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EVALUATION AND TOUR OF BURMA PHARMACEUTICAL INDUSTRIES AND THE BIOLOGICALS PRODUCTION FACILITIES

A Report Prepared By PRITECH Consultants:
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Doc # 1538B

Report of Tour of Burma Pharmaceutical Industries and the Biologicals Production Facilities

January 6 - 17, 1986

Purpose of Visit

To serve as consultants to the U.S. Agency for International Development and the Burmese Pharmaceutical Industries Corporation (BPI) in increasing production of Tetanus Toxoid.

As secondary visit objectives, the team is to review production of Diphtheria - Tetanus Toxoid combined and Diphtheria - Tetanus Toxoid conbined with Pertussis Vaccine.

Summary of Visit

The team toured the vaccine production facilities of BPI as well as the pharmaceutical plant and the pharmaceutical research and development establishment.

A detailed review of the methods for producing Tetanus and Diphtheria Toxoids was carried out, and the project to employ a fermentation process to culture the tetanus micro-organisms was examined.

The program to develop a Pertussis Vaccine was reviewed.

During the course of the visit, Dr. Cooper presented a lecture on microbiological control in pharmaceutical and vaccine production to 38 members of the BPI staff, and Dr. Manclark reviewed the scientific principles and current state of knowledge of Pertussis Vaccine with the Biologics staff.

Visits were also made to the Department of Health Laboratories and the Tuberculosis center for the Rangoon District.

Senior People Contacted

U Maung Maung Mya,	Director Biologics Dept.
Daw Thein Thein Nyunt,	Deputy Asst. Manager, Biologics Dept.
U Chan Thein,	Biologics Dept.
Daw Lu Lu,	" "
U Saw Wallace,	" "
Daw Khin Su Su,	" "
Daw Myint Myint Aye,	" "
U Tin Oo	" "

U Thein	Deputy General Manager, Industry I
U Thein Han	Assistant General Manager, Industry I
U Khin Win	Deputy Assistant General Manager, Industry I
Dr. Chin Shein	Medical Division
U Tin E	Personnel Dept.

U Ba Nyunt	Managing Director, Pharmaceuticals
U Saung Myint	Assistant General Manager, Sterile Products
U Win Maung	" " " Tablets
U Maung Maung Chu	" " " Alcohol
Daw Tin Tin Aye	Manager, Quality control
U Htoon Hia	Deputy Assistant General Manager, Quality Control
Daw Mar Win Lay	Quality Control
U Hia Thein Aung	Research Department
U Aung Aung	" "
U Win Lain	" "

Dr. Ko Ko Gyi	Director of Research and Development
U Saw Myint	Director of Planning
Dr. Mehm Soe Myint	Director of National Health Laboratory
Dr. Daw Khin Soe	Chief of Food & Drug Laboratory

Present Situation - Facilities for Biologics Production

The plant is at least 30 years old, and maintenance has not kept pace with the increasing demands of an aging facility.

Some basic equipment required for vaccine production is adequate, but there are serious shortfalls. The steam autoclaves are functional, but the steam supply may not always be dependable. Only one incubator has cooling capability to maintain proper temperatures of incubation during hot periods.

Since there are no barrier systems with a supply of sterile-filtered air, the carrying out of aseptic processes such as sterile transfers and sterile filling involve considerable hazard of microbial contamination. This situation also affects the credibility of steribility test results.

A new suite is under modification for the production of Tetanus Toxoid. The walk-in incubator is of modern design and should prove capable of handling the large volume of cultures required in an upgraded production program. However, this new production unit has not incorporated any of the modern concepts of conditioned air and the use of high efficiency particulate filters (HEPA) needed in such a facility.

The room which houses the tank fermenter intended for cultivation of the tetanus micro-organism as an alternative to stationary bottle or pot cultures and is probably adequate but the associated and necessary services required to operate this unit may not be satisfactory. This includes a sterile air supply and steam supply.

Another critical shortcoming in the design of the existing plant and the unit under modification is the lack of an adequate gowning room adjacent to the rooms where sterile product is exposed such as where sterile transfers and sterile filling operations are carried out. It has been shown and reported in current literature that personnel in these critical areas are associated with most of the microbial contamination. Therefore, proper gowning procedures are very important, especially where barrier systems such as laminar flow sterile air are not used over exposed product.

While the state of the facilities as described above may not be totally to blame for the high discard rate (50%) of tetanus cultures, this situation has a significant impact on the objective of increasing tetanus toxoid production.

Plans for Increasing Tetanus Toxoid Production

The current volume of toxoid now being produced is about 3 million doses including monovolent tetanus toxoid, formal toxoid for the military, and combined Diphtheria - Tetanus Toxoid.

The intended goal is about 9 million doses of tetanus toxoid in several forms including monovolent tetanus toxoid, Diphtheria-Tetanus Toxoid, and Diphtheria-Tetanus Toxoid combined with Pertussia Vaccine.

Due to the limitations observed in the tetanus fermenter unit, it is recommended that this project continue as an experimental program only and not be part of the expansion program for tetanus toxoid at this time.

The team believes that with additional technical advice in areas such as adequate aseptic handling and in seed culture maintenance, it is possible for the operation to expand to meet the goal of 9 million doses of tetanus toxoid per year in the present facilities and utilizing the tetanus production unit now under modification. One important factor in meeting this goal is a reduction of the rate of contamination of tetanus cultures which should be achievable if an intensive study of the process is undertaken. Contaminated seed cultures are frequently the source of this type of problem but contamination during aseptic transfers may also be involved.

Potential and Feasibility of Upgrading the Present Biological Facilities

In general, it is the team's view that the poor condition of most of the buildings and associated structures would virtually preclude basic structural improvements or modifications. For example, it probably would not be feasible to install a form of central air conditioning to allow input of sterile filtered air to the sterile rooms and the sterility test area. On the other hand, it should be possible to purchase laminar flow benches and portable laminar flow curtained units with which would be employed in sterile transfer operations and in carrying out filling operations and bench type bacteriology. One potential problem with these laminar flow units is that they tend to further increase room temperature. Perhaps, window air conditioners with suitable baffling could alleviate this problem. It should be kept in mind that these laminar flow units require proper maintenance, and it must be determined whether this type of talent is available or whether this service can be contracted locally.

The steam supply seems to require an audit by a competent engineer. It is possible that appreciable modifications to this supply unit may be necessary. The alternative is to purchase and install individual steam generators for each autoclave and other equipment requiring a dependable source of dry steam with at least 50 lbs pressure.

The sterile-filling operation is currently a manual procedure employing glass-sealed ampules. It is possible that this unit cannot handle the target volumes mentioned earlier.

Additional filling capability should be available in the facilities of the Pharmaceutical Development Department and in the sterile Pharmaceuticals department. If this is not feasible upgrading of the biologicals filling capability will be necessary.

Quality of Vaccines

One somewhat intangible aspect of this audit is a determination as to whether the vaccines produced meet the recognized international standards of potency and safety. The team judgement is that potency levels for Tetanus and Diphtheria Toxoids are adequate and in the case of the military Tetanus Toxoid may even be higher than necessary. The animal safety tests performed seem to be executed properly. If the vaccines can be properly handled it would be advisable to send samples to a recognized testing laboratory for potency and safety determinations. Pertussia Vaccine is not yet in production.

There may be some concern about sterility of the final container products. The sterility test as carried out at BPI and for that matter as performed in other parts of the world is not a very sensitive test and may fail to detect a low level of contamination in final containers. The means of reducing this risk to an acceptable level is to incorporate a good anti-microbial preservative in the product and to use proven aseptic procedures which will minimize the chances of accidental contamination during the various stages of processing. In view of the comments made earlier, there is a possibility that some low level of non-sterility may exist in these final products.

Pertussis Vaccine

Dr. Manclark's report will detail the status of this project to develop production and testing procedures for Pertussis Vaccine. The adequate transfer of this technology has not yet taken place and our short visit will not replace this need. It will be necessary for an individual(s) with adequate background in bacterial vaccine production and testing to be exposed to an extended period of training at a well established production facility and a suitable period at a regulatory or testing laboratory.

The alternative which has been chosen by several countries is to have an arrangement with an established company which produces the product commercially and is amenable to a total transfer of technology. The terms of such an arrangement may vary with each manufacturer but should include a period of cooperation beyond the introductory date of the product.

Training of Laboratory Workers

The above paragraphs deal with the transfer of technology to one or more individuals already formally educated in microbiology and who can readily absorb the principles and details involved. However training of individuals in the more basis jobs is also an important aspect of the manufacture of safe and potent biologics. Our observations during our tour of the biologies and pharmaceutical facilities suggest that this program may need further implementation. Successful programs of training can be readily evidenced when observing the behaviour of personnel in areas where product is exposed. The operators in the sterile filling unit in the biologicals unit seem competent and knowledgeable, however, some laboratory workers in the tetanus area did not seem adequately concerned about aseptic precautions.

Comparative Costs

The available cost figures for the several Tetanus Toxoid containing products available from the accounting office of BPI indicate that these costs are higher than comparable vaccines obtainable from UNICEF. However it must be kept in mind that these comparisons may be flawed. One considerable influence upon the BPI costs is the assignment of plant overhead by the BPI accounting department; the assigned portion of the total cost of operating the BPI facility. This assignment if altered could easily put the domestic vaccines in a more favorable comparative position. Secondly it must be kept in mind that the biologicals operations employ a considerable number of people. Finally the purchase of imported vaccines would probably require hard currency. There is another somewhat intangible factor which also plays a role, namely the question of national pride in having the capability of producing their own vaccines for their health programs.

It is my view in this instance as it was in a previous tour of another South East Asia country that the above considerations tend to deemphasize the importance of comparing domestic production costs with imported vaccines.

Conclusions

The team believes it is possible for the biologicals department of BPI to increase production of Tetanus Toxoid from 3 million doses annually to 9 millions doses in its present facilities including the proposed tetanus production unit under renovation. Sterile filling facilities are limited and may require assistance from the Pharmaceutical Development Dept. or Pharmaceutical Production.

The Pertussis Vaccine Development Program will require a transfer of technology which could be achieved by sending a suitable employee(s) abroad for training or by reaching an agreement with a manufacturing firm to transfer technology to the BPI site.

Comments concerning the biologcals production facility are included.

Submitted by:

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Report to the Government of the Social Republic

of the Union of Burma

and

The United States Agency for International Development

An evaluation of the Burma Pharmaceutical Industries ability to produce Tetanus Toxoid Adsorbed Vaccine of acceptable quality, in the volume and at a price that is economically feasible for the proposed neonatal tetanus immunization project. The consultation was carried out by Dr. Murray S. Cooper and Dr. Charles R. Manclark between January 6 and 17, 1986.

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Introduction

This is a report of the Burma Pharmaceutical Industries (BPI) ability to produce Tetanus Toxoid Adsorbed Vaccine of acceptable quality, in the volume and at a price that is economically feasible for the proposed neonatal tetanus project. The consultation was carried out by Dr. Murray S. Cooper and Dr. Charles R. Manclark between January 6 and 17, 1986. Each consultant prepared and submitted a separate report. In addition to Tetanus Toxoid Adsorbed Vaccine (TTAds) production, the consultants also reviewed the production and control testing of all biologics manufactured by the BPI, with special emphasis being given to Diphtheria and Tetanus Toxoids Absorbed Vaccine (DT Ads), Diphtheria and Tetanus Toxoids and Pertussis Vaccine Absorbed Vaccine (DTP Ads) and any other product which may impact on the ability of the BPI to produce Tetanus Toxoid Adsorbed.

It is possible to produce vaccines and related biologicals with very modest equipment and knowledge. To produce vaccines that are safe and effective and are manufactured efficiently at low cost requires both knowledge and experience. Manufacture of vaccines involves the use of virulence factors from the etiologic agents of diseases the vaccines are designed to prevent. If these virulence factors are improperly inactivated, there is the potential for great harm when the vaccine is administered. If the manufacturer is overzealous in the inactivation of the virulence factors, the resultant vaccine may not be clinically effective. If the prospect also exists that the final product will be contaminated with adventitious materials or microorganisms, this will negate any ability to produce an effective

vaccine. Therefore, adequate facilities and equipment, knowledge of the basic science attendant to the production of a vaccine and an awareness of the limitations of the manufacturing process coupled with proper and well executed control procedures are all essential for the delivery of safe and effective vaccines.

Tetanus Toxoid Adsorbed - Production

The production culture is the Harvard strain of *Clostridium tetani*. The lyophilized culture is grown out in tubes of thioglycolate broth. Records show that a true seed-let system is not used since some cultures were transferred more than seventy times before returning to the freeze-dried culture. Production is in four liter stainless steel jars incubated at 35°C for seven days. Purity is checked with gram-stained smears and all uncontaminated jars are pooled and filtered as *toxin.* There are two crude filtrations through paper pulp and cotton fiber followed by a sterilizing filtration through a Mandler candle. Determinations for Lf and MLD are done at this point. The Lf is usually about 30 (greater than 20 Lf is acceptable to BPI) and the MLD is 1:200,000 to 1:300,000 (the antibody used for the Lf determination was produced in horses immunized with tetanus *toxin*). Toxoiding is accomplished by adding 0.5% formalin for 30 days at 35°C. Material which passes a guinea pig toxicity test (5ml injected subcutaneously into each of 3 guinea pigs; examined and shown to be free of tetanus toxin symptoms for 30 days) is labeled as toxoid and transferred to the purification laboratory.

Purification

Several production lots of tetanus toxoid are pooled in a 250 liter stainless steel tank. The pH is adjusted to 7.0, solid ammonium sulphate added to 25% (w/v) and then held overnight at $5^{o}C$ to $10^{o}C$. The precipitate is collected on Povic filter sheets in a filter press and then dissolved in about five liters of physiological saline. The redissolved toxoid is dialysed against 100 liters of distilled water at $5-10^{o}C$ for 48 hours with no stirring followed by a second dialysis against fresh distilled water. The toxoid is checked and shown to be free of ammonium ion (a distillation-titration method performed by the quality control laboratory) and then diluted to twenty liters with physiological saline. The toxoid is sterilized by passage through a Millipore® membrane filter (BPI personnel and protocols show 0.25 micron filters - but probably in error since Millipore® only makes a 0.22 micron filter). The final bulk is checked for freedom from toxicity (guinea pig), potency, Lf, protein nitrogen, total nitrogen, pH and sterility. Based on comparisons of Lf before and after toxoiding, there is a yield of about 20-40 percent of the starting material. A tank fermentor is present in the tetanus toxoid production unit. The fermentor was provided by the United Kingdom. It was fabricated by Stainless Metalcraft and contains the following information on the nameplate: CHATTERIS, CAMBS, DESIGN CODE B.S/515, PT 2. JDB NO. 21177. The chamber and jacket have been tested and certified at 20 PSI. The chamber has a total capacity of 200 liters with a working capacity of 160 liters. Construction of chamber and jacket appears to be of high nickel content stainless steel.

The chamber has no baffles. Agitation is by an electric motor driven shaft through the top of the fermentor which drives a paddle-type impeller located at the bottom of the chamber.

The chamber has more openings than is necessary and the valves and shields for the valves are designed in such a way as to make sterilization difficult. These design problems will complicate the use of the fermentor but will not prevent its use for tetanus toxoid production. The following is a serious problem, however, and must be corrected before the fermentor can be used for the growth of Clostridium tetani for the production of tetanus toxoid. The air supply is passed through three filters before entering the tank. The first filter is to remove particles and the second two filters are meant to sterilize. The first sterilizing filter will retain particles greater than 0.9 microns; this will not sterilize air. The second sterilizing filter is mounted on the chamber and contains a layer of glass wool sandwiched between wire mesh. The seal between the filter element and the filter jacket was not intact. This type of filter is difficult to sterilize, but even if sterilized with seals intact, it is probably not able to effectively filter the air passing through it.

Sterility of the air used for aeration cannot be maintained with the present filters. It is suggested that the 0.9 micron filter be replaced with a filter that can exclude 0.22 microns. The second filter mounted on the tank can be removed and discarded. A sterilizing filter to remove bacterial cells

in the air discharged from the culture chamber should be installed in place of the course Mandler filter currently used. Air is provided from a pump located next to the fermentor. A more dependable source of air which can insure an easily regulated flow without surges is necessary. There is a need for training the personnel who will operate this equipment. Much can be learned through empiricism, it is imperative, however, that some of the personnel have knowledge of the principles of growth of C. tetani and the production of tetanus toxin. At the present time, emphasis should be placed on increasing the production of tetanus toxoid in jars. Once the necessary repairs and modifications have been made on the fermentor and a knowledge of fermentor technology obtained, the fermentor can be used on an experimental basis until consistency is obtained in the production of tetanus toxoid. At that point the toxoid produced can be used to supplement or replace the toxoid produced by the jar method.

Formulation

Tetanus Toxoid Absorbed Vaccine is formulated to contain 6-8 Lf tetanus toxoid and 1 milligram aluminum as aluminum hydroxide. (Alhydrogel®).

A second formulation is prepared for use by the army. It contains 20 Lf of crude unadsorbed tetanus toxoid (one Health Department Official stated that he preferred 25 Lf). Each recruit is given a primary series of three injections at three week intervals followed by booster injections each year of the ten year enlistment.

Is BPI able to make good Tetanus Toxoid Adsorbed Vaccine?

The BPI product is quite acceptable when judged by the method of manufacture and the potency (greater than 8 unit) and freedom from toxicity obtained. It would be impossible or unfair to compare the BPI product to one made by US manufacturers, however, since there is little attention given by BPI scientists to the application of good manufacturing practices regulations in the production of this vaccine.

Is BPI able to make good Tetanus Toxoid Adsorbed Vaccine at a reasonable price?

Probably not. Cost estimates available from BPI indicate that this vaccine costs $0.093 per dose to produce (see Appendix VI). The UNICEF price for TT Ads is 0.0135 US dollars per dose (10 dose vial) or 0.01 US dollars per dose (20 dose vial). For additional information see Appendix V. There are many ways to calculate costs. If you assume that all products cost about the same to produce, the 6,066,330 doses of biological products produced by BPI (Appendix III) required an expenditure of 3,405,990 kyats (see Appendix II) or about 23 cents per dose.

Is BPI able to expand production of Tetanus Toxoid Adsorbed Vaccine?

At the present time between 40 and 50 percent of the vaccine produced is rejected because of microbial contamination. There was some contradiction in the answers provided by BPI personnel but apparently about 10-15 percent of the final bulk product is contaminated during the filling process with a

30-40 percent loss of product due to microbial contamination during the growth of production cultures. Conditions for filling final products in the Bio Products area of BPI leave much to be desired. The filling facility is working at its capacity now and could not be expanded. If arrangements could be made to fill biologics at the Development Center for Pharmaceutical Technology (DCPT) there would be substantial saving of product. If the DCPT is not available for filling even the pharmaceutical filling area of BPI might be a reasonable, although not ideal, alternative. The Bio Products area has two unused laminar flow benches. Although they are only about one year old, they are not operational. An inside room should be selected for a filling area (the outside walls usually have mold and mildew growing on them). It should be cleaned, painted, sealed, and cleared of all equipment (including clothing) not needed for the filling operation. The laminar flow hoods should be installed in the room and all work done in the hoods. The BPI uses flame sealed ampules for most of its products. This requires sealing the ampules outside the protected sterile area. A vial filler and sealer is available and could be installed in one of the laminar flow hoods and thereby reduce the risk of contamination during sealing. A similar aseptic laminar flow facility should be installed for the transfer of seed cultures and for the inoculation of production cultures.

As mentioned earlier in this report, the army uses crude unadsorbed Tetanus Toxoid containing 20 Lf per dose. After a primary series of three doses there are annual booster doses which means that about twelve doses are

received in a ten year enlistment. Crude Tetanus Toxoid is too reactogenic, the unadsorbed vaccine is even more reactogenic, a dose of 20 Lf is excessive, and the use of annual boosters is unnecessary and not good medical practice. If the recruits were given four doses of Tetanus Toxoid Adsorbed over the ten year period, the annual requirement for vaccine for the army would drop from 342,000 doses to 57,000 doses (see Appendix III). If the toxoid required for the 342,000 doses of crude vaccine is purified with a 40 percent efficiency the net annual gain would be about 80,000 doses of Tetanus Toxoid Adsorbed Vaccine.

To expand production is usually a matter of balancing the costs and availability of incubator space, autoclave size, and the availability of fermentors. At the present time, the purification of tetanus toxoid could be increased about four to eight times with existing personnel and facilities. This would necessitate a seven-day work schedule, but it could be done. The bottle-neck in production, however, is the production area. The tetanus toxoid production unit will be moving into a renovated building soon (no tetanus toxoid unit should ever be located in an area where other drugs or biologics are produced). The amount of toxoid that will be produced will be limited by the amount of space contained in the incubator for growth of C. tetani and inactivation of the toxin. The eight incubator shelves will hold 88 total jars (88 X 8 liters per jar = 704 liters) with space on the floor for 25 bottles each containing 12 liters (total volume equal 300 liters) of toxin undergoing inactivation. Although the number of jars could be

increased up to 30 per week, there would be insufficient incubator space available to store toxins undergoing inactivation. If such space could be provided, tetanus toxoid production could be tripled. If the contamination losses could be eliminated, production would increase by six-fold over the current level..

Should USAID use Tetanus Toxoid Adsorbed produced by the BPI in the proposed neonatal tetanus immunization program ?

Probably not and if it were my decision alone, I would not use the vaccine. The manufacture of biologics is not an exact science. There is often an excessive reliance on the results obtained in the recommended control tests. The Tetanus Toxoid Adsorbed produced by BPI meets all the usual control tests but these tests have limitations. Validation of each step in manufacture provides a higher level of control and virtually no attention has been applied to the validation process or other good manufacturing practices by BPI personnel or management.

In addition to providing health care to Burma, I should imagine that the USAID is interested in creating a favorable impression of the United States, its culture and its technology. It is unlikely that a vaccine accident could occur during an immunization campaign but it is probably more likely to occur with a BPI vaccine than with one produced under US license. Such an accident would not only be a detriment to the vaccine program but might create a false impression of our technology.

Vaccines are available through UNICEF but since the supply of some vaccines is marginal in the United States, products manufactured by a U.S. manufacturer may not be available through this source. If there is an interest in purchasing vaccines produced under U.S. license, you may wish to consider Connaught Laboratories Limited of Willowdale, Canada, Institute Sieroterapico Vaccinogeno Toscano Sclavo, Siena, Italy, and the Swiss Serum and Vaccine Institute, Berne, Switzerland. Connaught laboratories and SCLAVO manufacture Tetanus Toxoid under U.S. Government license and SCLAVO and Swiss Serum and Vaccine Institute are U.S. licensed manufacturers of Tetanus Toxoid Adsorbed. These companies could provide vaccine for use in Burma.

Diphtheria Toxoid - Production

The PW strain of *Corynebacterium diphtheriae* obtained from the Lister Institute is used. There is no seed lot system, growth of the production culture is on a meat digest medium supplemented with ferrous sulfate in Thomson bottles. No determination of total iron content of the medium is done. Cultures are grown for five to six days at 35°C. Each bottle is checked for purity with a gram stained smear, the growth from the bottles is pooled and allowed to settle at room temperature for sixty to ninety minutes. After the cells have settled the supernatant is passed through a paper pulp filter followed by an asbestos sterilizing filter in a filter press. Tests for Lf, pH, protein nitrogen and total nitrogen are done. The Lf averages between 80-100 per milliliter of filtrate. Formalin is added in two steps to a final concentration of 0.5 percent. Toxoiding is done at

35°C for four weeks. Upon completion of a satisfactory freedom from toxicity test in guinea pigs, the material is labeled as toxoid and tested for Lf, protein nitrogen, and total nitrogen. There is no significant change in the Lf before and after toxoiding but the flocculation for the toxoid requires two to three times more time.

Purification. The toxoid is concentrated twenty-fold by ultra-filtration through parlodian candles. Analytical grade ammonium sulfate is added to 22 percent. The precipitate that forms is discarded and ammonium sulfate is added to the supernatant to 36 percent. The precipitate is dissolved in physiological saline and dialysed against distilled water (5 liters toxoid versus 100 liters distilled water) for 48 hours. The toxoid is checked for ammonia and Lf and diluted to 600-800 Lf with physiological saline. Merthiolate® is added and then the toxoid is sterile filtered through a 0.45 micron Millipore® filter. The toxoid is then tested for Lf, pH, toxicity, potency, protein nitrogen, total nitrogen and sterility. Routinely >1000 Lf and usually 1500 to 2000 Lf per milligram nitrogen is obtained; this exceeds the WHO requirement. About three units of antibody are produced in guinea pigs.

Formulation. Diphtheria toxoid is used in two products, DT Adsorbed and DTP Adsorbed. DT Adsorbed contains 30 Lf of diphtheria toxoid, 6-8 Lf of tetanus toxoid and 1 milligram aluminum as aluminum hydroxide (Alhydrogel®) per single human dose. No DTP Adsorbed Vaccine has been produced but the

proposed formulation is 30 Lf (30-33) diphtheria toxoid, 10 Lf tetanus toxoid, 4 PU (less than 20 opu) pertussis vaccine and 1 milligram aluminum as aluminum hydroxide (Alhydrogel®) per single human dose.

Is BPI able to make good diphtheria toxoid for use in DT Adsorbed and DTP Adsorbed Vaccines?

The BPI product is quite acceptable when judged by the method of manufacture and the potency and freedom from toxicity obtained. As with tetanus toxoid, it would be impossible or unfair to compare the BPI product to one made by US manufacturers, since there is little attention given by BPI scientists to the application of good manufacturing practice regulations in the production of this vaccine.

Is BPI able to expand production of diphtheria toxoid?

About fifty percent of this current toxoid is rejected because of microbial contamination. If the contamination problem can be eliminated there would be a resultant doubling of production. Space is available in the incubator to double the amount of C. diphetheriae grown and double the amount of toxin undergoing detoxification. The facilities for purification could be expanded four to eight times with no problem. A conservative estimate would be that diphtheria toxoid production could be increased four-fold if the contamination problem can be controlled.

Pertussis Vaccine - Production. Pertussis vaccine is used as a component of DTP Adsorbed. To date, the BPI has been unsuccessful in their attempts to produce potent, non-toxic pertussis vaccines. A detailed review of the BPI manufacturing process revealed many problems. To detail the problems and provide solutions would require more time than was available during the consultation. It is unlikely that BPI can meet the projected production goals for 1986 and 1987 (see Appendices III and IV)

The following observations and comments deal with other products manufactured by BPI and are provided for information only. No in depth analyses of the products were made.

Tetanus Antitoxin (Equine)

Some thought should be given to moving away from the use of Tetanus Antitoxin (Equine) and move toward the use of Tetanus Immune Globulin (Human). Burma has a unique situation in which it has a large population of army and retired army personnel who have been hyperimmunized with incredible amounts of tetanus toxoid. This population could provide an ideal source of Tetanus Immune Globulin (Human). The use of Tetanus Immune Globulin should obviate the problems usually associated with Tetanus Antitoxin.

TAB Vaccine.

This is a vaccine composed of *Salmonella typhi*, *Salmonella paratyphi* A, and *Salmonella paratyphi* B. This vaccine is not considered useful in modern

vaccine prophylaxis and should be discontinued in favor of a single component typhoid vaccine.

Rabies Vaccine

This is a sheep brain vaccine. Real thought should be given to using a more modern vaccine inactivated by some other method than that currently used by BPI. The NIH potency test should be used instead of the Habel test for potency.

General Comments on the BPI physical plant and its Suitability as a biologics production facility.

A great deal could be said about the BPI plant but simply stated, it is not a facility that should be used for the manufacture of biologics. There are many basic design flaws in the buildings which make it impossible to control temperatures during manufacturing and maintain asepsis. The roof leaks and the resultant water runs down the walls and into the work areas and incubators and provides support for the mold and mildew that abounds on these surfaces. During the monsoon the lower floors flood and Russel vipers and cobras often enter the building. Some attempt has been made to condition the air supply to the work areas but, as an expedient the air was vented through the shafts previously used for exhaust air. As a result there is not a proper flow of air through the work areas and the new system has actually compounded the contamination problem. No attempt is made to provide cooled,

filtered air under positive pressure to the laboratories. In addition, equipment which generates considerable heat such as autoclaves, ovens, and incubator shakers increase the ambient temperature to 40-43°C during the warm months. Two Finnish refrigerator-incubators are available at BPI but neither is being used as an incubator at present. The incubators in use for all products are usually operated at 35°C and have no ability to control temperatures when the ambient temperature exceeds 35°C.

The animal production facility is completely inadequate. Buildings are open and the availability of animal food attracts a plethora of vermin, mice, rats and other rodents which in turn attract snakes. In my discussions with the vivarium personnel it was clear that there was no real understanding of the animal needs for biologics production and control. Mice, rabbits, and guinea pigs seemed in apparent good health but in many instances weight gains were less than expected. Although vitamin C is added to the drinking water for guinea pigs, both guinea pigs and rabbits are given green feed with the attendant risk of diarrheal disease. There seems to be little understanding of the requirements of laboratory animal husbandry and of such basic concepts as the foundation-production colony system. The mouse strain may not be suitable for potency testing and could be replaced with a breeding nucleus of N:NIH(S) mice from our National Institutes of Health, but to do so would be impractical until an improved animal facility is available.

General Comments. The US Government is interested in widening the role of commercial manufacturers in the pharmaceutical industry. Our manufacturers are quite interested in new markets but are often reluctant to transfer technology to a potential competitor. A point that is often overlooked is the fact that our pharmaceutical industry is not only a producer, it is also a user of materials. One needs only to walk through the Development Center for Pharmaceutical Technology which was built by the Japanese (at a cost of about 8 million dollars plus 4 million dollars from Burma) to see how this has been used by the Japanese to expand their markets. Once the building was completed, Japanese scientists and technicians were brought to Burma to train local personnel. Later on Burmese workers were sent to Japan for additional training. As a result of this, all became imbued with the Japanese methods. As you walk through the DCPT you will note that Japanese reference books, equipment and reagent catalogs are everywhere and the shelves are loaded with Japanese manufactured chemicals, reagents, etc. The equipment is serviced by Japanese technicians as needed and virtually all replacement parts are from Japan. So, for the expenditure of about eight million dollars the Japanese have built a state-of-the-art pharmaceutical plant (an excellent contribution to Burma), have had a real influence on the thinking of Burmese scientists and citizens, and have produced a ready market for Japanese goods which support the pharmaceutical industry. This has been accomplished in many parts of the world by the Japanese and I think that the US Government is missing an opportunity to do the same. In Burma, the building of a proper biologics production facility in cooperation with the SRUB would be such a project.

In most other countries of the world, manufacturers willingly open their doors to foreign scientists and in some instances provide support for these scientists to visit and study in their establishments. Perhaps the US Government could be instrumental in encouraging our manufacturers to provide easier access to their plants so that foreign scientists can benefit from the US experience.

Cold Chain. One of the major concerns of any immunization project is whether an adequate cold chain can be maintained so that potent and safe vaccines reach the consumer. There is also the concern that the vaccines are properly used by the health professional or paraprofessional. Rather than establishing a cold chain with its needs for refrigerators, power supplies, etc., has any thought been given to using a different approach? Why not organize an immunization team composed of personnel well trained in the administration of vaccines and provide them with a refrigerated truck for the vaccines? A second vehicle could carry support materials and personnel. The team would be preceeded by a group that would publicize the immunization program and work with the local health care personnel to organize the immunization day. The teams would circulate throughout the country providing immunizations on a continuing basis. This system has the prospect of providing effective vaccines at less cost and should be evaluated for a country like Burma.

APPENDIX I

ORGANIZATIONS VISITED AND PERSONNEL CONTACTED

7 and 17 Jan 86
Pharmaceutical Industries Corporation
Ministry of No. Industry
U Ba Nyunt, Managing Director
U Saw Myint, Director (Planning)
U Ban Yi

7-17 Jan 86
Burma Pharmaceutical Industries

Biologics Group
U Swe Hlaing, Deputy General Manager (Planning)
U Maung Maung Mya, Acting Deputy General, Manager (Production)
U Chan Thein, Deputy Assistant General Manager, Rabies Laboratory
U Tun Myint, Assistant manager, Tetanus Toxoid Production
U Tin Soe, Assistant Manager, Diphtheria
Toxoid Production, Diphtheria and Tetanus
Toxoid Purification, Diphtheria and Tetanus
Toxoid Vaccine Production
Daw Myint Myint Aye, Manager, Sterility Testing, Media Laboratory
Bacterial Vaccines, Pertussis Vaccine Laboratory.
U Saw Wallace, Veterinary Surgeon, Small Animal Unit, Verterinary
Department
U Than Yin, Deputy Manager, Biologics Testing Laboratory
Biologics Department
Daw Khin Su Su,. Deputy Assistant General Manager,
Serum Concentration Laboratory, Freeze-drying Laboratory,
Microbialogical Laboratory, Biochemical Laboratory

8 Jan 86
Development Center for Pharmaceutical Technology
Dr. U Koko Gyi, Director
U Kyaw Sein, Manager
U Soe Thein, Engineer

10 Jan 86
Department of Health of the Ministry of Health
Dr. Aye Kyu, Assistant Director (EPI)

14 Jan 86
National Health Laboratory
Dr. Mehm Soe Myint, Director (Pathologist)
Dr. Khin Khin Soe, Chief of the Food and Drug Administration
Dr. Thiri Tun Myint, Assistant Pharmacalogist,
Pharmacalogy Section, Food and Drug Quality Control Laboratory

Union Tuberculosis Institute
Dr. Khin Maung, Medical Superintendent

6-17 Jan 1986
U.S. Officials in Rangoon - USAID/Burma
Mr. Charles D. Ward, Jr., AID Representative
Mr. Terry J. Barker, Program Officer
Dr. John J. Naponick, Burma Health Officer (Rangoon)
Dr. Kay Wachsmuth, Consultant
Enteric Diseases, CDC, Atlanta, Georgia 30333

APPENDIX II

BURMA PHARMACEUTICAL INDUSTRY

(Biologics Department) (Kyats in Thousands)

PARTICULARS	1982-83	1983-84	1984-85
INCOME	4,158.34	4,166.90	2,921.89
SALES 4,158.34	4,166.90	2,921.89	
EXPENDITURE	4,541.17	4,533.61	3,405.99
DIRECT LABOR	1,222.40	1,099.11	1,083.08
RAW MATERIAL	2,349.40	2,689.56	1,555.61
FACTORY OVERHEAD			
Maintenance & Repairs	16.32	24.84	2.34
Factory Variable Overhead	70.67	39.74	35.23
Indirect Labor	211.32	161.90	191.79
Insurance	256.55	100.00	192.35
Fixed Overhead	23.10	53.42	33.59
Depreciation	21.00	21.00	21.00
ADMINISTRATIVE EXPENSES	162.13	135.49	144.85
SELLING AND DISTRIBUTION EXPENSES	0.36	0.20	0.05
COMMODITY TAX	207.92	208.35	146.10
LOSS	(-)382.83	(-)366.71	(-)484.10

APPENDIX III

BIOLOGICAL PRODUCTS

Sr. No.	Items	Existing BPI production capacity* (in dose per year)	Additional quantity to be produced after expansion (in dose per year)
	Tetanus Vaccine		
1.	Tetanus Toxoid (Adsorbed) 1 ml	2,022,000)	6,000,000
2.	Tetanus Toxoid (Adsorbed) 5 ml	5,000)	
	Crude Tetanus Vaccine		
3.	Tetanus Toxoid (formal toxoid) 1 ml	30,000	X
4.	Tetanus Toxoid (formal toxoid)20 ml	312,000	X
5.	Dephtheria/Tetanus Vaccine (Adsorbed) 1 ml	750,000	2,000,000
6.	Diphtheria/Tetanus/Pertussis Vaccine (Adsorbed) 1 ml	X	1,000,000
7.	Antisnake Venom 10 ml (in freeze dried form)	30,000 ampoles	70,000 ampoles (in freeze dried form)
8.	Antisnake Venom 10 ml (in liquid form)	55,000 ampoles	X
9.	Anti-Rabies Vaccine (freeze dried) 2 ml	3,000	X
10.	Anti-Rabies Vaccine (freeze dried) 10 ml	126,530	X
11.	Cholera Vaccine 20 ml	1,090,000	X
12.	Plague Vaccine 10 ml	1,000,000	X
13.	T.A.B. Vaccine 10 ml	600,000	X
14.	Tetanus Antitoxin 1,500 I.U.1 ml	22,000	X
15.	Tetanus Antitoxin 10,000 I.U. 2.5 ml	20,800	X
	Biological products in doses, sub-total	6,066,330	9,070,00

Note: Smallpox vaccine production of 4 million doses per year was stopped due to small-pox eradication.

*Actual doses delivered. Does not take into account losses encountered during the manufacturing process.

APPENDIX IV

EPI VACCINE REQUIREMENT FOR 1986-90 (in doses)

	1986-87	1987-88	1988-89	1989-90
Measles Vaccine				
TARGET POPULATION (under one year)	90,383	116,805	141,953	157,436
Vaccine Requirement	120,209	155,350	188,797	209,390
Polio Vaccine				
TARGET POPULATION (under one year)	177,039	238,099	293,486	346,867
Vaccine Requirement	706,386	950,015	1,171,009	1,383,999
DTP Vaccine				
TARGET POPULATION (under one year)	722,487	782,585	844,938	901,672
Vaccine Requirement	2,882,723	3,122,514	3,371,302	3,597,671
TT Vaccine				
TARGET POPULATION (Pregnant Women 2 doses)	980,082	1,065,777	1,150,694	1,227,958
Vaccine Requirement	2,607,019	2,834,966	3,060,844	3,266,369

APPENDIX V

1985 COSTS OF VACCINES PURCHASED WITH REVOLVING FUNDS BY THE PAN AMERICAN HEALTH OFFICE (WHO)

Vaccine	Costs per dose - US dollars	
	10 dose vial	20 dose vial
Tetanus Toxoid Absorbed	0.0135	0.01
Diphtheria and Tetanus Toxoids Absorbed	0.018	0.014
DTP Absorbed	0.021	0.016
Td (Adult) Absorbed	0.014	0.014

APPENDIX VI

Costs of Vaccines Produced by BPI for use in Burma

Vaccine	Ampule volume	Dose volume	Doses per ampule	Ampules per box	Kyats per box	Kyats per dose	U.S. dollars per dose*
Tetanus Toxoid Adsorbed	1 ml	0.5 ml	2	10	14.00	0.70	0.093
Tetanus Toxoid (Crude-formal)	1 ml	1.0 ml	1	10	9.05	0.90	0.120
Tetanus Toxoid (Crude-formal)	20 ml	1.0 ml	20	10	65.10	0.32	0.043
Diphtheria and Tetanus Toxoids Absorbed	1 ml	0.5 ml	2	10	19.95	1.00	0.133
Tetanus Antitoxin (Equine) 1500 IU	1 ml	1.0 ml	1	10	14.15	1.42	0.189
Tetanus Antitoxin (Equine)10,000 IU	2.5 ml	2.5 ml	1	10	15.75	1.58	0.211

* Assume 7.5 kyats per US dollar