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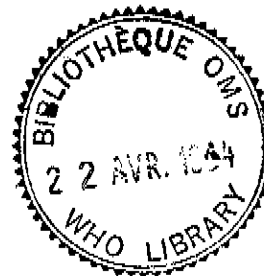
CVI MISSION TO EGYPT

TASK FORCE ON SITUATION ANALYSIS

NOVEMBER - DECEMBER 1992



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Report
CVI Task Force on Situation Analysis
Egypt
29 November - 4 December 1992

Executive Summary

The purpose of the visit of this team representing the Task Forces on Situation Analysis of Vaccine Supply and Vaccine Quality Control of the Children's Vaccine Initiative was to work with national authorities and participating donors to develop a strategic vaccine supply plan for Egypt for the next ten years. Special thanks are due to the Chairman of the Board and the staff of Vacsera for opening their files and their facilities to us, and to the Executive Director, EPI.

The terms of reference, to work towards development of a strategic plan for all EPI vaccines, had to be curtailed due to the time available. Priorities were based on the huge need for OPV for the polio eradication initiative, the need for TT of high quality for the initiative to eliminate neonatal tetanus, and a specific request regarding needs for DTP vaccine production. Although BCG demand and wastage were addressed, its production and quality control were not evaluated. Yellow fever and hepatitis B vaccines were not included in this analysis.

It has become increasingly clear that the traditional donors of vaccines for immunization programmes will be phasing out their direct support of vaccine procurement in this decade, and donors in Egypt are no exception. It is therefore important to recognize that Egyptian Ministry of Health authorities are already engaged in a series of meetings with donors, including WHO, UNICEF, and USAID, to discuss strategies for sustainability in vaccine supply. The team hopes that this report will be a useful resource to this group.

As Egypt has attained high immunization coverage and a reduced rate of population growth, the demand for vaccine has stabilized, except when new immunization strategies are employed, for example, for polio eradication. The team has analyzed the projected demand figures, and has made suggestions for their revision. It is essential that vaccine demand specifications and changes in these figures based on timely and continuous monitoring of use be communicated to the supplier as far in advance as possible.

Production and quality control at Vacsera along with current capacity and needed inputs were analyzed for OPV, TT and DTP. In general the team commends Vacsera for the quality of its products and the technical expertise and dedication of its staff. With implementation of GMP and Quality Assurance procedures, the National Control Laboratory should be well-equipped to assure the safety and efficacy of locally produced vaccines. Some recommendations will be made on the separation of this laboratory from the in-process testing laboratories, and on GMP and Quality Assurance procedures. To assure the quality of biological products produced in Egypt, there must be appropriate licensing requirements and adequate monitoring of production processes and products. It is essential that the National Control Laboratory function in such a way as to assure credibility in the quality of local production, particularly if supply of vaccines for export is envisioned.

Filling of imported OPV bulk is providing sufficient vaccine to meet the needs of EPI. It is estimated that ample filling capacity is present to exceed the projected 56 million doses of OPV required annually for the next several years. Analysis of potency data from both the production laboratory and the national control laboratory indicates a consistently potent product on release. Validation of the potency testing by WHO laboratories lends credence to these data. Some needs for capital expenditure and modification of filling procedures will be covered in the specific recommendations to follow; however, the general impression is that, as long as bulk vaccine is supplied to Vacsera, sufficient quantities of a quality product can be produced.

The tetanus toxoid production facility has the capacity to produce 25-30 million doses per year, more than enough to meet national needs for all tetanus toxoid-dependent products. The team found the facility and its staff to be competent and functioning well. Recommendations are included on the filling facility which should improve its sterile operation.

After a two-year gap in production of pertussis vaccine, Vacsera staff have resumed its production. However, to date no lots of DTP vaccine have been produced and released by Vacsera. The necessary mixing and testing will take at least five months; therefore, imported vaccine will be needed in 1993, after which local production may be able to fulfil most if not all of the demand. It is noted that a request to UNICEF for provision of some DTP vaccine has already been initiated for 1993. Recommendations for DTP production and filling, including capital expenditures and staffing, are given.

The present analysis suggests that Vacsera can provide, therefore, OPV and TT to meet Egypt's demand, and the team concludes that dependence on donations for these two vaccines is unnecessary (except for provision of OPV bulk). For DTP, as the capability to produce approved DTP is uncertain as yet, importation of the total demand will be necessary at least for the short term. Although BCG production was not evaluated, it is important to note that if it is to satisfy the national needs for BCG vaccine for school entry, Vacsera will not be able to provide BCG in 20 dose vials to meet the need for newborn immunization. Because of the high wastage levels seen to date with the larger vial sizes provided by Vacsera, Egypt will still need to import BCG vaccine for newborns. In addition, importation of measles vaccine, OPV bulk, and DTP

vaccine (at least for the short term) will be needed. This amounts to expenditure of about $2.5 million per year to import vaccines under even the most optimistic of scenarios. Means of increasing government financing to cover at least part of these costs on an increasing basis need to be investigated. One mechanism is to use the Vaccine Independence Initiative, which can increase the impact of government expenditure for vaccines by providing access to the UNICEF procurement system along with the possibility of paying for vaccines on delivery rather than in advance.

A major factor in any consideration of sustainability in vaccine supply for Egypt is the long term viability of Vacsera as a biologicals production institution. It is clear that revenues to Vacsera from production and provision of the EPI vaccines do not cover its costs. At the same time the prices for its EPI vaccines are nearly identical to those of UNICEF, making it difficult for Vacsera to compete for public sector procurement. Unless it is able to significantly increase productivity and expand its more lucrative private sector market, Vacsera's EPI vaccine operation will need continuing subsidy to provide high quality vaccines. Consideration of the most cost-effective role for and the best structure for Vacsera as a vaccine supplier to Egypt will be critical to any vaccine supply strategy.

KEY RECOMMENDATIONS

Vaccine Demand

A vaccine supply strategy by definition will depend on defining the amounts of each vaccine needed, the presentation and characteristics of the vaccine to be used, and the timeframe for provision of the vaccine. This requires careful planning well in advance.

- Projected demand figures must reflect true vaccine usage, based on target population size and growth (or decline), field wastage figures, if available, and immunization strategies in use. Timely and continuous monitoring of vaccine usage and communication of projected changes in demand must be communicated to the supplier as far in advance as possible.

Vaccine Procurement/Production

In a climate of lessening donor support to vaccine supply, governments must explore sustainable means to procure or produce vaccines. A critical part of the strategy for Egypt will be defining the place of Vacsera in vaccine supply. A "blended" approach to the procure/produce option is recommended, consisting of continuing to improve the productivity and viability of Vacsera as a producer while remaining open to divesting of operations which remain seriously uneconomic, exploring increased local financing options including "fee-for-product" and increased GOE support, increasing procurement efficiencies through participation in UNICEF's Vaccine Independence Initiative, and continuing to press donors for needs which cannot be satisfied through these measures. Specific recommendations are given:

- Explore other methods whereby the population might pay all or part of the costs of vaccines, starting with those that are relatively popular. The potential viability of this option was illustrated in the way that the population clamoured for hepatitis B vaccine, and was willing to pay a substantial sum for it.

- Discuss with USAID and UNICEF the potential value of participating in UNICEF's Vaccine Independence Initiative. The VII is intended to: improve the planning and efficiencies of vaccine procurement, improve vaccine related coordination between the Ministries of Health and Finance, allow the country to benefit from the lower prices available to UNICEF, and enable payment to be delayed until the vaccines are received in country.

- Initiate discussions with the MOH and other ministries regarding the fundamental mission of Vacsera and the extent to which the GOE wishes to preserve that mission regardless of cost.

- Initiate discussions with the MOH and other ministries regarding an organizational structure which would give Vacsera more flexibility to hire, fire and reward employees and disinvest itself of burdensome operations.

Management Issues for Vacsera

It has been noted above that Vacsera's long-term economic and financial viability can only be assured through important increases in its productivity. While this review did not have sufficient time to conduct a complete institutional analysis, there are several concepts which Vacsera might consider as ways to improve its organizational and management efficiency. The recommendations of the team are:

- Establish a commercially oriented marketing department to carefully examine existing and potential future buyers and develop a whole new pricing policy and strategy. While Vacsera's long-term ambition may include an expanded private sector market in Egypt and exports to regional countries, before investing for increased production for those markets, Vacsera must be careful to assure that those markets indeed exist and that their product is attractive in terms of quality, reliability and cost.

- Explore ways by which Vacsera's research department might more directly support and improve Vacsera's priority products and processes.

- Undertake an overall organizational needs assessment to more clearly identify the gaps between employee capabilities and Vacsera's needs.

- Prepare and initiate a more comprehensive and strategic personnel training programme.

- Engage a management and accounting firm familiar with the manufacture of vaccines and biologicals to conduct a detailed review of Vacsera's cost, estimate the financial savings from and recommend specific cost reductions, and refine Vacsera's cost and revenue accounting structure.

- Closely monitor trends for all Vacsera products. If losses continue to be sustained for certain products, explicitly and openly evaluate (according to previously agreed criteria) the merits of continuing to produce that product.

- Examine the feasibility of optimizing Vacsera's assets by selling off or leasing underutilized space or facilities.

- Examine the feasibility of modifying employee schedules and the work week to provide for longer work shifts in the production areas.

National Quality Control and Licensing

To assure the quality of biological products produced in Egypt, there must be appropriate licensing requirements and adequate monitoring of production processes and products. A totally separate National Control Authority charged with this function of which the National Control Laboratory was an integral part would be essential for assurance of the quality of vaccines produced at Vacsera, particularly if export is envisioned.

- Identify key components of a National Control Authority for Biologicals which would exist as part of the MOH, independent of Vacsera, and make recommendations to the MOH on the development of such an agency. This work is best done by an outside consultant working with the National Control Laboratory staff and the MOH.

- Separate the National Control Laboratory functions from those of in-process testing.

- Continue work done in collaboration with the Centre for Biologics Evaluation and Research staff in reviewing and suggesting QA/QC capabilities.

- Actively initiate, through the GMP staff, such activities as inspections of the production unit, selecting samples for testing, directing the development of Standard Operating Procedures, and other related activities to assure that production is being carried out under GMP conditions. Although maintenance of the cold chain is a critical function, it should be the responsibility of a different staff.

- Enhance compliance with GMP's accomplished through training on and off site. Completion of training in two two-week segments; total time required, approximately 6 months.

- Provide several items of laboratory equipment (including a spectrophotometer, automatic pipeting devices, etc.)

- Provide one PC for logging information regarding vaccine lot protocols and improved record accessibility.

Vaccine Production

General

Many of the observations made on areas where production could be improved are common to all production and filling units observed. These are included in this general section.

- Begin the implementation of GMP procedures at Vacsera in all locations. Many of the suggested changes require a change of behaviour, but will cost little.

    - Improve documentation in all areas by developing a complete written record of all steps taken to produce each lot. Include in batch records fill line checks and operator sign-in.

    - Carefully and fully write all process documents, with a second responsible officer signing the master for correct content.

    - Institute procedures to check thoroughly the operation of laminar flow hoods on a daily basis.

    - Calibrate the temperature recorders, and incorporate into the excellent system of subcontracting cold room and incubator temperature control checking of thermostat operation.

    - Better control over the cold chain can be accomplished by the installation of recording thermometers on freezers and incubators containing critical and costly materials. The longest time required is for the procurement process; installation can be done in approximately one week.

    - Investigate and fully document all batch problems.

- Fund a budget item of up to $100,000 for maintenance of equipment to provide the necessary equipment repair and spare parts needed to keep the equipment operational.

- To allow the National Control Laboratory to function independent of production, train staff from the production areas in the necessary testing and begin to develop the requisite laboratory testing functions within the production units.

- Additional recommendations for equipment and training for vaccine production are given in **Annex V**.

DTP/TT

- The activities of staff within the filling facility should be immediately corrected to be compatible with those essential for clean room operation.

- Perform necessary repair and maintenance on the water supply.

- Completely overhaul the filling line to improve the speed and performance of its function. The timetable would depend upon the commercial availability of parts and service technician time. Estimated time for completion, approximately one month.

- Hire four staff for DTP production and filling operations. Anticipated time for recruitment, 1 year. An additional year would be required for them to become fully trained.

- Accomplish compliance with GMP's through training on and off site. Training can take place in two two-week segments; total time required, approximately 6 months.

- Institute a better coordination between production and testing procedures, so that the work flow can be expedited.

- Vacsera should continue efforts to complete the current effort to demonstrate that its DTP experimental product is approvable for commercial use. In doing so, it must complete the production of three commercial scale lots, show that it passes all applicable control tests, and have them evaluated by the National Control Laboratory. In addition, the National Control Laboratory should have final container materials from each of these lots tested in an independent outside contract laboratory. This can be arranged on request to the Biologicals Unit, WHO. If all of these activities are successfully accomplished, the National Control Laboratory will be in a position to approve the product for commercial distribution and sale to the government can commence.

A rough timetable for the events outlined in the above recommendation follows:

Activity	Time Frame	Comments
Blend DTP bulks	Approximately three to seven days	
DTP final container filling for three lots	Approximately three to seven days	
Test three DTP final container lots	Approximately 10 weeks	This is correct if three test can be run in parallel
Test three DTP final container lots at outside laboratory	Approximately 12 weeks	These tests could be run in parallel
Review of Application for approval by National Control Laboratory	Approximately 7 days	

OPV

- Consider modification of the filling procedure or vial labelling so that the vials contain the stated number of doses.
- Order and install recommended new equipment to improve the sterile filling operation and the storage of bulk vaccine.
- Improve housekeeping, particularly in the mixing room, by painting.
- Test the individual potencies of the three polio types on final product on a random sample of lots. Occasional back-up testing outside the country can also be arranged on request to the Biologicals Unit, WHO.

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INTRODUCTION

In response to critical issues of vaccine supply for national immunization programmes, specifically to ensure that tetanus toxoids and other locally produced vaccines are of acceptable quality and to assure adequate affordable quantities of oral poliovaccine (OPV) for the polio eradication initiative, two Task Forces, on Situation Analysis of Vaccine Supply and on Vaccine Quality Control, of the Children's Vaccine Initiative (CVI) have been formed. The CVI is a partnership of public and private organizations working together to make available at an affordable price all the vaccine needed, of high quality, to immunize all the world's children against all vaccine-preventable diseases, at birth, orally, with a heat-stable vaccine.

The purpose of the visit of this team representing these two Task Forces was to develop a strategic plan for vaccine supply for the next ten years in Egypt, with specific attention to the feasibility of local production of tetanus toxoid (TT), diphtheria and tetanus toxoids and pertussis vaccine (DTP), oral poliovaccine (OPV) and BCG vaccine at the Egyptian Organisation for Biological and Vaccine Products (Vacsera) to meet all of the country's needs for these vaccines. The Terms of Reference of the team are given in **Annex I**. Persons working with the team in Cairo are listed in **Annex II**, and the schedule of work is given in **Annex III**.

Current Situation

Demographics and Economics of Egypt

Egypt has a population of 52 million inhabitants, a crude birth rate of 0.0338, and 1.7732 million newborns in 1990, estimated from 1989 figures. Government figures give the number of surviving infants in 1991 as 1.64 million. The number of births has decreased for the past three years (Data from EPI Project). The Gross National Product is US$ 34.67 million, and the GNP per capita is US$ 645.65.

Vaccine Use Data

Immunization coverage data reported by EPI for 1991 and 1992 are given in **Table 1**. Immunizations are delivered through 3437 health units in all Egypt. The session frequency is determined by the governorates, at one to two sessions weekly, depending on the target population. Different antigens are given at different sessions.

Wastage rates have been calculated based on EPI figures for the reported number of doses issued compared to the reported number of doses used. For the first two quarters of 1992, these figures are given in **Table 2**.

Table 1. Vaccine Coverage Data in Egypt

Vaccine	BCG	DPT3	OPV3	measles	TT2
1991	92%	86%	86%	89%	71%
1992 to June	92%	90%	90%	85	46%

Table 2. Wastage Factors (Rates) in Egypt Determined by Usage Data, Jan-Jun, 1992

Vaccine	Wastage factor (rate)
BCG (20 infant dose vials)	1.6 (38%)
measles (10 dose vials)	1.3 (23%)
OPV (20 dose vials)	1.5 (33%)
DTP (20 dose vials)	1.25 (20%)
DTP + IPV (20 dose vials) quadruple vaccine	1.32 (24%)
TT (20 dose vials)	2.56 (61%)

Vacsera supplies BCG in 40 infant dose vials, which will probably result in higher wastage factors. Data from 1989-90 on BCG based on use of larger vials showed wastage factors of 2.6 (62%). Vacsera's total BCG drying capacity for BCG is 4,000,000 doses per year in this presentation, which with wastage will cover only the needs for school entry children.

A recurring complaint from EPI staff to Vacsera is that vials of OPV are not yielding the stated number of doses. This may lead to higher wastage or a shortage of vaccine at the periphery. Studies at Vacsera indicate that due to vial construction, the total number of doses may not be delivered. Vacsera is now considering labelling modifications, usage instructions, or adding some percentage of overage to address this problem.

Vaccine use over the past four years is in **Table 3**. Vaccine sources are given in **Table 4**. Tetanus toxoid is produced at Vacsera, which also blends and fills OPV. Some DTP vaccine has been made in the past and more is planned (**Table 5**). Prices which the government pays for vaccines from Vacsera are close to UNICEF prices, delivered.

UNICEF has been supplying OPV in bulk, and BCG, DTP, and TT to supplement local production. IPV, combined in a quadrivalent form with DTP, has been supplied with the first dose of OPV, paid for by the Egyptian government. Hepatitis B vaccine has been introduced nationwide via a donation from USAID. Vacsera is now examining alternatives either to produce it under technology transfer or to import it in bulk and fill it at Vacsera. WHO supplied some TT, 185,000 doses, in 1991.

Table 3. Vaccine Use, 1989-1992						
Year	doses	BCG	DTP	OPV	measles	TT
1989	doses issued	4,321,980	6,454,560	9,617,320	2,184,060	3,757,520
	doses used	1,513,644	6,331,320	5,670,135	1,614,459	913,412
1990	doses issued	5,486,800	6,849,100	22,293,600 (includes campaigns)	1,882,250	3,434,630
	doses used	1,516,524	6,016,068	6,068,088	1,470,080	1,001,610
1991	doses issued	5,415,000	not available	26,000,000 (includes campaigns)	1,500,000	9,850,000
	doses used	not available	not available	not available	not available	not available
1992 through June	doses issued	996,588	4,640,740 (995,494 as DTP-IPV)	4,418,032	859,980	1,691,600
	doses used	718,151	3,654,003 (751,031 as DTP-IPV)	2,857,534	666,789	650,491

Table 4. Vaccine Sources, 1990-1992						
Year	Source	BCG	DTP	OPV	measles	TT
1990	UNICEF	3,000,000	10,000,000	bulk	1,500,000	5,000,000
	local	1,760,000	none	17,577,600	none	none
1991	UNICEF	4,000,000	7,000,000	bulk	1,500,000	5,000,000
	local	1,415,000	none	26,315,600	none	1,160,000
	other	--	1,300,000 donation as DTP-IPV	--	--	185,000 WHO
1992	UNICEF	4,000,000	7,000,000	bulk	2,500,000	5,000,000
	local	1,750,000	none	27,370,600 to 31 October	none	not available
	other	--	1,300,000 donation as DTP-IPV	--	--	--

Table 5. Vaccine Produced by Vacsera 1989-1991, Millions of Doses					
Vaccine /Year	BCG	DTP	OPV	TT	DT
1989	0.700	2.8	3.1692	1.987	2.166
1990	1.3112	--	17.578	--	2.764
1991	2.8612	--	26.3156	1.160	3.7
Stated capacity	4 in 40 d vials, 2 in 20 d vials	4.0	45	4	4

Identity of Donors

The major EPI donors are WHO, UNICEF, Rotary, and USAID. UNICEF provides vaccines and cold chain equipment, as well as other items and studies essential to the success of EPI. UNICEF has indicated that it will be phasing out its support to Egypt, but has pledged to continue to provide the needed vaccines at least through the end of 1993. It is not clear what the level of UNICEF support will be after that time. Rotary, through its PolioPlus grants, has supported polio eradication activities, including funding OPV through UNICEF. The PolioPlus grant has now been exhausted, and it is not clear what Rotary's future contribution, if any, in terms of funds for vaccines, will be. WHO provides technical expertise and fellowships, and these will continue. USAID has had a major involvement in EPI through the Child Survival Project, which was funded for five years at US$ 67 million. This project will be ending at the end of 1995. The donors have been meeting regularly with the Ministry of Health officials to develop a sustainability plan for vaccines for Egypt.

National Licensing Procedures

These requirements have been developed for pharmaceuticals, and have been extended to vaccines. The procedure requires submission of a file for evaluation by a series of boards which analyze the scientific and technical data. The facilities are inspected and a license is granted for about two years. The process of initial licensing takes up to one and one-half to two years. The file contains a description of the manufacturing process, a copy of the leaflet, and control tests done on the final product, as well as other information deemed necessary by the boards. Where relevant, clinical information may be required.

To date, none of the EPI vaccines produced by Vacsera are licensed in Egypt. A submission has recently been made for licensing of TT.

Perceived Needs and Constraints for Vaccine Self-sufficiency

Communicated to the team at the outset of the mission were the following concerns about the ability of Egypt to approach sustainability in vaccine supply:

1. Need for the government to recognize that donors were pulling out, and to begin to plan for the future
2. Some equipment needs for the OPV and DTP production areas to provide enough vaccines to meet the demands of the government
3. Need for implementation of GMP's and QA procedures at Vacsera
4. Need for better planning for vaccine needs, and timely communication of changes in demand to Vacsera
5. Inability of Vacsera to raise prices to cover the true costs of vaccine production. Consequently staff salaries are low.

Assessment of Demand

Table 6 summarizes EPI's estimates for vaccine requirements for the routine EPI in Egypt for 1993-1996. These requirements were calculated by EPI using the following assumptions: number of births in 1989 as a starting point, wastage for all vaccine 25% or 1.33, growth rate of 3.5% per year, three doses for DPT and OPV plus one booster at 18 months (a fourth OPV dose is now recommended, but was not included in the EPI estimate; it has been included in the team's projection in **Table 7**), TT requirement calculated for two doses to pregnant women equalling the number of births. Full (100%) coverage is assumed in EPI's calculations, and for the other calculations mentioned. UNICEF Egypt has also estimated requirements, but has used a newborn population of 2 million and an annual increase of 3%.

Table 6. EPI Egypt Estimate of Vaccine Requirements to 1996

Year	Polio	DTP	Measles	BCG	TT
1993	10,838,252	10,838,252	2,615,053	2,645,407	5,116,356
1994	11,217,591	11,217,591	2,706,579	2,737,996	5,295,429
1995	11,610,207	11,610,207	2,801,310	2,833,826	5,480,769
1996	12,016,564	12,016,564	2,899,356	2,933,010	5,672,596

The team feels it would be useful to take into account the declining birth rate and the reported wastage factors seen with vials as supplied by Vacsera, and has calculated the values seen in **Table 7A**. All values in **Table 7A** are calculated assuming the figure for surviving infants given by the Government of Egypt (GOE) for 1992, 1.644 million, with no change for subsequent years. The team has discussed its estimates with EPI, the MOH, UNICEF, and USAID, and all were provisionally satisfied with the figures. Careful monitoring of vaccine usage, with revision of demand at least quarterly, and possibly monthly, will be necessary.

For neonatal tetanus elimination, immunization campaigns for pregnant women in seven high risk governorates are planned, two rounds each, for an additional 2 million doses per year. These were not included in the EPI estimates, but have been included in **Table 7A** through the end of 1995, when the global target of elimination of neonatal tetanus is projected to be met.

For polio eradication, the Ministry of Health, which declared a target for polio eradication of 1994, has already embarked on many activities to achieve this purpose, consistent with a Polio Eradication Plan encompassing the strategies recommended by WHO technical groups. The increased utilization of OPV for this purpose is about 40 million doses, leading to an estimated demand for OPV annually as given on the next page:

Routine Immunization	**12 million**
Annual Mass Campaigns (two rounds, reaching all children under five years of age, conducted in low season for poliovirus transmission, continued annually until wild poliovirus is eliminated)	**24 million**
Containment Measures (a certain number of doses, about 2000, of OPV given to children around a case of polio)	**3 million**
Mop-up Operations, 2 rounds (limited to high-risk governorates based on surveillance data, immunizing all children under five, house-to-house, in the low season for poliovirus transmission)	**12 million**
Reserve	**5 million**
Total	**56 million**

Despite accelerated immunization activities, a well-functioning Acute Flaccid Paralysis surveillance system, and the development of two viral diagnostic laboratories, the team believes that eradication of polio by 1994 cannot be achieved in Egypt, particularly as it is bordered by countries which have not yet begun eradication activities. The number of polio cases is decreasing, and it is expected that given thorough and meticulous execution of the planned strategies, polio control can be a reality in Egypt by the end of 1994. Going from polio control to freedom from circulating wild polio virus will necessitate continuation of supplementary immunization strategies probably for another three years after 1994, with maintenance of high immunization coverage and aggressive response to a single detected case of polio after that time.

Accordingly, the supplementary immunization vaccine needs for OPV estimated by EPI given below have been incorporated into **Table 7A**, and extended through 1997, with amounts calculated for outbreak response (assuming two doses to all children under five on detection of a single case of polio) beyond that date.

Table 7A. Calculated Demand Figures, 1993-1999

Year		1993	1994	1995	1996	1997	1998	1999
Required doses, millions	BCG, 1 dose to infants	2.63	NO CHANGE FROM 1993 FIGURES					
	DTP, 3 doses plus booster	8.75	NO CHANGE FROM 1993 FIGURES					
	measles, 1 dose	2.2	NO CHANGE FROM 1993 FIGURES					
	TT, 2 doses to pregnant women	4.93	NO CHANGE FROM 1993 FIGURES					
	TT, campaign in high-risk governorates	2	2	2				
	OPV, 4 doses plus booster	12.33	NO CHANGE FROM 1993 FIGURES					
	OPV, supplemental activities	44	44	44	44	44	22	22

Assumptions: for BCG, 1.6 wastage factor; for DTP and measles, 1.33 wastage factor; for TT, 1.5 wastage factor overall, with 2 million doses for campaigns in high-risk areas through 1995; OPV for routine system, 5 doses and 1.5 wastage factor; OPV supplemental activities, using EPI projections of 44 additional doses per year through 1997, then reducing to nation-wide outbreak response for all children under 5 with 2 rounds, if a case of polio is reported.

Table 7B. Costs of Imported Vaccines, 1993-1999								
Year		1993	1994	1995	1996	1997	1998	1999
Cost of imported vaccines in US $1000 including 20% freight, and 8% annual increase in UNICEF prices from 1992 prices	BCG	221.4	239.1	258.3	279.0	302.0	325.6	351.6
	DTP	651.9	382.2 plus	LOCAL PRODUCTION				
	measles	456.5	493.0	532.4	575.0	621.0	670.7	724.4
	TT	LOCAL PRODUCTION						
	TT high-risk	LOCAL PRODUCTION						
	OPV, bulk costs	266.3	287.6	310.6	335.4	362.2	391.2	422.5
	OPV supplemental, bulk costs	950.4	1026	1108	1197	1293	699.6	755.6

Production Assessment

OPV

Capacity of Filling Operation. OPV is being filled from concentrated bulk purchased by UNICEF into locally purchased packaging components. This section of Vacsera should be capable of filling 60 million doses of OPV as defined in the demand projections, without adding a second shift, or purchasing major filling equipment. Actually, the section is already operating at this level of capacity. It is currently filling 10,000 vials daily, which equates to a capacity of at least two million vials annually, based on a 200 work day year, and three hours per day effective filling line operation, which is management's estimate of the maximum productive time available yearly.

Fortunately, the current very large forecast demand for OPV will require only 1.5 million vials for machine filling (20 and 50 dose vials) and 400,000 hand filled vials (10 dose vials). This represents roughly 150 machine fills per year (or only 75% of existing 'capacity'), and 200 hand filled batches.

It should be noted that 150 of the forecast hand filled batches are for EPI use. The remaining 50 batches are planned for private sale at LE 0.68 per dose or approximately US$ 0.21. The MOH price is LE 0.20 per dose or $0.06.

GMP's in Filling Operation. In general, Vacsera is operating a reasonably productive, good quality OPV bulk filling area. However, there are numerous GMP errors which would prevent this department from passing a formal full scale GMP audit, a prerequisite to exportation. While the operating staff observed in filling and related work have superior skills and discipline to that observed in the equivalent DTP filling area, there are a wide range of areas which could be corrected at no or low cost.

- Process documents, in particular for the bulk dilution process, need to be carefully and fully written, with a second responsible officer signing the master for correct content, and the quality control office also approving and maintaining a master copy. The source and basis of formulas used, e.g. the dilution formula "," should be clearly documented.

- Batch records to include filling line checks and operator sign-in could be instituted.

- Repainting, particularly in the mixing room, could improve housekeeping.

- Instituting procedures to check thoroughly the operation of laminar flow hoods on a daily basis could also be completed by the current staff with no outside assistance or cost to the institute.

- Calibrating the temperature recorders, and checking thermostat operation needs to be incorporated into the excellent system which subcontracts cold room and incubator temperature monitoring and control.

- Problem batch investigations should be fully documented, even and perhaps especially when the problem could not be clearly identified. Problem identification is often very difficult to confirm; usually the production laboratory resolves the problem without a conclusive idea of the cause. This situation applies to the most advanced, highly funded laboratories as well as those less fortunate. However, the GMP's require the documentation of the investigation. Often the process of documenting the problem analysis will solve a variety of processing problems.

Potency of Product. Much concern has been voiced by some segments of the Egyptian population on the potency of the OPV filled at Vacsera. A review of the documentation indicated that potency determinations were in accord with those conducted by the manufacturers of the monovalent bulk lots imported, that calculations for dilution were being made correctly, and that the total virus titre of the filled bulk was as expected. Test data from both the production laboratory and the National Control Laboratory were in agreement and showed a consistent level of potency for vials selected randomly from each fill lot, regardless of vial size.

Last year five lots were tested by WHO contract laboratories and found to have potency above the required levels and in agreement with values found at Vacsera. Nevertheless, it would be important to have the individual potencies of the three polio types tested on final product on a random sample of lots. Occasional back-up testing outside the country could also be arranged on request to the Biologicals Unit, WHO.

Though the potency of the vaccine as it leaves Vacsera is satisfactory, the integrity of the cold chain in the field has also been questioned. The latest field efficacy data show an efficacy of 90%, consistent with earlier observations. It would be useful, if possible, to extend these studies to determine field efficacy by polio type. The Executive Director, EPI, has suggested testing the potency of samples from various points on the distribution system. Careful monitoring of the cold chain may give an indication of spots where vaccine might be exposed to a titre loss. Vaccines could then be selected from these sites and tested in Egyptian laboratories in coded fashion. WHO could review the protocol and arrange duplicate testing of a random selection of samples if desired.

Tetanus Toxoid

Production. The staffs in the tetanus production unit are knowledgeable about the fermentation and the downstream purification of tetanus toxin and preparation of tetanus toxoid. They have used both 140 and 350 litre fermenters for production. The team was impressed with their application of ultrafiltration technology for toxoid concentration and dialysis. Although the toxin level (Lf per ml) in their cultures is low, the yields of toxoid have been very consistent between 70% to 80%. The facility for tetanus production is well maintained.

Vacsera is doing some things remarkably well. The TT staff have replaced the diafiltration step with an ultrafiltration process that both saves time and improves quality (We recommended the process be published.). The processing vessels requested are primarily to permit the TT area to reach the 25 million dose level and are needed immediately.

Filling. The team did not review procedures for this product in detail. The same type of containers are said to be used as with DT. The bulk is transferred in these containers to the DT filling area for the filling of final containers.

Capacity. It was estimated that on the basis of two fermenters (140 litres and 350 litres) being in operation, the unit should be able to produce 1.0×10^6 doses of tetanus toxoid per week. Based on this, Vacsera should be capable of producing 25 to 30 million doses of tetanus toxoid per year with the existing staff and facilities. The plant is making over four million doses of DT annually for routine use, and over a million doses of TT.

Assessment of Product. Based on the testing results supplied to us by the National Control Laboratory, Vacsera should be capable of producing high quality tetanus toxoid preparations. They should be able to produce sufficient amounts of toxoid for TT, DT and DTP preparation for Egypt's EPI.

DTP and DT

Production. The area is currently being used for the production of diphtheria toxoid and pertussis component. The evaluation team was impressed with the diphtheria material being produced which had consistently excellent Lf levels per ml and a high yield of diphtheria toxoid (see below).

The DP staff appear to have modified a very sophisticated Westfalia continuous separator and made it function well for both diphtheria and pertussis separations. Many UNICEF-assisted projects have not been successful in achieving this.

The large DP fermenter has not been used and appears to have been a bit dismantled to keep the others running (two 140 litre in TT and DP, and one 350 litre in TT). To reach the production demand forecast the unit will need to bring all its fermenters into fully operational state.

The space for production appears to be adequate for the production of DT and TT and DTP separately, devoting the facility to serial production. A complete analysis of the utility requirements was not done. The water supply was evaluated and found to need repair and maintenance. HEPA filtered air is provided for the building. The storage area for raw materials did not appear to be well organized. (See Filling section for further details on this facility)

The Vacsera staff identified maintenance of equipment as one of their major problems. The vaccine production staff maintains their own equipment. This is particularly difficult since, for example, some items like the fermenters were no longer being made, compromising the availability of replacement parts and increasing their cost. They do not have off-shore maintenance contracts.

The long range plan developed by Vacsera for achieving independence from product sources from outside of the country appears to be based on a needs analysis. As noted above, there are not enough data on the current method of DTP production at this point to make accurate predictions. The proposed increase of additional workers seems a reasonable suggestion, but would need to be fine tuned later based on the success achieved in preparing vaccine lots. Since all of these new workers would have to be trained by the current personnel, they should be brought in gradually so as not to suddenly overtax the capacity of the current staff with "on-the-job" training duties.

Filling. Evaluation of the DTP filling area indicated that GMP's were not being adhered to in a number of instances. A window in the corridor adjacent to the DTP filling area was open to the outside, as was the door to the suite. Employees were noted to be eating in the facility. A filling operation was in process; the employees were gowned and masked, but not wearing gloves. A laminar flow tent was in place over the filling operation; however the equipment did not cover the entire area involved in the filling. On the automated filling line, unaffixed labels had been left unsecured.

Vacsera has made an excellent decision to standardize filling of DTP and TT in the same vial, with colour coded caps for DTP, TT and DT. However to make it work reliably under the projected increase in workload, a complete renovation would be needed. It is suggested that the filling room be brought to Class 100 standard and that smooth walls and flooring would be advisable.

From the team's perspective DTP filling is a hypothetical discussion, as the plant has never made DTP which was used in normal programmes in Egyptian infants. Some years ago less than five batches were filled during the RIVM/Netherlands bilateral assistance period, but the plant has not produced DTP independently since then.

The forecasted EPI programme need is for nine million doses of DTP, and about seven million of TT. The question for filling capacity is how many vials of each will need to be processed through the existing filling line, and if that exceeds its capacity. Based on the above, the line will need to fill 1.2 million vials per year (16 million/15 doses per vial). Currently the line (a Bausch and Stroebel with auto wash, sterilize, fill, stopper, cap, and labelling all in line which would cost about $1.5 million today) is filling 9,300 vials per day (three hours effective) on a routine basis. At this level of effective use the line could fill all the DTP and TT needed by the MOH in 133 days. As the plant uses a 200 day per year effective work period, the line would be used about 66% of its current useful capacity.

This would leave the line available to fill DT (which is not requested by EPI, but is a product with significant demand in the country), and other products useful and permissible to fill in the facility. This excess additional capacity can be approximated at 600,000 vials/year (70 days not used for DTP and TT x 9,300 vials/day).

However, the existing filling line is being operated in a seriously deficient manner. The line needs an urgent overhaul to include correct change parts for the new Egyptian moulded glass vials (the line was originally to run on imported 10 ml tubing vials, and is now using 7.5 ml moulded vials). The line also needs a laminar flow hood that fits the line correctly. The original has a half meter gap between the exit of the vial sterilization tunnel, and the beginning of the filling line. Considering the level of sophistication of the equipment, and the virtually critical need for pure air at this point of the process, this is a surprising design error. It should be corrected at once. As with the OPV clean room, there is no or minimal air quality monitoring in process. Again, an air quality monitoring set is recommended (along with training in how to properly establish a monitoring programme, see below). The cost of repairing or replacing these items is attached in DTP equipment needed. Virtually all the DTP equipment recommended is needed URGENTLY. The auto labeller has not worked for five years and is in need of both spares and an overhaul.

Closely related to the function of the filling line equipment is the building it functions in. While originally designed to be a normal aseptic production area, it has not been maintained sufficiently to assure that level of performance. The critical service equipment water for injection treatment and storage, and air purification need immediate review, overhaul and retraining if necessary. The water system provided by the RIVM project has ceased operation and been replaced with a thermocompression still, the water storage tank air vent has not been checked or changed in an unknown period (the system operator was unaware of the filters function), nearly all gauges are nonfunctional, and no documentation of the units operation were evident. This does not mean the plant has unsterile water, it means the system is not maintained or operated in an acceptable manner. Again, training and overhaul is urgently needed (see **Annex V** for costs).

Capacity. Thus far, despite efforts between 1985 and 1991, the total production of DTP vaccine has only been 12.5 million doses. No material was made in 1991. Production was resumed in September of 1992. None of the earlier material produced has been successfully tested for potency by Vacsera, although five lots are said to have been tested in the Netherlands in 1988 with passing potency results. The new production material is currently in process, and at least one bulk pertussis lot has been evaluated for potency and passed the test. The production unit is also planning to employ a new separator apparatus which may increase the ease and speed of production. This has been used successfully a few times.

Based on the results of the four recent production runs, the team found that Vacsera scientists can consistently produce pertussis cell density in the 140 litre fermenter to an average of 55-65 OU/ml, and to consistently obtain high yields (average 75-80%) of final detoxified pertussis cells. Both fermenter results and downstream process results are remarkable. The potency of the final bulk needs to be evaluated.

The team recognizes that Vacsera scientists are highly motivated and knowledgeable, and there is good potential for the production of high quality pertussis component for DTP production. They have never used the 350 litre fermenter to grow pertussis culture, and were advised to start to operate this fermenter as soon as possible to establish optimal conditions for pertussis cell production in it. At this point the team is unable to estimate the maximum capacity for annual production of the pertussis component at Vacsera.

The same group of staff is also responsible for the production of diphtheria toxoid. They have used only the 140 litre fermenter for this purpose. The team was impressed with the consistently high titre in the fermenter (an average of 200-250 Lf/ml). The average yield of diphtheria toxoid was about 65%. It is estimated that they could produce 0.5 million doses of diphtheria toxoid from each 140 litre fermenter every two weeks. This mean that it is possible to produce at least 20 million doses working 40 weeks per year.

Standard Operating Procedures for diphtheria, pertussis, and DTP production were not available. Batch records for each lot of product were not well organized, and data were kept in several locations. Vacsera should write SOP's for each product, and should initiate GMP training for the production staff as soon as possible.

Compliance with GMP's. TT and DP bulk manufacture were not observed. The DTP filling area, and related wash/preparation were functioning and briefly observed. From the brief observation period, it appears that the DTP work area is in serious need of sterile technique and basic GMP retraining. A few observations:

- The building is HEPA filtered throughout, meaning very high purity air is supposed to be in the entire complex. However, the same building has open windows and outside doors, and essentially no effort is made to reduce the dust level of incoming staff and visitors. The doors need to be repaired so they close automatically (the current door fit is very poor), the windows need to be closed permanently, and the air conditioning system maintained. This is fundamental to operating buildings of this type.

- Clean rooms are supposed to be clean. The room needs to be emptied of all extraneous items and scrubbed immediately. Clean room operators wear sterile or at minimum very clean gloves in the filling operation. They do in OPV, they should in DTP. Personnel should be minimized in the clean room, especially under the laminar flow hood. Not more than two people need to be in the room, and as few under the hood at any time as necessary. The filling line does not operate properly now so the line is being continuously 'assisted', i.e. rejects are being reprocessed for recapping or restoppering. It's a bit like riding in a Mercedes with ten people pushing it.

- The wash/sterile preparation room is also serving as the cafeteria. When we entered the area staff quickly tried to hide plates and pots before they were noticed. The staff obviously know this violates all rules of sterile processing, but continue to eat in the building.

It is the team's impression that the DP production and DTP filling area are operating on two levels. Level one is essentially a vaccine development lab staffed by dedicated scientists struggling to make some very complex equipment operate properly. Level two are the workers who primarily prepare materials and operate the filling and packaging area. This area reflects very little of the discipline and training that are essential and basic to this type of operation. The cadre of 'trainers and policemen', production supervisors, who know the rules and enforce them is missing. This is easy to criticize and hard to overcome. It will require hiring, training and keeping the right people. This is addressed below in training needs.

Assessment of Product. The data show that Vacsera can consistently produce a high quality and safe diphtheria component for DT use. The pertussis component produced recently by the modified continuous separation method (Westfalia system) needs to be tested. The team suggests that this product be tested both at Vacsera and at outside laboratories to evaluate the safety, potency and consistency of production of the pertussis component.

It was predicted that with additional effort (i.e. longer working hours or the use of more than one shift), Vacsera would be able to produce lots in a matter of about five months and could increase its effectiveness to meet Egypt's projected needs perhaps beginning in 1994.

Assessment of Quality Control System

At present, the National Control Laboratory is an integral part of Vacsera, which makes independent control and release of products impossible. The activities of the sector on Control and Research, in which the National Control Laboratory is situated, also include implementation and monitoring of GMP's. The National Control Laboratory has been functioning also as an in-process testing laboratory for some products.

National Control Laboratory

That there has been significant progress in this area over the past several years was documented by our review of the records and conversations with Vacsera employees in the course of reviewing the DTP family of products. There has been a marked improvement in the quantity and quality of record keeping, with the use of reporting forms which contain summary reports of test results clearly and completely. Individual records of the results of testing from laboratory notebooks in which they are recorded through the final summaries appear to be complete and accurate. There has been good progress in the development of Standard Operating Procedures. A review of a number of these documents indicate that they are clear and complete.

There continues to be the tendency for the National Control Laboratory to function as the primary and only test laboratory in many instances. This is perhaps understandable given the stage of development of Vacsera's programme but is unacceptable for independent product release.

There is also a need for better coordination between production and testing procedures. It is important to evaluate the ability to perform all tests on a product early in the process of development of manufacturing. For example, with pertussis, greater assurance that the product can be effectively and efficiently made would be available if it had been possible to conduct potency tests in-house, and then to use these to monitor production serially throughout the production process.

It will be important to continue consultations that will focus on this area. The ongoing project with the Centre for Biologics Evaluation and Research of the United States Food and Drug Administration can address some of these activities.

GMP's and QA

A recent addition to the Sector on Control and Research is a group under the responsibility of the General Director for GMP. It would be hoped that this group would be actively initiating such activities as inspections of the production unit, selecting samples for testing, directing the development of SOP's, and other related activities to assure that production is being carried out under GMP conditions. Unfortunately, this has not yet happened. This group's efforts at monitoring compliance with GMP's were, at this point, limited to evaluation of the cold chain and selection of samples from some production lots for testing.

It is evident from reading the above description of the production processes that GMP is not yet the rule at Vacsera. A review of some of the deviations from GMP noted with production staff was received with interest and some surprise. GMP training and monitoring must be initiated as an immediate priority.

General Licensing and Quality Control Procedures

As outlined in Section 2, the current national licensing procedures were developed for pharmaceutical products and have not been appropriately adapted to biological products. There is no independent agency with the technical expertise to license biological products and no functioning mechanism to implement the necessary inspections, review of clinical data, and appropriate testing which would be necessary to assure the quality of the vaccines and other biologicals being produced. The National Control Laboratory in the Sector on Control and Research is attempting to fill the role of a release authority, but is compromised by its need to act also as an in-process control laboratory. An independent National Control Authority within the MOH is a must. Thought needs to be given to the role of the National Control Laboratory *vis-à-vis* the National Control Authority, and its relation to Vacsera. We would recommend that it be independent of Vacsera, with new training and facilities to be developed for in-process control testing within the production laboratory.

Financial Evaluation and Production Options

Options for Meeting Egypt's EPI Vaccine Requirements

The projected constraints in donor resources are discussed above. At the same time, the Government of Egypt faces ongoing budgetary restrictions. Egypt's EPI has at least four options which it might consider to meet its EPI vaccine requirements:

a) **Maintain the Status Quo**: UNICEF has made clear that it cannot continue to donate the levels of vaccine and bulk that it has in the past and that are projected for the future. Through GOE resources, cost recovery possibilities or other donors, alternatives to the current financing arrangements must be found.

b) **Complete Local Production**: For the foreseeable future this is not a viable technical option. No local production of measles, OPV bulk, or hepatitis B bulk is being advocated presently.

c) **Import All Required EPI Vaccines**: From purely economic and financial perspectives, this is currently an attractive option. Over the near term, imported vaccines through efficient procurement systems such as UNICEF's will become even more price competitive with Vacsera-produced vaccines than they are now, and there is no assurance at this time that Vacsera can remain price competitive.

d) **Blended Approach**: A "blended" approach consists of: 1) continuing to improve the productivity and viability of Vacsera as a producer while remaining open to divesting of operations which may remain seriously uneconomic; 2) exploring increased local financing options including "fee-for-product" and increased GOE support; 3) increasing procurement efficiencies through participation in UNICEF's Vaccine Independence Initiative; and 4) continuing to press donors for needs which cannot be satisfied through these measures.

The "blended" approach is recommended. For political and security reasons, supply assurance and national pride, the GOE is likely to remain fully committed to sustaining Vacsera as its national organization responsible for EPI vaccine production and procurement. Even if non-economic production activities were abandoned, Egypt would still need to retain many of Vacsera's procurement capabilities. In addition, from an economic/financial perspective, there is nothing illogical or even "un-businesslike" about lucrative aspects of a company cross-subsidizing unprofitable elements of that business if those elements: 1) do not jeopardize the profitable aspects; 2) help provide visibility and a positive image for the company; and 3) fill a valid need. Under this approach, it is further recommended that Egypt:

- Undertake the organizational and management recommendations for Vacsera contained on the next page;

- Explore other methods whereby the population might pay all or part of the costs of vaccines, starting with those that are relatively popular. The potential viability of this option was illustrated in the way that the population clamoured for hepatitis B vaccine, and was willing to pay a substantial sum for it.

- Discuss with USAID and UNICEF the potential value of participating in UNICEF's Vaccine Independence Initiative (VII). The VII is intended to: improve the planning and efficiencies of vaccine procurement, improve vaccine related coordination between the Ministries of Health and Finance, allow the country to benefit from the lower prices available to UNICEF, and enable payment to be delayed until the vaccines are received in country.

Vacsera's Financial Health

In recent years a significant drop in the rate of inflation and the virtual disappearance of any shadow pricing for foreign exchange have greatly improved the economic returns and financial health of productive enterprises in Egypt. Despite these positive developments, however, this assessment believes that the financial situation of Vacsera's vaccine production operation may be the biggest obstacle to long-term viability. Based on Vacsera supplied figures, this assessment reviewed the cost and price structures for three EPI vaccines: Polio, DTP and Tetanus Toxoid. The results of this review are summarized in **Tables 8A-8C**. Potentially significant findings include:

- **Polio:** Given current costs, pricing structures and projected production for 1993, the Vacsera polio filling and finishing operation will lose $24,000 per year ($2.5 million if true economic costs including UNICEF donated vaccine are considered). Even excluding the cost of the donated bulk, Vacsera's costs are more than 20 percent above the UNICEF price. The losses on polio production are large enough to cancel out the very modest profits realized for DTP and TT.

- **DTP:** When last produced and sold, Vacsera essentially broke even on the costs and sales of its DPT vaccine ($103 per 1 million doses). At the same time, its public sector price was identical to UNICEF's.

- **TT:** Vacsera makes a slight profit on this vaccine while keeping its prices competitive with UNICEF's.

- On all three vaccines, an average of approximately half of all costs go to support the personnel, buildings and equipment of Vacsera's "non-product" departments (e.g. Administration, Public Relations, Research, Planning). These costs seem particularly high given the fact that Vacsera is dealing with few regulatory/licensing issues and funds little research and development (most research is donor funded).

Table 8A. Product Balance Sheet - OPV								
REVENUE/INCOME								
Sector	% Sales	Purchase Revenue less Price tax of 10%		Vial Size	Price per Dose		Revenue per Dose	
					LE	$	LE	$
GOE	0.98	4.44	4.00	20	0.222	0.067	0.200	0.060
		11.11	10.00	50	0.222	0.067	0.200	0.060
Private	0.02	6.78	6.10	10	0.678	0.205	0.610	0.184
		11.89	10.70	20	0.595	0.180	0.535	0.162
1992 UNICEF PRICES (20 DOSE) 0.070								

COST OF GOODS SOLD (All costs in LE per 1 million doses produced)		
1. Chemicals	Bulk, stabilizer, etc	63,000 contributed by UNICEF
2. Filling	Inputs including vials, stoppers, labels, etc	40,000
3. Direct Personnel	Salaries and benefits of all people involved in OPV production	4,000
4. Water/Electricity	OPV only	6,000
5. Direct Services	Communications, transport, postage, etc for OPV only	1,500
6. Indirect Personnel	Pro-rated share of personnel from "non-product" departments	6,000
7. Indirect Building/Equipment	Amortization of polio equipment and Vacsera buildings. Equipment amortized over 5-20 years, buildings over 50, includes spare parts for OPV production	170,000

COST OF GOODS SOLD (All costs in LE per 1 million doses produced)			
8. Other Equipment	Pro-rated share of all vehicles and equipment from "non-product" departments, including furniture, computers, testing and research equipment, and vehicles, water, electricity	15,000	
9. Indirect Services	Other miscellaneous expenses including communications, transport, postage, etc for "non-product" departments	2,000	
SUBTOTAL		307,500	
10. Loss/wastage	@ 15 per cent	46,125	
TOTAL COST PER 1 MILLION DOSES		353,625	
COST PER DOSE		LE 0.354	$ 0.107
PROFIT (LOSS) PER 1 MILLION DOSES	GOE PRIVATE	(150,749) 5,132 (145,617)	(45,543) 1,550 (43,993)
PROFIT (LOSS) FOR 56 MILLION DOSES		(8,154,552)	(2,463,611)
SUBTOTAL (assuming no cost of bulk)		244,500	
10. Loss/wastage	@ 15 per cent	36,675	
TOTAL COST PER 1 MILLION DOSES		281,175	
COST PER DOSE		LE 0.281	$ 0.085
PROFIT (LOSS) PER 1 MILLION DOSES	GOE PRIVATE	(79,748) 6,581	(24,093) 1,988

Table 8B. Product Balance Sheet - DTP (All costs in 1989/1990 prices)								
REVENUE/INCOME								
Sector	% Sales	Purchase Price	Revenue less tax of 10%	Vial Size	Price per Dose		Revenue per Dose	
					LE	$	LE	$
GOE	0.97	2.94	2.65	20	0.147	0.044	0.132	0.040
Private	0.03	4.44	4.00	20	0.222	0.067	0.200	0.060
1990 UNICEF PRICES (20 DOSE) 0.043								

COST OF GOODS SOLD (All costs in LE per 1 million doses produced)		
1. Chemicals	Media, ingredients, etc	14,800
2. Filling	Inputs including vials, stoppers, labels, etc	12,363
3. Direct Personnel	Salaries and benefits of all people involved in DTP production	2,646
4. Spare Parts	Parts and consumables (oil) to keep DTP equipment in good operating condition	4,046
5. Water		400
6. Electricity		250
7. Direct Services	Communications, transport, postage, etc for DTP only	1,166
8. Indirect Personnel	Pro-rated share of personnel from "non-product" departments	3,778
9. Indirect Building/Equipment	Amortization of DTP equipment and Vacsera buildings. Equipment amortized over 5-20 years, buildings over 50	74,680

COST OF GOODS SOLD cont. (All costs in LE per 1 million doses produced)			
10. Other Equipment	Pro-rated share of all vehicles and equipment from "non-product" departments, including furniture, computers, testing and research equipment, and vehicles	2,130	
11. Indirect Services	Other miscellaneous expenses including communications, transport, postage, etc for "non-product" departments	250	
SUBTOTAL		116,509	
12. Loss/wastage	@ 15 per cent	17,476	
TOTAL COST PER 1 MILLION DOSES		133,985	
COST PER DOSE		LE 0.134	$ 0.040
PROFIT (LOSS) PER 1 MILLION DOSES	GOE PRIVATE	(1,635) 1,974 340	(494) 597 103
PROFIT (LOSS) FOR 9 MILLION DOSES		3,057	924

Table 8C. Product Balance Sheet - TT								
REVENUE/INCOME								
Sector	% Sales	Purchase Revenue less Price tax of 10%		Vial Size	Price per Dose		Revenue per Dose	
					LE	$	LE	$
GOE	0.91	1.83	1.65	15	0.122	0.037	0.110	0.033
Private	0.09	2.61	2.35	15	0.174	0.053	0.157	0.047
1992 UNICEF PRICES (20 DOSE) 0.033								

COST OF GOODS SOLD (All costs in LE per 1 million doses produced)		
1. Chemicals	Ingredients	10,000
2. Filling	Inputs including vials, stoppers, labels, etc	13,090
3. Direct Personnel	Salaries and benefits of all people involved in TT production	2,184
4. Water	TT only	140
5. Electricity		3,053
6. Direct Services	Communications, transport, postage, etc for TT only	765
7. Indirect Personnel	Pro-rated share of personnel from "non-product" departments	7,174
8. Indirect Building/Equipment	Amortization of TT equipment and Vacsera buildings. Equipment amortized over 5-20 years, buildings over 50	33,000
Spare parts	TT equipment only	10,000
9. Other Equipment	Pro-rated share of all vehicles and equipment from "non-product" departments, including furniture, computers, testing and research equipment, and vehicles, water and electricity	7,000

COST OF GOODS SOLD cont. (All costs in LE per 1 million doses produced)			
10. Indirect Services	Other miscellaneous expenses including communications, transport, postage, etc for "non-product" departments	780	
SUBTOTAL		87,186	
12. Loss/wastage	@ 15 per cent	13,078	
TOTAL COST PER 1 MILLION DOSES		100,264	
COST PER DOSE		LE 0.100	$ 0.030
PROFIT (LOSS) PER 1 MILLION DOSES	GOE PRIVATE	8,678 1,127 9,805	2,622 340 2,962
PROFIT (LOSS) FOR 7 MILLION DOSES		68,632	20,735

- Vacsera follows a price structure which is artificially set by the Government (the buyer of 95 percent of these three products) and not responsive either to market forces or to the long-term financial well being of Vacsera. There is no apparent relationship between the public and private sector prices for these three vaccines.

- Vacsera does not follow a fully consistent system of cost accounting and there are some differences between figures provided by the production people and those supplied by the financial management department.

- Vacsera's losses from production and sale of EPI vaccines may be offset by profits from other products such as anti-snake and scorpion venoms, anti-tetanus serum, cholera vaccine and diagnostics.

In essence, since its costs are equal to its sales prices, and its sales prices are equal to those of its principal competitor in the public sector (UNICEF), Vacsera finds itself trapped in an economically and financially unsustainable position. Without charging higher prices for its products, it cannot earn the profits which should be plowed back into training, equipment and the research necessary to improve its products and processes. At the same time, if it charges the public sector higher prices, it would be non-competitive with UNICEF prices. If inflation in Egypt continues at a rate of 10 - 15 percent, these problems will likely be exacerbated *vis-à-vis* its competitors in Europe, the US and Japan. The limited set of options Vacsera might explore to extricate itself from this trap include:

- **Increase productivity** through employee training programs, increasing the utilization of the production buildings and equipment, and by eliminating or reducing expenses for unproductive personnel and physical plant;

- **Improve and expand Vacsera's ability to attract and satisfy the growing demand from the private sector**, in Egypt and in other countries, where it can charge higher prices for its products.

The production related investments discussed above will improve the quality of Vacsera's products and make them more likely candidates for export. Most, though not all the investments will also result in increases in productivity. Unfortunately, the assessment team did not have sufficient time to analyze the impact of those investments on productivity. The high priority investments discussed in **Annex V** are considered absolutely essential to Vacsera's continued vaccine operations and should help improve its overall competitive and financial picture.

General Organizational and Management Considerations

Overview

When Vacsera was established in 1973, it was primarily concerned with the production of smallpox, cholera, typhoid and rabies vaccines. Today it produces approximately 65 different products in various presentations. Vacsera is fully owned by the GOE. Its employees are civil servants and Vacsera's funding comes through the Ministry of Health with various approvals required from the Ministries of Planning and Finance. Vacsera follows GOE rules and regulations and the prices of the products it sells to the public sector are set by the government. The modest "profit" that Vacsera makes is returned to the Ministry of Health rather than being ploughed back into the organization.

Nevertheless, Vacsera is now called an "economic organization" and has a certain degree of operational autonomy. Legally the Chairman is guided by Vacsera's twelve person Board of Directors and reports directly to the Minister of Health. In practice, these people are seldom involved in the day-to-day operation of the organization.

A cursory review of Vacsera's staffing pattern suggests that, of the 920 people on the staff: a) there may be a large number of highly trained professionals, a large number of lower level administrative and support personnel and a shortage of skilled workers essential to the production activities; b) staffing for the production departments appears to be at levels which are appropriate or slightly below levels required, while there appear to be staff surpluses in some non-product-oriented departments. Vacsera may wish to conduct a more careful examination of its staffing pattern.

While some workshops and overseas training are provided through several donor-funded projects, there is no evident organization-wide personnel training and development policy or programme and there is only a vague appreciation of the specific skill weaknesses that need to be addressed. There are no formal written position descriptions or qualification requirements for most positions.

Personnel salaries (averaging between LE 100/month for a new college graduate and LE 250/month for department directors) and incentives are clearly inadequate to attract and keep good people. While the Chairman has managed to creatively reward some employees with project funded bonuses and overseas training, she has very limited flexibility or resources in this regard.

The Planning Department prepares annual work plans which set production targets and estimate resources required and schedules. The Chairman is kept informed through monthly progress reports which are sometimes shared with other department directors and discussed at senior staff meetings.

With substantial donor support, the Research Department is conducting some interesting research on schistosomiasis and other diseases of epidemiological importance to Egypt and the developing world. Its activities, however, are only tangentially related to Vacsera's priority production areas and do little to improve production, processes or quality control.

Information on the direct costs of vaccine production is prepared by the production units and collected monthly by the costing department. That department then estimates and prorates indirect costs to each product. Vacsera's books are audited regularly by the Ministry of Finance and by the Central Agency for Accounts. According to Vacsera management, no private audits or commercial review of the costing structure has ever been conducted.

A 41-workstation, donor funded computer network is helping to track raw material and final product inventories, sales by client and testing done on Vacsera's farm animals. It is planned that, by early in 1993, the system will be able to automate payroll and keep track of a variety of personnel information. Budgeting, general accounting, costing and production planning and lot tracking are to be added by June 1993. All of these routine functions are currently done by hand and by pen or pencil contributing to the serious documentation and information-availability problems noted elsewhere in this report. Automation of these functions, together with installation of a few additional personal computers in critical offices, should improve this situation.

As noted above, the GOE is virtually Vacsera's only customer for vaccines used in the EPI (at least 95% of total production). While an MOH sales entity (Organization for the General Trade of Drugs) is a middle agent for most of Vacsera's non-vaccine products, vaccines are sold only at Vacsera. To date, very little thinking has gone into identifying new markets or developing new marketing strategies.

Annex I

Terms of Reference for Team Visit

1. Ascertain forecast demand for EPI vaccines in Egypt, in particular those being produced for EPI use (BCG, DTP, TT, OPV).

2. Evaluate the production lines, particularly for OPV and DTP, analysing

   (1) present capacity
   (2) potential capacity
   (3) bottlenecks in production
   (4) actual stock on hand

3. Assess the quality control of vaccines particularly with respect to Good Manufacturing Practices and offer assistance to assure independent quality control of vaccines produced to ensure compliance with WHO requirements.

4. Analyze the costs of vaccines produced, the capital investment needs to expand/renovate the current plant, the resources available from sale of vaccines to the government, and the role of long term government/donor investment into vaccine production.

5. Determine strategies for financing importation of components needed to develop sustainable vaccine production.

6. Analyze Egyptian requirements for licensing of vaccine, national regulations for pharmaceutical inspection and for production and quality control of vaccines.

7. Before leaving the country, develop, in conjunction with national authorities, a plan to approach sustainability in vaccine supply for Egypt, including steps to take, timeframes, and donor inputs necessary.

Annex II

List of Persons Working with Team in Egypt

Ministry of Health

- Dr Mohamed Sobhy Abdel Reheem, First Undersecretary for Prevention and Primary Health Care Services
- Dr Mohamed Said El Sharkawy, Director, Communicable Disease Control
- Dr Esmat Mansour, Executive Director, EPI
- Dr Atef Hassan, Cold Chain and Immunization Officer, EPI

Vacsera

- Dr Raga'a Hassan Ali, Chairman
- Dr Mashaalla Hosny, Under Secretary for the Sector of Control, Research & GMP
- Dr Laila Basyouny, General Director, Control
- Dr Madiha Omer, Director, Bacterial Control Department
- Dr Mohamed Yassni, General Director, GMP
- Dr Nabil Guirguis, General Director, Research Department
- Dr Abdel Reheem El-Beltagy, Under-Secretary for the Sector of Production
- Dr Abdullah El-Beri, General Director, TT Production
- Dr Aida Roushdy, Technical Consultant
- Dr Odette Kallini, General Director, OPV Production
- Dr Nahed Fikry, OPV Production
- Dr Mohamed Hedia, Filling
- Mr Mikhail Boutros, General Director, Finance and Administration

WHO

- Dr M.I. Al-Khawashky, WHO Representative
- Dr M. Wahdan, DDP, EMRO

USAID

- Ms Joy Riggs-Perla, Director, Office of Health
- Dr Felix Awantang, Project Officer
- Mr Sameh Angayer, Programme Specialist
- Dr Reginald Gipson, Chief of Party, Clark-Atlanta University Child Survival Project
- Mr Al Baron, Evaluation and Monitoring, Child Survival Project

UNICEF

- Mr Namasi, UNICEF Representative
- Ms Moira Hart, Chief, Health and Nutrition
- Dr Ibrahim El Kerdany, Senior Programme Officer, Health and Nutrition
- Dr Magdy Bayoumi, Project Officer, Health

Annex III

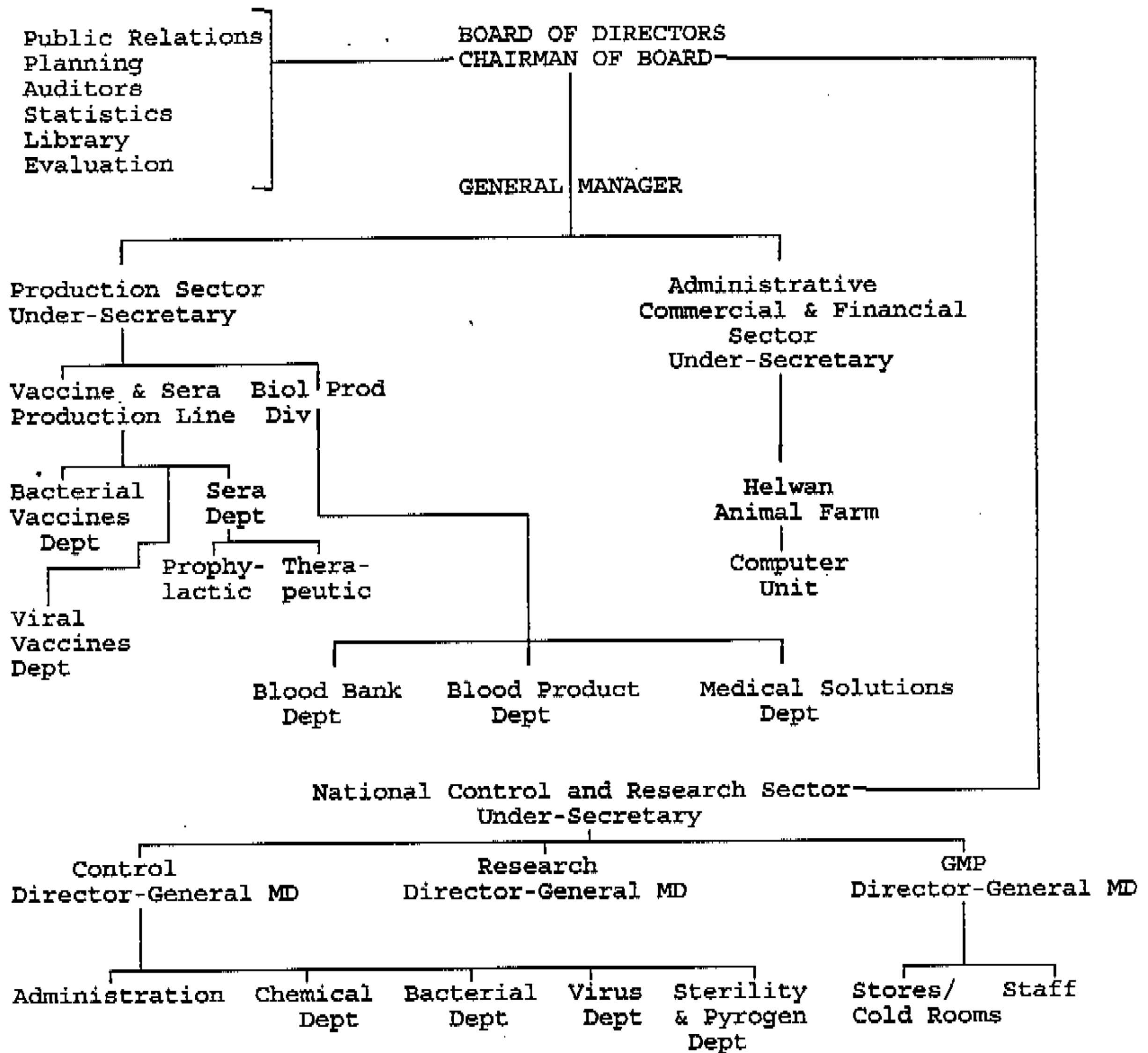
Schedule of Team Activities

Sunday, 29 November	09.30	Meeting with WHO Representative (Milstien and Parkman)
	10.00	Meeting with Dr Sobhy, First Undersecretary for Prevention and Primary Health Care Services, Dr El Sharkawy, Director Communicable Disease Prevention, and Dr Esmat Mansour, Executive Director EPI and Child Survival (Milstien and Parkman)
	11.30	Meeting with Dr Raga'a Hassan Ali, Chairman, Vacsera, and staff (Milstien and Parkman)
	12.30	Meeting with Dr Mashaalla Hosny, Under-Secretary for Control, Research, and GMP, Vacsera, and staff, and tour of Quality Control facilities (Milstien and Parkman)
	15.30	Meeting with Ms Joy Riggs-Perla, Director, Office of Health, USAID Mission, and Dr Reginald Gipson, Chief-of Party, Clark-Atlanta Child Survival Project and staff (Milstien and Parkman)
	19.00	Team discussions
Monday, 30 November	08.15	Meeting with UNICEF staff (Holmes and Milstien)
	09.30	Briefing on activities of Vacsera and tour of facilities; intensive activities with DTP and OPV production staff and filling lines (Gilmartin, Parkman, and Shih)
	10.00	Meeting with Dr Esmat Mansour on demand forecasting for vaccines (Holmes and Milstien)
	13.00	Information exchange at Vacsera (entire team)
	19.00	Team discussions
Tuesday, 1 December	09.30-14.30	Vacsera (entire team)
	16.00	Team discussions

Wednesday, 2 December	09.30	Vacsera (entire team)
	14.00	Discussion of recommendations with Dr Wahdan, Dr Esmat Mansour, and Dr Raga'a Hassan Ali at Child Survival Project (entire team)
	17.00	Team discussions and report writing
Thursday, 3 December	09.30	Discussion of recommendations with Dr Sobhy, Dr El-Sharkawy, Dr Raga'a Hassan Ali, and WHO Representative (entire team)
	12.00	Discussion of recommendations with Vacsera staff (entire team)
	14.30	Discussion of recommendations with UNICEF and USAID staff at UNICEF (entire team)
	17.00	Team discussions and report writing
Friday, 4 December	08.00	Team discussions and report writing

Annex IV

Organogram of Vacsera



Annex V

Cost Implications of Recommendations

OPV Equipment

HIGH PRIORITY NEEDS

1. **Bulk Concentrate -70 C Ultra Low Temperature Freezers**

The current freezers are more than 15 years old, have no temperature indicator or recorder, are said to be operating at -55° C, but there is no way to confirm this (the thermometer used once a week now is very inaccurate for this type of critical industrial use). Considering over a million dollars of bulk concentrate sits in these freezers, representing about a year's supply of OPV, their replacement is critical. Specify as per Sanyo, 500 litre capacity, dual sealed compressor type with seven day recorder and temperature alarm. Quantity three.

Budget 3 @ $7,000 $ 21,000

2. **Additional Modifications to New Filling Area**

These are for additional HEPA filtered areas, added ventilation to the hallway outside the filling area to reduce dust levels, a second set of doors at the entry. These are local purchase costs and should be purchased immediately with the engineering firm which is nearly completing the new clean room. It is immediate because the modifications will cost significantly more to make if delayed after the work now in process is completed (we have about two weeks before the area will be finished).

HEPA filters $3,500
Ventilation $3,500
Additional Doors $2,000
Budget $ 9,000

THE FOLLOWING ARE HIGH PRIORITY NEEDS, BUT NOT CRITICAL TO IMMEDIATE FUNCTIONING. THEY SHOULD BE SUPPLIED IN THE NEXT SIX MONTHS

3. **Instrumentation**

These include multichannel pipettes, pH meter, top loading balances quantity two, exact specifications should be requested. All items are routine essential parts of this type of production.

Budget $ 10,000

4. **Filtration membranes, holders, pumps and related supplies**

Again exact specifications need to be provided and reviewed, but this is essentially resupplying items in routine use for some years. Source is all Millipore, USA and must remain that company to be consistent.

Budget $ 15,000

5. **Air Quality Monitoring Set**

This includes a particle counter, a DOP generator for challenging and certifying performance of laminar flow Hoods, a slit to agar plate sampler and plates, and a precision anemometer.

Budget $ 20,000

6. **Spare Parts for the Existing Filling Line**

Again, specifications need to be provided in detail, but these should not exceed the amount budgeted.

Budget $ 20,000

7. **Laminar Flow Benches**

To replace the current system for hand filling and also for use in blending operations. Should be sufficiently long so that three operators can sit: three meter width, vertical airflow, quantity two

Budget $ 30,000

8. **Reagents and Supplies**

Every production laboratory has a routine need to import a variety of low value but essential items such as pyrex graduated 20 litre bottles for mixing bulk, magnesium chloride and Hanks solution media mix. Currently the laboratory is buying locally, trying to minimize cost. This is not optimal for product quality, time consuming, and more costly than if Vacsera were given an annual account to order and import resupplies from as they specify. This could be done on a reimbursable basis or on a programme funded basis. For the type and level of operation, this will be about $20,000 annually.

Budget $ 20,000/yr

LOWER PRIORITY EQUIPMENT

The following were requested and viewed as desirable, but not immediate, needs. Both items are high value and require very careful specification. Both items require substantial lead time to purchase, inspect, test, ship, install, and commission before routine use can be expected.

9. **Two thousand litre autoclave**

To replace or augment two existing large autoclaves. There is one new autoclave which has not yet been used in the new production area, but its capacity will limit turnaround speed somewhat. The large autoclaves on the upper floors of the building are not up to current control and recording standards, but probably have several years of working life remaining.

A new autoclave of this size that meets European GMP requirements is a considerably more complex machine than those in use now. A unit that meets USA GMP requirements would include a computer with sophisticated programming and documentation. These documentation and 'validatability' requirements can add more than $ 100,000 to the budget below. It is not recommended, both for cost of maintenance and dependence reasons as flying computer technicians from the manufacturer is a practical impossibility over the expected 30 year life of a machine like this. Again, the cost of maintenance and complexity should be carefully considered before providing this item.

Budget	$150,000

10. **WFI System**

The existing system in the OPV work area will be barely adequate for the production demand of the new wash/sterilizer system being put in place. However, a new system in the current building with several floors and multipoint distribution will be an involved undertaking. It will require careful specification and a local engineering firm familiar with this type of work to complete it properly.

Item	Cost
Pretreatment and deionizer	$ 40,000
Distiller	$100,000
Storage at 90°C	$ 80,000
Distribution recirculating	$ 80,000
Budget	$300,000

Totals

Category	Amount
Urgent Immediate	$ 30,000
Urgent	$ 115,000
For Consideration	$ 450,000
Yearly Supply Support	$ 20,000

DTP Equipment

1. **Storage Vessels for TT**

Same as those already delivered, quantity six, specify 100 litres with vibromixer agitator.

Budget, six @ $ 10,000	$ 60,000

2. **Fill/Packaging Line Overhaul**

This should include B&S technician visit, spares for two years operation and new change parts for locally made vials.

Budget $ 75,000

3. **Replacement Laminar Flow Hood**

This is for over the filling line. Size and shape to be specified exactly.

Budget $ 25,000

4. **Repair/Rehabilitate**

Provide new supply of spares for existing fermenters and repair.

Budget $ 70,000

5. **Air Quality Monitor Set as per OPV Above**

Budget $ 20,000

6. **Supplies and Reagents**

To include ultrafiltration elements, media materials and reagents for quality control. Again as with OPV this laboratory needs a budget to stock imported items quickly and from first quality. Based on similar arrangements UNICEF has already, this should not exceed $50,000 annually for the quantity of DTP and TT forecast.

Budget $ 50,000/yr

7. **Building HVAC Assess and Repair**

This should include the HEPA system, with a new supply of spares to last two years, plus retraining of current facility engineer, or consider adding this function to the very efficient cold chain subcontract arrangement now in place.

Budget $ 60,000

8. **Water for Injection System**

Needs complete assessment and overhaul/repair where necessary. Current engineer needs retraining or it may be more effective to subcontract this function.

Budget $ 40,000

9. **Repair/Replace Doors and Windows**

This is for all those not operating properly. This should be contracted locally.

Budget $ 10,000

Totals

Immediate	$ 360,000
Yearly Supply Support	$ 50,000

DTP and OPV Training Requirement

A variety of suggestions are being offered in this mission report. DTP will need more assistance than OPV. Pertussis fermentation is still to be mastered and then adjuvant mixing and filling will follow. It is very important that the consultants used for each area be qualified in production, able to assist in the most constructive manner, and not changed. A series of short visits by a variety of experts WILL NOT HELP.

DTP

One consultant for a three year basis, using approximately three months' time at Vacsera per year. The goal should be full self-sufficiency in DTP production. This will need to be augmented with short training courses in focused areas. Detailed Terms of Reference, a training plan, and a schedule need to be developed. Priorities are: pertussis fermentation, clean room operation, SOP preparation, GMP training for all staff, department management, and planning. The training programme should be flexible. It should permit termination of the consultant very quickly is the relationship is not beneficial.

Budget, three years @ $ 100,000 $300,000

OPV

OPV filling is already functioning at a high level of efficiency. One consultant on a flexible schedule to spend about two months at Vacsera per year for two years is recommended. In addition, short seminars on clean room operation and GMP are recommended.

Budget, two years @ $ 80,000 $160,000