PN-ABC-014
ISN 60207

Resources for Child Health
REACH

JSI A John Snow, Inc. project

Proposed Production of Tetanus Toxoid
for Neonatorum use at National Institute of Health

Islamabad, Pakistan

April 12, 1987

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AID Contract No: DPE-5927-C-00-5068-00

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EXECUTIVE SUMMARY

1. The Report deals with the National Institute of Health's (NIH) request for USAID to fund the purchase of a 150 litre fermentor for production of Tetanus Toxoid for neonatorum use (T.T).

2. The potential maximum annual demand of T.T. was estimated at 22,000.000 (22,000K) doses annually for 1987, '88', '89 and '90 and 6.000 K in 1991 and onwards.

3. It is recommended that local basic production of T.T. be commenced as soon as possible.

4. N.I.H. currently have a small production of T.T. in outmoded facilities, using outmoded equipment and a technology which requires upgrading.

5. The Rijks Instituut Voor vulksgezondheid (RIV) in the Netherlands likely will transfer technology and provide equipment to N.I.H. for productions of Diptheria Toxoid, Tetanus Toxoid and Pertussis vaccine. This plant however is unlikely to be in production until mid 1991.

6. N.I.H. have fermentation experience using a 150 litre fermentor.

7. It has been calculated that the maximum annual production capacity using a 150 litre fermentor is 20.000 K doses of T.T. (10 LF/dose).

8. An overview is provided of the major requirements for large scale T.T. production.

9. It is considered that by commencing separate basic production of T.T. soonest, two years can be saved, rather than await the, as yet not confirmed, Dutch assistance.

10. The Consultant recommends that N.I.H. be informed that USAID is prepared to assist in establishment of basic T.T. production by providing a fermentor and selected other equipment, subject to N.I.H. developing an integrated Project Proposal.

11. The make-up of such a Project Proposal is outlined.

12. A methodology for interim supply of T.T. is outlined, employing material from the RIV if possible combined with product to be obtained from UNICEF.

1. Subject:

- N.I.H. Pakistan's request to USAID to fund the purchase of a 150 litre New Brunswick fermentor for the production of Tetanus Toxoid. (T.T.)

2. POTENTIAL DEMAND FOR TETANUS TOXOID NEONATORUM

- According to W.H.O. (Dr. Witt) not less than 25% of the deaths in the 0-1 year of age group in Pakistan are still attributable to neonatal tetanus.
- This is in line with the fact that T.T. coverage is still low in comparison with other antigens.
- The current Pakistan T.T. neonatorum project (Interprovincial Workshop - 1987) aims at coverage of all pregnant women and married women of child-bearing age.
- Based on the above, the following maximum quantities of T.T. will be required:
  * 1987;'88,'89,'90 - 22,000 K doses annually
  * 1991 onwards - 6,000 K doses annually

  (for basis of calculations see Appendix I)

3. POTENTIAL WAYS OF SUPPLYING T.T.

- The T.T. either can be imported, produced locally or a combination of both.
- Due to the continually increasing world-wide demand of T.T. (either singly or in combination with diphtheria toxoid and/or pertussis vaccine), coupled with the few remaining manufacturers with export capacity, continuous reliance on imports is not advocated.

- In view of N.I.H.'s growing experience in vaccine production, and the size of Pakistan's population, it is recommended that local basic production be commenced as soon as possible with interim T.T. imports.

4. CURRENT PRODUCTION OF T.T. AT N.I.H.

- Presently N.I.H. manufactures T.T. in 5 litre glass flasks using a technology which is outmoded.
- The annual production is approximately 1,000 K doses per annum (at 15 Lf/dose).
- It is unknown whether the quality of this T.T. meets W.H.O. specifications (the Consultant has recommended that N.I.H. arrange with W.H.O. appropriate testing to determine compliance.)
- The output is sold to the Armed Forces and to Government clinics. It is not used in the E.P.I.
- The product is prepared using the Copenhagen 401A strain and a modification of the Dutch composition of growth media.
- The glass flask method does not lend itself readily to large-scale production.
- The production facilities are outmoded, do not meet current Good Manufacturing Code standards and are small.

- The equipment is very severely outdated.
- The staff comprises 1 Officer in Charge; 1 technician for media preparation; 1 technician for harvesting and decalcification and 2 lab. attendants for washing and sterilizing.
- The product is filled, labelled and packaged outside the T.T. poduction facility.

5. POTENTIAL PRODUCTION OF T.T., DIPTHERIA TOXOID AND PERTUSSIS VACCINE USING ASSISTANCE BY THE GOVERNMENT OF THE NETHERLANDS

- The Consultant visited the Rijks Institute voor Volksgezondhia - Bilthoven (RIV) and met also with officials of the AID organization of the Netherlands Ministry of Foreign Affairs.
- A report of this visit can be found in Appendix II.
- No definitive date for commencement of the Dutch Project could be ascertained.

6. FERMENTATION EXPERIENCE AT N.I.H.

- N.I.H. currently run two fermentors; one with a capacity of 16 litres (experimental size) made by New Brunswick Company and purchased by N.I.H. and one New Brunswick 150 litre fermentor donated by U.S.A.I.D.
- The latter fermentor is used for cultivation of Cholera vaccine, Typhoid vaccine and Paratyphoid vaccine A & B.
- The two fermentors are well maintained and well operated.
- The 150 litre fermentor cannot be used for T.T., unless it is transferred to a facility dedicated to T.T. production only.
- Such a move would deprive N.I.H. of Cholera, Typhoid and Paratyphoid Vaccines production capacity.

7. ANNUAL PRODUCTION CAPACITY FOR T.T. USING A 150-LITRE FERMENTOR

- It has been calculated that a 150-litre fermentor should give N.I.H. a maximum annual capacity of 20,000 K final doses of T.T. with a potency of 10 Lf/doses (W.H.O. standard).
- Details of the calculation can be found in Appendix III.

8. MAJOR REQUIREMENTS FOR LARGE SCALE T.T. PRODUCTION

- Dedicated storage facilities for the tetanus culture.
- Washing and sterilizing facilities
- Water treatment plant
- Fermentor
- Incubators
- Ultra-Filters
- Bulk Toxoid storage facilities
- Bulk storage tanks
- Ampoule washing equipment
- Filling equipment
- Labelling equipment
- Laminar flow hoods
- Storage facilities for final products
- An isolated facility with appropriate interior finishes, and HEPA filtered air in specified areas.

9. COMMENTS ON N.I.H.'S REQUEST FOR A FERMENTOR

- It is extremly unlikely that basic production of T.T. from the Dutch project will commence much before mid 1991.
- By commencing separate basic production of T.T. it is estimated that approximately 2 years can be saved. (see Appendix IV).
- However, as will be noted from the above, provision of a fermentor alone will not provide the required T.T.
- Emphasis should be laid on the need for the final product to conform to W.H.O. specifications (a requirement in use of the vaccine in the EPI).

- N.I.H. have the ability to manufacture large quantities of T.T., although it is deemed advisable that additional training be obtained (e.g. from RIV).
- Staff complement has to be increased along the lines outlined in Appendix V.

10. CONSULTANT'S BASIC RECOMMENDATION

- It is recommended that N.I.H. be informed that USAID is prepared to assist in the establishment of basic T.T. productions by providing a fermentor as well as some selected other equipment subject to N.I.H. developing an integrated project proposal. (see below).

11. PROJECT PROPOSAL BY N.I.H.

- Such a proposal should contain the following:

a. Building

* Location;
* Lay-out;
* Interior finishes to be used;
* Air purification schematic

b. Services

* Availability of water, electricity, steam, gas and stand-by electricity

c. Equipment

* List of major equipment (including basic specifications) with an indication which equipment will be purchased by N.I.H. itself and which is requested from USAID.

d. Project Execution Time-Frame

* Major activities with a time-frame against each.

e. Proposed Staffing

* How and where additional staff training will be obtained.

- It should be noted that the Consultant has discussed each of these items already with the appropriate N.I.H. staff and has requested them to commence collection of the necessary data. Hence N.I.H. should be in a position to prepare such a proposal with little delay.

- It is recommended that the project proposal be scrutinized by an appropriate outside Consultant.

12. INTERIM SUPPLY OF T.T.

- N.I.H. to ascertain immediately whether the Netherlands Govt. is prepared to implement the DPT project and, if so, what quantities of finished T.T. can be provided and when and the same for bulk T.T. concentrate.

- Based on above, place appropriate orders with UNICEF for finished, ready-for-use T.T. until approximately mid '88 and for T.T. bulk concentrate from mid '88 to second quarter of '89. (This is based on time-frame indicated in Appendix IV).

13. PERSONS INTERVIEWED:

13.1 N.I.H. Islamabad

- Maj. General (Retd.) Dr. M.I. Burney - Executive Director
- Mr. Zafar Ali - Acting Chief, Bacterial Production.
- Mr. Arfan Mahmood - Senior Scientific Officer (in charge of Fermentation)
- related staff members (of Bacterial Production Dept).

13.2 USAID:

- Mr. Peter Davis
- Mr. Raymond S. Martin,
- Ms. Heather Goldman

13 3. REACH

- Dr. N. Hirschhorn

A P P E N D I C E S

APPENDIX I

CALCULATION OF T.T. NEONATORUM REQUIREMENTS

- Estimated number of pregnant women annually: 4,000 K.
- Estimated number of married women of childbearing age: 16,000 K.
- Dosage schedule : 2 doses per women. (during 1987-1990)
- Wastage factor : ± 25-30%

Demand Calculation:

- 100% coverage of all pregnant women: 4,000 K x 2 doses plus ± 30% wastage equals 12,000 K doses.
- 25% coverage of married women of childbearing age: 4,000 K x 2 doses plus ± 25% wastage equals 10,000 K doses.
- By 1991 coverage of pregnant women only estimated at 4,000 K plus ± 30% wastage equals 5,200 K doses.

Appendix II

VISIT TO RIJKS INSTITUTE VOOR VOLKSGEZONDHEID (RIV) NETHERLANDS

SUBJECT

- Proposed technology transfer by RIV for production of Diphtheria Toxoid, Pertussis Vaccine and Tetanus at N.I.H. Islamabad

MAIN POINTS

- RIV stated that in principle the Netherlands Government is prepared to fund this project.

  (Note: Upon checking in Islamabd with Gen. Burney it was discovered that this decision has not as yet been communicated to the N.I.H.)

- Anticipated time-frame indicated by RIV is as follows:

  * buildings completed by end '88;
  * equipment installation completed by mid '89;
  * commencement of final, ready-to-use product from imported bulk concentrate by mid '89;
  * basic production (5 lots) completed by end '90

- Annual plant capacity proposed:

  * T.T. - 8 million doses
  * D.T. - 8 million doses
  * DPT - 16 million doses

- Number of fermentors to be installed:

  * for D & P - 1 x 300 litre
  * for T.T. - 1 x 300 litres

- RIV discussed N.I.H.'s capability to produce T.T. particularly related to the processing of the toxin (produced in the fermentor) to the final, ready-to-use product.
  (Note: Upon checking at N.I.H. it was found that Gen. Burney already has arranged to Mr. Zafar Ali to visit RIV in September '87 for a 6-8 week period for training. During this visit Mr. Zafar Ali should be in a position to obtain all necessary technology to process the toxin into the toxoid using the RIV technology).

PERSONS INTERVIWED:

- Prof. Dr. E.J. Ruitenberg - Adjunct Director General
- Dr. R.H. Tiesjema - Head Bacterial Production/Technology Transfer

Appendix III.

ESTIMATED MAXIMUM ANNUAL PRODUCTION CAPACITY USING A 150 -L FERMENTOR

- Effective fermentor capacity: 115 litres
- Crude toxin output : 90 LF/ml
- Total crude toxin output per fermentor load:
  115,000 x 90 Lf = 10,350,000 Lf
- Wastage factor in conversion to toxoid, purification and co-centration: ± 55%
- Total final toxoid output per fermentor load: 4,6000,000 Lf.
- This equals 460,000 doses of 10 Lf.
- Number of fermentor runs per year : 40
- Total capacity per year : 40 x 460,000 = 18,400,000 doses of 10 Lf each.

Appendix IV

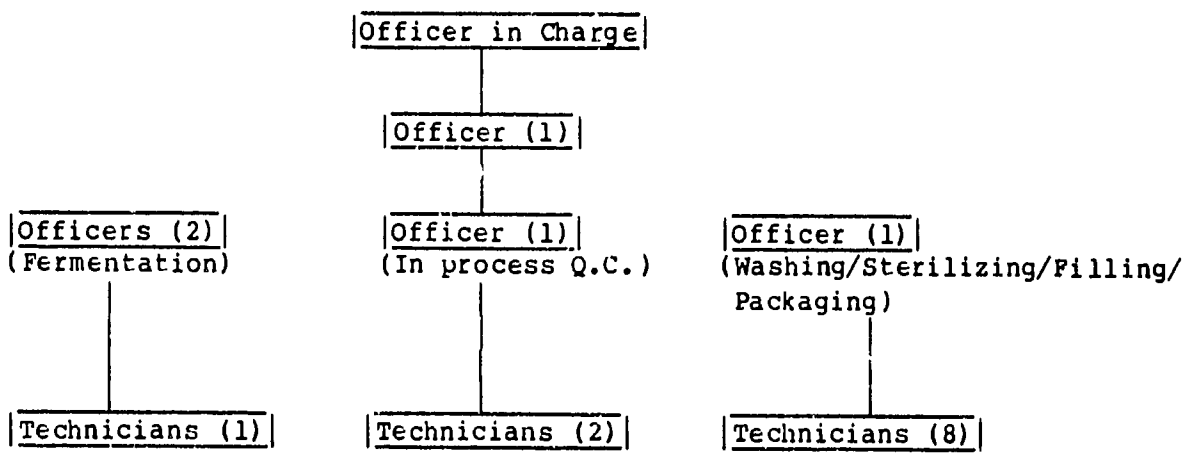
TENTATIVE TIME-FRAME T.T. PRODUCTION BY NIH

1.	Finalization of project proposal	May	'87
2.	Official USAID Approval	June	'87
3.	Completion of Building and Services	March	'87
4.	Completion of Equipment Installation	June	'88
5.	Completion of Validation of Building & Equipment	Aug.	'88
6.	Commendement of Trial Runs	Aug.	'88
7.	Completion of Trial Runs	Nov.	'88
8.	Commencement of Basic Production	Nov.	'88
9.	Completion of First Five Consecutive Production Batches	March	'89

Appendix V

SUGGESTED STAFF COMPLEMENT

T.T. PRODUCTION



NOTES ON EPI VACCINE PRODUCTION IN THIRD WORLD COUNTRIES BY GOVERNMENT VERSUS PRIVATE INDUSTRY

B Y

ROBBERT E. BINNERTS
BINNERTS & CO. INC.*
OTTAWA, CANADA

PRIVATE INDUSTRY EPI VACCINE PRODUCTION IN THE DEVELOPED WORLD.

- The last twenty years have seen a very significant reduction in the number of private companies engaged in manufacture of EPI vaccine.

- Currently in the developed world only the following full line (i.e. all six EPI vaccines) private manufacturers remain:

  - o Behringwerke - Germany (a subsidiary of Hoechst);
  - o Merieux - France (a subsidiary of Rhone-ponlence which has been nationalized);
  - o Sciavo - Italy (a subsidiary of ENI - an Italian state organization);
  - o Connaught - Canada

- In addition there are some private companies manufcturing one or two EPI biologicals; namely:

  - o Lederle - USA (DPI and OPV);
  - o Connaught - USA (DPT);
  - o Wyeth - USA (DPT);
  - o R.I.T. Belgium (measles and OPV);
  - o Well-come - U.K. (DPT and OPV)
  - o M.S.D- US (Measles).

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* Binnerts and Co. Inc. are consultants in the vaccine field specializing in feasibility studies, and technology transfer projects.

- The principal reasons for the rapid demise of private biological manufacturers are:
  - o. constantly increasing government regulations;
  - o. the very high costs of liability (especially in the U.S.);
  - o. constantly rising cost of R&D;
  - o. relatively low returns on vaccine sales;
  - o. the fact that many private biological producers were subsidiaries of large pharmaceutical concerns. Hence cessation of biological production did not affect the bottom-line significantly.
- The above is already demonstrated by the small number of private vaccine producers which quote on UNICEF tenders for EPI vaccine.

EPI VACCINE PRODUCTION IN THE THIRD WORLD

- Until the EPI became truly effective, demand for EPI vaccines in Third World Countries was remarkably low.
- The principal customer was and remains the Government, and hence it can dictate price. (Private market for EPI vaccines remains insignificant in all Third World countries).
- Vaccine production is both capital and trained labour intensive.
- EPI vaccine production in Third World countries can only be cost effective with a captive market of a minimum of 50 million inhabitants with a high birthrate and realistic pricing of the vaccines, coupled with indigenous manufacture of production components (vaccine vials, stoppers etc.)

- The above is well illustrated by the fact that in the Third World there is no private industry producing EPI vaccines with the exception of the Serum Institute in Poona-India which supplies DPT to the Indian Government.
- Moreover with the exception of NIH Pakistan, only the simple vaccines such as BCG and DPT are produced by Government organizations (all of which are heavily subsidized by the State)
- Establishment of private industry vaccine producers is further hampered by the fact that once the EPI has achieved its target coverage, vaccine demand will be reduced to the new-born market only.
- Even in many Third World countries with a sizeable population (such as the Philippines) where the Government does not undertake vaccine productions, no private industry has stepped in.
- In certain Third World countries, the Government will not allow private production of EPI Vaccines (e.g. Pakistan, Indonesia and Egypt).

REPORT ON
MEASLES VACCINE LYOPHILIZATION CAPACITY
AT NIH, ISLAMABAD, PAKISTAN

BY
ROBBERT E. BINNERTS
BINNERTS & CO. INC.
APRIL 10, 1987.

SUBJECT:

- NIH, Pakistan's request to USAID to fund the purchase of a Freeze-drier for NIH's Measles Vaccine Production.

ASSESSMENT OF CURRENT SITUATION:

- No official, written request from NIH to USAID has been made.
- With technology transfer from Connaught Laboratories, Ltd. Canada, NIH have erected an up-to-date freeze-dried Measles vaccine facility.
- The plant is in active production, manufacturing vaccine meeting WHO standards (as confirmed by duplicate quality control tests undertaken by Connaught).
- The current freeze-drier is a Model 54FS75 manufactured by the Hull Corporation, Hatboro, PA 19040, USA and installed in 1983.
- Since that time one compressor has had to be replaced by Hull.

ANNUAL CAPACITY OF CURRENT FREEZE-DRIER:

- The freeze-drier has a capacity of 30 K doses/cycle.
- The current freeze-drying cycle is 96 hours.
- without allowing for down-time and for production losses, the drier is capable of handling 6,480 K doses/annum.
- Allowing for 1 months's down-time/year and 10% production loss, the annual capacity is reduced to 5,000 K doses.

ANNUAL ESTIMATED DEMAND FOR PAKISTAN'S EPI:

- According to indications supplied to the Consultant by the EPI Cell, Pakistan's foreseen maximum annual demand during the next five years is 5,000 K doses (allowing for wastage in the field and some reserve stocks).
- Hence, provided there is no major breakdown of the current freeze-drier, there is sufficient existing freeze-drying capacity to meet Pakistan's annual demand.

OBSERVATIONS ON REQUEST FOR ADDITIONAL FREEZE-DRIER:

- The NIH Measles Vaccine Plant is capable of providing a maximum of 8,000 K doses of Bulk material/annum, but does not have the capacity to freeze-dry it.

- A world-wide shortage of Measles Vaccine is beginning to be experienced due to the drastically increased up-take by UNICEF, coupled with the very limited number of commercial manufacturers.

- Hull Corporation does not have a service representative in Pakistan; all service demands are handled out of the US as are all spare parts.

  Consequently, should the current freeze-drier experience a major breakdown, Pakistan's ability to satisfy its Measles Vaccine demand may be seriously jeopardized as imports of emergency vaccine supplies from foreign sources at short notice may be impossible.

- Ability by NIH to build up reserve stocks of ready-for use vaccines, would be provided by means of an extra freeze-drier.

- Provision of an extra freeze-drier also would enable NIH to export Measles Vaccine and obtain foreign exchange for import of production component, chemicals and spare parts.

RECOMMENDATIONS:

- Funding by USAID of another freeze-drier to NIH Measles Vaccine facility.

RECOMMENDED COURSE OF ACTION:

- The Hull Coporation be requested to prepare a proposal along the following parameters:

  - Capacity identical to current freeze-drier.
  - Equipment to be installed next to current freeze-drier.
  - Two double-stage compressors.
  - Cooling tower.
  - Essential accessories and spare parts (see appendix).
  - Shipping, installation and run-up.

- The Hull proposal to be sent to Connaught for initial consideration.

- It is strongly recommended that this purchase be sole-sourced for the following principal reasons:

  - Standardization of equipment in NIH;
  - Similarity of equipment obviating extensive rest-runs to appropriate freeze-drying cycle;
  - Indentical preventive maintenance by NIH;
  - Interchangeability of spare parts.

PERSONS INTERVIEWED:

- Major General (Retd) M.I. Burney, Executive Director, NIH.
- Mr. Shahid Akhtar, Head Measles Vaccine Production, NIH.
- Dr. Manuel Carpio, Asstt. Director Technology Transfer, Connaught Laboratories.
- Dr. Witt - WHO Consultant EPI.
- Col. Mohammad Akram Khan, EPI, NIH.

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