

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

REPORT # 9

JUNE 1990

by

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GLOSSARY OF TERMS AND ABBREVIATIONS:

BLG	- Biologics Division of WHO
CIDA	- Canadian International Development Agency
DT	- Diphtheria Toxoid
DTP	- Diphtheria and Tetanus Toxoids combined with Pertussis Vaccine
ED	- Executive Director
GMP	- Good Manufacturing Practices
GOP	- Government of Pakistan
JW	- Jorgen 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 Instituut voor Volksgezondheid & Milieu
TT	- Tetanus Toxoid
USAID	- United States Agency for International Development
WHO	- World Health Organization

1. INTRODUCTION

This report covers the second visit by J.C.W. Weber to Islamabad. The visit took place from Thursday, June 21 till Sunday, July 1, 1990. Associated meetings in Toronto (Mr. Jim Keeling, Consulting Engineer), New York (Mr. John Gilmartin, UNICEF) and Bilthoven, Holland (Mr. Theo Evers, RIVM) are reported in the appendices.

During this visit most of the meetings were held together with Major General M.I. Burney (MIB) and Dr. Rushna Ravji (RR). Most of the observations and recommendations in this report were based on consensus achieved at the meetings. Some of the statements are, however, the sole responsibility of JW.

The following members of NIH participated in most of the meetings as time permitted:

-Mr. Zafar Ali, Chief, Biological Production

-Mr. Arfan Mahmood, Project Manager

In addition, the following members of the future Tetanus Toxoid plant staff were present at some of the discussions:

-Mr. Akbar Baig, Scientific Officer

-Mrs. Farida, Scientific Officer

-Mr. Abid Hussain

It was very regrettable that the designated Senior Scientific Officer, Mrs. Mumtaz Begum, was absent during this visit by JW.

Visits were made to the following sections for assessment relative to

(a) Potential interactions between sections

(B) Assessment of the general status of GMP compliance within the NIH.

- Measles Vaccine. Mr. Shahid Aktar. (Viral Vaccines Coordinator)

- Rabies Vaccine. Mr. Abdus Samad Khan (Sr. Scient. Officer)

- Polio Vaccine. Mr. Abdus Haq Soomro (Officer-in-charge)

- General Quality Control (Potential National Control Laboratory) Mr. Zia Khan (Officer-in-charge).

Briefing and de-briefing meetings were held with the Executive Director, Dr. Abdul Ghafoor.

Additionally JW had the following meetings:

- Re. Tetanus Toxoid requirements and EPI:
Dr. Akram together with General Burney and Dr. Ghafoor.
- Re: General Pakistani Vaccine situation and funding questions:
Mrs. Louise Marchand, CIDA, Canadian High Commission
Mr. Kunio Waki, UNICEF.

OBJECTIVES

The principal objectives of this visit to Islamabad were:

(1) Review and assessment of the following items:

- Status of building, facilities and services.
- Standard Operating Procedures for both production and Q.C
- Training programme.
- Staffing plans and available candidates.
- Expected status of project by September 30, 1990.

(2) Assist in:

- Determining realistic time schedules.
- Locating hard currency funding for post-Sept.30 needs.

(3) Make recommendations regarding:

- Issues under (1) and (2) above.
- The purchase of Tetanus Toxoid concentrate to
(a) cover interim requirements till plant is fully operational and (b) serve as trial material for the diluting, filling and packaging functions.
- Requirements for continuity after Sept.30.
- The National Control Authority and the National Control Laboratory.
- Training programmes.
- Job descriptions and personnel requirements.
- Staff relations.

2. CURRENT STATUS

2.1 Project Management by NIH

The appointed Project Manager (PM), Mr. Arfan Mahmood, had been distracted in several directions, such as air conditioning repairs in a government building, and an, also totally unrelated, assignment in Bahrain.

As a result, he had not kept up with all the key functions, and Gantt charts were incomplete, while follow-up with PWD had been left primarily with MIB.

Regularly scheduled meetings and co-ordination efforts were not satisfactory and seemed to have been largely dependent upon the USAID consultant, General Burney, rather than on the responsible NIH staff.

2.2 Building Erection

Apart from walls left incomplete pending arrival of equipment, the structure was basically in place.

The floors were being prepared at the time of JW's visit.

In general, the building seems to be proceeding moderately ahead of the "Activity-Time Frame Chart" (Time-chart) included in Report # 8 with respect to structural details.

2.3 External services

The situation with respect to boilers and stand-by generators had not improved.

The boilers, which were brought in during 1987 were not hooked up and were still awaiting some legal investigation. The generator had been wrongly placed originally (blocking the opening of a boiler port) and required moving. This latter activity was now scheduled for July 1990. However, the procrastination with respect to these matters combined with similar costly bureaucratic delays in other areas of NIH raised serious doubts in this consultant's mind with respect to the ability of the current system to support and sustain the efforts required to complete the project.

A suggestion by Mr. Arfan to utilize the steam from the other end of the building on an emergency basis was good, but regrettably a temporary emergency facility could easily, in the current situation, become a permanent feature leading to serious steam shortages in other areas of the Institute and be used to justify further delays.

2.4 Internal Services.

The blueprints covering installation of electricity, plumbing and air-conditioning were said to be completed. They were now subject to a PCI and approval by a Government Finance Committee. Most of these approvals were given during the week of June 24.

The blueprint were not made available to the consultant engineer, Mr. Jim Keeling, who had to work entirely from sketches. It was not clear to which extent the drawings and requirement estimates he prepared were utilized. They should be useful when checking the final specification before proceeding. This is not likely to alter the cost picture, but should provide some insurance against errors and unexpected cost overruns later.

2.5 Internal Training

A proposal was handed to JW by Mr. Arfan prior to departure. The review with recommendations of this will be presented in Appendix 4.

2.6 External Training

-2.6.1. Training at RIVM, Holland.

This was discussed at JW's meeting with Mr. Theo Evers and Dr. J.T. Hendriks at RIVM on June 19th. (See report, Appendix 5) The Rijksinstituut will not be ready to accept trainees until after 1st October, 1990 due to renovation of tetanus area. The final selection of trainees has not been done. See Recommendations, 3.6.1.

-2.6.2. Training at NBS, N.J., U.S.A.

The candidates are still Messrs. Arfan and Baig. They are hoping to go in July, but NBS have in a fax suggested that both come together during the week of August 13.

Two 'phone talks with NBS revealed this:

-July 9. Mr. Ivan Vazquez (Sales person) said that Mr. Arfan had already trained on the IF-150 fermenter and indeed used for about 3 years as it was identical to the one shipped earlier to NIH.

-July 10. Mr. Jerry (?) Gerber, Training Manager said that there was no IF-150 in New Jersey to train anyone on. I suggested possible training by an NBS person in Islamabad. He will get back to USAID and keep me informed.

2.7 Fermenter

The fermenter is now in a building awaiting installation.

2.8. Ancillary Equipment to be funded by USAID.

It appears that the equipment is in various stages of preparation and shipment and should reach Islamabad on time.

2.9 Tanks

As per 2.8

2.10 Production Components

-2.10.2 Compatibility Testing. Components/Equipment.

A very limited, and insufficient, compatibility test had been performed with the vials using the Measles Vaccine Department's filling equipment. Proper data were not available.

The Cozzoli Company has received 300 (!!) vials from NIH for testing on the equipment. No information on results were available.

-2.10.3 Compatibility Testing. Components/Product.

The need for a compatibility test to ensure product "survival" when in contact with the inner vial surfaces and stoppers was requested at the April visit. No effort was undertaken as yet.

-2.10.4. (Formerly 2.10.3) Tetanus Bulk Concentrate.

Request for bids had been sent to eligible US manufacturers by USAID, but the price was determined to be unacceptable.

In June requests for bids were sent to a number of selected international manufacturers. Only two bids had been returned by July 1st.

2.11 Computerization.

There was no evidence of progress.

2.12 Production Procedures and SOP's.

A set of SOP's was provided to JW and reviewed. Those dealing with QC testing were quite adequate and detailed, while the SOP's for production were sketchy, inadequate and in some cases needed significant changes. JW reviewed them and gave the documents with comments to Mr. Zafir Ali for revision.

The SOP's were still not based on "collaborative efforts" but authored singly by Mrs. Mumtaz with some editing by Mr. Zafir Ali.

2.13 Staffing.

An organization chart was prepared by Mr. Arfan during the consultant visit. This is basically reasonable, but there are a number of functions for which no trained staff seems to be available. There appeared to be problems with both hiring and retaining staff, partially due to lack of incentives both in terms of remuneration and promotion potentials.

2.14 Overall Impression

-There are a number of highly dedicated, skilled staff members.

-The Executive Director's chair has been filled with a person dedicated to progress. However, it appears that too much decision making either rests at this level or, worse, are funnelled through the E.D.'s office for resolution at the Ministry level.

-The function of Chief, Biological Production is seriously overloaded.

-The relevant ministry or ministries appear not to be fully cognizant of the ramifications of the delays in funding and remedial activities seen throughout the NIH. The leaking roof in the Rabies Vaccine Facility and the air handling system in Polio are examples. In both cases production has been held up for many months due to lack of governmental approval. The cost in such delays both in terms of lost production, idle staff and (presumably) delayed immunization far exceeds the cost of the repair.

These and other incidents are well known to the funding agencies, and it is difficult to see significant additional funding being recommended unless this situation is corrected.

3. RECOMMENDATIONS

3.1 Project Management

Mr. Arfan must devote his time on a top priority basis to the project management. He should keep regular activity charts (if not Gantt charts) and hold at least weekly meetings monitoring all activity.

It is essential that he keeps the Executive Director, General Burney and Mr. Zafir Ali all informed about any slippage in timing and any item that need to be moved by a higher authority. The weekly meetings should include General Burney, Mr. Zafir Ali, the senior future staff members and those responsible for the trades (Electricity, plumbing, steam, painting etc.) as required to keep the information flow and more important the activity flow free of obstacles.

It is recommended that the PM keeps MIB informed on a daily basis.

To function efficiently, the PM should have access to a clerk/typist with office facilities and the necessary transportation.

3.3 External Services

It is recommended that USAID and Dr. Ghafoor separately or jointly inform the appropriate government authorities of the costly and unacceptable delays which have occurred, not only with respect to the boiler situation, but also in relation to the indefensible delays in repairs to the polio and rabies facilities.

The addition of an emergency steam line from the other end of the building should be completed, but not relied upon for long-term use.

3.4 Internal Services

The "Review of Mechanical and Electrical Drawings ----etc" by J.E. Keeling should be fully utilized in the checking of final blueprint and as work progresses.

3.5 Internal Training.

See Appendix 4.

3.6 External Training

3.6.1 Training at RIVM, Holland.

There is reason to question the long term commitment of Mrs. Mumtaz. She is quite familiar with TT production, but it may be wasteful to invest in her training at RIVM if more committed personnel, such as Mrs. Farida and Mr. Hussein could go and gain the necessary knowledge.

Again, whoever is elected to go should be fully informed on both the microbiology and technology with respect to TT production and have participated actively in the penultimate edition of the SOP's.

3.6.2. Training at NBS, N.J., U.S.A.

In view of the information from NBS the necessity of further training for Mr. Arfan should be reviewed. It would of course be very useful if Mr. Baig could get outside training, but the fact that no comparable equipment is available at NBS makes it rather meaningless.

It would, however, be most useful if NBS could send a trainer/technician to Islamabad when the fermenter is in place, and that should be negotiated with the company. I will keep in contact with NBS and see what they suggest and are willing to do.

3.7, 3.8 and 3.9

No further recommendations at this time.

3.10 Compatibility Testing.

I repeat the recommendations from Report No. 8:

"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 include 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."

Serious production delays can be encountered later if these items are not thoroughly investigated and documented now. Stability tests should be undertaken both with currently available TT, with the TT concentrated (when diluted) 'bought in and, eventually, with the product produced in the new fermenter.

Note: This is not merely a recommendation. It must be done properly as soon as possible.

3.12 Production Procedures and SOP's

It bears repeating that the SOP's must be a collaborative effort between the supervisory staff and the operating staff. The procedures relating to cleaning, washing and sterilizing, people and material flows etc. must be written both in English and in Urdu, and both understood and approved by those who will be doing the job. Without a sense of ownership in the procedures, there is little guarantee of compliance with them.

3.13 Staffing

It is recommended that selection of potential staff be done as soon as possible with backup personnel identified also. That way, when the various operation starts and the training programmes commence, it will be possible quickly to assemble the required teams.

Serious consideration must be given to the medium and long term commitment of current and potential staff members. Many different circumstances can result in people leaving their job, therefore the stability of the human resources should be optimized through careful selection including thorough interviews.

Potential career paths should be made clear, but of course not promised.

ADDITIONAL RECOMMENDATIONS:

During a meeting with Dr. Ghafoor, a number of recommendations were made with respect to the success and welfare of the TT project within the NIH organization. These recommendations are summarized in Appendix 6.

APPENDICES

APPENDIX 1.

ACTIVITY LOG for VISIT JUNE 1990 and RELATED ACTIVITIES

TRAVEL & ACTIVITIES IN ISALAMABAD

<u>DATE</u>	<u>No of DAYS</u>	<u>ACTIVITIES</u>
June 17/20	2	Travelling to Islamabad (Stop in Holland)
June 19	1.5	Meeting at RIVM
June 21	1	Meeting at NIH
June 23	1	Meetings with Mr. Zafir Ali, Dr. Ghafoor, Dr. Akram (EPI) and Gen. Burney. Reviewing progress at TT building.
June 24	1	Working meetings at NIH
June 25	1	a.m. NIH meetings. Review Rabies Vacc. Prod.. p.m. Meeting, USAID
June 26	1	a.m. Review Measles Vacc. Prod. p.m. USAID
June 27	1	Working at NIH
June 28 NIH	1	a.m. Debriefing at USAID and at with Drs. Ghafoor, Goldman and Rushna p.m. Mrs. Louise Marchand, Development, Canadian High Commission
June 30	1	Working meeting with General Burney
July 1	1	a.m. Meeting at UNICEF, Mr. Kunio Waki p.m. Wrap-up at NIH
July 2/3	2	Return travel

RELATED ACTIVITIES PERFORMED IN CANADA AND USA

June 1	1	Meeting at UNICEF, New York with Mr. John Gilmartin, Procurement.
July	2.5	Report writing, discussions with CLL, NBS

Total Days: 18

APPENDIX 2

PLANNED FUTURE ACTIVITIES

(Subject to Approval by USAID)

Sept 9 or 13 Arriving Islamabad

Sept 24* Leaving Islamabad

* This is the latest date I can leave Islamabad and be home and complete my report etc. prior to September 30.

Activities to be planned for the September visit (in addition to the review of progress, consultations with staff and management and updating of schedules:

1. GMP course
2. Planning for the future
3. Firming up of management structure
4. Ensuring information source for after September 30.

Any additional activities related to the TT project at NIH, including the attempts to locate additional funding, must be based requests from NIH, GOP or USAID.

APPENDIX 3

KEY TARGET DATES

(Please, note: The dates below are best estimates)

Plant Construction

-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

-Installed and accepted	November 30
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Production Equipment

-(i) USAID Purchases	
-Installed and validated	May 1991
-(ii) NIH Purchases	
Received in Islamabad	December 31
-Installed and validated	April 1991

Validation of Total System

-Completed	May 1991
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SOPs and Protocol Forms

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

(Appendix 3 continued)

Bulk Toxoid

- Ordered	July 20, 1990
- Delivered and cleared	Sep. 15, 1990

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	December 31
- <u>Full Scale Basic Production Starts</u>		<u>February 1992</u>

Note: These dates are based on the current status, experience from other biologics manufacturers and observations at NIH of delays and "glitches" likely to occur.

The Project Manager should update this time table together with his Gantt chart and keep the senior management of NIH as well as the consultants informed.

APPENDIX 4

INTERNAL TRAINING

(The following programme is based on a proposal prepared by Mr. Arfan Mahmood. This draft proposal is returned to Mr. Arfan herewith.)

IN-HOUSE TRAINING PROGRAMME

Phase 1, Theoretical.

A. Basic Outline

1. Introduction to Clostridium Tetani, tetanus toxoid and the disease.
 - General Introduction
 - Epidemiology
 - Action of the bacillus
 - Concept of "toxoid" and immune mechanism
2. Importance of Quality Assurance, Safety and Individual Responsibility

Suggested "Faculty"

Opening address: Executive Director
Epidemiology: General Burney
Bacteriology: Mr. Zafir Ali
QA, Safety etc: Executive Director or MIB

Attendees: All staff

Time: 2 hours for one day. To be repeated when a significant complement of new staff is engaged.

B. Processing

- General process outline
- Growth and passaging of C. tetani
- Fermentation
- Detoxification
- Purification
- Dilution
- Filling and packaging
- In-process tests including criteria

During this part, each step to be discussed in outline, then in detail. The lecturer to assure that each member has understood and appreciated the importance of the details discussed.

- Concepts of G.M.P. incl. Quality Assurance, Quality Control Test criteria, Standard Operating Procedures, Record Keeping.

Suggested Faculty:

Technical Information: Mr. Zafir Ali
Mrs Mumtaz Begum
and/or Mrs. Farida
Mr. Arfan Mahmood

G.M.P. etc: JCWW in September

Attendees: All technical staff

Time: Four to five days @ 2 hours, including question and answer period.

Phase 2, Practical.

The practical training to be undertaken by all senior technical personnel. The training periods to be set according to requirements, and should not be discontinued until Mr. Zafir Ali, Mr. Arfan Mahmood and Mrs. Mumtaz Begum (Mrs. Farida) in consultation with MIB, are satisfied that the technicians can perform their tasks without errors, efficiently and with complete comprehension of the activity.

APPENDIX 5

MEETING AT RIVM

On Tuesday June 19 JCWW met at the Rijksinstituut voor Volksgezondheid en Milieuhygiene in Bilthoven, The Netherlands.

Present:

Mr. Theo Evers, Deputy Head, Bureau of International Cooperation and
Dr. J.T. Hendriks, Bureau for International Cooperation.

About RIVM:

The Director General is: Mr. van Noort
The Scientific Director: Professor Sannngster

RIVM originally turned down the request for training for these reason:

1. RIVM very busy with other items (e.g. China project)
2. Timing bad
3. Prefer to teach groups with members from several nations
4. The NIH, Islamabad request covered DPT..... too much !
5. NIH engaged in too many other projects.

There was a more favourable view on the situation now, but training could not start till after October 1, as the Tetanus Toxoid facility is closed till then for renovation.

They will consider a maximum of two trainees.

There should be a good understanding of English, and the trainees should be technically well prepared.

The names of the proposed trainees should be given as well as a minor curriculum vitae so the RIVM group can assess the learning level.

Application for the training as well as potential financial assistance for travel, lodging and board should be made from the GOP via the Embassy of the Netherlands in Islamabad. They will channel the requests to the appropriate agencies in Holland, i.e. RIVM and the Dutch Agency for International Development.

APPENDIX 6

ADDITIONAL RECOMMENDATIONS

At a meeting on Thursday June 28 JCW met with Dr. Ghafoor, Dr. Heather Goldman and Dr. Rushna Ravji in the Executive Director's office for a debriefing.

The following recommendations were made:

1. Continuing Consultancy by Gen. Burney.

It would be very beneficial to the NIH if the Institute were to retain Major General Burney's services as consultant after September 30, when USAID has completed their obligations to the project.

The General's scientific knowledge, his international reputation as well as his familiarity with the NIH and "how to get things done" would make his contributions in terms of coordination of special projects and government relations over the next several years invaluable.

2. National Control Authority.

Pakistan needs a National Control Authority with respect to biologics which will function independently of the producing institutes.

There is an increasing stress at the WHO on the importance of the National Control Authority, the National Control Laboratory. Guidelines have recently been re-drafted regarding the functions and responsibility of the NCA and NCL, the authority of these organizations. It is essential that they possess the necessary skills and competence in order to function effectively and be recognized beyond the national borders.

There have been recommendations made regarding the collaborative efforts on training and sharing of expertise between developing countries.

3. Good Manufacturing Practices and Quality Assurance

These concepts need much strengthening at the NIH. It is important that the fundamentals of joint and individual responsibility be fully understood and appreciated at all levels. The fact that unsafe, poor or unhygienic practices "hurts us all" and may cause sickness and death to the people, especially children who depend on the products must be emphasized repeatedly.

Staff must be encouraged to report errors and appreciate that they can do this with impunity.

4. Personnel Matters

-The staff complement necessary to run an effective and efficient Tetanus Toxoid plant must be firmed up.

Existing "personality clashes" must be investigated and dealt with in a manner which ensures the future of the project, and also is seen as just.

Team building must be taught and encouraged. The creation and maintenance of a smoothly working team is a major asset to any project. Everyone must have a sense of pride and ownership in the project as well as a realization that his/her contribution is essential for the overall success is essential to the ultimate success.

-It would be very beneficial to the efficient technical management of the NIH biologicals production if there were a definitive division between bacterial vaccines and viral vaccines. The current head of biologicals production in general is a good bacteriologist with a sound and thorough knowledge of bacterial vaccines. His knowledge of viral vaccine is significantly less.

There is more than enough to do in the bacterial vaccine field to allow Mr. Zafir Ali to be distracted by the many general administrative duties related to all the other product. It seems to me that it is imperative to the NIH to demonstrate its continuing competence by making a complete success out of the TT project and at the same time improving the viral vaccine projects.

5. Problem Solving

It is obvious to this consultant that some projects such as Rabies and Polio have suffered greatly from interminable delays in the resolution of relatively simple problems such as a leaky roof or shortness of air filters.

The cost of these long interruptions in production are enormous compared with the cost of the required remedies.

These serious obstacles to efficient vaccine production are known to several of the international development agencies and are signalling caution. There appears to be significant reluctance to proceed with further funding until there is some evidence that these obstacles can be overcome on a consistent basis.

It is absolutely essential that the appropriate authorities review their system and priorities and ensure prompt attention to such matters.