

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

**REPORT # 10
SEPTEMBER 1990**

by

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GLOSSARY OF TERMS AND ABBREVIATIONS:

BLG	- Biologics Division of WHO
CIDA	- Canadian International Development Agency
ED	- Executive Director (Dr. Abdul Ghafoor)
GMP	- Good Manufacturing Practices
GOP	- Government of Pakistan
JW	- Jorgen C. W. Weber, Consultant
MIB	- Major General M.I. Burney, Consultant
NV	- 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
RR	- Dr. Rushna Ravji, USAID
TT	- Tetanus Toxoid
USAID	- United States Agency for International Development
WHO	- World Health Organization
ZA	- Mr. Zafir Ali

1. INTRODUCTION

This report covers the third and last scheduled visit by J.C.W. Weber (JW) to Islamabad.

The visit took place from Thursday, September 13 till Monday, September 24, 1990. Associated meetings in Toronto, Canada (Connaught Laboratories Ltd.), in Siena, Italy (Sclavo S.p.A.) and at the Biologics Division of WHO, Geneva, Switzerland are reported in the appendices.

During this visit most of the meetings were held together with Major General M.I. Burney (MIE) and Dr. Rushna Ravji (RR) who in collaboration have kept the project moving. The observations and recommendations in this report were in general shared by the three of us, although the way they are expressed as well as some of the concepts are the sole responsibility of JW.

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

-Mr. Zafar Ali, Chief, Bacterial Vaccine Production.

-Mr. Arfan Mahmood, Chief Engineer, (Previously designated Project Manager for the TT project)

-Mrs. Farida Muqis, Scientific Officer.

-Mrs. Mumtaz Begum, Sen. Scientific Officer (Previously designated Officer-in-Charge for the TT project.)

Mr. Akbar Baig, Asst. Engineer went to the United States for training in fermenter technology at the New Brunswick Scientific Corporation together with Mr. Arfan. (NBS did not have a model of the relevant fermenter (IF-150) in stock, but it was decided to sent both Mr. Arfan and Mr. Akbar anyway). Regrettably, Mr. Akbar had failed to return at the time of JW's departure from Islamabad.

Activities included several visits to the building site, meetings with the Public Works Department, a seminar on Good Manufacturing Practices and Quality Assurance (please, see Appendix 4) meetings with Colonel Akram of EPI and with CIDA.

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

A briefing meeting was held with Drs. Heather Goldman and Rushna Ravji of USAID, while Ms. Anne Aarnes with Dr. Rushna attended the final debriefing meeting on September 23.

OBJECTIVES

The principal objectives of this trip were basically the same as for previous visits:

(1) Review and assess the following items:

- Status of building, facilities and services.
- 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.
- Find a suitable training facility for the scientific staff.
- Edit and re-write the Standard Operating Procedures for the production and QC
- The formulation of realistic and workable job descriptions

(3) Make recommendations regarding:

- Issues under (1) and (2) above.
- The potential purchase of additional Tetanus Toxoid concentrate to cover the hiatus in supply which can be expected to occur between the time the first shipment from Sclavo is exhausted and the time the TT facility is fully operative and capable of satisfying the EPI requirements.
- Continuity of the project after Sept.30, 1990.
- The National Control Authority and the National Control Laboratory.
- Training programmes.
- Staff Organization

(4) -Presenting a seminar on the "Concepts and Philosophy of Good Manufacturing Practices" (Appendix 4)

2. CURRENT STATUS

2.1 Project Management by NIH

The appointed project manager, Mr. Arfan Mahmood, had again failed to fulfil his key functions. The situation I found in this respect had not improved since my June visit, but rather deteriorated. It appeared that most of Mr. Arfan's time had been spent first in preparation for his trip and then travelling on a combined training trip and vacation.

During my visit this time, Mr. Arfan was most of the time too busy with other responsibilities *.

The upkeep of the Gantt chart, an essential part of effective project management, was left entirely in MIB's hands, as were most of the other responsibilities of the Project Manager.

The periodic reporting to JW, as had been requested and agreed to, never took place. Hence much time during the first couple of days of this visit were spent updating myself on items which could well have been reported in advance.

* E.g. liquid nitrogen production. One was left to wonder who looked after that facility while he was travelling abroad.

2.2 Building Erection

This item is generally on schedule now. The outstanding items are listed in Appendix 3 (Key Target Dates).

2.3 External services

The physical situation with respect to boilers and stand-by generators had still not improved, and the scheduled activity for July had not occurred.

However, at a meeting with the PWD on September 18 chaired by the ED and attended by a number of senior staff members as well as by JW, assurances were given regarding the expeditious resolution of the problems. (The minutes of the meeting, as prepared by Mr. Zafir Ali, are attached as Appendix 5).

2.4 Internal Services.

Significant progress had taken place.

There was some thought that a fourth air conditioning unit would be required to achieve a degree of pressure differential between the potentially (though not likely in aerosol form) spore containing area and the next stage of processing (where the bacteria would have been filtered out). The resolution to this (a simple baffle in the supply line) had been given by JW in June, but was not finally settled till a meeting with the AC contractor on Sept 15.

The placement of equipment in the Washing & Sterilizing Area and the need for proper drainage were still items that needed to be settled. It appeared that REB must have been misunderstood with respect to the use of floor drains with the result that no allowances were made for drains in this area, not even for drainage from the autoclaves. The PM's concept of how an autoclave functioned was rather bizarre.

2.5 Internal Training

The internal training programme was still at the planning stage.

2.6 External Training

-2.6.1. Training in Tetanus Production.

-2.6.1.1 RIVM, Bilthoven, The Netherlands

In spite of numerous telephone discussions this plan became increasingly unlikely due to, I believe, RIVM's pre-occupation with some major technology transfer projects.

-2.6.1.2 Connaught Laboratories Ltd., Toronto, Canada

Meetings with several members of CLL indicated that at this time Connaught was not interested in technology transfer, nor in a position to offer training. This may be related to the recent purchase of the company by Institut Merieux of France.

-2.6.1.3 Sclavo S.p.A. Siena, Italy

In view of the USAID purchase of TT concentrate from Sclavo it was decided to discuss training with that company. See report of JW's visit on September 11. (Appendix 6).

-2.6.3 Training at New Brunswick Scientific Corporation

As noted above Messrs. Arfan Mahmood and Akbar Baig had spent some time at NBS. Akbar Baig had not yet returned. No report on the visit was available.

2.7 Fermenter

Still awaiting installation.

2.8. Ancillary Equipment funded by USAID.

I have been informed that all the USAID funded equipment either has arrived in Islamabad or is in transit from Karachi. Hence this major part of the project has met the deadline, mainly thanks to the ingenuity and efficiency of the USAID procurement section.

2.9 Tanks

As per 2.8

2.10 Production Components

-2.10.2 Compatibility Testing. Components/Equipment.

The results of the testing by the Cozzoli Company were not available.

-2.10.3 Compatibility Testing. Components/Product.

The initial data of a fairly extensive compatibility experiment were shown to JW on his arrival. The results looked promising, but additional testing (longer term) is being carried out.

-2.10.4. (Formerly 2.10.3) Tetanus Bulk Concentrate.

An order for 35 mega Lf has been issued by USAID to Sclavo S.p.A., Italy.

2.11 Computerization.

No evidence of progress was presented.

2.12 Production Procedures and SOP's.

A revised set of production SOP's was provided to JW and reviewed and edited. They were still far from adequate and the editing job was lengthy and laborious.. It appears that a full understanding of the function and importance of these documents is still lacking.

Similar to the previous set, these SOP's were still not based on "collaborative efforts", but appeared to have been authored singly by Mrs. Mumtaz with some editing by Mr. Zafir Ali. MIB had also done some editing, but this had not been followed up by the originator(s).

2.13 Staffing.

Additional staffing had been requisitioned, and a plan was presented to JW by ZA.

2.14 Overall Impression

While significant progress was seen in some areas it was evident that far too much responsibility and actual designing and planning work was left to MIB.

I do not believe it is exaggerated to say that without the General's constant vigilance the project would have ground to a halt.

The appointed PM, Mr. Arfan had not fulfilled his responsibilities and appeared to have only limited interest in doing so.

The Chief of Bacterial Vaccines, Mr. Zafir Ali, on the other hand seemed to have taken a much more active hold and interest in the project. As his specialty is the scientific/technical side of vaccine production, not the engineering side, ZA will need good engineering support staff.

It was gratifying to see that a strong representation from the Executive Director had succeeded in finally activating the PWD.

3. RECOMMENDATIONS

3.1 Project Management

Mr. Arfan Mahmood is either not interested in the position of Project Manager, or he lacks understanding of the implications of the responsibility. In either case it is this consultant's recommendation that Mr. Arfan's responsibility for the TT project is confined to working on the installation and ensuing "trouble shooting" related to the equipment, air conditioning and other engineering services within his field of expertise.

I furthermore recommend that ZA assumes the activities and responsibilities of project management himself, keeping the ED and MIB fully informed of all stages of the project and of any slippage in timing.

The formal involvement of JW as a consultant in this project after September 30 is undecided and not probable. However, in order to complete certain items which can be handled on a "long distance basis", it is requested that JW be kept regularly informed about progress via copies of Gantt chart updates as well as the pen-ultimate copies of SOP's, production protocol forms, job descriptions, labellings etc. This activity may be regarded as voluntary and will not be billed to NIH, unless the Institute specifically requests additional efforts which entails expenditure of money or requires substantial time.

Weekly meetings should be called by ZA and include MIB as well as the future officers of the department. ZA has demonstrated the ability to maintain proper minutes of meetings but this responsibility should be delegated to a senior member of his staff. I would propose Mrs. Farida.

It is essential that ZA delegates a significant quantity of his responsibility to his subordinates, and gets used to allow decision making at a lower level.

3.3 External Services

The results of the meeting with the PWD on September 15 gave reason for optimism. See ZA's minutes of the meeting (Appendix 5).

3.4 Internal Services

Recommendations were made with respect to drainage of autoclaves and general drainage of the W & S area.

The project engineer needs some updating in the use and functioning of autoclaves in order to give adequate instructions and advice with respect to the installation.

3.5 Internal Training.

In addition to the internal training programme suggested in Appendix 4 of Report No. 9, there has been some discussion of obtaining outside help for a QC course. This was discussed at WHO. Please, see Appendix 7.

3.6 External Training (Sclavo, Italy.)

The technology at Sclavo was very similar to the one to be applied at the NIH. One important item is the order in which the toxoid is processed.

It is strongly recommended (and I believe agreed by all concerned) that the training should be attended by Mr. Zafir Ali and Mrs. Farida Muqis. (Mrs. Mumtaz will soon be leaving for Norway and cannot be included in the current staff planning). Mr. Hussein's should be trained by Mrs. Farida and ZA and later, when his language skills are improved, sent to a training course.

During my visit I drafted a letter for the EI to send to Sclavo. (See Appendix 6).

If a positive reply is NOT received to this request every effort must be made to find another source of training. Please, let me know immediately so that I may make some effort to help finding an alternative.

I wish to stress that the trainees should go to Sclavo with copies of Standard Operating Procedures for both production and testing. They can then amend these as they go along and become introduced to new techniques which may improve the procedures.

3.7, 3.8 and 3.9

No further recommendations at this time.

3.10 Compatibility Testing.

I would very much appreciate seeing the final results of the ongoing testing.

Similar compatibility/stability testing need to be undertaken as soon as product is available. It must be done both with the intermediate product from Sclavo and later on again with the product produced at the new NIH plant.

This is essential as one of the means of ensuring product efficacy in the field..

As stated in the earlier report, mock runs must also 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, reviewed with MIB and kept on file by the production manager.

3.12 Production Procedures and SOP's

It is absolutely essential that the SOP,s are joint efforts and written or re-written in such a way that the operator at the stage of production or testing described fully understands it and is committed to it. Some operations may have to be written in both English and Urdu to ensure absolute comprehension. This applies to all stages of operation including washing and sterilizing of equipment, cleaning of facilities and the "traffic rules" within and between the restricted areas.

3.13 Staffing

While active recruiting and interviewing was being carried out by ZA, the only committed staff members for the new TT plant were ZA himself, Mrs. Farida, and Mr. Akbar (if he has returned).

It is clear that the Institute is suffering from "divided loyalty" by the staff due to the fact that most staff members must have an additional job to "make ends meet". This would, in the long run, seem a very costly way of running an enterprise. The short working day (allowing for the workers to rush off to the next job) has a deleterious effect on the continuity and commitment so essential to a biological manufacturing facility. I recommend that efforts be made to persuade the GOP, and especially the Ministry of Health, that a vaccine manufacturing unit is very different from most if not all other activities under the Government. It requires highly skilled, dedicated workers at all levels in order to follow the exacting requirements needed to make a safe and efficacious product.

Vaccine manufacturing cannot be a part time job. If treated as such, severe product losses with concomitant prohibitive costs become inevitable.

It is further recommended that every effort be made to add job enrichment and incentives in the form of training, promotion potentials and other rewards, e.g. bonus, educational travel etc.

The goals of the NIH to become an internationally acclaimed institute producing exportable products cannot be realised without significant reorganization as well as changes in staffing policies.

The TR plant could be quite successful if Mr. Zafir Ali and Mrs. Farida are given the necessary support staff as well as financial backing and ongoing training and updating in the relevant technologies.

APPENDICES

APPENDIX 1.

ACTIVITY LOG for VISIT SEPTEMBER 1990
and RELATED ACTIVITIES

TRAVEL & ACTIVITIES IN ISALAMABAD

<u>DATE</u>	<u>No of DAYS</u>	<u>KEY ACTIVITIES</u>
Sept.09 & 12	2	Travelling to Islamabad (Stop in Italy)
Sept.10	1	Travelling Rome to Siena
Sept.11	1	Meeting at Sclavo, Siena
Sept.13	1	Meeting at NIH. (RR, MIB, ZA)
Sept.14	0	Review and editing of SOP,s.
Sept.15	1	First facility review, Working meetings.
Sept.16	1	a.m. NIH. Review of Gantt Chart. p.m. USAID, Drs. Rushna and Goldman
Sept.17	1	Review SOP,s with TT staff. Revise plans for W & S area with MIB, ZA and Mr. Rashid from MV area.
Sept.18	1	Meeting. PWD (with ED)
Sept.19	1	Presenting GMP Seminar to NIH Staff Meeting with Dr. Ghafoor
Sept.20	1	Working meeting at NIH
Sept.21	0	Holiday
Sept.22	1	Inspection of Bldg. Site with ZA Debriefing Mtg. with Dr. Ghafoor
Sept.23	1	Final review at NIH Debriefing Ms. Anne H. Aarness
Sept.24 & Oct. 3	2	Return travel
Sept.25 till Oct. 1	0	Personal business
Oct. 2	1	Meeting at WHO, Geneva

RELATED ACTIVITIES PERFORMED IN CANADA

Sept.4	1	Meeting at Connaught Laboratories
Oct. 12 & 13	2	Report writing

Total Days: 19

APPENDIX 2

PLANNED FUTURE ACTIVITIES

(Not part of USAID contract, but related to future funding of the NIH TT project as required)

-Meeting with Anne Woodbridge, CIDA, Ottawa, Canada

-Additional discussions with UNICEF

-Possible discussion with UNDP

In order to make these activities more effective, I would need a realistic estimate of 1991 requirements of hard currency separated into:

1. Requirements for additional concentrate
2. Other requirements to ensure the completion and the efficient operation of the TT facility.

For this purpose a letter from Dr. Ghafoor outlining this information when it becomes available would be most helpful before I make further approaches to these and possibly other funding agencies. Some assurance that some of the recommendations made with respect to the TT facility are being/will be introduced would be helpful in future discussions.

Please note:

The most effective route of approach is letter(s) to the respective agencies. Please, furnish copy to me if you wish me to attempt any intervention.

APPENDIX 3

KEY TARGET DATES

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	Oct. 31, 1990
-Internal installation	Nov. 15
-Internal services validated	Feb. 13, 1991

Heating and Air handling

-Installed and accepted	December 30
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Production Equipment

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

Validation of Total System

-Completed	May 1991
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SOPs and Protocol Forms

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

(Appendix 3 continued)

Bulk Toxoid

-Ordered	July 20, 1990
-Delivered and cleared	Sep. 30,

Other Items

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

Production

-From bulk toxoid	Started	May 31, 1991
	Completed	Oct. 31
-Basic Production, 3 Qualifying lots,	Start	July 1
	Finish	December 31
	Tested	Feb. 1992

-Full Scale Basic Production Starts March 1992

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

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

APPENDIX 4

INTERNAL TRAINING incl. G.M.P. SEMINAR

The training programme outlined in Appendix 4 of Report No. 9 has been amended below to take into consideration staff changes and to stress certain aspects:

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

The lecturer must ensure that each member has understood and appreciated the importance of the details discussed.

Suggested Faculty: Mr. Zafir Ali
Mrs. Farida

Attendees: All technical staff

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

Please, note:

The Question and Answer period is a very essential part of the lecture in order to achieve the highest possible level of participation.

Phase 2, Practical.

The practical training to be undertaken by all senior technical personnel. While this kind of training needs to be particularly intensive during the first working period for any new staff members, it must be an ongoing activity which should never be considered fully completed.

GMP SEMINAR

A seminar on Good Manufacturing Practices and related subjects (i.e. Quality Assurance) was conducted by JW on September 19.

It was well attended by about 35 staff members.

Following a reading from the holy Koran the Executive Director introduced the speaker and the subject.

The seminar was basically conducted as a discussion, introducing various aspects of GMP and bringing in the relevance to the daily routines at NIH. Several members of the audience participated actively leading to a lively discussion.

Relevant reading material and a QA/GMP check list was handed out to the participants.

General Burney closed the meeting.

It is recommended that appropriate senior staff members conduct such discussion seminars from time to time in order to maintain the focus on GMP and in order to allow new queries and subjects to surface. An additional advantage is the "cross fertilization" between the various production areas as well as Quality Control.

APPENDIX 5

**MINUTES OF MEETING WITH PUBLIC WORKS
DEPARTMENT** as prepared by
Mr. Zafir Ali.

The part of these minutes relevant to the Tetanus Toxoid Facility are presented on the following two pages.

NO.F.1-18/BPD
NATIONAL INSTITUTE OF HEALTH
(Biological Production Division)

Islamabad, the 19th Sept, 1990.

Subject:-MINUTES OF THE MEETING

A meeting was held in the conference room of NIH, Islamabad, on 18-9-90 at 11.30 A.M. with the Officers of Pak. PWD, (E/M), under the Chairmanship of Dr. Abdul Ghafoor Executive Director, NIH, to discuss the pending work of various projects and maintenance work of of Pak.PWD (E/M). The following officers attended the meeting:-

1. Maj. Gen.(Retd.)M.I. Burney, USAID Consultant
2. Mr. Zafar Ali, Chief, BPD.
3. Mr. Zair Khan, PSO, Q.C. Department.
4. Mr. Arfan Mahmood, SSO/CE, BPD
5. Mr. A.Q. Mohmand, SSO, DC&RD.
6. Mr. Mohammad Riaz, Superintending Engineer, Pak.PWD,
7. Mr. Zahid Pervaiz, Executive Engineer, Pak.PWD,
8. Mr. Mohammad Naem, Asstt. XEN,
9. Mr. Mohammad Yunas Khan, Asstt. Engineer & 4 members of Staff.
10. Mr. Khalid Mansoor, Sr. Accountant.
11. Mr. Tariq of M/s Freezol, Islamabad.

The Chairman (Dr. Abdul Ghafoor) started the meeting with his remarks on the progress of work, discussed in the last meeting with the Chief Engineer and Director General Works, regarding Airconditioning, Steam Supply and Electrification etc. of various On-going Projects and General maintenance of the Institute.

1) TETANUS TOXOID PROJECT

A) On query by the Chairman, Gen. M.I. Burney and Mr.σ.C.W. Weber(USAID foreign Consultant), the Superintending Engineer (Mr. Riaz) assured that the work on Boilers & Stand-by Generator will be started very soon and will be completed by 20th October, 1990. As regards the main Electricity

: 2 :

supply by commissioning a Transformer, the S.E. assured the house that the same will also be completed between 5th to 10th October, 1990.

B) AIRCONDITIONING

The ducting work of A/C in the T.T. Project is in progress. The main A/C Unit will be provided by the Contractor not later than 20th October, 1990. The S.E. stated that 2 units are already available, the third of 20 ton unit is to be made available for which he instructed Mr. Tariq to act accordingly. Further, the Contractor informed that he will make search for this 3rd Unit and will inform the Executive Director, NIH, regarding its availability by 20th Sept, 1990, after confirming from various authentic sources.

C) COLD ROOM AND INCUBATOR ROOMS:

The S.E.(E/M), Pak. PWD, stated that tender has been called for. The lowest bidder has quoted a very low price for the completion of the job and it is doubt that the Contractor will be able to carry out the job with good quality material. Therefore, the S.E. is trying to find out the genuineness of the firm and after assurance of the quality of work, the contractor will be awarded the contract at an early date and it will be completed by the end of December, 1990.

APPENDIX 6

MEETING AT SCLAVO S.p.A., Siena, Italy

On my way to Islamabad I stopped in Italy to visit Sclavo in Siena.

Sclavo is the largest biological company in Italy and one of the major, respected vaccine makers in the world.

I met with the following members of Sclavo's management:

-Dr. Tito R. Ubertini, Technical Director, Responsible Head of Establishment

-Dr. Riccardo Vanni, Director, Biopharmaceutical Division

-Dr. Francesco Pascucci, International Marketing and Sales Director

Sclavo had very recently been sold to an Italian blood products manufacturer: Marcucci - Guelfo. The policies to be introduced by the new senior management had not been fully clarified yet, and some uncertainty was evident.

I was taken through the Production, Quality Control and Filling, Packaging and Warehouse area (the latter being situated a few kilometres outside Siena.) The facilities were large and modern, and the technology the very latest. I was very impressed with the new Bacterial Vaccines facility and especially the Tetanus Toxoid area. Sclavo appears to have a stable, dedicated staff of senior scientists and technologists.

(It is worth noting that I had my impressions confirmed during my later visit to WHO)

I requested an arrangement with Sclavo for the training of two NIH scientists (Mr. Zafir Ali and Mrs. Farida) at Sclavo for a period of about two weeks. This was received very positively, and Dr. Vanni asked for a letter from the NIH or GOP outlining the request. Such a letter was drafted for Dr. Ghafoor, who edited it and had it mailed on or about the 24th of September.

The draft as prepared by JW is shown below:

DRAFT

National Institute of Health
Islamabad, Pakistan

September 22, 1990

Dr. Riccardo Vanni
Director
Bio-Pharmaceutical Division
Sclavo S.p.A.
Via Fiorentina, 1
53100 Siena
Italy

Dear Dr. Vanni

Following your discussion with Mr. J.C.W. Weber of Canada (currently consultant to USAID and NIH regarding our Tetanus Toxoid project) I am writing you requesting permission to send two of my senior staff members for a brief training period (3 - 4 weeks) to your company.

Mr. Weber reported to us the results of his visit and discussions.

He informed us that he had found Sclavo's facilities of the highest technical standards with a devotion towards progress and the highest standards of quality.

The two individuals will be responsible for the production of Tetanus Toxoid for use in the prevention of Tetanus Neonatorum, a major cause of infant mortality in rural Pakistan.

The tetanus toxoid facility, which is nearing its completion at the NIH campus here in Islamabad, has been largely financed through the support of the United States Agency for International Development (USAID).

By way of explanation: the 35 million Lf of Tetanus Toxoid Concentrated purchased on our behalf by USAID will be diluted, filled and packaged in the new plant while the basic fermentation facility is being completed, validated and qualifying lots prepared for the approval by the authorities. It is of the greatest importance to the tetanus portion of the EPI programme in Pakistan that there is no significant interruption in supply.

The two persons we have selected for training are:

- Mr. Zafir Ali, M.Sc.(Microbiology), Senior Scientist and Chief, Bacterial Vaccines

and

- Mrs. Farida Muqis, M.Sc.(Bacteriology), Scientific Officer.

(Draft letter continued)

While Mr. Zafir Ali will have the overall responsibility for the toxoid production, it is anticipated that Mrs. Farida Muqis will oversee the day to day running of the plant.

The subjects we would ask you to cover with the trainees are the production (fermenter technology), filling, and testing of Tetanus Toxoid as well as the essential aspects of Quality Assurance and GMP.

We should note that Mr. Zafir Ali has many years of experience with Tetanus Toxoid, while Mrs. Farida's main activities have been with other bacterial vaccines.

The best time for the training to take place would, from NIH's point of view, be the beginning of November, 1990.

The travel and living expenses for the two trainees would be covered from here, but we would sincerely appreciate it if you would make reservations for accommodation in reasonably inexpensive facilities.

It would be most useful if they had access to a small kitchen.*

We very much appreciate your kind consideration of this for us very crucial matter, and look very much forward to hearing from you.

Yours sincerely

Abdul Ghafoor
Executive Director

* Please, let us know the approximate cost of accommodation and living expenses in order for us to budget for the trips.

P.S. For the sake of expedience we would request that you kindly telefax your response to U.S.A.I.D., Islamabad c/o Dr. Rushna Ravji. (Fax No: 92-51-824086

-----End of Draft Letter-----

NOTE:

I repeat the importance of the two trainees bringing pen-ultimate drafts of SOP,s in order to have a good review with the technical personnel at Sclavo and with the option to make final changes at this time based on new technology and techniques encountered.

APPENDIX 7

MEETING AT WHO, GENEVA

I visited Geneva to discuss the possibility of a training course in Quality Control Procedures at the NIH in Islamabad and an appropriate laboratory for the testing of the initial lots of TT produced in the new facility.

I met with the following persons:

- Dr. David Magrath, Chief, Biologics
- Dr. Julie Milstien, Scientist, Biologics and EPI
- Dr. Francois Tasse, Scientist, EPI

1. Training course

WHO normally only gives regional training courses, e.g. there will be a training course in polio Q.C. for the Eastern Mediterranean Regional Office (EMRO) in Cairo soon. NIH is entitled to send attenders to this course.

Dr. Milstien is planning a visit to Islamabad before the end of the year. I have asked her to contact the NIH in respect of on site training.

Dr. Milstien has been very involved in WHO training, specifically as related to EPI and diagnostic procedures.

NIH should also approach WHO with a request routed through EMRO.

Also: The Japanese through JAICA have donated much money to the establishment of QC facilities and procedures, (including at the Pakistan NIH, of course). NIH could approach JAICA directly or via Western Pacific Region of WHO in Manila (WPRO) with a request for additional support.

In conclusion: Dr. Magrath is now aware of and sympathetic to the problem, and will do his best to facilitate matters as they are referred to him.

2. Testing Laboratory for Final Tetanus Toxoid.

It was suggested that Sclavo be asked to perform the back-up control testing, especially in view of the fact that the initial TT is made from their concentrate.

An alternate testing laboratory is RIVM. Their facility is recognized by WHO as a collaborative laboratory.

I would recommend that both approaches be followed. While test results generally vary a little between laboratories, it would give some additional assurance to the NIH while also maintaining a dialogue with RIVM.

Please note: Dr. Magrath requested a copy of this report. It will be forwarded to him simultaneously with the copies to Islamabad.

APPENDIX 8

ADDITIONAL RECOMMENDATIONS

A number of recommendations were made under this heading in Report No. 9. Two of these are repeated below for emphasis.

1. 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.

2. 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.

APPENDIX 9:

3. Quality Control

It is recommended that a significant reorganization of the central Quality Control department takes place at this time, while the new facility is being completed to ensure that all necessary disciplines and techniques are available, that the QC department is entirely separate from the production areas and able to render both a service and a verdict on the product.

While a central QC departments can render a valuable service by doing in-process testing for the production areas, the production areas must never be responsible for their own final bulk or final container testing.

The concept of QC and QA is the subject of a separate letter to the ED.