, the total costs of vaccine production should be determined by the end of the third quarter of 1995. This assessment is urgently needed before any initial investment into a new facility is made. If necessary, a technical consultant(s) should be engaged for this analysis which should be done in conjunction with a detailed technical review of manufacturing processes (see section 3.1).

3.5.2 BPS as a business

If local vaccine manufacture continues, it is important that the BPS is run more along business lines to improve cost-effectiveness. This should also include the ability to sell its products to users, in this case the Department of Health. The options for increasing autonomy, internal control and accountability of BPS, as a government agency, as a government owned company, or as an independent commercial enterprise, should be explored, including consideration of the options for commercial partners or joint ventures.

3.5.3 Regulation of BPS

From a regulatory standpoint, the vaccines to be produced at Los Baños could be regarded as "new" products being manufactured in new facilities. As such, and in keeping with the mission's recommendations regarding the National Control Authority, the Los Baños facilities should be subject to licensing and inspection. The products manufactured should be subject to evaluation, registration and testing.

3.5.4 Anti-venom

The BPS currently manufactures a number of horse serum-derived reagents and anti-venom products, including anti-venom for the Philippine Cobra. The manufacture of such materials requires a large number of horses; appropriate stable facilities; a significant area for the horses to graze and exercise; separate laboratory facilities for processing; and BPS personnel to care for the horses, "milk" the snakes, and conduct the manufacturing process. Approximately 3000 doses of anti-venom are produced annually. Although there is obvious well-founded national pride in the anti-venom for the Philippine cobra, the manufacture of this material requires significant investment of resources to produce what is a relatively small number of doses each year. Consideration should be given to retaining the serpentarium to allow the "milking" of the snakes, but sending the venom to another manufacturer for the production of the anti-venom on a contract basis.

3.6 National Control Authority

Although the Bureau of Food and Drugs (BFAD) does, in principal, have NCA responsibility for biological products including vaccines, it currently does not play a significant role in their regulation or testing. While it does have laboratory facilities, including animal houses for testing drugs, it currently has no real capacity to conduct laboratory testing of vaccines and related biologicals. The mission was advised that some consideration had been given by the Department of Health to establishing a testing laboratory within the School of Public Health at the University of the Philippines. Having the vaccine control laboratories directly under BFAD's control, in the same way that the drug testing laboratories are, would be a consistent and logical approach for the Philippines, although there is no reason why they could not be located elsewhere. However, if the vaccine control laboratories were with an organization other than BFAD, the final review and authority to release vaccine should reside with BFAD. Even if the decision is made to cease vaccine production, there would still be a need for BFAD to adequately test and regulate imported vaccines.

4, CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

The continued production of vaccines meeting the minimum standards of quality, safety and efficacy will require a massive commitment, in financial, technical and management terms, from the Government of the Philippines. The Government will need to address three central issues: (1) the provision of the necessary initial, and ongoing, funding; (2) the long-term political commitment to local manufacture; and (3) the provision of appropriate management and training. In the light of the findings of this mission, the Government should consider again the

available options for vaccine self sufficiency. Essentially these options are: (1) the cessation of local manufacture and procurement of all vaccines from outside sources; and (2) continued local production of some vaccines in a sustainable way,

The review of the proposed new vaccine production facilities has revealed that the cost of construction and equipment, in particular the provision of specialized air handling services that are required to allow the manufacture of vaccines that would meet minimum standards of quality, safety and efficacy, are much greater than originally envisaged by the Department of Health. The total cost of the revised plans, including equipment, for a baseline of continued production of tetanus toxoid and BCG vaccines is approximately 540 million pesos, or US$ 21 million (Annexes 2 and 3). This total includes provision for the commissioning, start-up and validation of the new facilities (12.1 million pesos) and an allowance for contingencies (66.1 million pesos).

In order for the Government of the Philippines to be able to make rational decisions about the future of local vaccine manufacture, detailed information on the total costs of vaccine manufacture should be closely re-examined. If the decision is made to continue local manufacture, it is absolutely vital that the Government commit to providing ongoing funding for construction, equipment, maintenance, operational costs, personnel and training. This will also require a commitment to establish, adequately equip and fund a designated National Control Laboratory.

4.2 Recommendations

(1) The Department of Health should accept revised site and individual building plans (Annex 1), incorporating modifications which will allow: compliance with minimum requirements for good manufacturing practice (GMP); more cost-effective distribution of essential services and utilities throughout the complex; a reduction in redundancies in facilities; greater efficiencies in materials and personnel flow; and increased production capacity.

(2) If it is decided to continue vaccine production, consideration should not be given to the production of other vaccines until such time as the successful and ongoing manufacture of tetanus toxoid and BCG has been demonstrated. Even then, a careful and formal assessment of the need for commencing the manufacture of any additional vaccines should be carried out before a final decision is taken.

(3) To enable the Government to make informed decisions about the future of local vaccine manufacture and to ensure cost-effective production, a detailed technical review of manufacturing processes should be immediately commissioned, and the total production cost of vaccine production should be determined by the end of the third quarter of 1995.

(4) Urgent consideration should be given to procuring sufficient appropriately controlled and monitored cold-room space to accommodate the storage of the necessary quantity of EPI vaccines, pending construction of the new facilities.

(5) The Department of Health carefully examine, technically and financially, the proposed equipment list for the new manufacturing facilities (Annex 5), and if necessary make commitments of funding to purchase this equipment.

(6) The Department of Health, when seeking tenders for major equipment purchases, should make the provision of installation, adequate after sales service and on-site training, in both

operation, calibration and routine and preventative maintenance, conditions of the tender process.

(7) The Department of Health should expedite a review of the classification and salary scales of BPS personnel in order to attract and retain suitably qualified and experienced staff.

(8) An appropriately qualified Project Manager should be recruited immediately with the responsibility and authority to coordinate and oversee all aspects of the design, construction, fitting-out, commissioning and validation of the new facilities at Los Baños.

(9) The Department of Health should approve the appointment of four new senior management positions reporting to the Director of BPS, namely: Manufacturing Manager, Quality Assurance Manager, Engineering Services Manager and Financial Affairs Manager.

(10) The organizational structure of BPS should be amended (Annex 6) so that the Officers-in-Charge of Quality Control and Quality Systems (or Compliance) Programme report to the Quality Assurance Manager and the Officers-in-Charge of BCG, Tetanus, Anti-Venom and Central Services report to the Manufacturing Manager.

(11) The Department of Health should ensure that the Quality Assurance, Manufacturing, Engineering Services and Quality Control Managers receive adequate training in current principles and practices of vaccine production and quality assurance at another vaccine manufacturer, ideally within the region (e.g. Japan or Australia).

(12) The Director and senior management staff of BPS should undertake a skills audit of the BPS by the third quarter of 1995 to identify the disciplines and particular skills which are not well represented by the existing staff and which will be required for the operation, management and future development of the new facilities. The BPS Management should maintain a training register and develop a training plan and programs to ensure that staff are adequately trained for their duties and responsibilities.

(13) By the end of the first quarter of 1996, the Department of Health should initiate a programme to provide basic GMP training and technical support in the further development of documentation, records, standard operating procedures and basic quality management systems within BPS. It is very important that this training is consistent with the document entitled "Bayanihan-NDP, supplementary notes to the ASEAN GMP", which was recently released to the Philippines Drug Manufacturing Industry.

(14) Legislation covering therapeutic goods (drug products) should be amended to include biological products and to formally establish BFAD as the National Control Authority (NCA) for biological products, including vaccines.

(15) By early 1997, the Department of Health should strengthen BFAD so that it is adequately resourced to undertake the effective inspection, evaluation, review of testing and release of biological products, including vaccines. It also includes a need to identify suitable laboratory facilities to allow potency and other tests of the quality and safety of biologicals to be carried out.

(16) The NCA should develop Philippine National Standards for vaccines, based upon WHO Standards, and publish these as part of the established standards legislative process.

(17) The Department of Health and BPS should fully explore options/possibilities for increasing autonomy, internal control and accountability of BPS, e.g. as a government agency, as a government owned company or as an independent commercial enterprise. This should include a consideration of the options for commercial partners or joint ventures.

(18) Any new manufacturing facilities at Los Baños should be subject to product registration for change in the site of manufacture, be issued with a license to operate (LTO) after attaining substantial compliance with GMP, and be included in the routine GMP inspection programme of BFAD. Basic WHO requirements for validation should be addressed during equipment and facilities commissioning and initial production at Los Baños.

(19) The manufacture of anti-venom for the Philippine cobra requires significant investment of resources to produce what is a relatively small number of doses each year. Further consideration should therefore be given to the possibility of retaining the serpentarium to allow the "milking" of the snakes, but sending the venom to another manufacturer for the production of the anti-venom on a contract basis.

5, ACKNOWLEDGEMENTS

The members of the team would like to express their thanks to Dr J. Tan and the Philippines Department of Health for the invitation to participate in the Vaccine Mission. The team is also grateful for the support, cooperation, assistance and hard work of the many individuals and representatives of a number of organizations, without whom this mission would not have been possible. Notable among these are: the Acting Secretary and senior officials of the Department of Health; the Director and staff of the Biologicals Production Service; the staff of the Bureau of Food and Drugs; and the architects and consulting engineers of RSD Gutierrez; the Dean of the School of Public Health at the University of the Philippines.

SCHOLARSHIP SCREENING COMMITTEE
ASSESSMENT SHEET

TITLE OF COURSE _____ BRIEF DESCRIPTION _____

DURATION _____ BASIC COURSE REQUIREMENTS A) AGE _____ B) EDUCATIONAL QUALIFICATION _____

COUNTRY OF TRAINING / VENUE _____ C) POSITION LEVEL _____ D) BACKGROUND EXPERIENCE _____

PROGRAM / SPONSORING AGENCY _____ AGENCIES INVITED _____

NO. OF SLOTS _____

NAME	NOMINEE(S) PROFILE						DOCUMENTARY REVIEW (60 PTS.)			TOTAL SCORE (60 PTS.)	PERSONAL INTERVIEW (40 PTS.)						TOTAL SCORE (40 PTS.)	OVER-ALL SCORE (100 PTS.)	REMARKS
	SEX	AGE	CURRENT POSITION	AGENCY/ REGION	(BACHELOR/ MASTERS) COURSE	ACAD. INST	Scholastic Record: RELEVANCE TO FIELD OF STUDY (20PTS.)	Scholastic Record: ACADEMIC PERFORMANCE IN BACHELOR'S PROGRAM (20PTS.)	RELEVANT WORK EXPERIENCE & TRAINING (20PTS.)		RELEVANCE TO PRESENT WORK ASSIGNMENT (10 PTS.)	KNOWLEDGE OF SUBJECT MATTER (10 PTS.)	COMMUNICATION SKILLS (10 PTS.): ORAL (5 PTS.)	COMMUNICATION SKILLS (10 PTS.): WRITTEN (5 PTS.)	ATTITUDE/ BEHAVIOR/ LOGIC, ETC. (5 PTS.)	INNOVATIVENESS APPLIED TO AGENCY (5 PTS.)			

CONSENSUS

DESK OFFICER

NEDA _____ DFA _____ DECS _____

CSC _____ ACADEME _____

NOTED BY :

Executive Officer

OVERALL CRITERIA FOR EVALUATION

A.	*Scholastic Record*	*40 pts.*
B.	*Work Experience and Training*	*20 pts.*
C.	*Interview Score*	*40 pts.*

A. Scholastic Record (40 pts.)

1. Relevance to the Field of Study (20 pts.)

This refers to the relevance (or closeness) of the nominee(s) undergraduate course to the program he/she is applying to. The closer (or more related) the undergraduate course, the higher the points.

This is based on the assumption that the possibility of finishing the program is increased if the program is close to (or related to) his graduate course.

2. Academic Performance in Bachelor's Program (20 pts.)

This refers to the nominee(s) performance during his undergraduate course. This is further broken down as follows:

2.1. No. of Failures (10 pts.)

Based on Transcript of Records, no failure earns the maximum of 10 pts. While 5 or more failing grades earns 0 pts.

The grades to be considered should be those referring to the core subjects of the course. The table below maybe useful:

Failures	Points
0	10
1	8
2	6
3	4
4	2
5 or more	0

2.2 Grades (10 pts.)

Based on the Transcript of Records, the grades of the nominee(s) shall be evaluated as follows :

Grade	Points
1.00 – 1.75 (Excellent)	10
1.76 – 2.00 (Above Ave.)	8
2.01 – 2.50 (Average)	6
2.51 – 3.00 (Below Ave.)	4
3.01 down (Fair)	2

Points of (2.1) and (2.2) are added to get the total point score.

B. Relevant Work Experience and Training (20 pts.)

1.Number of years of relevant work experience (10 pts.)

This refers to the number of years of relevant work experience of the nominee(s), especially with the nominating agency. Priority shall be given to those who have had relevant work experience for at least 5 years but have not undergone relative training. This is to gauge the nominee's sense of company loyalty and to approximate willingness to return after training to apply his/her acquired knowledge.

5 years & above	=	10 pts.
4 years	=	8 pts.
3 years	=	6 pts.
2 years	=	4 pts.
1 year or less	=	2 pts.

2. Nominees with relevant training shall get additional 10 points.

C. Interview Score (40 pts.)

1. Relevance to Present Work Assignment (10 pts.)

This refers to the relevance of the program to the nominee(s) present work assignment. Preference shall be given to those who will have immediate impact in their present assignments upon their return. This is in line with the program's objective to introduce new approaches through foreign training and scholarships in order to encourage development within the particular local fields.

Very relevant	=	10 pts.
Relevant	=	8 pts.
Slightly relevant	=	6 pts.
Not relevant	=	0 pt.

2. Knowledge to the subject matter (10 pts.)

3. Communication Skills (10 pts.)

Oral	5 pts.
Written	5 pts.

4. Attitude/Behavior/logic/ maturity of judgement / ability to project one's self (5 pts.)

This refers to the overall attitude of the nominee, including his enthusiasm and determination as projected in his/her interview. It includes nominee's ability to articulate himself well, expressing confidence and mastery in his field that may merit him/her the scholarship or training abroad.

5. Innovativeness Applied to Agency (5 pts.)

This refers to the possible multiplier effect the nominee is capable of doing in transferring the knowledge he/she gained from the program. Potential benefits also refer to his/her ability to initiate changes and new programs to improve the quality or work in his given field. This is expected to be done after he/she comes back his/her training and will be commensurate to the amount of time spent abroad. Potential benefit may also be measured according to the degree of maturity and judgement the nominee exhibited during his/her interview.

POST-TRAINING REPORT

NAME OF PARTICIPANT :

OFFICE / AGENCY :

COURSE TITLE :

DURATION :

COUNTRY PROGRAM :

PLACE OF TRAINING :

The Post-Training Report should be submitted to the Scholarship Affairs Secretariat (SAS)-NEDA within sixty (60) days upon completion of the training. It must contain the following:

I. Evaluation of the course, the content delivery, applicability to Philippine situation to include positive and negative factors

II. Problems Encountered

III. Recommendations

IV. Re-entry Plan

V. Others

POST-TRAINING REPORT

I. EVALUATION OF THE COURSE, THE CONTENT DELIVERY, APPLICABILITY TO PHILIPPINE SITUATION TO INCLUDE POSITIVE AND NEGATIVE FACTORS

This includes the scholar's ideas and expectations on the course in both technical and administrative matters. Technically, the impression must indicate the manner that the course design was prepared, the effectiveness of the lecturers and the programming of lectures. The impression must also indicate the efficiency of the overall administrative and logistic report, the allowances, social workers, student advisers, accommodations.

The evaluation should be an analysis of the training program which should mention: (a) the importance of the course in relation to the priorities of the Medium Term Philippine Development Plan (MTPDP) and the agency's training needs; (b) the need for modification in the coverage of the training which matches with the agency's training needs/expectations; and (c) other agencies or institutes relevant to participate in the training, and

Relevance to the present work of the scholar and applicability and availability of materials used during the training in his present place of work – to maximize multiplier effect of the training.

II. PROBLEMS ENCOUNTERED

This portion should indicate the difficulties experienced in the country of training, school facilities, lodging, training staff, languages, schedules, etc.. It must also indicate, e.g. the donor agency's reporting to the institutes, rapport with the adviser.

III. RECOMMENDATIONS

This includes suggestions and comments on the training attended for the improvement of the program. Modifications on the course modules, lecturers, site visits, accommodations, allowances, terms of the grant, etc. must be expounded. Recommendations must respond to the issues/problems earlier identified in order to have meaning and significance.

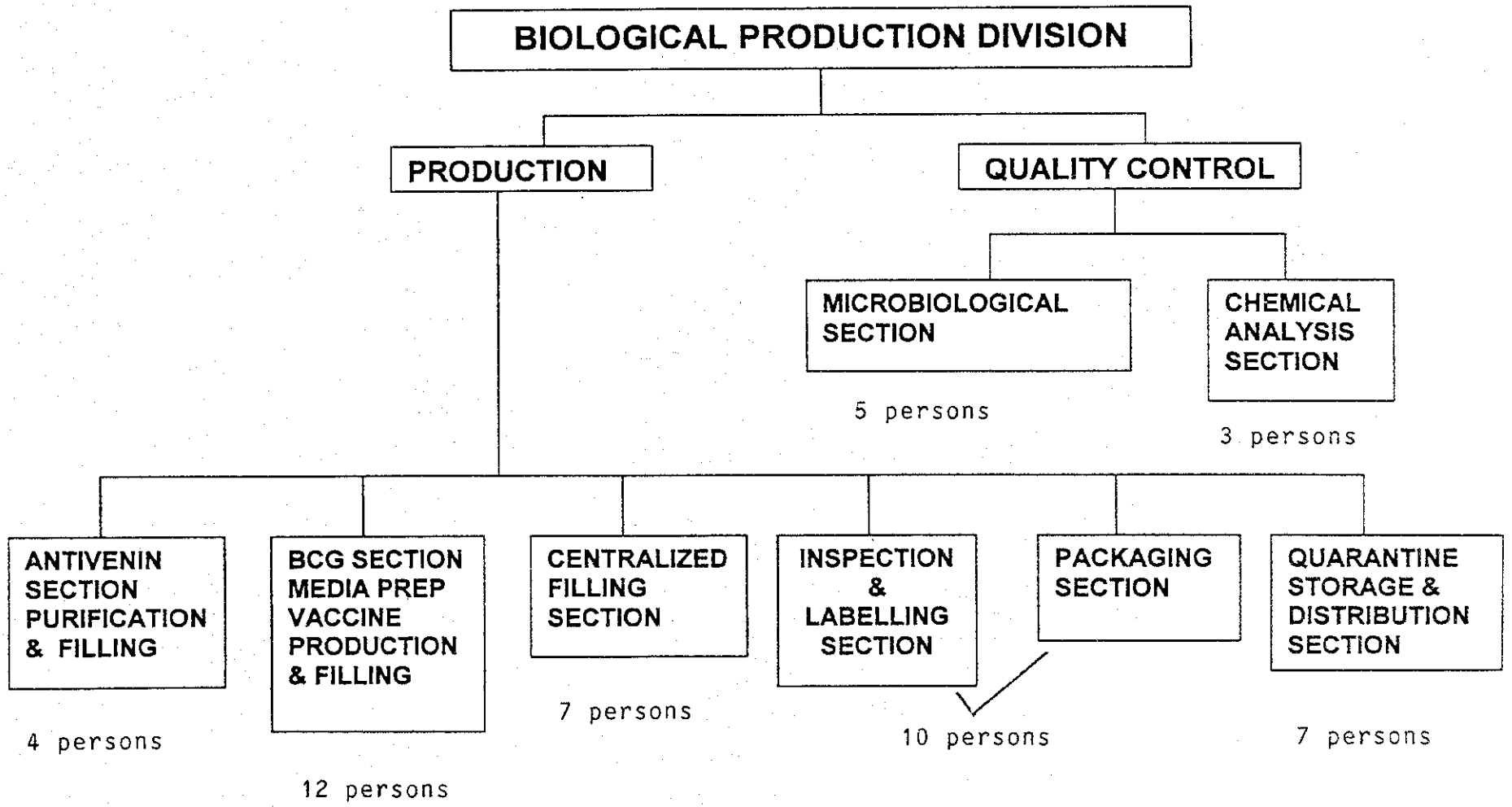
IV. RE-ENTRY PLAN

This must explain how the technology gained will be transferred/applied to the nominating agency. The proposed entry plan may be explained through set of activities to be undertaken within the unit/staff/office/agency. The proposal may indicate the budgetary requirements for the implementation of said activity. The assistance from the donor institute or the government coordinating authority may likewise be needed to make effective proposal. This must also include the scholar's proposal to utilize the knowledge learned upon return to his/her country (Philippines). The re-entry plan must at least cover 2-3 years plan of action with clear quantifiable targets (supported by schedule of activities) to address actual gaps in his/her office/organization. This consideration is closely linked to how multiplier effects should be maximized.

V. OTHERS

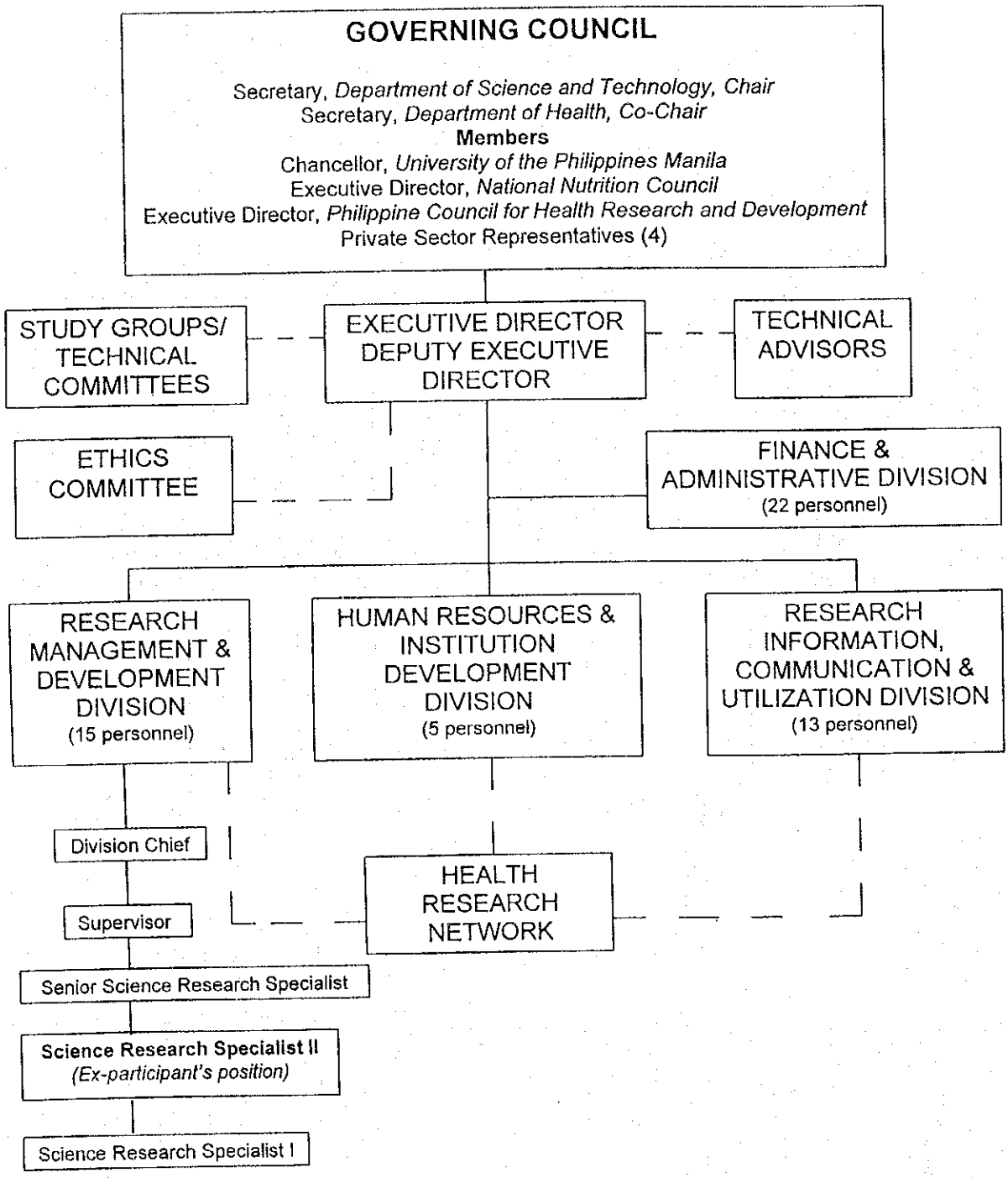
This may include items that would contribute to improvement/ effectiveness of the program. A free-wheeling discussion of other points of interest which would directly or indirectly influence the formulation of course designs/programs that would be more responsive and practicable to Philippine conditions. Special concern which a particular individual/scholar would wish to highlight.

ORGANIZATIONAL CHART

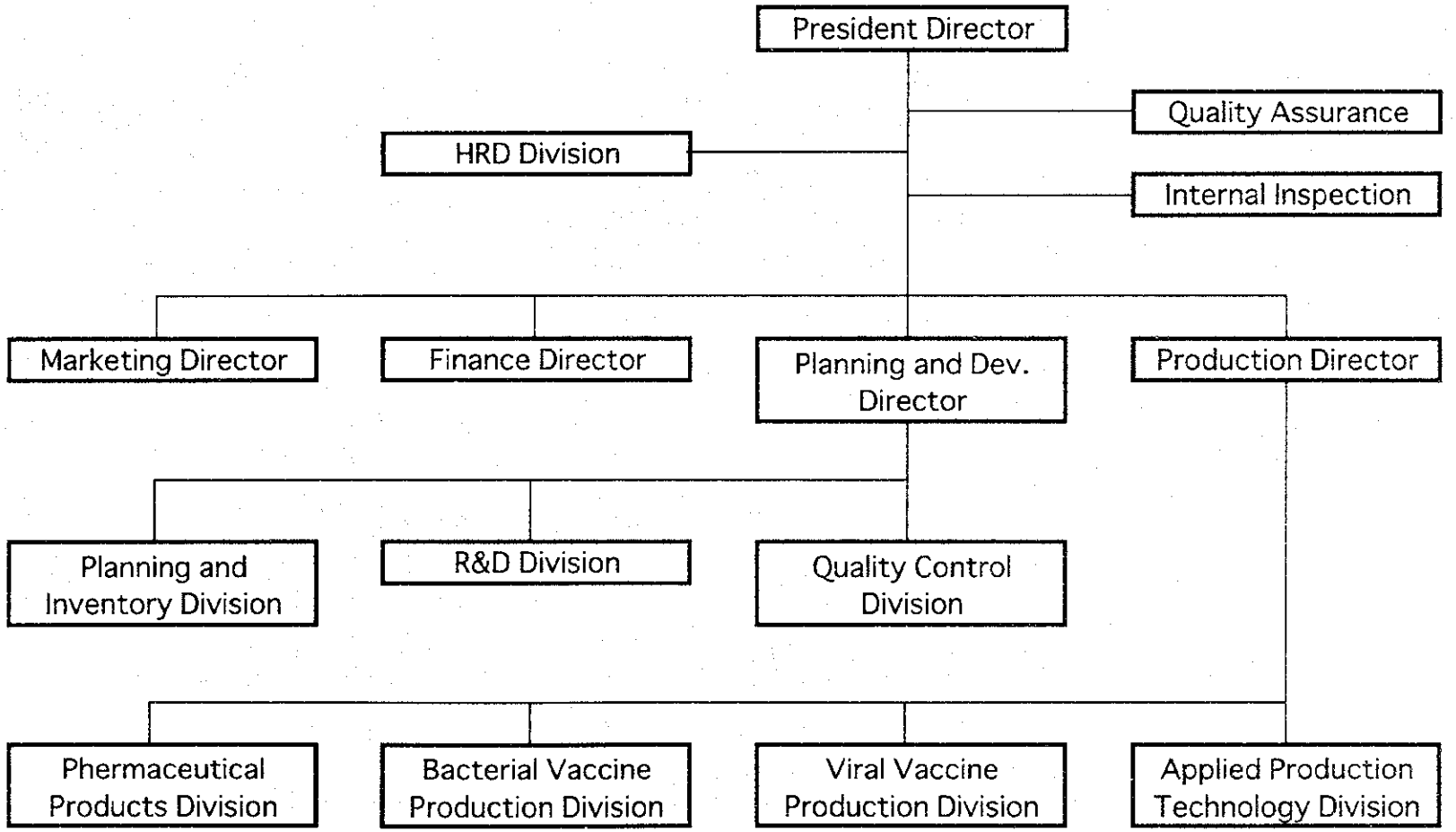


Annex A

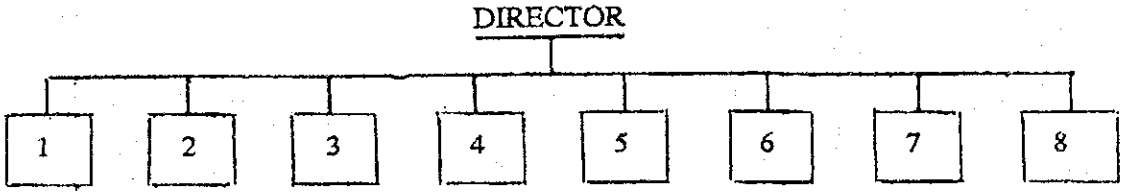
Organizational Structure of PCHRD-DOST



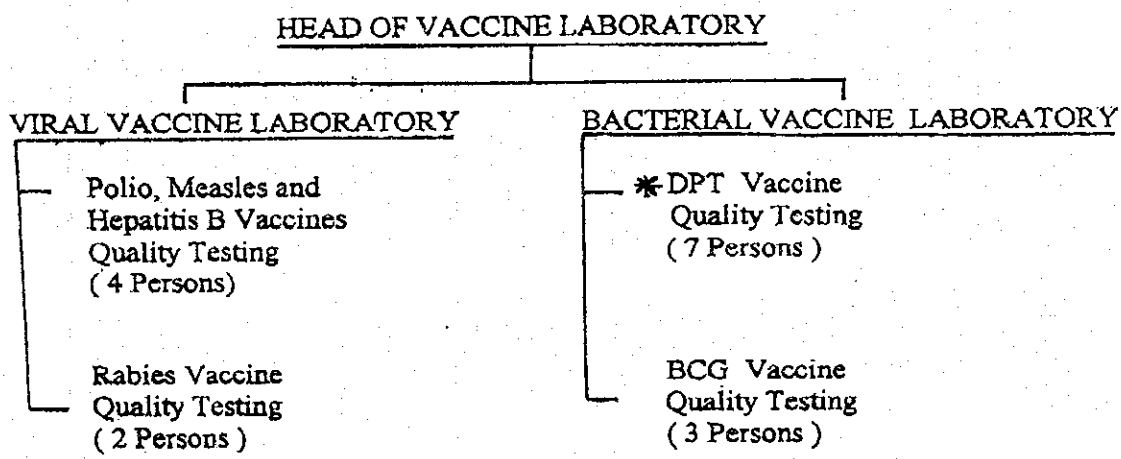
Ornanizational Chart of BIO FARMA



NATIONAL QUALITY CONTROL LABORATORY OF DRUG AND FOOD



DIVISION OF VACCINE QUALITY TESTING



Note :
1. Division of Food and Beverages Quality Testing
2. Division of Drug Quality Testing
3. Division of Narcotic and Hazardous Quality Testing
4. Division of Cosmetic and Medical Devices Quality Testing
5. Division of Traditional Drug Quality Testing
6. Division of Vaccine Quality Testing
7. Division of Toxicology
8. Division of Microbiology

5．安藤団員の小講義要約とスライド

ワクチンの最近の問題について

Ⅰ　ワクチンの安全性への対応

低開発国ではワクチンの有効性が最優先されるが、先進国ではワクチンのターゲットとなる感染症の発生数が激減しており、ワクチン接種事故が生じると大きな問題となる。そのため有効性と副反応の差し引きでワクチンの価値が論議され、特に副反応の少ないワクチンが求められている。

1　チメロサール

チメロサールは防腐剤として不活化ワクチンに添加されるが、水銀を含むため人体への影響が懸念されている。現在のチメロサール減量化への対応として、申請書の変更・高感度測定法の導入・水銀含量の測定・機器のバリデーションを実施している。

2　ゼラチン

ゼラチンはアレルギー原として作用しアナフィラキシーショックを起こすので、ワクチンの添加物として抗原性の低いものを用いるとか、あるいはゼラチンフリーワクチンの開発を進めている。

3　ヒト血清アルブミン

ヒト血清アルブミンには、パルボウイルス・ＨＩＶ・ＨＢＶ・ＨＣＶの混入の可能性に加え、未知の感染性因子が含まれていることが疑われる。ゼラチンやヒト血清アルブミンは生きたウイルスの安定剤としての役割があるので、これに代わる副作用がなく（少なく）、それぞれのワクチンウイルスに適したものを探さなければならない。

4　プリオン

プリオンは感染性を持つ蛋白で、ＢＳＥ（狂牛病）はプリオンが原因で発症する。あるワクチンの製造には牛由来の原料を用いるのでプリオン混入の可能性が疑われるが、いまだ確実にプリオンを測定する方法を人類は手にしていない。そこで、ＢＳＥが確認されていない地域の牛由来の原料を用いることで、ワクチンへの混入を避ける方策としている。

Ⅱ　改良型ワクチン

近年、ワクチンの開発には種々の規制があり、多大な時間と費用が必要となる。ここでは、日本脳炎ウイルスを動物愛護の点で問題のあるマウス脳で増やすのではなく、細胞培養で増やす方法の開発と、おたふく風邪ウイルスの弱毒化に問題のあったＭＭＲワクチンではなく、安全性の確認された麻しんワクチンと風しんワクチンの混合ワクチンを簡単に紹介する。

1　組織培養日本脳炎ワクチン

１９９６年から、Ｃｅｌｌ　ＢａｎｋやＳｅｅｄ　Ｖｉｒｕｓ等の基礎的研究から始め、培養のスケールアップ・施設の新設バリデーション・臨床試験用ワクチンの製造までが終了し、安定性試験・前臨床試験が始まっている。これから臨床試験・製造承認申請と続く予定である。

2　麻しん一風しん混合（ＭＲ）ワクチン

それぞれの単味ワクチンは既に市販され有効性・安全性・安定性は証明済みであるので、混合による影響を臨床試験で調べ始めている。

Ⅲ　その他

インフルエンザワクチンの製造量・成分の変遷をみると、典型的な「社会情勢とワクチンメーカーの対応」関係を知ることができる。また、ワクチンの特許の役割を示す典型的な例として生水痘ワクチンの現状を示す。

最後に、発展途上国にワクチンを供与するための日本国内での寄付集めの新聞広告を示し、人々の好意が大きな役割を果たしていることを理解してもらう。

1　インフルエンザワクチン

１９５３年にインタクトワクチンが発売された後、次第に社会に受け入れられ、集団接種へと移行して製造量が爆発的に増加した。その約１０年間に発生した副反応の反省をふまえ、ＨＡコンポーネントワクチンが開発された。その後約２０数年間、集団接種が維持されたが効果を疑問視するジャーナリズムのキャンペーンに動かされて、ついに集団接種は中止に追い込まれた。任意接種になり製造量が激減して数年のうちに高齢者が集団生活している老人ホームや保育所等（ハイリスクグループ）でインフルエンザによる死亡が多発した（数千人規模）。こういった報道や厚生省の注意喚起により、製造量は再び増加に転じている。

2　生水痘ワクチン

生水痘ワクチンの岡株は、製造特許を世界でも大手のSKBやＰＭに供与して、世界標準となっている。

Current Topics in Vaccines

Follow up inquiry commission for the completed trainee of vaccine quality control technology course

CONTENTS

Thimerosal (Background)

Thimerosal has been used as an additive to biologics and vaccines since the 1930's

⇓

Review and assess the risk of all mercury containing food and drugs (1997)

⇓

U.S. vaccine manufacturers responded to (1998)

⇓

FDA request to provide more detailed information about the thimerosal content (1999)

⇓

Statement established the goal of removing the vaccine preservative thimerosal (1999)

⇓

EMEA published statement on thimerosal containing medicinal products (1999)
(European Agency for the Evaluation of Medicinal Products)

⇓

Ministry of health and welfare start to guide of thimerosal decreasing in Japan

⇓

Response of BIKEN

① FDA application/ Thimerosal free ↔ Preservative free

② Application of poralographic method/ Test for thimerosal content

③ Measurement of mercury content

④ Validation of instruments

Action plan for thimerosal in Biken

Vaccine	PLAN
Influenza	Preparing for application of minor change
Japanese encephalitis	Already decreased to 1/10 content
DTacP combined	Investigating for other preservative or low thimerosal content
Other bacterial	Investigating in parallel with DTacP vaccine

Gelatin (Cause, Effect and Reaction)

Background 1:

Increase in amount of gelatin containing food

↓

Oral sensitization through intestine

↓

Increase of gelatin allergic reaction

↓

Report of Anaphylaxie shock by gelatin containing snack

Background 2:

Development of heat stable vaccine (10× gelatin content)

↓

1994 Allergie(Anaphylaxie)

Kitasato: Mumpus 41 (11)

Measles 80 (5)

Takeda: Measles 4

↓

1995

Anaphylaxie shock by MMR vaccine (USA)

Reaction of vaccine producer

① Change to low antigenic gelatin

② Development of gelatin free vaccine

↓

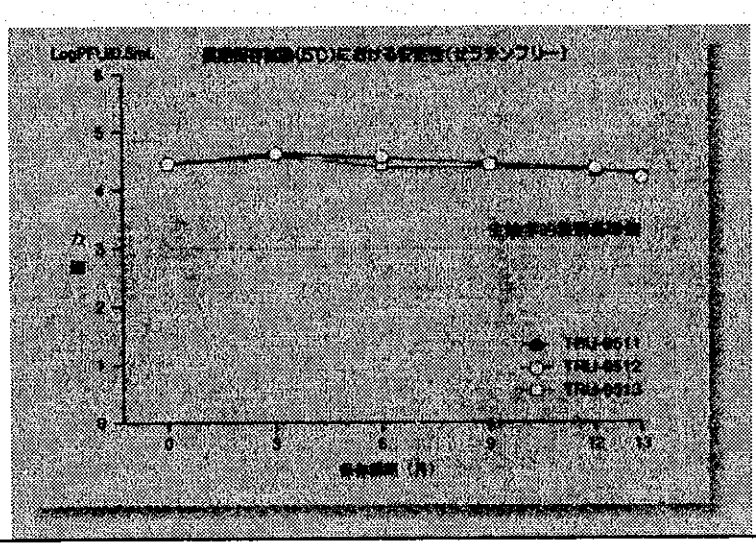
Now, gelatin free vaccines are mainstream

Reaction of vaccine producer in Japan

	December, 1997 Vaccine Producer in Japan							January 2001
Main Vaccines	A	B	C	D	E	F	G	H	C
Freeze-dried live attenuated measles vaccine	—	○	●	●	●				▨
Freeze-dried live attenuated rubella vaccine	○	○	○	●	●				○
Japanese encephalitis vaccine	●	●	●	●	●	●	●		○
Adsorbed DacPT combined vaccine	○	●	●	○	○	○			○
Diphtheria-Tetanus combined toxoid	○	●	●	○	○	○			○
Adsorbed Diphtheria-Tetanus combined toxoid	—	—	●				—		○
Freeze-dried live attenuated mumps vaccine	○	○							
Freeze-dried live attenuated varicella vaccine	—	—	▨						○
Influenza HA vaccine	●	—	●	●	●	●			○
Adsorbed Tetanus toxoid	○	●	○	○	○	○			○
Freeze-dried inactivated rabies vaccine	●	—		—					
Recombinant adsorbed Hepatitis B type vaccine	○	—	●						(●)
Recombinant adsorbed Hepatitis A type vaccine	○	—			○	○			
Live Oral Poliomyelitis vaccine	—	—	—	—	—	—	—	●	—

○: Gelatin free
▨: Gelatin hydrolysate ※: D-solbitol
●: Gelatin included
—: No licence

gelatin free rubella vaccine



Reaction of vaccine producer in Japan

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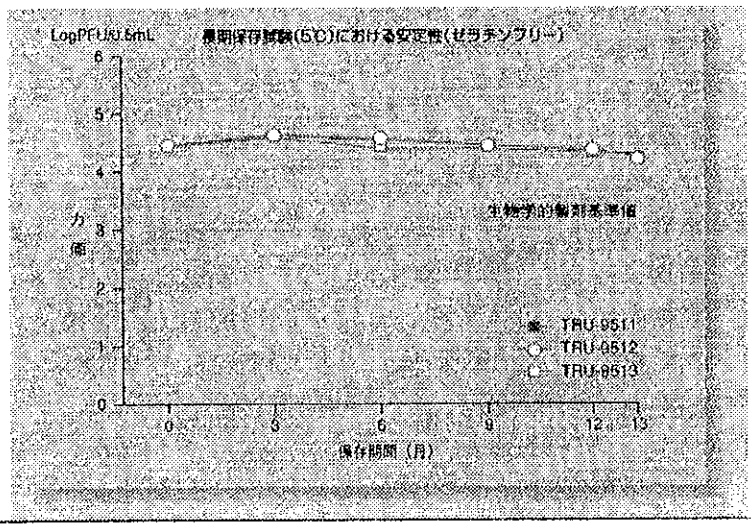
Adsorbed DacPT combined vaccine	○	●	●	○	○	○			○
Diphthena-Tetanus combined toxoid	○	●	●	○	○	○			○
Adsorbed Diphtheria-Tetanus combined toxoid	—	—	●				—		○
Freeze-dried live attenuated mumps vaccine	○	○							
Freeze-dried live attenuated varicella vaccine	—	—							○
Influenza HA vaccine	●	—	●	●	●	●			○
Adsorbed Tetanus toxoid	○	●	○	○	○	○			○
Freeze-dried inactivated rabies vaccine	●	—		—					
Recombinant adsorbed Hepatitis B type vaccine	○	—	●						(●)
Recombinant adsorbed Hepatitis A type vaccine	○	—			○	○			—
Live Oral Poliomyelitis vaccine	—	—	—	—	—	—	—	●	—

○: Gelatin free
: Gelatin hydrolysate
●: Gelatin included
—: No licence
※: D-sorbitol

gelatin free rubella vaccine



Human serum albumin

Suspicions on contamination of

- Parbovirus B19
- HIV
- HBV & HCV
- Unknown infectious agent


エイズ感染者100万人超のタイ

ワクチン治験に黄信号

弱者重視へ「路線回帰」

Human serum albumin

Suspicions on contamination of

- Parbovirus B19
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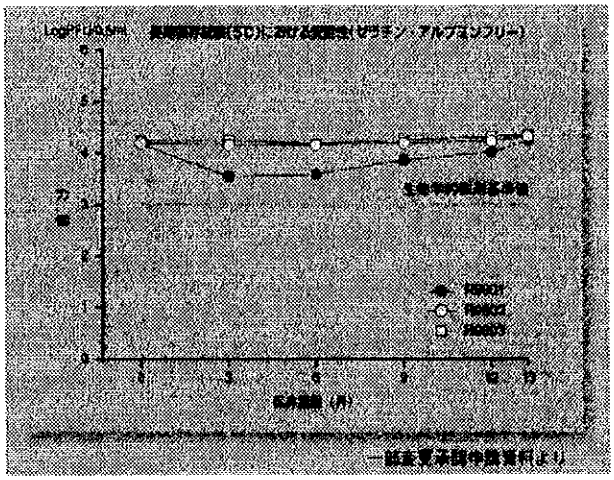
Albumin free rubella vaccine



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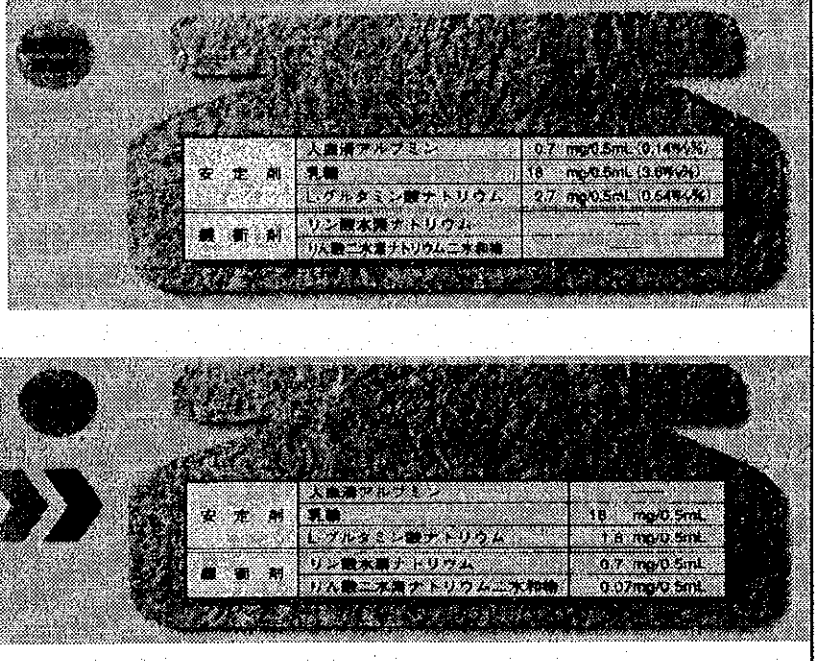
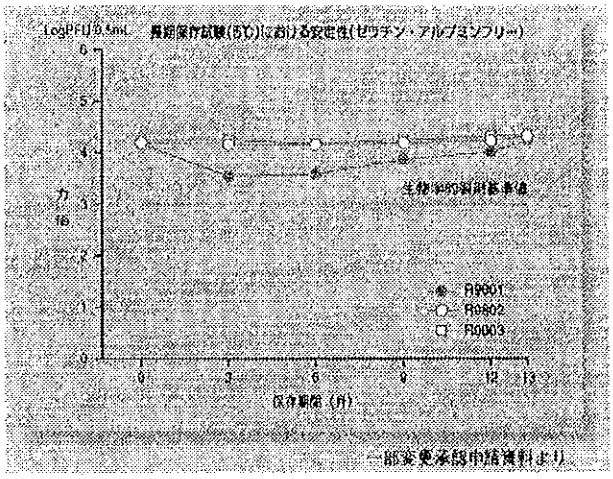


Albumin free rubella vaccine



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