

Situation Analysis: Thailand

23-29 April 1996



CHILDREN'S VACCINE INITIATIVE

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CHILDREN'S VACCINE INITIATIVE

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UNITED NATIONS DEVELOPMENT PROGRAMME

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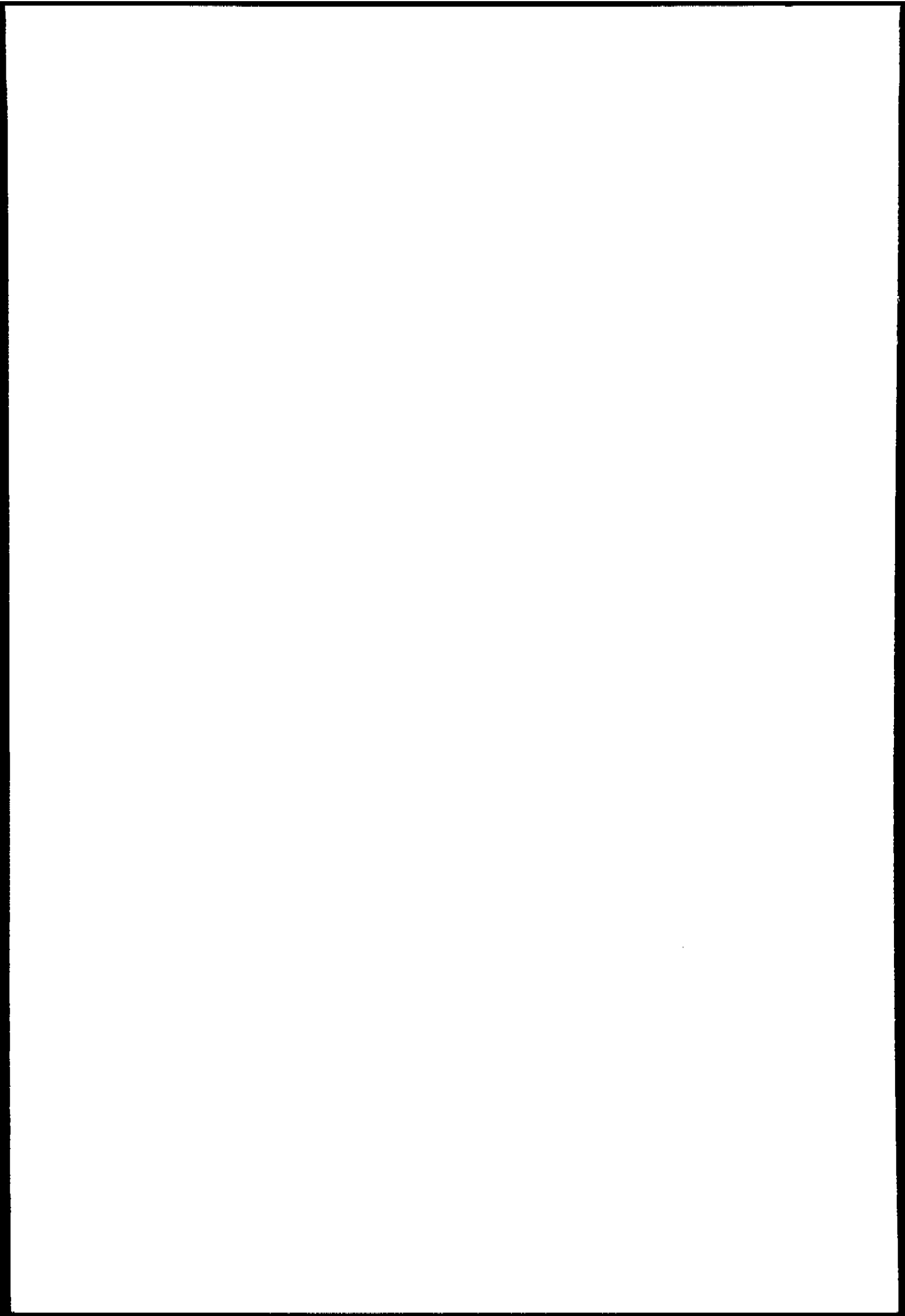
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Acronyms

BCG	bacille Calmette-Guérin (vaccine)
BOB	Bureau of Budget
BOI	Bureau of Investment
CDC	Communicable Diseases Control
DTP	diphtheria-tetanus-pertussis vaccine
DTP-HepB	diphtheria-tetanus-pertussis - hepatitis B vaccine
DTP3	diphtheria-tetanus-pertussis vaccine, third dose
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration
GMP	good manufacturing practice
GPO	Government Pharmaceutical Organization
HBV	hepatitis B vaccine
JE	Japanese encephalitis
JVA	joint venture agreement
I _f	(floculation units)
MMR	measles mumps rubella (vaccine)
MOPH	Ministry of Public Health
OPV	oral polio vaccine
OPV3	oral polio vaccine, third dose
QA	quality assurance
QC	quality control
R&D	research and development
SOP	standard operating procedure
Td	tetanus and diphtheria toxoids, with reduced diphtheria content for adults
TT	tetanus toxoid (vaccine)
WR	WHO country representative



Executive summary

The short assessment of the Thai vaccine situation included an examination of the FDA, NIII (Division of Biological Products, Department of Medical Sciences), Government Pharmaceutical Organization (GPO) Biological Products Department and the Thai Red Cross Society's BCG Vaccine Laboratory. The evaluation covered programme planning, vaccine quality, technical/production, national control, economic/financial viability and management aspects.

The achievements of the EPI in coverage and disease reduction are excellent. The level of technical expertise and the strong desire to continue to produce vaccines whilst striving to keep astride of world wide developments in terms of products and quality standards are also impressive.

In general it was found that the challenges facing the vaccine production industry are as follows:

- **Limited political support.** Funds for the immunization programme are large. Similar levels of support should be provided to the biotechnical industry.
- **Poor visibility.** As the junior partner of GPO, vaccine production is overshadowed by management's attention to pharmaceuticals.
- **Quality and GMP.** There is a need for a dedicated Quality Assurance programme in both GPO and Thai Red Cross facilities, separate from production and quality control.
- **Production scale.** Because of the small national market, production must be maximized to be efficient. There is a need to upgrade equipment in some areas along with development of technologies for JE and tetanus production.
- **Access to long term R&D** to ensure an ongoing pipeline of up-to-date products and assistance with basic research.
- **Management objectives.** Set new challenges to the industry to set and achieve targets whilst focusing on satisfying Thai public markets as well as additional volume elsewhere
- **The National Control Authority lacks the necessary authority over government producers**

Although these challenges seem many, the path which the government is following is moving in the right direction. The suggestions made in the report are in most cases re-enforcement of what is currently being planned.

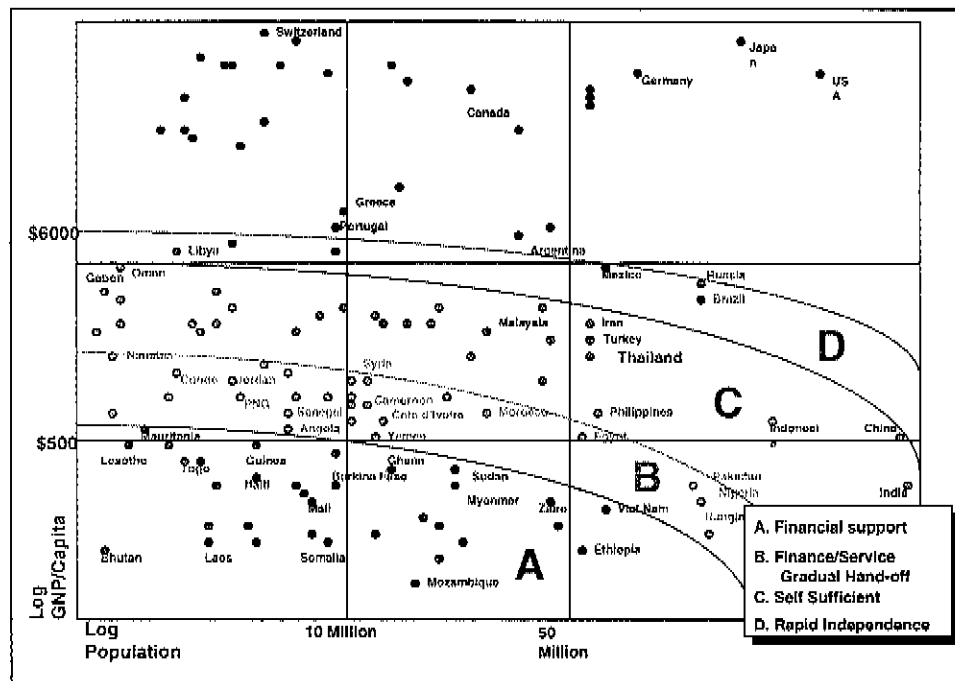
Specifically a four point plan is suggested:

- Legislation to give the National Control Authority statutory powers to include control of government producers.
- Choose a joint venture partner with the objectives to: upgrade the primary production as well as filling and packaging; obtain access to export and private markets so as to achieve economies of scale; and to establish the necessary links in Research and Development to insure new product development.
- Establish rapidly, a new stand-alone company (owned and managed initially by GPO) of vaccine production assets, with the objective to obtain the administrative economies of scale and separation of quality assurance, quality control and production; and obtain critical mass of technical expertise in the country. (Note: ideally this new company would include the BCG laboratory, as currently production, quality control and quality assurance is performed by the same person and there is little back-up. Therefore, the BCG (and anti-sera) laboratory producer would benefit by being part of a focused producer—at least administratively—with the production assets remaining where they are. This would mean the new company would be most likely be jointly owned by GPO and the Thai Red Cross with the Red Cross having normal shareholder rights.)
- Investment in management, people and equipment to: improve GMP/quality assurance; enhance production technology; set and achieve budget targets; upgrade human resource management and leadership.

Introduction

Thailand, like many countries has reached a point where it must decide if it wishes to have a long-term future in biotechnology. We believe that Thailand should take advantage of its position and rapidly develop its vaccine industry. WHO has found the grid drawn below useful in determining each countries relative advantage for vaccine production. The two axis represent relative wealth and population: the larger and richer the country, the more possibilities exist for having a viable vaccine production.

Figure 1: Global targeting strategy



Thailand has a population exceeding 50 million and is a country of intermediate wealth. Thailand belongs to Band C. For Band C countries with populations over 50 million, it has been found that where there is an established industry with competent staff, vaccine production has a good chance of becoming or staying viable in the long term.

Deciding to rely on international suppliers of vaccine is the most valid option for most small countries. The population size of Thailand can barely support a vaccine industry and so the possibilities for export should be examined. There are already many companies producing DTP (Figure 2) and its components and competition for exports will be strong.

Figure 2: Countries manufacturing DPT components

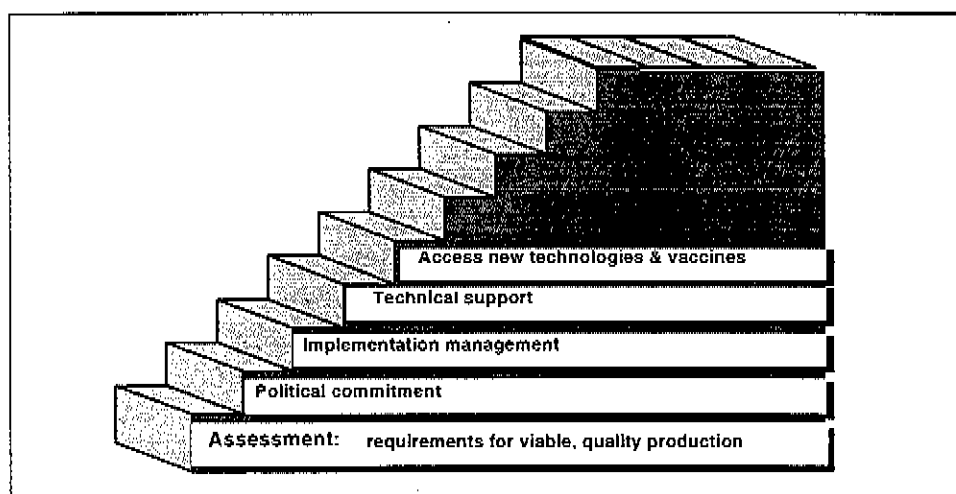
Argentina	Ecuador	Myanmar
Australia	Egypt	Netherlands
Austria	Finland	Philippines
Bangladesh	France	Poland
Brazil	Germany	Romania
Bulgaria	Hungary	Russia
Canada	India	Serbia
Chile	Indonesia	South Africa
China	Iran	Switzerland
Colombia	Israel	Thailand
Croatia	Italy	Turkey
Cuba	Japan	Uruguay
Czech Republic	Jordan	UK
Denmark	Korea	USA
DPR Korea	Mexico	Venezuela
		Vietnam

With so many potential competitors, Thailand must have a viable production industry based on its national market. Vaccine production is scale intensive and so Thailand should try to maximize and consolidate its production.

Thailand has expressed a wish to have a strong biotechnology industry and to become a leader in this field within its region. This goal will not be achieved unless the industry receives an increased level of support, first from the government and, secondly from outside partners with a strong research and development (R&D) programme in biotechnology.

The level of support from the Government for vaccine production is not yet clear. Without clear support, including legislative changes, the industry has little chance of long term success. To be successful there are several mandatory steps which need to be taken.

Figure 3: Mandatory steps through which producers must proceed



Starting at the bottom of the steps, public sector companies wishing to have a long term viability need to proceed stepwise. Companies trying to access new technologies or requesting technical fixes are unlikely to be successful if the other steps have not been completed.

First the company must have realistic data on its current position and have a good view of where it is going. Then it must have sufficient political and legislative support to allow for any necessary changes. The company can then adjust management to implement the new business plan. Only then can technical fixes and access to new technologies be worthwhile.

The mission examined various aspects of the immunization programme and was for the most part encouraged by its findings. Government support for immunization is undeniable and the successful programme puts to shame most of the world. However it is by no means clear that the Government has focused its support to include adequate financing and political support of the small but important vaccine producers. Assessments have been made of the industry but they have been limited in scope.

Based on assessments made globally and examination of the very limited opportunity to observe the Thai programme we believe that Thailand should increase its support to the vaccine producers with the intention of becoming a market leader in the future.

However based on current facilities and operations it would be cheaper, in the short term, for Thailand to obtain its vaccines from international suppliers. International suppliers have the possibility of production prices which Thailand could not be expected to match within the next 20 years. Importation of vaccine is always an option but does not meet the vision of the people we have met.

Management summary

The team focused the management and economic assessment on two areas. First, we focused on providing assistance with the joint venture project. Second, the team made a very basic assessment of the economics of the overall production—emphasizing DTP/Td/TT and JE vaccines (note: we made some observations as to BCG and anti-sera).

Joint venture

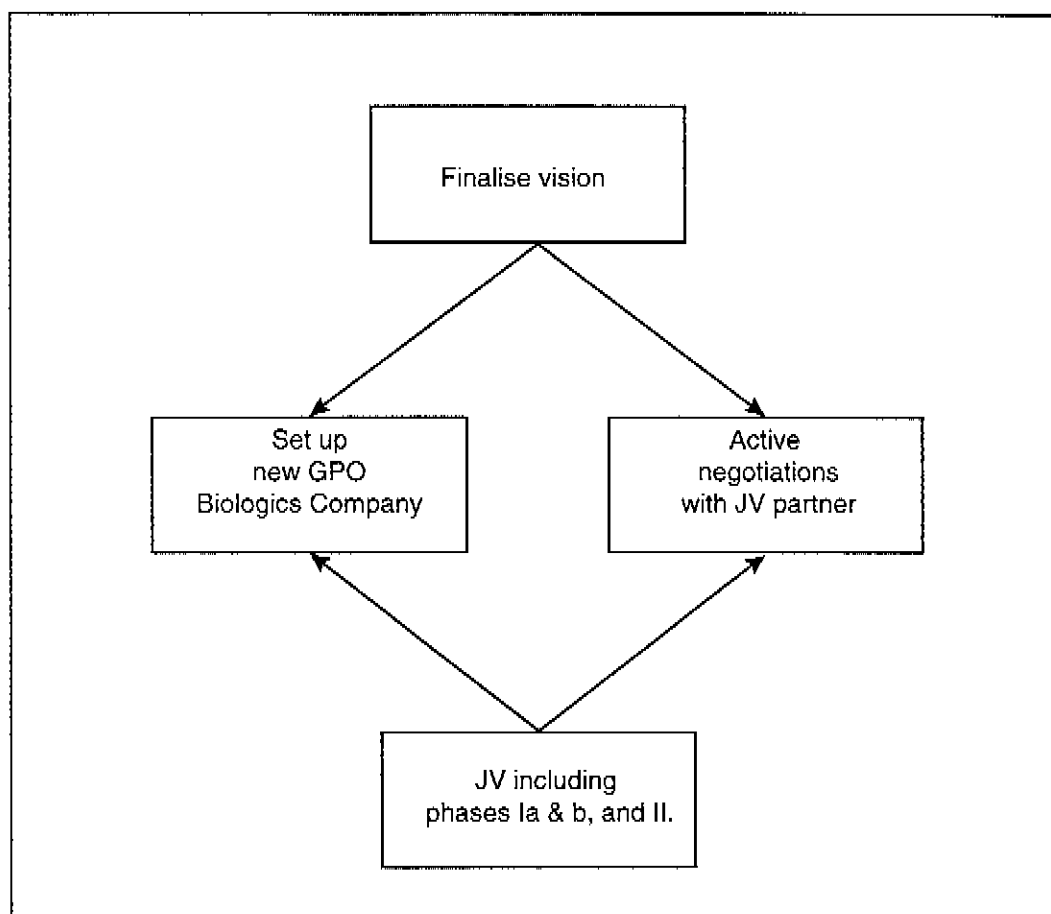
GPO should actively seek out a potential partner for their biological products. The underlying logic is that GPO and Thailand as a country has—and wants to continue to have—the basic skills needed for a biotechnology industry. However, the country is in need of a technology partner both for production and research and development (R&D) if they are to be up to date and fully competitive. To this end, Thailand has done a basic financial assessment of the joint venture possibilities.

The mission agreed that the overall strategy is very sound. However, if Thailand's objectives are to be fully met, we suggest that there are a number of issues which need to be re-addressed in terms of negotiation a joint venture agreement.

To this end, GPO and the team have devised a two point plan of attack for proceeding with the overall strategy whilst improving any joint venture arrangement (see Figure 4). First, it is our recommendation that GPO setup a wholly owned subsidiary containing the Biological Products Department. This company would have its own Chief Executive or Managing Director who would report to the Managing Director of GPO. The main difference in terms of what exists today with the Biological Products Department is that this new company would be responsible for proposing and meeting its own budget, objectives and goals (and serve as a precursor to the organization which must be setup in any event as part of any joint venture). Additionally, it would give a strong signal to the staff that the Biological Products Department is capable in the short to medium term of standing on its own and therefore has a future independent of any negotiations with a joint venture partner. In short, such a tactic would provide an immediate boost to morale and provide the focus needed to keep the production of vaccines progressing towards overall international quality and production standards.

Such a structure usually has its own board of directors where the managing director of the holding company (in this case GPO) serves as the Chairman. This would also allow GPO to formalize through board positions its relationships with outside advisers and experts currently assisting them with the Biological Products Department.

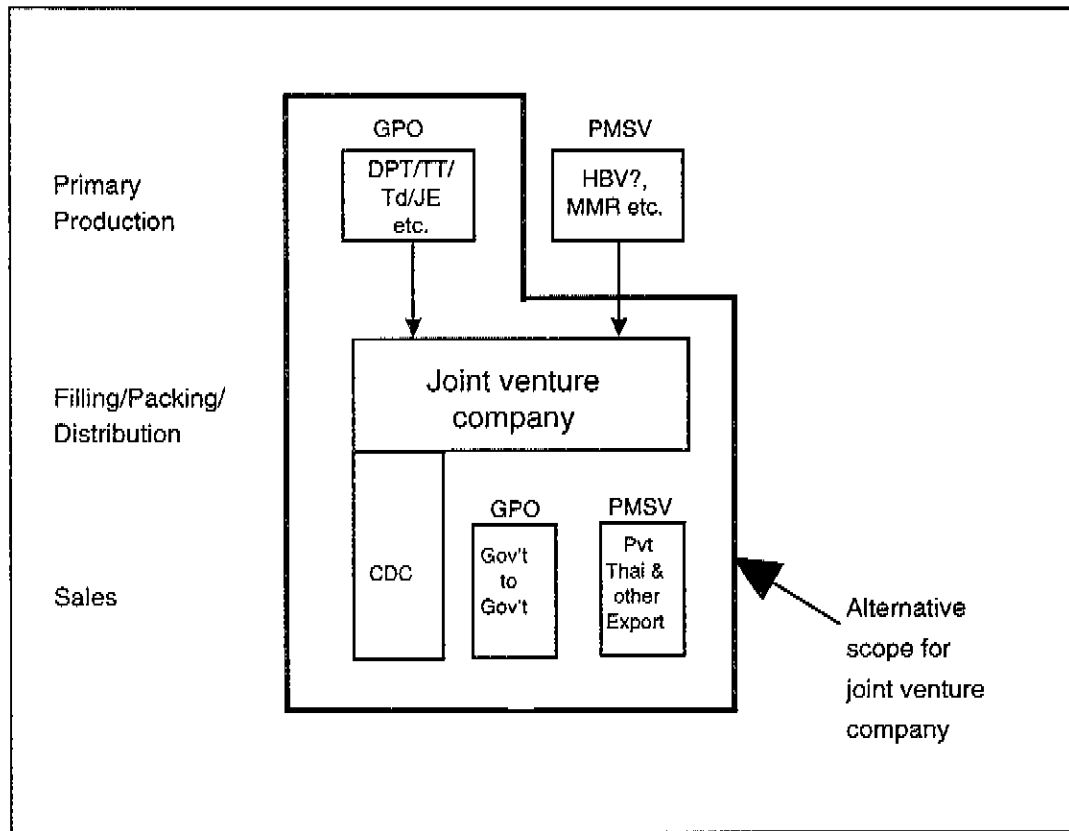
Figure 4: Possible process for completion of joint venture project



Second, in parallel with setting up the biologics company, GPO would be able to negotiate a strong Joint Venture Agreement (JVA) with its partner of choice. A joint venture company should first seek an arrangement which has filling facilities with limited cooperation on primary production, R&D and sales and marketing. Longer term any negotiating team should require the agreement to cover (see Figure 5):

- all GPO's production capacity for vaccines and sera (including a strategy for DTP-HBV);
- the filling and packaging;
- R&D explicitly defined (including HBV combination vaccine);
- management control, training and financial objectives clearly defined;
- sales and marketing to include both private and public Thai markets and to clearly define target export markets for the joint venture.

Figure 5: Scope of joint venture agreement



Based upon some recent experience, we believe that negotiating a good joint venture proposal should be possible given the rapidly changing attitude of transnational vaccine producers toward joint ventures. WHO has observed a complete change in attitude from one where the transnationals resisted broad ranging ownership/joint venture arrangements to one where many are now seeking such arrangements in certain geographies. It is our feeling that Thailand is offering a unique opportunity based on:

- its own market for both traditional and new vaccines;
- its access to other countries;
- its regulatory environment and ability to insure world class standards in quality control;
- its capacity for performing clinical trials;
- its overall levels of infrastructure and education.

Basic economic assessment

Although it is impossible to perform a full feasibility study in such a short assessment, it is our objective to provide GPO and the Thai government with a basic view as to the overall financial feasibility of producing vaccine in Thailand.

required. Based on this rough analysis—accounting for real depreciation (in other words the amount of depreciation needed to support future investment in fermenters, filling lines etc.)—we found that GPO can become competitive with world prices.

For JE, for example, the cost per dose if they produce 2.0 million doses means that GPO would be very competitive vis-à-vis the prices available to CDC from international producers. In order to reach this position as outlined in Table 1 it will require GPO to commit itself to adopting the freeze dried form using the Beijing strain (note: because of the fixed nature of investment, for little added investment, GPO could also produce over three million doses per year of JE).

Table 1: JE Cost per dose

	.6 Million	2.0 Million
Direct costs (production and direct overheads)	18.1 Million Baht	33.5 Million Baht
Cost/dose	-30 Baht	-17 Baht

In terms of DTP/Td/TT production, GPO is currently 30% higher cost (not including indirect overheads) to the UNICEF benchmark of 2.75 Baht per dose of DTP. In order to achieve similar costs as the UNICEF price GPO would need to increase the efficiency of their production (see Table 2). This could be accomplished both through upgrading the technology (e.g. fermenters for T) and an increase in the volume to at least 2 x the requirements for the Thai market. Therefore, it would be in the interest of the Thai government and GPO that any Joint Venture arrangement builds in sufficient access to export markets so as to insure the volume required to achieve efficient economies of scale.

Table 2: "DTP" Cost per dose

		Thai Demand			2 x Thai demand	
Direct Costs production and direct Overheads)		26.3 Million Baht			39.5 Million Baht	
	TT	Td	DTP	TT	Td	DTP
Cost/dose	1.30 Baht	1.40 Baht	3.50 Baht	.95 Baht	1.05 Baht	2.60 Baht

It should be noted that the above cost estimates include the cost of the new equipment and a nominal rent (2500 baht/sq. meter/year). The estimates do not include the cost of acquiring the necessary technology nor does it detail the timing of the investment and as such uses today's Baht and US Dollar as the basis.

It should be emphasized that the above analysis of the figures is in no way a feasibility study and is intended to test (using gross assumptions and analysis) the overall viability of Thai production from a financial perspective only. The overall estimated trends in cost/dose with changes in volume appear in line with our international experience (70 to 80% scale curve).

Finally, we wish to thank Messrs. Raboo and Tianchai and Mrs. Nantanee and Miss Nartaya for their assistance in making the above estimates on such short notice.

Overall observation of BCG and antisera production

We have not performed a detailed analysis of the production of BCG or antisera in the country. Our principal observation for both the BCG and antisera areas is that if Thailand wants to maintain suitable production for these products then they should seriously consider consolidating at least the people assets of their production into a single management structure with GPO's vaccine production. By consolidating the expertise it encourages cross assistance in Quality Assurance, Quality Control, R&D and Production techniques as well as Marketing and Finance. Additionally, it means that any one unit is not so dependent on one or two people.

Bureau of investment (BOI)

When considering the best way forward for vaccine supply in Thailand the policies and privileges of the BOI may be crucial. The BOI supports private enterprises and has a set of incentives which apply to new companies which qualify. Should a new vaccine production company be established which has 51% private ownership (Thailand had been considering a Joint Venture with a 49% private ownership by an external partner and a 2% internal ownership by the Crown. This arrangement would qualify as a private company) then

- corporate income taxes would be exempted for eight years and a 50% reduction for an additional five years.
- double deduction from taxable income of water, electricity and transportation costs for ten years.
- 25% deduction from net profit of the costs of installation.

Other incentives are also important, including:

Guarantees

- against nationalization
- against competition for State owned Enterprises
- against price controls.

Protection

- imposition of taxes against competitive products
- import ban on competitive products
- possibility of other tax relief for the benefit of the enterprise.

Such support makes the establishment of a new company very attractive.

Department of Communicable Disease Control

Recommendations

1. CDC should become a more demanding customer. Vaccines from any source should meet standards of safety and efficacy acceptable to the MOPH.
2. CDC should examine its forecasting tools to determine if a change in methods would provide additional information. Such information may enable a fine tuning of the forecast to more accurately predict how changes in strategy and vial size would effect vaccine usage. Adjustment could then be made which would reduce vaccine wastage below its current levels.

Observations and comments

The EPI in Thailand is excellent. With nearly 100% coverage of all target groups (Table 3), active surveillance and significant disease reductions, the country is achieving ambitious targets.

**Table 3: Results of immunization coverage
surveys 1990, Bangkok**

Vaccine	BCG	DTP3	OPV3	Measles
Coverage %	99.5	95.7	95.7	81.9

Immunization coverage was very high for all antigens in 1990. Coverage has improved since then and is currently close to 100%.

Discussions revealed that Thailand wishes to improve four areas :-

Research and Development

Thailand should be more active in biomedical research and able to solve many of the technological problems related to production. Thailand is active in the field trials of new vaccines and new disease control strategies. It is the long term wish of Thailand to play a regional leadership role in this area.

Implementation

Thailand has a very effective implementation programme. The programme needs to prepare itself for additional activities related to disease control for an increasing number of diseases. It is the long term wish of Thailand to be able to help its neighbors in their programmes.

Production

Thailand has two active production units, GPO and Red Cross. Both of these enterprises are producing vaccine but need support to improve their output in terms of quality and quantity. Thailand wishes to have a strong biotechnology industry and is prepared to take additional action to ensure the growth of vaccine production. Currently it is thought that improvement would be best achieved through the establishment of a joint venture with a major research based vaccine producer.

Human development

While Thailand has a good cadre of vaccinologists there are insufficient to support the expansion of the industry and a significant proportion of technical staff have received consistent and extensive training. Strengthening of the vaccine production, implementation and research will require even more ambitious plans for training and development.

These visions of Thai future all require changes to the way vaccines are handled now. Many of the activities that will need to be changed are under different branches of various ministries. There are ways in which CDC should change its behavior to support the vision that has been outlined.

Become a demanding customer

CDC should require that all vaccines used within the EPI are manufactured to the same high standards. Currently the two producers in Thailand are exempt from any form of external independent evaluation. While many of the functions expected of a National Control Authority are currently conducted on a request basis by the FDA and NIH, no one outside of the producers has any legal right or responsibility to comment on standards. Such situations have been shown, in many countries, to result in lower standards of production and quality assurance and reduced investment in maintenance and upgrading.

CDC should require competitive pricing from its suppliers. Currently CDC is required to pay higher than market prices when purchasing vaccines from GPO. The higher prices in fact subsidize the two vaccine producers. It may not be necessary for the CDC EPI budget to be used for such subsidy. While CDC is required to purchase at higher than necessary prices there is less incentive for the producers to continually seek ways to reduce their production costs. Vaccine production is highly dependent on volume. The current practice of manufacturing less than 50% of the total national requirements of DTP is inefficient but has been allowed to continue. Thailand could save money by either expanding or by abandoning DTP production.

CDC should insist on deliveries according to its needs. Vaccine imported from international suppliers of vaccine can be delivered with a flexibility that matches programme needs. By being required to purchase from local producers, the programme is disadvantaged. Currently vaccine is produced in many small lots. Production failures or unexpectedly low yields make delivery erratic. The creation of regional cold rooms has helped the delivery situation. Further improvements should be requested to meet programme needs.

CDC should examine its forecasting methods and realize the inherent advantages of using different vial sizes for different strategies. Currently, vaccine wastage is calculated as being fixed according to the vaccine. In reality vaccine wastage depends on other factors including vial size, session size and chosen strategy. Opportunities to adjust vial size from the local producer exist and should be examined.

Table 4: Where immunization takes place (% per location)

	Outreach	Hospital	Health center	Private
Central U	1.5	55.7	18.4	24.4
Central R	1.5	32.8	54.9	10.8
Northwest U	1	43.4	20.6	28.1
Northwest R	0	22.7	76.8	.5
North U	0	68.2	11.9	19.9
North R	0	27.5	68.5	4
South U	0	58.4	21.3	20.3
South R	5.1	33	59.9	2

Immunization at hospitals occurs for a high percentage of infants. Even in rural areas 30% of immunization occurs in hospitals (Table 4). Health centers are open only monthly whereas hospitals are open at least weekly for immunization. This would indicate that in Thailand availability is more important than proximity when mothers decide to get their children immunized.

The Government adds antigens to the programme as they become available. As can be seen from table 5 below the total cost of the traditional vaccines is no longer a very high percentage of the total expenditures for vaccines.

Table 5: Total vaccine costs

Vaccine	DTP	OPV	Measles	Hep b	Tetanus toxoid	Rabies	Japanese enceph.	Rubella
Doses	5 209 560	28 297 680	1 406 000	4 679 696	3 771 680	405 000	1 016 000	2 160 000
Cost per dose	0.22	0.09	0.26	1.80	0.08	7.00	0.68	0.31
Total funds	1 146 103	2 546 791	365 560	8 423 453	301 734	2 835 000	690 880	669 600
% of total	7	15	2	50	2	17	4	4

Hepatitis B accounts for more than 50% of the funds spent on vaccine. This vaccine should be the first priority when examining ways to improve efficiency. When DTP-Hep B is introduced, it is planned to reduce the number of doses per child to 3. Making a reduction to three doses per child now could reduce the programme cost to CDC, by more than US\$ 2 million per year.

The annual forecast of vaccine requirements provided to GPO are made by CDC but are for planning purposes only. Orders are by GPO directly from the provinces. Forecasts have been quite accurate for the past several years. Forecasts have been made for the coming five years.

The programme strategy requires that all of the approximately 8230 health centers offer immunization services on one fixed day per month. While such a strategy used to mean poor coverage the compliance rate in Thailand is very good and coverage is high. The infrequent service concentrates the target population and there are approximately ten newborns each month at each health center.

The Ministry of Public Health

The Ministry of Public Health includes the Office of Food and Drug Administration (FDA), which has the overall National Control Authority function for Thailand, and the Department of Medical Science, Division of Biological Products which has specific National Control Laboratory functions for biologicals.

National Control Authority

Recommendations

1. Revision of the current legislation, which grants specific exemption from licensing and registration requirements to the two local vaccine producers, is necessary to enable the FDA to conduct a complete National Control Authority programme. Removal of the exemption would also benefit the Thai Red Cross and GPO, in the short term by providing them with feedback in regard to GMP issues which may require improvement, and in the long term by providing them with the opportunity to gain certification and obtain a Certificate of Free Sale for their vaccines.
2. To maintain the separation of the National Control Laboratory from the Producer, the Division of Biological Products should devolve their research into production issues to the GPO.
3. If the NIH Division of Biological Products were to institute the practice of protocol review, they would be able to be more selective in the batches tested, and in the tests performed on the batches selected.
4. The NIH Division of Biological Products has a stated lack of experienced staff, primarily due to the poor image of Quality Control work (in particular *in-vivo* testing), and the lack of salary to compensate for this. Changing the current work organization to a more flexible system (including product-based work as well as the current test method based work) with more comprehensive training, and salaries more in line with those offered by private sector pharmaceutical companies may influence this situation.

A. Office of Food and Drug Administration (FDA)

The FDA has overall responsibility for regulatory affairs in Thailand, which includes pre-marketing licensing and registration of drug manufacturing, importing, and sale, and post-marketing quality surveillance. This function also includes GMP inspection of manufacturers, with a concerted campaign of training that involves inspectors being sent to many countries for training, and those inspectors combining their variety of experiences to set up a programme to train more inspectors "in-house" Thailand participates in the WHO Certification Scheme, and can issue a Certificate Of Free Sale.

Adverse drug reactions are also monitored, and this includes the number and type of adverse reactions to vaccines. Adverse drug reaction monitoring was instituted in 1983, and the expanding network of reporting centers has contributed to the increasing number of reports.

The FDA has dedicated staff with experience in pharmaceutical regulation, and are re-designing their work to give more responsibility to people with appropriate expertise. They acknowledge their lack of expertise in biological products, and the expertise of their colleagues in the Division of Biological Products, in the Department of Medical Science. The FDA have staff acting as the Secretariat to the Committee on Biological Products, and coordinate, through joint planning with the Division of Biological Products, the monitoring of vaccine quality.

It was explained that Thai law currently specifies exemption from the licensing requirements for "the production, importation, and sale of drugs are processed by ministries, public bodies or departments in duty bound to prevention or treatment of disease, Thai Red Cross, Government Pharmaceutical Organization (GPO)."

The specific exemption of the two Thai vaccine producers from the licensing and registration requirements applicable to all other private enterprise pharmaceutical companies is of considerable detriment to the vaccine producers, as there is a wish to support the development of vaccine production, which could otherwise include registration, licensing, and certification. The revision of the law, to remove the exemption for the Thai Red Cross and GPO, would enable the FDA to conduct a complete National Control Authority programme. Removal of the exemption would also benefit the Thai Red Cross and GPO, in the short term by providing them with feedback in regard to GMP issues which may require improvement, and in the long term by providing them with the opportunity to gain certification and obtain a Certificate of Free Sale for their vaccines.

B. Department of Medical Science, Division of Biological Products

The Department of Medical Science comprises 22 Divisions, housed in a modern complex in the MOH precinct in Nonthaburi. The Division of Biological Products is the National Control Laboratory for biological products, with responsibility for Vaccines, Toxoids, Serum, and Blood Products. Their stated role is Quality Control testing, which includes the preparation and maintenance of National Reference Preparations, monitoring of the vaccine cold-chain in the distribution system (through surveillance sampling and testing), the drafting of suitable National requirements for biological products, research and development on quality control techniques, including sero-surveillance and quality of production, and work with the FDA on marketing applications for biological products. The Director also has a seat on the sub-Committee for registration and licensing of new drug products

The Division of Biological Products has large, modern facilities, with five laboratories which include six sterile rooms and a wide variety of state-of the art equipment, including, electrophoresis and nephelometry equipment, and an oxygen demand monitoring Warburg apparatus (for viability testing of BCG), purchasing underway for a coagulometer and HPLC, and access to a protein synthesizer, and DNA sequencer. This is complemented by the very good technical infrastructure, which includes access (with other users) to well-designed animal test facilities,

which are supervised by a veterinarian (who demonstrated a very thorough knowledge of the equipment and procedures to maintain both the "conventional" and isolated animal experimental facilities).

The Division (when fully staffed) has 39 staff, with 19 scientists, nine administrative staff, five technical, and six laboratory workers, and is divided into six "methods-based" Sections: Administration, Chemical and Physical Control, Biological Assay, Safety Control, Biological Standardization, and Biological Development and Application.

The Biological Standardization and Biological Development and Application Sections are currently run by one person, due to the high turnover of experienced staff. This person is also the QA coordinator, and part of this function is to liaise with the QA Director, who reports, in turn, to a QA committee to coordinate this activity over the 22 divisions. The QA programme was instituted only recently, and is an ongoing process that could perhaps be facilitated by the engagement of an external source of information on quality systems as applied to biological products.

The Biological Development and Application Section includes sero-surveillance, aimed at monitoring and improving the efficacy of the national immunization campaign, and this function is a valuable addition to the Quality Control activities. However, the Section also involves itself in research into production issues, in collaboration with the GPO. This is beyond the scope of activities for a National Control Laboratory, and this function should be devolved to staff of the GPO (even though some work could be conducted in the Division's facilities and discussed with Division staff) in order to maintain the separation of the National Control Laboratory and the Producer.

The staff of the Division appear knowledgeable and enthusiastic, and the good facilities are complemented by a five-year plan for the work of the Division and for the training of the staff. However, quality control testing by the Division has recently taken up to one year from the date of submission of the sample, due to the high staff turnover, problems with supply and health of experimental animals, and a less flexible testing regime which requires the performance of every test on every sample. GPO does not currently submit production protocols or QC test data and results to the Division. If the Division were to institute the practice of protocol review, they would be able to be more selective in the batches tested, and in the tests performed on the batches selected. The resultant reduction in routine test work would allow more time for implementing the QA system and for training.

Staff of the Division saw their major problems as a lack of experienced staff, primarily due to the poor image of Quality Control work (in particular *in-vivo* testing), and the lack of salary to compensate for this. This is a problem with no easy resolution, though changing the current work organization to a more flexible system (including product-based work as well as the current test method based work) with more comprehensive training, and salaries more in line with those offered by private sector pharmaceutical companies may influence the situation.

Thai Red Cross

BCG Production

The BCG production facility is located at the Queen Saovabha Memorial Institute (QSMI), Thai Red Cross Society complex.

The QSMI was founded over six decades ago as the Pasteur Institute of Bangkok, with the initial mission to produce rabies vaccine and snake antiserum.

This was later expanded to include production of other vaccines such as smallpox, cholera, BCG and typhoid. Presently only BCG and tuberculin are being produced.

The BCG facility was constructed in the early fifties and the production of vaccine began in 1953.

The working seed has been obtained from Statens Serum Institute in Denmark. Contents of the seed ampoule are grown for up to a maximum of nine passages. Production is done in 500 ml. culture flasks on a weekly basis. The bacterial mass is pooled together and homogenized by the use of steel balls. When the final bulk is prepared, filling is done manually, into 5 ml. amber vials. 0.5 ml. fill representing ten doses is freeze dried using 48 hr. drying cycle. Freeze drying of the vaccine is done with the use of the two "EDWARDS" freeze dryers, but we have been told that a new unit has been ordered, as a replacement to the older of the two units.

Current production capacity of about 3.0 million doses annually is sufficient for the domestic requirements.

BCG vaccine is produced in an old facility and needs significant up-grading to meet the basic GMP requirements.

QC testing is adequate, but there is no internal control of procedures and no evidence of documentation. All quality control tests are done in the same facility by the two QC staff, and based on the results obtained, vaccine is released by the head of the BCG production. The QC function should be independent of production.

There is an identified need for more research on quality issues. This could be addressed in two ways. The suggestion from the staff was for an additional staff member, with designated responsibility for quality assurance. The proposed management team option of a joint GPO/Thai Red Cross vaccine administration could include a single QA management for co-ordination of this function across all vaccine production and quality control.

Recommendations

1. Purchase automatic or semi-automatic equipment for filling, stoppering, capping and sealing.

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2. Production facility needs to be upgraded by repairing and repainting of the wall and floor surfaces.
 3. Production and QC responsibilities should be separated. QC tests and releases of the BCG Vaccine should be independent of production.
 4. A quality assurance function should be instituted, separate from both production and QC. This could be addressed in two ways. The suggestion from the staff was for an additional staff member, with designated responsibility for quality assurance. The proposed management team option of a joint GPO/Thai Red Cross vaccine administration could include a single QA management for co-ordination of this function across all vaccine production and quality control.
 5. Establish maintenance crew to assist in commissioning and validation, and, in particular, repair of equipment.

Government Pharmaceutical Organization: The Biological Product Department

Quality Control

A well organized quality control department is an essential pre-requisite for the successful production of biological products. The quality assurance division at GPO, headed by Mrs. Suchada Subhachaturus, is located on the second floor of Building 21, where the first floor of the building is being used by the Anti-venom Serum Production Division. All required in vivo and in vitro tests for locally produced and imported vaccines are performed by the QC division, and based on the results, released for use by the head of the QC.

The QC facility is crowded and very old and must be urgently upgraded to satisfy the minimum GMP requirements. The equipment presently used is also very old and must be replaced to provide quicker and more accurate assessment of the quality of vaccines tested.

The QC department is also responsible for the quality assurance activities of the organization but the programme is in the process of being established. The head of the department will be attending training in July at Bio-Farma in Indonesia. The quality assurance programme would be greatly facilitated by the separation of QA from QC.

Recommendations

1. Establish a Quality Assurance Management function, to provide leadership and guidance to production and QC staff in the preparation and application of SOPs and compliance with GMP.
2. Expand the QC facility and provide more space for proper separation of biological and chemical testing.
3. Replace all exposed wood with the appropriate metal laboratory furniture.

Diphtheria toxoid

Production of diphtheria toxoid is done using one 55 liter New Brunswick fermenter. Annual production of 65-70 batches accounts for about 50% of the 5.0 million doses requirement set by the CDC. This is mainly due to low yields as well as production losses of about 40% due to contamination and in process losses during purification and detoxification.

The facility for production of diphtheria toxoid (Building 32) is in good condition and would require minimal capital to be brought to GMP standards.

Standard operating procedures are in the initial stages of preparation, and should be completed during 1996.

Pertussis vaccine

The present production of pertussis vaccine is done in the second 55 liter New Brunswick fermenter located next to the fermenter being used for the production of diphtheria toxoid.

Both units are 10-12 years old and are being used on the continuous basis. Pertussis strain used is 26426, obtained from the Institute of Immunology Zagreb, Yugoslavia, containing agglutinogens 1,2 and 3.

Similar to production of diphtheria, 65-70 production batches are made annually. Losses of about 20% are mainly due to bacterial contamination.

The staff of 20 (5 scientists and 15 technical/administrative) is shared by diphtheria and pertussis production.

Upon completion of testing and release by quality control, the concentrates are transferred to the Mixing Department Building 31/2 for final bulk preparations.

The standard operating procedures are at the same level of creation as the SOPs for diphtheria.

Recommendations

1. Develop a system for investigation of the reasons for the high discard rate.
2. Speed up preparation of SOPs and training of production staff in GMP practices.
3. Investigate the possibilities of increasing the production batch size by purchase of additional fermenters and related equipment.
4. Consideration should be given to the physical separation of the production activities of diphtheria and pertussis.

Tetanus toxoid

Tetanus toxoid is produced from the Harvard strain by the static method, using 30 liter capacity stainless steel containers. About 70 batches each containing 100 liters (5 x20 liter per container), are being produced annually.

Approximately 70% of the production is discarded. 30 % of the material is lost due to contamination, and 40% due to low Lf levels and losses during detoxification, precipitation and purification.

Due to this, only 50% of the required vaccine can be produced.

Tetanus toxin is produced in a separate, free-standing building (Building 37) which was renovated in 1993.

However, it is evident that this production unit is totally lacking production discipline and needs urgent establishment of the proper production control and good manufacturing practices to protect both production staff and the product.

Toxoid purification is done in Building 31/1, which is physically separated from the toxin production building.

Recommendations

1. Stop production of tetanus toxin until proper production procedures are in place.
2. Prepare all required standard operating procedures and re-train the staff in good laboratory practices.
3. Re-construct the entrance to the toxin production area to accommodate installation of showers for the staff entering and leaving the production area.
4. Prohibit entrance of non production staff to the building at all times.
5. Set proper procedures for transfer and delivery of materials, product and staff to and from the area.

Japanese encephalitis vaccine

JE vaccine is a liquid preparation of JE virus, Nakayama-NIH strain, grown in neural tissue of mice.

Infected mouse brains are harvested, homogenized and inactivated for 60 days at 4 degree C with formalin. After concentration and purification the vaccine is filled as a single or ten-dose configuration.

JE vaccine production is located on the second floor of Building 30 and employs four scientific and ten technical and administrative staff.

Due to low potency yields, (one dose per mouse), production capacity of the JE unit is limited to about 400 000 to 500 000 pediatric doses per year, compared to the requirement of 1.5 to 2.0 million doses.

Recommendations

1. Establish a development project to improve the yields from the present one dose/mouse to the original 2-2.5 doses per mouse.
2. Establish a development project to investigate the possibility of JE vaccine production in tissue culture.
3. Investigate possibility of changing from Nakayama to Beijing strain.

Distilled water

The Biological Products Department at GPO has its own distilled water plant.

Water is produced in Building 41 in a 25-30 years old unit of 250 liter per hour capacity.

Through SS piping installation the water is transferred to a jacketed 3000 liter stainless steel tank and circulated at 80 degree C to two points of the complex :

- a. Hepatitis B filling area (Building 30)
- b. General filling area (Building 38)

All other production units receive distilled water in the plastic containers or have their own production units.

From the discussion with the staff it appears that required tests are being performed at all points regularly.

A replacement unit, capable of producing 500 liters per hour has been ordered from AQUANOVA, Finland.

Standby generator

Biological Products Department is equipped with a small (130-140 kW) standby generator to provide emergency power to selective cold room storage areas, Hepatitis B production and storage area and distilled water circulating tank.

Hepatitis B

Final bulk preparation of Hepatitis B vaccine purchased as concentrates from Smith Kline, as well as filling and freeze drying is performed on the first floor of Building 30.

The facility is well designed with modern equipment and high level of sanitation. The capacity of the unit is sufficient for the present CDC requirements.

GMP overview

Insufficient time was available to do an in-depth GMP analysis of the production of vaccines at GPO.

However the following items need to be addressed:

1. A QA system is required rather than the current philosophy of testing quality into a product.
2. It should ensure that the entire process is designed to produce a product of a consistent quality, safety and efficacy
3. More attention to GMP is required and higher level of understanding by all staff is required to achieve the desired ends.

This should require that:

1. All manufacturing processes should be clearly defined and be known to be capable of achieving the desired ends.
2. All necessary facilities should be provided, including:
 - a. Appropriately trained personnel
 - b. Adequate premises and space
 - c. Suitable equipment and services
 - d. Correct materials, containers, and labels
 - e. Approved procedures
 - f. Suitable storage & transport
3. A full set of Standard Operating Procedures detailing exactly what is required, in a form understandable to the relevant staff is available.
4. Adequate training is provided.
5. Full records of the manufacturing process should be kept in each area.
6. Batch History records should be available.
7. A batch recall system should be developed.
8. A programme of self-audit, to ensure compliance with the above points, should be instituted.

GMP findings

Due to the limited time available, and the nature of the mission, a full GMP audit was not conducted. However the following points would need to be addressed in order to provide assurance that a vaccine of a consistent quality safety and efficacy is produced.

1. Processes were apparently not adequately defined but depended upon the skills and experience of the staff involved. Documentation that was available was often not signed, dated or complete.
2. Production and QC staff appeared to be achieving adequate results in relatively poor conditions. While some staff had received adequate and extensive training, training of all staff did not appear to be planned, and recorded.
3. Premises were nearing the end of their useful life and did not generally lend themselves to the maintenance of the physical parameters of GMP. In general the buildings were old, and of poor design which did not lead to logical work flows. Improvements could easily be made.
4. There was some evidence that the provision of vials and packaging materials was functioning satisfactorily. It is understood that this may in part be due to the purchase, testing, and release of these materials by the pharmaceutical section, which has a well developed QA system.
5. A unified approach needs to be adopted to the documentation system within the Biological Products Department. There was some evidence to suggest that whilst all divisions were aware of the importance of GMP issues as they relate to documentation, different divisions were taking different approaches. Quality Assurance needs strengthening to ensure there is a common approach.
6. Insufficient time was available to examine the receipt, storage and use of raw materials and the storage and distribution of vaccines after release.

Annex 1: Tentative timetable

Day	Team 1	Team 2
Tuesday, 23/4: am pm	WHO CDC GPO	
Wednesday, 24/4: am pm	CDC CDC	Thai Red Cross GPO
Thursday, 25/5: am pm	Bureau of Budget FDA	Division of Biological Products FDA
Friday, 26/4: am pm	Informal discussion re: report	
Saturday/Sunday, 27-28/4:	Write report	
Monday, 29/4: am pm	Final discussion (at GPO) Presentation of report (at CDC)	

Annex 2:

List of participants

Mrs. Amporn Ruangchan, Deputy Managing Director, GPO
Mrs. Patchara Kootiratrakarn, Deputy Managing Director, GPO
Mr. Tamnu Chantorn, Director Biological Products Department, GPO
Dr. Sit Thirapakpoomanunt, Chief of Serum Division, GPO
Mrs. Suchada Subchachaturus, Director, Biological Standardization Division, GPO
Mr. Ruangchai Kaweepornpoj, Toxoid Division, Biological Products Division,
GPO
Dr. Nopadol Somboon, Managing Director GPO
Mr. Chanasak Dechkum, Toxoid Division, Biological Division, GPO
Mr. Witthaya Suwannawong, Toxoid Division, Biological Division, GPO
Dr. Wacheerat Kangsanant, Director Experimental Animal Division, GPO
Miss Nartaya, GPO
Mr. Raboo, GPO
Mr. Tianchai Lakornrach, GPO
Mrs. Nantanee, GPO
Dr. Vason Pinyowiwat, MOPH, CDC
Dr. Damrong Boonyoen, Director-General, CDC
Dr. Boonlert Lumlertdacha, Thai Red Cross
Ms Thipchuta Bharnthong, Senior Medical Scientist, BCG Vaccine Production
Laboratory, Thai Red Cross
Dr. Henry Wilde, Queen Saovaktra Memorial Institute, Chulalongkorn University
Prof. Dr. Pakdee Pothisiri, Secretary General, FDA
Mr. Yuwandee Patanawong, Drug Control Division, FDA
Mr. Suboonya Hutangkabodee, Director Technical Division, FDA
Dr. Yuppadee Javrongrit, Inspection Division, FDA
Dr. Teeranart Jivapaisarnpong, Chief Biological Standardization Section,
Department of Medical Science
Dr. Jarong Wongwanich, Director Division of Biological Products, Department of
Medical Science
Mr. Chakramon Phasukavanich, Deputy Secretary General, BOI
Mr. Ampol Thiamsam, Bureau of Budget
Mr. Ampol Thimasan, Specialist in Programme and Project Evaluation
Dr. Brian Dobberstyn, WR/WHO
Dr. Godfrey Walker, MO/WHO