PHC 158

CONSULTANCY ON THE ESTABLISHMENT OF A FACILITY FOR THE PRODUCTION OF TETANUS TOXOID AT THE NATIONAL INSTITUTE OF HEALTH ISLAMABAD, PAKISTAN

REPORT # 8*

APRIL 1990

* Following the sequence started by Binnerts & Co. Inc. - Last report # 7, dated May 1989.

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GLOSSARY OF TERMS AND ABBREVIATIONS:

BLG	- Biologics Division of WHO
CIDA	- Canadian International Developments Agency
DT	- Diphtheria Toxoid
DTP	- Diphtheria and Tetanus Toxoids combined with Pertussis Vaccine
GMP	- Good Manufacturing Practices (Current)
GOP	- Government of Pakistan
JW	- J.C.W. Weber, Consultant
MIB	- Major General M.I. Burney, Consultant
MV	- Measles Vaccine
NBS	- New Brunswick Scientific Corporation
NIH	- National Institute of Health, Islamabad
OIC	- Officer-in-Charge (Production Manager)
PM	- Project Manager
PWD	- Public Works Department, GOP.
QA	- Quality Assurance
QC	- Quality Control
REB	- The late Robbert E. Binnerts, Former Consultant
RIVM	- Rijks Institut voor Volksgezondheit & Milieu
TT	- Tetanus Toxoid
USAID	- United States Agency for International Development
WHO	- World Health Organization

1. INTRODUCTION

This report is prepared as an update of the information provided in the reports numbers 1 - 7 by the late Robbert Binnerts. It is based on the information obtained during my visit to Islamabad from April 1'st till 8'th incl.
The observations, conclusions and recommendations are the results of a joint effort between the two consultants to USAID: Major General M.I. Burney (MIB), and J.C.W. Weber (JW) in close collaboration with members of the NIH staff. Specific efforts were made to have one or preferably both the main players present during all the meetings:

-Mrs. Mumtaz-- Officer-in-Charge (OIC) (i.e. Production Manager)

-Mr.Arfan Mahmood-- Project Manager (PM).

(Dr. Zafar Ali, Director of Biologics Production regrettably had to go away due to illness in his family.)

Unless specifically noted, all items in this report are based on consensus between the two consultants, and the other members of the planning team.

The principal objectives of this visit to Islamabad were:

- Assessment of current status of the project
- Technical review related to Production, Quality Control and general adherence to Current Good Manufacturing Practices (GMP).
- Review and recommendations re building lay-out
- Preparation of a realistic activity schedule designed to meet the tight budgetary time frame
- Review of equipment specification list
- Make recommendations regarding staffing and training.

2. CURRENT STATUS

2.1 Project Management by NIH

2.1.1
Since Mr. Binnerts' last visit there had been a long hiatus with inactivity. Mr. Binnerts (REB) had been due here again in early August, but tragically died shortly before his departure. JW should have come to Islamabad in January, 1990, but was prevented from travelling due to an injury.

2.1.2
In February of this year USAID engaged the former Executive Director of the NIH, Major General Burney (MEB) as consultant, and significant progress was evident as a result.

2.1.3
The assigned Project Manager, Mr. Arfan Mahmood, appears to have been able to devote much more time to the project recently, and has an excellent grasp on the mechanical/technical details, including air handling systems, filling equipment and last, but not least fermenters. He is due to undergo further training in the mechanical aspects of fermenter technology soon at the New Brunswick Company in New Jersey, U.S.A.

2.2 Building Erection

2.2.1
Interior walls had been erected to the point where no significant adjustment was possible. Hence the efforts had to be concentrated on the optimal utilization of the facility as it now stands.

2.2.2
The building is very much behind schedule due to a variety of circumstances, some beyond control. Not enough effort was seen in terms of scheduling work on a concurrent rather than consecutive basis.

2.2.3
Some measurements, notably with respect to the Culture Room had been noted by MIB to be incorrectly applied, thus requiring new specifications for a laminar flow hood.

2.3 External Services

No progress since REB report of May/89. Executive Director requested by letter of March 31, 1990 PWD to accelerate this work.

2.4 Internal Services

2.4.1
No proper blueprints were available yet. They had been awaiting input from Canadian consultant. Some sketches showing air, electricity etc. as well as people, product and material flow will be available for JW to take to Consulting Engineer in Toronto, while some actual blue prints may have to be forwarded later if deemed necessary (in addition to the air handling plans mentioned under 2.4.2.)

2.4.2
Air handling plans had been reviewed 4-5 times prior to JW's arrival. The PWD staff seemed to have misunderstood the requirements for a clean air facility. This has, we hope, been settled at the meeting on 5th April, but the PM as well as the consultants will have to review the "final" blue print again, and JW will show it to the Toronto engineer.

2.5 Internal Training.

No actual schedule had been set up yet, nor were any plans available regarding a "curriculum" for the training programme and who should provide the training.

2.6 External Training

The list of staff members for overseas training provided by REB has been amended as follows:

Function	Person	Training Place
-Production Manager	Mrs. Mumtaz	RIVM, Holland
-Asst. Production Mgr.	Mr. Abid	-"-
-Project Manager & Maintenance Engineer	Mr. Arfan	New Brunswick Scient. N.J., U.S.A.
-Asst. Maint. Eng.	Mr. Baig (?)	-"- (after Arfan's return)

The time of the visit to RIVM has not been settled. There appeared to be some reluctance on behalf of RIVM.
JW contacted Bilthoven from Copenhagen on the way back to Canada and obtained the following information:

Dr. Theo Evers, Head of the Bureau for International Co-operation said that the request had originally been turned down because it "did not fulfil the necessary criteria". It had been under review again, but there was a great deal of reluctance, because the request (Letter from General Syed Azhar Ahmad of Feb. 18, 1989)had included a full training course in the production of diphtheria toxoid and pertussis vaccine in addition to the tetanus toxoid and the preparation of DTP vaccine.
I told him that only Tetanus was on the agenda at this time and requested a meeting. It was agreed that I would stop in Holland on my way to Islamabad in June --if this is OK with you. At that time we should be able to get an agreement in order.

It is imperative that the staff members going to RIVM are as well prepared as possible in advance in order to benefit maximally from the trip.

2.7 Fermenter

The fermenter had arrived and is sitting poorly covered by torn plastic on an open cement walk way between two buildings and is subject to dust and "curious fingers".

2.8 Ancillary Equipment to be Funded by USAID

The list was found to be in good shape when compared with Mr. Binnerts' original list. A few amendments were made.
The bids are required to be submitted by 25th April and contracts awarded by May 7th. This activity need extremely tight monitoring to avoid slippage with potentially very serious complications.

2.9 Tanks

MEB and JW were informed by Arfan that the Pope Scientific Company in Wisconsin had tanks in stock fitting the specifications, and would be able to deliver immediately upon contract award.

2.10 Production Components

2.10.2
JW was informed that compatibility tests with locally procured vials and stoppers had taken place. No data were presented.

2.10.3
It has been decided to purchase, with the help of USAID a quantity of Tetanus Toxoid Bulk Concentrate in order to utilize the filling and packaging equipment while the fermentation procedure is being developed in the plant. This will also enable the Health Authorities to proceed with the immunization of women in the child bearing age much earlier.

2.11 Computerization of Project Management

MEB has, through his own initiative and at own expense established a PERT project management computer schedule with a computer firm in Rawalpindi.
This is extremely useful, but reference is made to Point 3.1.1 under Recommendations.
It was clear that Mr. S.H. Rizvi, even if provided with a suitable computer programme, would not be able to get it running to a degree of usefulness within less than 3 months. The urgency of the project does not allow such delay.

2.12 Production Procedures

It was found that the senior managerial staff designated for the Tetanus plant did not have a detailed picture of each step in the procedure. JW believes that too much reliance has been placed on the training at RIVM as a basic training programme rather than what it should be, namely the final polish of already fully informed technologist.

3. RECOMMENDATIONS

3.1 Project Management

3.1.1.
It is the opinion of JW that until a suitable PERT or equivalent computer programme is available at NIH, the Project Manager (PM) should maintain a hand drawn GANNT chart, to be updated weekly or more often if important slippage or advances occur. This chart, with relevant comments, should be communicated to MEB at the time of each updating and to USAID and to JW (possibly via USAID office fax) at least every second week.

3.1.2.
The NIH, specifically Dr.Zafir Ali, should ensure that the PM is able to devote his entire working time to the planning, supervision and co-ordination of this project until it is completed (i.e. all construction, equipment and facility issues have been settled, the process has been tested out, validated and approved and the plant is turning out satisfactory product).

3.4. Internal Services

3.4.1 and 3.4.2
Copies of final blueprints (esp. air handling) should be forwarded to JW as soon as possible. Otherwise the only input from the consulting engineer in Toronto, Mr. Jim keeling of Proctor and Redfern will be based on the sketches only.

3.6 Internal Training.

A tentative schedule for this activity including a complete list of subjects, trainees and teachers should be drawn up by

3.7 Fermenter

The fermenter should immediately be protected properly, at least with a full and tight tarpaulin, but preferably inside a dust free building. The same applies to all new equipment which cannot be placed as soon as it arrives.

3.9 Tanks

If requested by USAID, JW will visit Pope Scientific Company to ascertain specification and timing.

3.10 Production Components

Compatibility testing of components with product (current Tetanus vaccine should be used till new product is available) must be undertaken on a systematic basis. An experimental design for the stability test of toxoid, both in the presence of proposed vials and stoppers must be set up. The design should included known toxoid and known components for comparison.
Note: This is a high priority item.

Similarly, mock runs must be undertaken with vials, stoppers and caps on the new filling and capping apparatus as soon as it is installed.
The results of these tests must be carefully documented, submitted to the consultants for review and kept on file by the production manager.

3.11 Computerization of Product Management

Although Mr. Rizvi is not ready to undertake this, he should a.s.a.p. obtain or set up such a programme in order that this and other projects can be run effectively on a later date.

3.12 Production Procedures

Mrs. Muntaz with the help of her Assistant Production Manager as well as of her colleagues at NIH should prepare a very detailed flow chart of all activities indicating every step, every connection, volumes, capacities etc. This should then form the basis of the Standard Operating Procedures (SOP) which should be drafted as detailed and accurately as possible prior to the visit to RIVM. (Note: There is a significant reservoir of talent, experience and knowledge available right on the premises of the NIH where help and advice can be obtained).
This is essential to ensure that maximum benefit is achieved during the training period.

APPENDICES

APPENDIX 1.

ACTIVITY LOG for VISIT APRIL 1990 and RELATED ACTIVITIES

TRAVEL & ACTIVITIES IN ISALAMABAD

March 30/31	Travelling to Islamabad
April 1	Meeting at USAID
April 2-5 & 7	Working at NIH with Maj. Gen Burney, NIH staff and PWD staff
April 8 (am)	Debriefing at USAID
(pm)	Meeting with First Secretary (Development) Canadian High Commission
April 9	Return Travel

RELATED ACTIVITIES PERFORMED IN CANADA AND EUROPE

April 10	Meeting at BLG, WHO. Dr. David Magrath re approval of facilities, testing of product, National Control Authority (NCA), Tetanus Toxoid availability, Training etc.
March 15	Meeting with Jim Keeling,Consulting Engineer, Proctor & Redfern, Toronto
April 17	Meeting with Dr. J. Siim (former Director of the Danish State Serum Institute) regarding DANIDA and 'phone discussion with Mr. Theo Evers of RIVM regarding training.
April 25	Meeting with Mr. Jim Keeling re sketches from NIH of TT plant.

APPENDIX 2

PLANNED FUTURE ACTIVITIES

(Subject to Approval by USAID)

May	Visit to Pope Scientific Co., Wisconsin re tanks if deemed necessary
June 1	Possible visit to UNICEF, New York re further (i.e. post Sept.30) funding for project.
June 18*	Visit to RIVM
June 20*	Arrival in Islamabad
July 02*	Leaving Islamabad
Sept 14*	Arriving Islamabad
Sept 30*	Leaving Islamabad

* These dates are tentative, and subject to JW's involvement in QA, GMP training and other activities to be determined.

APPENDIX 3

KEY TARGET DATES

Equipment from U.S.A.

-Final bid date	April 25, 1990
-Contract approval	~~May 7~~
-Arrival Karachi port (110 days after contract approval)	August 27
-Earliest arrival, Islamabad	November 1

Activities at NIH

(Please note: The dates below are LATEST DATES)

Plant Construction

-Completion of external construction	June 14, 1990
-Completion of internal lay-out	June 14
-Comp. internal construction	July 15
-Completion, internal painting, plastering, flooring etc.	Nov 29
-Inspection of building	Dec. 10
-Adjustments to building completed	Jan. 15, 1991
-Commissioning of building	Feb. 13

Services

-Steam, Electricity, Water, Gas into building	August 16, 1990
-Internal installation	September 30
-Internal services validated	Feb. 13, 1991

Heating and Air handling

-Blueprints and specs approved	June 30, 1990
-Installed and accepted	November 30

Production Equipment

-(i) USAID Purchases Received in Islamabad	November 15,'90
-Installed and validated	May 1991
-(ii) NIH Purchases Received in Islamabad	December 31
-Installed and validated	April 1991

(Appendix 3 continued)

Validation of Total System

-Completed	May 1991

SOPs and Protocol Forms

-Prepared	July 31, 1990
-Completed and approved	Nov. 30
-Training in use of Protocol Forms	Jan. 31, 1991

Bulk Toxoid

-Ordered	July 15, 1990
-Delivered and cleared	Feb. 15, 1991
(Note: Time frame depends on whether manuf. has concentrate in stock or must make from start.)	

Other Items

-Labels and direction inserts printed & approved	Dec. 31, 1990
-Chemicals available at NIH	March 31, 1991

Production

-From bulk toxoid	Started	May 31, 1991
	Completed	Oct. 31
-Basic Production, 3 Qualifying lots,	Start	July 1
	Finish	October 31
-Full Scale Basic Production Starts		November 1991

ACTIVITY-TIME FRAME CHART
BY ROBBERT E. BINNERTS

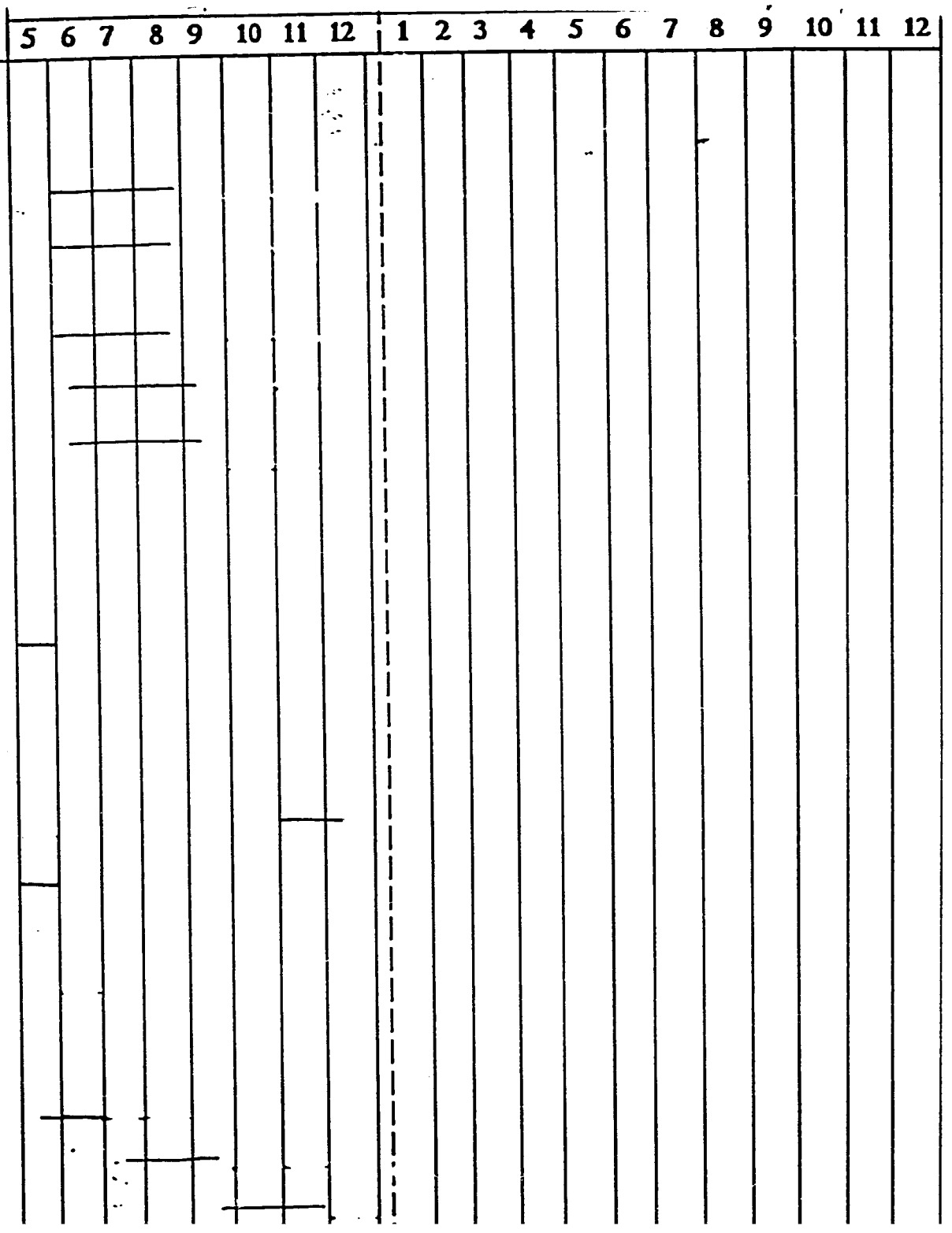
(REVISED MAY, 1990)

ACTIVITY-TIMEFRAME CHART
TETANUS TOXOID-PAKISTAN

of Maj. Gen. Burney
and J.C.W. Weber

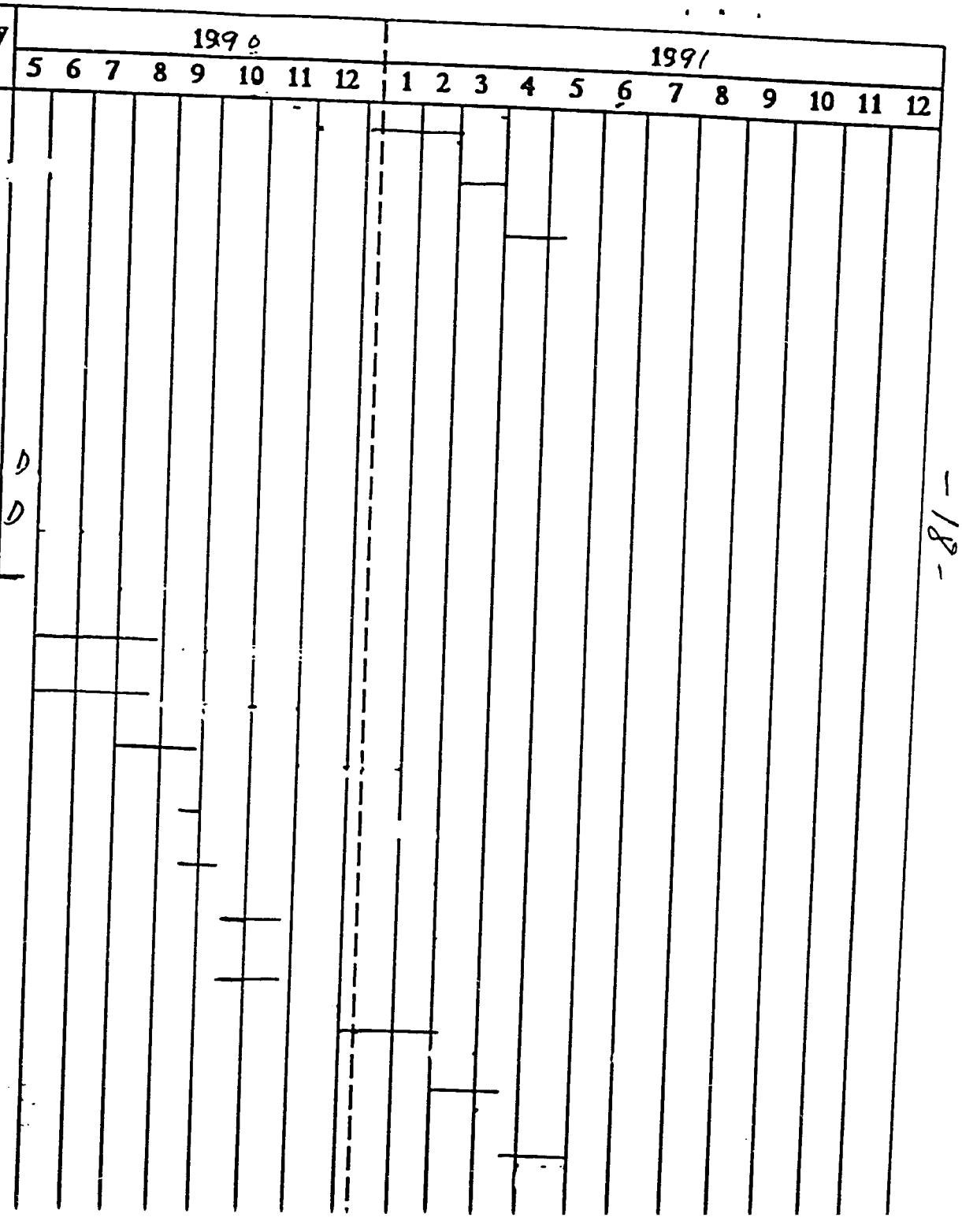
Acc't No.	Activity	Responsibility	1990								1991											
			5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
B	BUILDING ERECTION																					
B1	Determination Loads	NIH/PWD	D																			
B2	Indication Opening to be left in exterior wall. Lay-out	NIH																				
B3	Construction Exterior	PWD																				
B4	Finalization Interior Lay-Out	NIH/CONS																				
B5	Construction Interior	PWD																				
B6	Installation Floor Coverings	PWD																				
B7	Plastering & Painting	PWD																				
B8	Inspection	NIH/CONS																				
B9	Re-adjustments	PWD																				
B10	New Inspection & Take-over Building from PWD	NIH/CONS NIH																				

Acc't No.	Activity	Responsibility
ES	**EXTERNAL STUDIES**	
ES1	Functionalizing. Run-Up Steam Boilers	PWD/NIH
ES2	Steam-lead to Building	PWD/NIH
ES3	Functionalizing El Sub-Station	PWD
ES4	E1. Lead to Building	PWD
ES5	Functionalization Stand-By Generator	PWD
S	**EQUIPMENT STORAGE**	
S1	Availability Storage Space for Equipment and Production Components	NIH
IS.	**INTERNAL SERVICES**	
IS 1.	Placement of Equipment	NIH
IS 2.	Prop. Service Blueprints	
	– Electricity – Steam – Gas – Compressed Air – Water (all types) – HVA	PWD
IS 3.	Checking Blueprints	KEELING/Cons.
IS 4.	Installation	PWD
IS 5	Run-Up	NIH

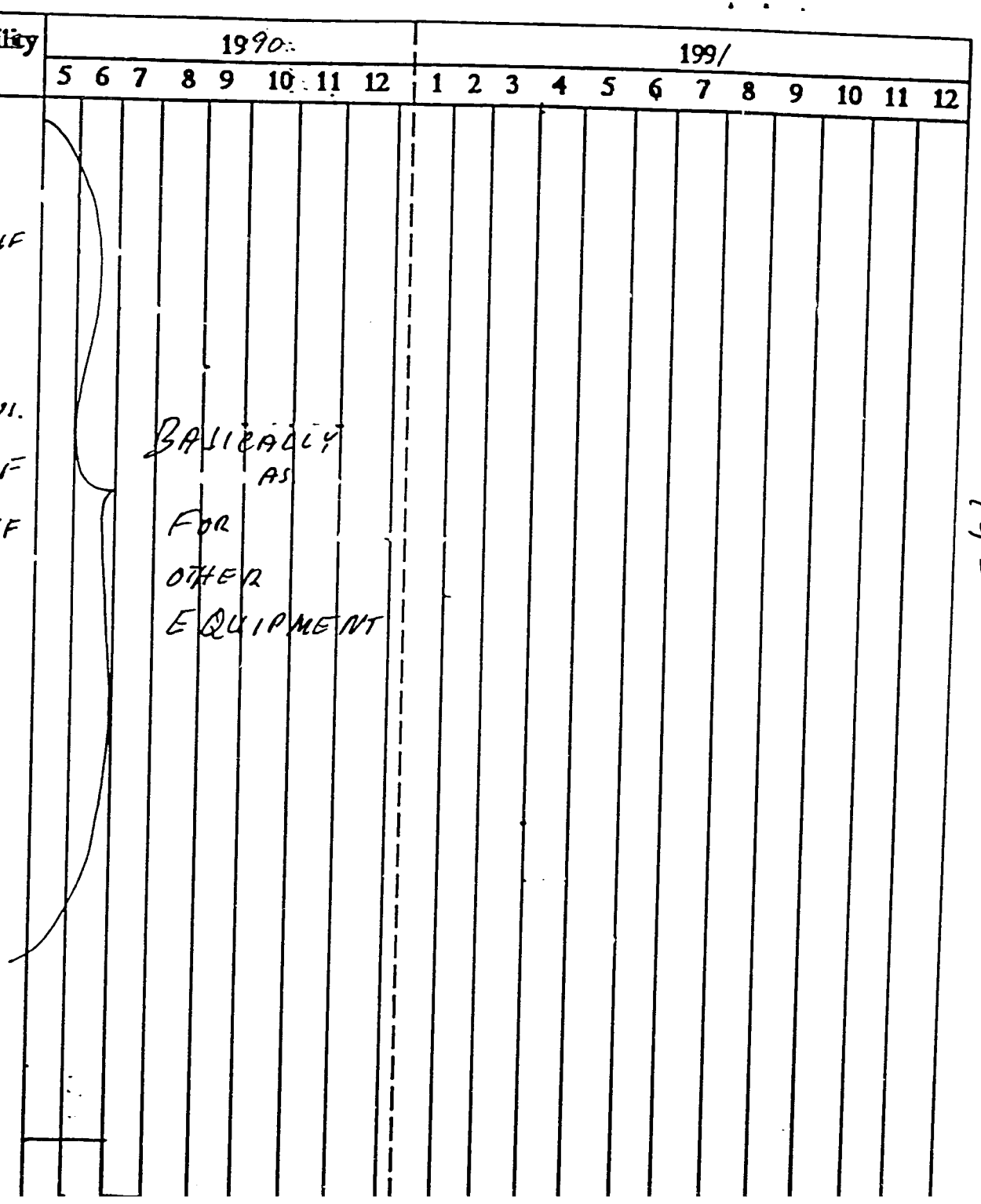


			5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
IS 6.	Re-adjustment	PWD/NIH																				
IS 7.	Validation	NIH																				
TI	TRAINING INTERNAL																					
TI. 1.	Prep. Manuals, Curric. Candidate Selection	NIH/CONS																				
TI. 2.	TRAINING COURSES (incl. GMP.)	NIH/CONS									SOME CONTINUATION											
TE	TRAINING EXTERNAL																					
TE 1.	Determine Training Recruitment/Duration	NIH./CONS																				
TE 2.	Determine appropriate time with NBS	NIH																				
TE 3.	Determine appropriate Foreign Institute and Time of Training	NIH/CONS																				
TE 4.	Undertake Training at NBS	NIH																				
TE 5.	Undertake Training at Foreign Institute						?	?														
F.	FERMENTOR																					
F1.	Follow up with NBS	AID	D																			
F2.	Shipment to Karachi	NBS	D																			
F3.	Custom Clearance	AID	D																			
F4.	Transportation to Islamabad	AID	D																			
F5.	Inspection for Insurance	NIH/AID	?																			
F6.	Storage at NIH	NIH	D																			

Acc't No.	Activity	Responsibility
F7.	Installation	NIH/NBS
F8.	Run-up	NIH/NBS
F9.	Validation	NIH/NBS
A.	ANCILLARY EQUIPMENT TO BE PURCHASED BY USAID	
A1.	Finalization Equipment Specs.	NIH/CONS.
A2.	Tendering	AID
A3.	Ordering	AID
A4.	Follow-up with Manufacturers	AID/CONS.
A5.	Production of Equipment	
A6.	Shipment	Manuf.
A7.	Custom Clearance	AID/NIH
A8.	Transportation to Islamabad	AID/NIH
A9.	Inspection for Insurance	NIH/AID
A10.	Storage at NIH	NIH
A11.	Installation	NIH
A12.	Run-up	
A13.	Validation	



Acc't No.	Activity	Responsibility
T.	TANKS	
T1.	Re-define specifications	NIH
T2.	Prelim. Drawings & Quote	MANUF
T3.	Approval of Drawings	NIH
T4.	Ordering	AID
T5.	Follow up with Manuf	AID/CONI.
T6.	Production of Tanks	MANUF
T7.	Shipment	MANUF
T8.	Clearance	AID
T9.	Transport to Islamabad	AID
T10.	Inspection for Insurance	NIH/AID
T11.	Storage	
T12.	Installation	NIH
T13.	Run-up	
T14.	Validation	NIH
AN	ANCILLARY EQUIPMENT TO BE PURCHASED BY NIH	
AN1.	Finalization Equipment Specs.	NIH/CONS
AN2.	Ordering	NIH



			5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
AN4.	Production of Equipment	Manuf.																				
AN5.	Shipment	Manuf.																				
AN6.	Customs Clearance 2	Manuf.																				
AN7.	Transportation to Islamabad	Manuf.																				
AN8.	Inspection	NIH																				
AN9.	Storage at NIH	NIH																				
AN10.	Installation	NIH																				
AN11.	Run-up	NIH																				
AN12.	Validation	NIH																				
V.	RUN-IN AND VALIDATION OF TOTAL SYSTEM																					
V1.	Run-in																					
V2.	Validation																					
V3.	Adjustment																					
V4.	Re-validation																					
SP.	STANDARD OPERATING PROCEDURES																					
SP 1.	Preparation ~~Finalization~~ of SOPs	NIH/Cons																				
SP 1.1	Completion of SOPs	NIH/Cons																				
SP 2.	Preparation of Protocol Forms	NIH/Cons																				
SP 2.1	Completion of P. Forms	NIH/Cons																				
SP 3.	Training in Use of Protocol Forms	Cons/NIH																				

Acc't No.	Activity	Responsibility	1990								1991											
			5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
C.	PRODUCTION COMPONENTS																					
C 1.	Preparation of Specs. for Bulk Conc. Toxoid and Quantity Required	NIH/Cons	D																			
C 2.	Tendering of Bulk Toxoid	USAID	D?																			
C 3.	Ordering of Bulk Toxoid	USAID																				
C 4.	Production of Bulk Toxoid	Manuf.				NOTE: ONE MANUFACTURER* HAS AVAILABLE CONC. IN THIS CASE SIX WEEK DELIVERY																
C 5.	Shipment Bulk Toxoid (Air)	Manuf.																				
C 6.	Clearance & Storage Bulk Toxoid	NIH																	FDA LICENSE!			
C 7.	Compatability Tests Vial & Stopper	NIH																				
C 8.	Delivery of Vials	NIH																				
C 9.	Ordering of Stoppers	NIH																				
C 10.	Production of Stoppers	Manuf.																				
C 11.	Shipment of Stoppers (Air)	Manuf.																				
C 12.	Clearance of Stoppers	NIH																				
C 13.	Drafting Text of Labels & Direction Sheets	NIH																				
C 14.	Approval Text of C13 by WHO (Probably not!)	Cons/ NIH																				
C 14.1	Approval of Text by NCA + Consultants																					
C 15.	Printing Labels & Dir. Sheets	NIH																				
C 16.	Preparation of Specs. for																					

Acc't No.	Activity	Responsibility	1990								1991											
			5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
C 17.	Tendering of Chemicals	NIH																				
C 18.	Ordering of Chemicals	NIH																				
C 19.	Delivery to Shipper of Chemicals	Manuf.																				
C 20.	Shipment of Chemicals	Manuf.																				
C 21.	Clearance of Chemicals	NIH																				
C 22.	Transportation to Islamabad of Chemicals	NIH																				
P.	PRODUCTION																					
P 1.	Production from Bulk Toxoid	NIH																				
P 2.	Basic production (3 lots)	NIH																				
P 3.	Q.C. of P2	NIH																				
P 4.	Duplicate Q.C. of P2	WHO																				
P 5.	Commencement Full Scale Basic Production	NIH																				

By Air mail.

F.1-18/89-BPD-619

18th Feb, 1989.

The Director,
Rijks Institute Voor
Volksgezondheid en milieuhygienic,
P.O. Box No.1,
The Netherlands 3720 BA, Bilthoven.

Subject:-TRAINING IN PRODUCTION & QUALITY CONTROL OF TETANUS TOXOID.

Dear Sir,

We are in a process of enhanced production of Tetanus Toxoid using Bio-reactor (Fermentor) at National Institute of Health, Islamabad. In this connection, two of our scientists are required to be trained in production and Quality control of Tetanus Toxoid and Diphtheria etc.

Therefore, the undersigned may please be informed about the possibility of above training at your Institute in the near future. Kindly intimate the date and schedule of the training programme or courses if you are holding at your Institute in near future, so that we could send our scientists for training in the field of Production and Quality Control of Bacterial Vaccines with special reference to Diphtheria, Tetanus & Pertussis.

Your cooperation in this regard is very much appreciated.

Yours sincerely,

Lt.Gen.
(DR. SYED AZHAR AHMAD
EXECUTIVE DIRECTOR.