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PREPARATION OF A MODEL PROGRAMME FOR INTEGRATED REGIONAL PRODUCTION OF BIOLOGICALS IN LATIN AMERICA

UC/RLA/87/276

Technical report: Production of vaccines in Latin America including a survey of production facilities, ancillary services and manpower*

Prepared for the Sistema Económico Latinoamericano (SELA)
by the United Nations Industrial Development Organization

Based on the work of Jack Cameron, CTA, microbiologist,
Richard F. Berney, mechanical engineer, Lars Holmstrom, economist,
Arðn Jakabos, plant engineer, Laszlo K. Nagy, microbiologist

* This document has not been edited.

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ABSTRACT

Project UC/RLA/87/276/11-51, "The preparation of a model programme for integrated regional production of biologicals in Latin America".

In this project, initiated by SELA, a team of 5 consultants (J. Cameron, CTA, Microbiologist, R.F. Berney, mechanical engineer, I. Holmstron, economist, A. Jakabos, plant engineer, L.K. Nagy, microbiologist) visited Bolivia, Cuba, Ecuador, Mexico and Venezuela between October and December, 1988. The team carried out a techno-economic survey of the biologicals industry (principally vaccine production and facilities) and related support sectors, manufacture and availability of production equipment, raw materials, packaging materials and consumables. It also reviewed the economics of production and the availability of manpower covering training, staffing and remuneration.

Within the region there is the technical ability to produce the vaccines most needed, those of the EPI (BCG, DTP, measles, poliomyelitis) and rabies. Regional, even national sufficiency, within a single country, however, is unlikely to be achieved in the foreseeable future, except possibly by Cuba, because of the poor condition of laboratories, absence of maintenance programmes for equipment and premises, lack of capital investment and the low priority given by governments to vaccine production, leading to poor salaries and a consequent inability to attract and retain good staff.

The economic analysis shows that in Mexico and Venezuela vaccine production has the potential to be profitable if refinanced, well organised and administered and carried out in premises meeting current standards of GMP. This last point means essentially the construction of new facilities.

It is recommended that the present situation be reviewed as soon as possible by SELA and individual governments to ascertain future commitments concerning investment and rehabilitation of the vaccine production sector. It is also recommended that the situation be further reviewed in 2 years with UNIDO participation.

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EXPLANATORY NOTES

Currency

$US equivalent, November 1988

Bolivia	:	2.4 bolivares
Cuba	:	0,76 pesos
Ecuador	:	465 sucres
Mexico	:	2230 pesos
Venezuela	:	7.50 bolívares (super preferred rate)
		14.50 (preferential rate)
		37.10 (free (public) rate)

Abbreviations

EPI : Expanded Programme of Immunization (of WHO)

FDA : Food and Drug Authority (US)

GGBR : Gerencia General de Biológicos y Reactivos (Mexico)

GMP : Good Manufacturing Practice

NIH (US) : National Institutes of Health

NIH (Mexico) : Instituto Nacional de Higiene

NIV : Instituto Nacional de Virología (Mexico)

OMS : Organización Mundial de la Salud

OPS : Organización Panamericana de la Salud

PAHO : Pan American Health Organisation

SELA : Sistema Económico Latinoamericano

WHO : World Health Organisation

Vaccines

BCG : Bacillus Calmette-Guerin, tuberculosis vaccine

DT : Diphtheria and tetanus toxoids

DTP : Diphtheria and tetanus toxoids and pertussis vaccine

OPV : Oral poliomyelitis vaccine (Sabin)

TT : Tetanus toxoid

(I)OU: (International) Opacity Units

INTRODUCTION

In February 1987 SELA requested UNIDO to review the feasibility of regional vaccine production in Central and South America. The function of SELA is to co-ordinate common positions by its 25 member states and to stimulate co-operation and the joint promotion of the region's economic and social advancement. It was constituted through the Panama Convention, an international treaty signed in 1975. The governments of Bolivia, Chile, Cuba, Guyana, Ecuador, Mexico, Nicaragua, Panama and Venezuela, all members of SELA, with a total population exceeding 128 millions, had indicated their interest in such a regional project which was also supported by PAHO.

Of the original group of 9 countries, 5 (Bolivia, Cuba, Ecuador, Mexico and Venezuela) were selected for a detailed review of their vaccine production capability. This review was also to include accessibility to and availability of essential ancillary industries, support services and delivery of vaccines to the field. The review was part of a more extensive regional economic programme which emphasised strengthening the production and trade of basic raw materials for the manufacture of essential drugs and vaccines in the region. Of the several technical co-operation activities being carried out by the member states in the group one is the present human vaccine production project.

The UNIDO document, UC/RLA/87/276 Rev. II "Model Programme for Integrated Regional Production of Biologicals in Latin America", a response to the request from SELA for a feasibility study, describes the situation concerning vaccine needs in Latin America and the difficulties in meeting them. Briefly, by 1990 there will be in the region about 15 million newborn children and 18 million pregnant women to be immunized. It is calculated that this will need about 135 million doses of bacterial and 71 million dose of viral vaccines. In 1984, with a nominal production capacity of 100 million doses of bacterial vaccines, the regional output was only 54 million; the corresponding figures for viral vaccines were 54 and 24 million. Some of these vaccines do not always meet WHO recommendations for potency, leading to a lack of confidence in local products and a reluctance to use them.

The seriousness of the shortfall in production is magnified by the significantly increasing demand due to growth of population and to increasing coverage of immunization programmes. There is also a view that to meet particular needs in certain areas, vaccines should be available for diseases other than those designated in the original EPI. Examples are rabies, widely produced in South America, meningococcal and Haemophilus influenzae B meningitis, hepatitis B, yellow fever, mumps and rubella. Although, at present, 11 Latin American countries produce bacterial vaccines (BCG, DTP, and tetanus toxoid) and 3 produce viral vaccines (oral poliomyelitis (Sabin) and measles) none is self sufficient, particularly in viral vaccine production. The demand, therefore, has to be supplemented by purchases either through the PAHO Revolving Fund or directly from transnational (multinational) producers outside the region.

To reverse the trends towards higher prices, dependence on the external supply of vaccines and the non-acceptability of locally produced products, integrated regional production, with emphasis on quality and guaranteed availability, is seen as a necessary first step. This will eliminate

dependence, guarantee availability and may reduce costs. A further factor in inter-regional supply will have to be better observance of WHO recommendations on testing and of GMP standards for production facilities. Variations from the norms recommended by WHO may be made at the discretion of National Control Authorities but for inter-regional supply the WHO norms should either be followed or alternative inter-regional norms agreed. Further factors which will contribute to the continuing viability of inter-regional supply are co-ordination of applied research and development leading to improved production methodologies and their rapid application. At a different level, the purchase of raw materials and equipment and the development of ancillary industries concerned with the supply of raw materials, culture media, plastics, animal cages, animal feed and processing equipment within the region will make an equally important contribution to the success of the project. An additional factor, implicit in the reference to improving methodologies, is a review of the manpower capability in the biologicals industry in the region.

To achieve the goal of self sufficiency in vaccine production in the region a team of 5 consultants was commissioned to review the present position and the contribution of associated activities in the region. More specifically a future programme will be based on the results of

a) a techno-economic survey of the biological industry in Latin America
b) a techno-economic survey of ancillary industrial sectors
c) the availability of human resources in university departments, research institutes and engineering companies.

The team consisted of:-

Jack Cameron, Chief Technical Advisor, Microbiologist
Richard F. Berney, Mechanical Engineer
Lars Holmstrom, Economist
Arun Jakabas, Plant Engineer
Laszlo K. Nagy, Microbiologist

All members of the mission did not visit all countries. To this extent the report is incomplete. Fortunately the largest current producer, Mexico, and the producer with greatest future production potential, Cuba, were visited by 4 members of the team (Cameron, Berney, Holmstrom, Nagy) and the survey of these 2, the most important countries, is complete. Of the other countries, all members of the team visited Venezuela and 3 (Cameron, Jakabos, Nagy) visited Ecuador and Bolivia. Production of bacterial vaccines in Ecuador is sufficient for national needs and of good quality, based on documents provided by the staff of the Institute "Leopoldo Yzquieta Perez". The Institute, however, is located in Guayaquil, 250 miles from Quito, and was not visited by the group. With hindsight this was a mistake and if the present situation is reviewed at a later date the laboratories in Guayaquil should be visited. There is no significant vaccine production in Bolivia. The number of working days spent by the different consultants in the different locations was as follows:

Member	Bolivia (La Paz)	Cuba (Havana)	Ecuador (Quito)	Mexico (Mexico City)	Venezuela (Caracas)
Cameron	2	10	3	10	10
Berney	-	5	-	5	9
Holmstron	-	5	-	5	9
Jakabos	2	-	3	-	10
Nagy	2	9	3	10	10

The project possibly could have been more productive had communication during its early stages been better. Not all countries knew in advance of the arrival of the team: the visit to Ecuador had to be rescheduled because it clashed with public holidays. The appropriate levels of government and administration in a number of cases were not aware of the team's terms of reference and much valuable time was spent arranging appointments. In La Paz (Bolivia) the group's visit was interpreted to mean that SELA, through UNIDO, would be designating the vaccines to be produced in a given area. As interpreted, this was not well received and had to be countered before discussions could begin. Elsewhere it was thought that UNIDO would be providing funds to rebuild institutes and that the team's role was to identify where capital would be most needed. These different points meant additional effort by the team and by the staffs of different institutes who, as a result, were required to make available at short notice all maintenance, production and quality control data.

RECOMMENDATIONS

Regional vaccine production, meaning a dependable supply of all EPI vaccines (and rabies vaccine) meeting WHO recommendations for safety and efficacy and produced in premises of current GMP standard, is not possible in the region at present. This arises from the poor condition of laboratories and the lack of maintenance of equipment and structures. These findings concern Mexico and Venezuela, currently the largest producers in the area. The laboratories in Ecuador, at Guayaquil, were not visited and there is no significant production in Bolivia. Cuba's potential, which eventually may make it a major contributor in the region, is as yet unrealized.

In spite of the shortcomings noted, several recommendations can be made concerning a) necessary changes in government attitudes and policies toward vaccine production and b) steps which should be taken to improve the present situation.

If these recommendations are followed the output and quality of products should improve and continuity of production should be assured. To achieve acceptability of premises, capital investment by governments for relocation and rebuilding is necessary.

The following are the recommendations:-

1. Through specifically designated officials, governments should be asked to formulate programmes and initiatives over a minimum period of 5 years to finance and redevelop national vaccine production. These programmes, with input from UNIDO, should make provision for improved staffing and salary scales at all levels and should cover the activities of research and development, production, filling, packaging and all aspects of mechanical and structural repair and maintenance. The improved salary scales are necessary to attract and retain the suitably qualified staff needed to carry out the forward looking type of rehabilitation programme envisaged.

2. The internal reorganisation should transfer financial and administrative responsibility to the heads of institutes. They in turn should be advised by professional administrators and economists, either as permanent members of staff or seconded from private commercial organizations.

3. Through SELA a much more serious effort than heretofore should be made to develop a working relationship with the private sector. In both countries the private sector is required by law to meet the various regulations which define standards for products and production facilities, regulations which the government production institutes themselves ignore (WHO and GMP standards).

At the technical level, it is unlikely that the present production facilities can be made acceptable as judged by international standards. Nevertheless, certain steps can be taken to improve the present situation:-

1. In conjunction with the present report a detailed examination of premises, processes and equipment should be undertaken with the help of independent experts. The recorded data should be used as the basis for a major programme of improvements.

2. An immediate emergency programme should be undertaken to develop maintenance schedules for all equipment and structures. This should serve to

extend the life expectancy of both equipment and buildings. Subsequently the recommendations in these programmes should be scrupulously observed and all activities recorded.

3. All capital equipment currently out of service should be brought into service either by repair or correct installation.

4. Operating manuals for all equipment should be obtained and made available to staff as necessary. These are as essential working tools as the equipment itself.

5. Flow diagrams for equipment in all processes should be drawn up to show that each item of equipment is compatible with its neighbour, e.g. a 1000l fermenter without a harvesting vessel large enough to accept its output or a freeze-dryer too small to process a large batch of a valuable live vaccine must be avoided.

6. Any further purchases of capital equipment or acceptance of donated equipment should be examined in terms of recommendation 4 to ensure that they are compatible with existing processes.

I. GENERAL DATA RELATING TO VACCINE NEEDS IN THE REGION
(J. Cameron)

A. Population Data

The total population of the 9 countries which originally expressed interest in the project is given below with projections to 1990 for the 5 countries which are the subject of the present report. These figures come from different sources.

Bolivia	6,733,637 (1988) :	7,000,000 (1990)
Chile	12,070,000 (1986)	
Cuba	10,190,769 (1987) :	11,000,000 (1990)
Ecuador	9,920,514 (1988) :	11,000,000 (1990)
Guyana	812,000 (1987)	
Mexico	81,912,000 (1987) :	92,000,000 (1990)
Nicaragua	3,500,000 (1987)	
Panama	2,280,000 (1987)	
Venezuela	18,753,389 (1988) :	21,000,000 (1990)

The total current population of the region is 146 million. The 5 countries of the report have a population of 128 million projected to reach 142 million by 1990, an increase of 14 millions or 11%.

The aim of the EPI is to ensure vaccine coverage for children. For this reason the diseases covered are those of early childhood, diphtheria, tetanus, tuberculosis, whooping cough, measles and poliomyelitis. Coverage has been extended to include protection against rabies (all ages) and to immunize pregnant women against tetanus. Thus in the review which follows most emphasis is given to the immunization of children 5 years old and younger. The methods of grouping children are not consistent: less than 1 year, 0 to 4, 1 to 4, 1 to 5, less than 5. Nevertheless the figures in the table, taken from various sources and incomplete, show that all 5 countries in the group have a regularly increasing birth-rate with possibly the exception of Cuba. This is one of the reasons for the increasing need for EPI vaccines. Annexes 1-3 give data for population, morbidity, and vaccine production, production capacity, utilisation and wastage for Bolivia, Ecuador and Venezuela. Corresponding data were not readily available from Cuba except for morbidity (3).

Country and age	Year and number of children (x10)*						
	1985	1986	1987	1988	1990	1995	2000
Bolivia							
Cuba (0-4)	0.81					0.97	0.96
Ecuador (1-4)			1.23	1.27	1.33		
Mexico (0-4)			10.93	11.14	11.56	12.65	12.72
Venezuela (0-4)	2.56	2.601	2.64	2.68	11.6	2.86	2.96
Ecuador (<1)			0.31	0.31	0.32		

*Various sources

B. Incidence of disease

PAHO data show that overall in North, South and Central America, excluding Bermuda, Canada and the US, morbidity of the EPI diseases declined between 1970 and 1984 except for tuberculosis (/).

	Morbidity (per 100,000)	
Disease	1970	1984
Diphtheria	4.0	0.7
Measles	>100	28
Poliomyelitis	2.5	0.07
Tetanus	3	0.8
Whooping cough	50	9

Tuberculosis, for which data are incomplete and sometimes confusing, increased from 71 to 99 cases (per 100,000) in Bolivia between 1985 and 1987. In Mexico one set of data shows an increase from 13 to 28 between 1981 and 1987, another from 20 to 22 between 1986 and 1987 (both sets of figures from Direccion General de Epidemiologia).

The tables which follow give the incidence of the EPI diseases and rabies for each of the countries visited (cases per 100,000).

Bolivia* (See Annex 1)

Disease	1981	1982	1983	1984	1985	1986	1987
Diphtheria	0.4	0.4	0.8	0.6	0.5	0.3	0.3
Measles**	109.1	12.2	16.9	20.3	3.4	6.6	14.5
Poliomyelitis	0.3	0.2	0.1	-	0	0.06	0.1
Rabies***	-	-	-	-	36.2	35.2	32.3
Tetanus: adult**	3.0	1.5	1.4	0.7	0.8	0.7	0.9
: neonatal	-	-	-	-	0.04	0.49	0.71
Tuberculosis	-	-	-	-	71.3	74.1	103.7
Whooping cough**	68.5	23.4	16.6	23.1	15.4	8.3	8.1

*Dirección Nacional de Epidemiología, Unidad de Estadística y Computación
**No se sabe el grupo etáreo
***Morbidity among those vaccinated only

Disease	1985		1986		1987	
	<5	>5	<5	>5	<5	>5
Diphtheria	0.01	0.45	0.04	0.2	0.05	0.2
Measles**	3.4	-	6.6	-	14.5	
Poliomyelitis	0	0	0.06	0	0.07	0.04
Rabies***	-	36.2	-	32.9	-	67.9
Tetanus: adult**	-	0.8	-	0.6	-	0.8
: neonatal	0.04	-	0.5	-	0.7	-
Tuberculosis	71.3	-	72.1	-	99.0	-
Whooping cough**	15.4	-	8.3	-	8.1	-

*Dirección Nacional de Epidemiología, Unidad de Estadística y Computación
**No se sabe el grupo etareo
***Morbidity among those vaccinated only

Cuba

Disease	1981	1982	1983	1984	1986	1987
Diphtheria	-	-	-	-	0	0
Measles	190.3	238.9	33.2	33.2	32.5	8.3
Meningitis	-	-	-	-	11.1	8.7
Poliomyelitis	-	-	-	-	0	0
Rabies	-	-	-	-	396.8	415.5
Tetanus	0.5	0.7	0.3	0.3	0.14	0.06
Tuberculosis	-	-	-	-	6.4	6.2
Whooping cough	3.9	9.3	2.8	0.8	3.4	1.0

*(1)(2)

Ecuador (See Annex 2)

Disease	1981	1982	1983	1984	1985	1986	1987
Diphtheria	0.4	0.3	0.3	0.8	0.5	0.2	0.2
Measles	5.6	19.1	28.1	76.6	12.6	8.7	15.9
Meningitis	-	-	-	-	0.3	0.2	0.4
Poliomyelitis	0.1	0.1	0.1	-	-	0.2	0.1
Rabies							
Tetanus: adult	0.9	1.6	1.9	1.8	1.03	1.0	1.1
: neonatal					1.0	0.7	0.8
Whooping cough	9.6	19.2	9.1	4.1	7.9	9.4	3.1

Mexico*

Disease	1981	1982	1983	1984	1985	1986	1987
Diphtheria	0	0	0	0	0.01	0	0.38
Measles	15.6	8.7	4.5	6.7	25.3	5.4	4.9
Poliomyelitis	0.3	0.1	0.3	0.2	0.1	0.1	0.04
Tetanus	0.5	0.4	0.5	0.5	0.4	0.4	0.4
Tuberculosis	13.2	11.3	11.7	10.2	10.1	7.5	7.0
Whooping cough	5.6	2.7	1.6	2.3	2.9	1.4	1.3

*Dirección Nacional de Epidemiología

Venezuela* (see Annex 3)

Disease	1981	1982	1983	1984	1985	1986	1987
Diphtheria	0.1	0	-	0	-	0.02	0.01
Measles	254.6	108.3	79.3	84.8	-	57.3	90.1
Poliomyelitis	0.6	0.3	0.1	0.1	-	0.15	0.4
Tetanus	-	-	-	-	-	0.41	0.02
Whooping cough	33.3	26.3	23.5	12.4	-	14.4	4.2

*Dirección Nacional de Epidemiología Prevenible para Vacunas

These tables show that in general the EPI diseases are under control. The exceptions appear to be tuberculosis and neonatal tetanus in Bolivia, rabies in Cuba and measles throughout the region. Thus the need for increased availability of vaccines is more to cope with the increase in population than to control any major spread of disease.

C. Vaccine Coverage

The following tables show vaccine coverage for the EPI diseases in the countries under review. The data are for children less than 1 year of age and receiving 3 injections of DTP vaccine, 3 doses of poliomyelitis (oral) vaccine and 1 dose of BCG and measles vaccine. The values are given as percentages.

Bolivia

Number of children	1981 206,066	1982 232,945	1983 239,497	1984 246,252
BCG	30	31	27	23
DTP	13	12	10	6
Measles	17	15	13	20
Poliomyelitis	13	12	10	46

Cuba

Number of children	1981 136,211	1982 139,759	1983 165,284	1984 166,261
BCG	97	97	96	97
DTP	67	99	99	86
Measles	49	55	94	82
Poliomyelitis	97	83	94	95

Ecuador

Number of children	1981 241,715	1982 249,840	1983 261,118	1984 264,299
BCG	82	99	85	99
DTP	26	35	31	48
Measles	31	44	34	54
Poliomyelitis	27	35	32	47

Mexico

Number of children	1981 2,400,956	1982 2,465,106	1983 2,336,807	1984 2,593,405
BCG	41	50	52	47
DTP	43	39	41	52
Measles	33	37	23	21
Poliomyelitis	99	99	88	99

Venezuela

Number of children	1981 491,907	1982 504,111	1983 515,190	1984 523,349	1985 530 [illegible]00	1986 540,000
BCG	77	76	82	92	-	-
DTP	54	53	58	33	59	54
Measles	43	45	42	41	57	45
Poliomyelitis	75	76	77	61	61	57

These figures show that vaccine coverage is good in Cuba, moderate in Ecuador, Mexico and Venezuela and poor in Bolivia. BCG vaccination coverage in Ecuador and poliomyelitis in Mexico are excellent.

The following table shows projected vaccine coverage in Mexico and Venezuela to 1990. These figures should perhaps be treated with caution, particularly the large increases in coverage against measles and tetanus predicted for Mexico. It is not clear that the necessary infrastructure is in place to handle such a large and rapid increase in coverage. The Mexican figures for poliomyelitis coverage seem somewhat erratic although in the past the authorities have made a major effort to stop the transmission of the wild virus which, if successful, may lead to a reduced need in later years for the present extensive coverage. The same concern about infrastructure applies also to Venezuela.

	Mexico*			Venezuela**		
Vaccine	1984	1987	1990	1984	1987	1990
BCG	47	60	70	92	90	90
DTP	52	50	70	33	50	70
Measles	21	80	90	41	60	90
Poliomyelitis	99	100	90	61	60	90
Tetanus toxoid	?	10	50	?	10	50

* Dirección General de Epidemiología
** División de Enfermedades Transmisibles y Accidentes. Departamento de Enfermedades prevenibles par vacunas (PAI)

D. Vaccine Demand, Production and Purchase (doses x10)

Cuba

Vaccine	Production	Purchase (doses x10)
BCG	10	-
DTP	-	1.0
Measles*	-	1.0
Meningitis	6.0	-
Poliomyelitis		2.5
Rabies (human)	0.1	-
(animal)	0.8	-

* Purchased as measles, mumps and rubella combination

Ecuador

Vaccine	Production (Demand)*			
	1985	1986	1987	1988
BCG	0.65	0.74	1.10 (0.86)	1.30 (0.36)
DT	0.51	0.16	0.45 (0.73)	? (0.90)
DTP	1.14	1.37	0.99 (1.92)	? (1.72)
Rabies (Human)	0.24	0.28	0.18 (0.31)	0.26 (0.24)
Tetanus toxoid	0.40	0.40	0.40 (0.47)	0.20 (0.20)

*Instituto Nacional de Higiene y Medicina Tropical

Annex 2, data provided by the National Institute of Hygiene, gives details of the child population up to 4 years of age for 1987 and 1988, projections to 1991, vaccine coverage, number of doses needed of BCG, DTP, poliomyelitis, measles and tetanus toxoid and estimated cost in $US. These are the most complete data provided by any of the countries visited.

Mexico

Vaccine	Estimated demand (doses x10)	
	1988	1989,1990
BCG	8	8
DTP	11	10
Poliomyelitis	31	33
Tetanus toxoid	2	2

Vaccine	Doses of vaccine needed for children (x10)		
	< 1 year	Older children	Total
BCG	4.2	3.8	8.0
DTP	6.8	2.3	10.1
Measles	2.3	2.1	4.4
Poliomyelitis	10.7	22.2	33.0
Tetanus toxoid (pregnancy)			

* Dirección General de Epidemiología

There are inconsistencies in these figures. The high demand for poliomyelitis vaccine arises from the national campaign to eliminate the wild virus. In the case of BCG and DTP, coverage is to be increased.

Venezuela

Vaccine	Production 1987 (doses x 10)*			
	Demand	Anticipated	Maximum	Purchase
BCG	0.6	0	0	0.6
DTP	4.0	3.5	4.0	0
Rabies (human)	0.16	0.16	0.16	0
(animal)	1.2	0.5	0.6	0.7
Tetanus toxoid	2.5	2.5	3.5	0

*Instituto Nacional de Higiene "Raphael Rangel"

In addition to the above there are purchases of measles (1.2 million doses), poliomyelitis (3.55), both EPI vaccines, rubella (0.3), yellow fever (0.9) and hepatitis B (0.001) vaccines.

Vaccine	Production*			
	1983	1984	1985	1986
DTP	2.5	0.6	2.9	3.0
Rabies (human)	0.1	0.1	0.1	0.15
(animal)	0.5	0.5	0.4	0.3
Tetanus toxoid	2.0	2.3	1.8	2.0

*Instituto Nacional de Higiene "Raphael Rangel"

It came as a surprise to learn that the authorities in Venezuela claim to find it cheaper to buy vaccine directly from an accredited supplier rather than through the PAHO Revolving Fund. This fund enables South American countries to pay PAHO in their own currency for vaccines purchased through the fund, PAHO later spending the currency in its country of origin.

E. Vaccine Loss

Loss of vaccine between leaving the production facility and being administered in the field is another factor putting extra pressure on the production facility and increasing production costs. The main reason for such losses is usually a breakdown in the cold chain, either during transportation or in incorrect storage prior to use. In the case of BCG vaccine, a loss of up to 50% may be accepted because production in multi-dose containers is so much cheaper than in single, double or triple dose containers that it is economical to accept the loss. On the other hand, any loss of imported vaccines in South America, e.g. measles, poliomyelitis, is much more costly than the loss of locally produced vaccine.

The following are data for losses of vaccine in the field in Venezuela.

Vaccine	1985			1986			1987		
	Sent*	Used	Lost	Sent	Used	Lost	Sent	Used	Lost
BCG	0.19	0.13	31	0.13	0.09	33	0.41	0.19	53
DTP	1.04	0.67	35	1.97	1.05	47	1.78	1.02	42
Measles	0.37	0.25	33	1.03	0.29	72	1.01	0.42	58
Poliomyelitis	1.19	0.74	38	1.90	1.27	33	2.01	1.15	43
Rabies (human)	0.02	0.02	0	0.02	0.02	0	0.03	0.03	0
Yellow fever	0.09	0.06	38	0.25	0.12	52	0.17	0.06	66

*Sent and used...doses x 10 ; lost...percentage.

F. Regional production capability

Regional vaccine production at present, interpreted either as the overall capability within the region or as the capability of a single country to supply the region with vaccines of a quality acceptable to WHO and produced in acceptable premises, is not feasible for a number of reasons:

1. None of the institutes visited meets current GMP recommendations for a production facility. Although the bacterial and viral vaccine facilities of the GGBR, Mexico, are the best they are yet not acceptable for this reason.

2. There is a general administrative and policy failure to accord vaccine production the priority, status, staff and finance needed for independent action to ensure that current standards of product quality and maintenance of premises and equipment are met.

3. For the future there are no credible government plans either for the construction of new premises or to improve existing premises to acceptable standards.

4. On occasion there is a failure to understand production problems which can lead to high losses of final product. This, in turn, highlights the need for further and better technical training to be followed, possibly, by some form of monitoring to ensure that understanding is complete. This is essential if the region is to become responsible for its own internal training.

A possible exception to points 1-3 is Cuba: new facilities under construction will be of GMP standard and vaccine production has a high priority. It is difficult to comment on the relevance of point 4 to Cuba because so little EPI vaccine work was available for review. Neither pertussis nor any of the viral vaccines is currently produced although measles has been produced experimentally. General technical expertise, however, is of a high order, e.g. genetically engineered hepatitis B vaccine and interferon A are being produced, both major technical achievements. Production of the additional EPI vaccines should be under way by 1991. Since Cuba will then be potentially a major producer in the region the question of regional supply should be re-examined in 2 or 3 years time. The new facilities, however, may be adversely affected by Cuba's many difficulties in gaining access to maintenance materials of acceptable standard, e.g. stainless steels. This leads to improvisation which, although highly praiseworthy, may in the long term prejudice the effective operation of equipment.

G. Quality control and product formulation

Currently there is confusion between WHO and US standards for the safety and efficacy of vaccines, perhaps understandable because of the prominence of PAHO and its consultants in the region. While this does not lead to major shortcomings in the quality of vaccines it does indicate a failure to appreciate that different standards do exist. If the present situation continues, with day to day technical assistance continuing to come largely from the US via PAHO, consideration should perhaps be given to the adoption of US standards.

The question of whether or not a regional quality control laboratory should be established should also be resolved. At present the laboratory in Mexico City is a WHO approved reference laboratory for a number of vaccines produced in Central and South America. It should not be assumed, however, that it can additionally serve as a regional quality control laboratory. To serve this function, discussions should take place and there should be formal agreement as to the status of the Mexican laboratory in the region.

Formulation of DTP vaccine varies within the region, mainly in the content of tetanus toxoid. WHO recommends a minimum of 5Lf in DTP with childhood immunization in mind. Where a full course of 3 injections cannot be assured or where pregnant women are immunized to prevent neo-natal tetanus a tendency to increase the immunising dose above 5Lf is understandable. Within the region it ranges from 7.5 to 20Lf: this is acceptable but 20Lf compared with 5Lf requires a fourfold increase in production. From a regional point of view, the formulation of tetanus toxoid and other vaccines should be standardised and the agreed standards adhered to, so as to ensure inter-regional uniformity and acceptability.

The production of single component vaccines, e.g. BCG, tetanus toxoid, is straightforward and production capacity in the region can meet demand. In the case of tetanus toxoid, it exceeds demand. The formulation of multicomponent vaccines, however, depends on the ability to produce all of the necessary components. In the case of DTP vaccines, availability of the pertussis component usually determines production capability for DTP. The use of older, static culture production methodology in some areas and unresolved toxicity problems in others limits pertussis production and, as a result, the regional demand for DTP vaccine cannot dependably be met.

II. PRIVATE INVESTMENT (J. CAMERON)

There was little desire on the part of any of the government officials met during the mission to consider the involvement of the private sector in vaccine production. On the other hand, 5 private pharmaceutical companies, Laboratorios Sanfer and Novum Corporativo in Mexico City, Laboratorio Palenzona and Pfizer in Caracas and Life Laboratories in Quito all indicated their willingness to discuss the possibility of a joint venture in vaccine production with the government. These 5 companies are well aware of and observe the high standards mandated in all areas of pharmaceutical manufacture. Two of them, Laboratorio Palenzona and Life Laboratories allowed the group to inspect their documentation on engineering and plant maintenance, production processes and quality control. There is no doubt that in Ecuador, Mexico and Venezuela there is both the academic and technical capability in the private sector to produce vaccines. At present, however, there seems to be little desire on the part of the different governments to discuss any possible joint ventures. This appears to arise within governments for two reasons, lack of any detailed knowledge of the industry and of accurate costing. As a consequence no serious discussions can take place with the private sector. As long as this state of affairs lasts money will continue to be spent in the present sub-standard facilities with little of real value to show for it and no prospect of acceptable regional vaccine production.

The level of record keeping and physical condition of laboratories in the private sector should be further commented upon. Apart from the incentive to succeed in the private sector, which is largely responsible for these positive attributes, there is also legislation in place which obliges such organisations to maintain both premises and records at acceptable levels. Were the vaccine production laboratories obliged to meet the same standards the poor level of mechanical and structural maintenance which the team observed would not arise. It is sad that, in the face of such positive legislation, premises belonging to the government, which introduced such forward looking legislation, should be allowed to deteriorate to the present state of unacceptability.

III. PRODUCTION OF BIOLOGICALS (L.K. NAGY)

To promote self sufficiency in biological products within the region, via the integration of their production and supply, it is of importance to examine the various factors (technological, engineering, commercial) which affect them so that a programme for integrated regional production may be prepared.

With respect to vaccine production the following aspects and factors were examined:

0. Product composition
1. Production
1.1 Technology and quality control
1.2 Capacity, consistency, wastage
1.3 Constraints
1.4 Research and development
1.5 Increasing production
2. Quality Assurance (QA), Good Manufacturing Practice (GMP), Quality Control (QC) at plant level
3. Supply of animals/animal testing facility
4. Availability of raw materials and other consumables
5. Manpower and training (in production, QA/GMP/QC)
6. Standardisation, Registration/Licensing and Quality Control of biological products at national level

In addition to vaccines, a list of other biologicals and their quantities produced in Mexico, Cuba, Venezuela and Ecuador is also provided.

A. Cuba

The following biological products were being produced in the country in 1988.

Bacterial vaccines

(1) Tetanus (Annex 4)
(2) BCG (Annex 5)
(3) Typhoid

Viral vaccine

(1) Rabies (Annex 6)

Blood products

(1) Albumin, (5, 10 and 20% solutions)
(2) Normal γ-globulin (10 and 16% solutions)
(3) Hyperimmune γ-globulin (anti-rhesus, -tetanus and -cytomegalovirus).

Diagnostics/Reagents

(1) Complement
(2) Antisera
(3) Toxoplasma antigen
(4) Streptolysin
(5) Antibiotic sensitivity disks

Manufacture of biological products at the Carlos Finlay Institute (C.F.E.) started some 15 years ago. Production of blood derivatives was already transferred to a new facility. Transfer of production of all other biological products is expected in 1989, following opening of the new National Centre for Bioproducts (BIOCEN).

Bacterial Vaccines - Carlos Finlay Institute

Tetanus Toxoid (TT)
(Annex 4)

In the preparation of this aluminium hydroxide adjuvanted purified toxoid of Cl.tetanus WHO recommendations are aimed at. Production processes and quality control tests are, with few exceptions, compatible with these recommendations. For conformity some additional tests would have to be carried out.

This vaccine has been produced at the Carlos Finlay Institute for the past 15 years. Its production is due to be transferred to BIOCEN during the first half of 1989. Method of toxin production will be changed to deep culture technology with a projected annual output of 20 x 10^6 doses. This may be increased, at a later date, to 40 x 10^6 doses p.a.

BCG Vaccine
(Annex 5)

Small quantities (0.2-10.0 x 10^6 doses) of this lyophilised, live vaccine, produced and tested by WHO recommendations, were in production at the Carlos Finlay Institute for the past 15 years. The vaccine was regularly (yearly) sent to the Statens Serum Institute, Dept. of BCG, for testing and was always approved. Its production is due for transfer to BIOCEN in the course of 1989. Projected output, using the same production technology, is between 3 and 6 x 10^6 doses.

Typhoid Vaccine

This heat/phenol inactivated, liquid, whole culture vaccine of Salmonella typhi type 2 is the oldest product of the Carlos Finlay Institute. In recent years the cultures were produced in a small (70L) fermenter. The nominal annual capacity was between 5 and 6 x 10^6 doses p.a. Its production is also due for transfer to BIOCEN.

Viral Vaccine - Carlos Finlay Institute

Rabies Vaccine
(Annex 6)

This is the only virus vaccine: it has been routinely produced (for

human use) for the past 17 years by the WHO-approved suckling mouse brain tissue method. It is tested to WHO recommendations. One or two batches per annum are sent to the Pan American Zoonosis Centre for testing. They have been approved on each occasion.

Work with a tissue culture-derived (BHK), chemically inactivated, liquid vaccine is in an advanced stage of development and is due to be completed by the end of 1990.

Blood derivatives

The new plant for the production of blood derivatives was opened in April 1988. Its present nominal production capacity is 80-100 tons of plasma p.a. This capacity may be increased to 200 tons p.a. Domestic demand takes up to 30% of blood products: the rest is available for export.

Production of blood derivatives is based on human blood-plasma fractionation by Cohn's method of progressive alcohol precipitation of plasma components, under strictly controlled conditions of temperature, pH, ethanol concentration, agitation, centrifugation and filtration.

The number of blood donors in 1988 was ca. 500,000. In addition to fresh blood, expired frozen plasma/blood is also used for processing.

The following blood derivatives are produced:

1) albumin as a 5, 10 and 20% solution
2) normal γ-globulin at 10 and 16% solution
3) hyperimmune - anti-rhesus, -tetanus, -cytomegalovirus globulins.

Substances in plasma tested for include cholesterol, IgG, IgA, IgM, IgE, glucose, creatinin, triglycerides, albumin, urea, calcium, bilirubin, transfertin and total protein.

Blood products are tested not only for antibodies to hepatitis B, tetanus, cytomegalovirus and AIDS but for antigens (B25 and B41) of the AIDS virus.

In the design and building of this modern plant GMP requirements were aimed at just as in all production activities. These include not only environmental monitoring of critical areas, proper segregation of in-process and finished products but preventive maintenance of plant and equipment.

In the pilot plant, development work is in progress for the preparation of - globulins, such as anti-haemophilia B and plasminogen activator for intravenous injection.

Total number of staff is 100, including 25 university graduates, 25 technicians and 36 maintenance staff, 6 of whom are graduate engineers.

EPI related vaccine development work in Cuba

Diphtheria Toxoid

Development work on the production of diphtheria toxoid was completed two years ago and use of the toxoid in clinical trials is nearing completion.

In the preparation and testing of the toxoid WHO recommendations were aimed at.

The production strain (PW-8) was obtained from Holland and the seed lot system was correctly employed for its use.

The production culture is grown in a fermenter (100-130Lf/ml) and the toxin is inactivated with formaldehyde (0.1%) and purified by precipitation with metaphosphoric acid.

An inspection of quality control tests shows that with very few exceptions these are compatible with WHO recommendations.

Diphtheria and tetanus toxoids were combined in two formulations: 30Lf + 10Lf and 15Lf + 5Lf/0.5 ml respectively, both adjuvanted with aluminium hydroxide. Five production batches were prepared and four of them have been on shelf-life tests for two years. Clinical trials with the two formulations started in 1986 and are near completion. The results are said to be good. Registration of D-T vaccine is anticipated during the first half of 1989.

Production of diphtheria toxoid at BIOCEN is planned on a campaign basis in 2 x 250L fermenters, sharing time with the production of pertussis cultures. Projected annual output of diphtheria toxoid is 15.0×10^6 doses initially, which may be increased substantially by the installation of an additional 250L fermenter.

Poliomyelitis vaccine

For many years a trivalent, oral (Sabin) poliomyelitis vaccine, derived from human diploid cells (MRC-5) and imported from the USSR, has been successfully used in Cuba. Transfer of technology for the production of this type of vaccine was agreed with the Soviet Union. Two Cuban nationals had already been trained in the USSR to establish vaccine production at BIOCEN, aided by expatriate experts.

Completion of EPI-related vaccine development and the introduction of satisfactory routine production of all EPI vaccines to WHO requirements would make BIOCEN a potential exporter of these products for the region.

Supply of animals for testing biological products in Cuba

The supply of laboratory animals for the routine testing of biological products is one of the functions of the National Centre for the Production of Laboratory Animals (CENPALAB). It is located 30km south of Havana and 5km from BIOCEN. It occupies 110 hectares, and when construction is completed (at present 40% of the establishment is in operation) the facilities will cover 55000m^2 to house production colonies, quality control, research departments and services.

The main function of CENPALAB are:

1) production of the main species and strains of laboratory animals, conventional, SPF and gnotobiotic, for institutions involved in biological research, production and evaluation of biological products.

2) Basic and applied research to ensure appropriate zoo technical and veterinary technology for the breeding and maintenance of production colonies.

3) Production of diagnostic kits for the detection of pathogenic viruses in laboratory animals and in poultry.

4) Production of concentrated food for laboratory animals.

In 1988 CENPALAB produced a large variety of conventional out- and inbred mice, rats, rabbits, guinea-pigs, dogs, gerbils, hamsters, pigs and primates (Annex 19).

Specific pathogen free (SPF) inbred and outbred nuclei of mice, rats, chicken, sheep, guinea-pigs and rabbits are also maintained in flexible small and large isolators.

In 1988 the construction of four large units has been in progress for the production of gnotobiotic animals designed for the annual production of ca. 500 000 mice, 150,000 rats, 100,000 chick embryos, as well as rabbits, guinea-pigs, hamsters, mini-pigs, sheep (and other species, if need be), to meet domestic and international demand. CENPALAB employs a strict programme of microbiological, parasitological, pathological, clinical and genetic control and monitoring of all species of animals in its well-equipped veterinary clinic and diagnostic laboratory. CENPALAB is running a small plant for the production of laboratory animal diets (25 formulations in 1988) equipped with state-of-the-art technology, with an annual production capacity of 12,000 tons. This plant will eventually produce 80 different formulae, sterilisable by autoclaving and irradiation, to meet all domestic demand and also for export.

In 1988 CENPALAB employed 155 people including 50 graduates (scientific, veterinary, medical, nutritional, engineering). When fully operational the number of staff will increase to 275.

Availability of raw materials and other consumables

Fine chemicals and reagents used for the production of biological substances are imported from Europe and elsewhere from well-known manufacturers (BDH, Merck, Flukka, etc.). There are no problems importing them apart from delays, which do not, however, interfere with production or quality control.

Some of the dehydrated media, media components (brain-heart broth, soya bean extract, peptone, etc.) are also imported; others are produced locally (Mueller-Hinton, SS, MacConkey, crystal violet, bile, thioglycollate, selenite, lactose media).

Bottles and vials are manufactured in the country. Their quality however is such that imported products from France are preferred.

Rubber closures are imported from France and Belgium as are aluminium caps and rings from Denmark and Italy. Some aluminium caps and rings are made locally, but due to variable quality of these products they are not used extensively.

Packaging materials, labels and leaflets are all produced locally from paper manufactured in the country.

Plasticware is not used in production and quality control and much of the glassware is imported.

All consumables are imported by a national buying agency Medi-Cuba.

Manpower and training at the Carlos Finlay Institute

There are 115 employees in production and quality control of CFE. These include 52 university graduates (microbiology, biochemistry, pharmacy, medicine, chemical, mechanical-engineering). The average industrial experience of the graduate staff is over 10 years.

The number of senior and junior technicians in these two departments is 62. Their entrance qualification is a diploma in microbiology, chemistry, or pharmaceutical production from Technical College. Industrial experience of technical staff ranges from 2 to more than 10 years.

The staff at the animal testing unit includes three graduates (microbiology, biology, veterinary medicine) with an average of over 10 years experience. Technicians in this unit have, on an average, 5 years experience.

In maintenance there are three graduates with university degrees in engineering and 14 technicians and skilled workers who have received appropriate nationally recognised training.

Post-graduate and on-the-job training at CFE have been both very active and extensive since the early 1980s in preparation for the staffing of BIOCEN.

Post-graduate and on-the-job training included working at specialised institutes (Center of Genetical Engineering and Biotechnology, Center for Immunoassay, Center for Biological Research and University departments).

Specialists in various aspects of production and quality control of bacterial and viral vaccines were trained in Hungary (Human Institute), Holland (RIV), Yugoslavia (Zagreb), France (Pasteur Institute), as well as at different centres for vaccine and culture media production in the USSR, Mexico (National Institute of Hygiene), Denmark (State Serum Institute) and Sweden.

Standardisation, Registration/Licencing and Quality Control of Biological Products at National Level in Cuba

There is a national system of standardisation and quality control in the country and the authority for their enforcement rests with the Ministry of Public Health (MPH).

At national level the appropriate department of MPH approves composition of products, their utilisation, production, testing and distribution. Thus, the system ensuresthat products are under control to the point of reaching the end user.

The standards set for medical biologicals are those of the WHO and are published.

With respect to biologicals the MPH is responsible for their registration and licensing as well as for granting export and import licences. For licensing of a product, a product licence application is submitted, furnishing details of pharmaceutical form, composition, uses, recommended dose and dosage schedule in addition to production processes, quality control tests and the results of clinical trials. If the submission meets the demands, the product is registered and a licence for its distribution is granted for a period of 5 years. Minor changes in the product, or in the raw materials used for its preparation may be introduced with approval of the licensing

authority. After the lapse of five years the licence is called in for renewal.

The responsibility for the routine testing of production batches rests with the Quality Control Department of the manufacturer who is legally responsible for their release for use. However, the central authority has the right of demanding samples of any batch for testing.

At the present time this function is carried out by the research laboratory of the Standardisation and Quality Control Authority. There are plans, however, for the establishment of a Central Quality Control Laboratory whose responsibilities will include statutory testing of registration batches of products by the tests specified in the product licence application. It will also have the right of carrying out spot checks on any batch of a product called in for the purpose.

In 1979 a GMP inspectorate was established with a view to the gradual introduction of the principles of GMP into all aspects of manufacture and quality control as well as to buildings, plant and equipment used for production.

B. Ecuador

The following products were manufactured in the country in 1988.

Bacterial vaccines

1. Diphtheria-Pertussis-Tetanus
2. Diphtheria-Tetanus
3. Tetanus toxoid
4. BCG
5. Typhoid (type 2)

Viral vaccines

1. Rabies (human)

Reagents

S.typhi H-901 flagellar agglutinogen
S.typhi O-901 somatic agglutinogen
S.paratyphi A flagellar agglutinogen
S.paratyphi B flagellar agglutinogen
P.vulgaris OX2 somatic agglutinogen
P.vulgaris OX19 somatic agglutinogen
Tuberculin PPD (RT23)

These biologicals are produced at the Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Yzquieta Perez" at Guayaquil. In the time available it was not possible to visit the laboratories and conduct a review of production technologies and quality control. A list of products, however, their formulation and the quantities of vaccines manufactured since 1984 were made available (Annex 7).

C. Mexico

The following vaccines were produced in the country in 1988.

Bacterial vaccines

(I) Diphtheria-Pertussis-Tetanus (DPT Annex 8, Annex 9)
(II) Tetanus toxoid (TT Annex 10)
(III) BCG (Annex 11)
(IV) Typhoid (Annex 12)

All bacterial vaccines as well as antisera and reagents in Mexico are produced at the National Institute of Hygiene (NIH), Mexico City. In the preparation of these vaccines WHO recommendations are aimed at.

Viral vaccines

(V) Trivalent oral (Sabin) poliomyelitis (Annex 13)
(VI) Measles (Annex 14)
(VII) Rabies (Annex 15)

Viral vaccines in the country are produced at the National Institute of Virology (NIV), Mexico City. In the preparation of these vaccines WHO recommendations are aimed at.

Other biologicals produced in the country are:

Antisera	Bottles
Anti-rabies	16,000
Anti-scorpion	143,000
Anti-viper (polyvalent)	16,000
Anti-tetanus	9,000
Anti-diphtheria	1,200

Reagents	Bottles
Coccidia	12,000
Histoplasma	12,000
Streptolysin	8,000
Tuberculin	36,000
Anti-rabies conjugate	1,000

Bacterial Vaccines - National Institute of Hygiene

I. Diphtheria-Pertussis-Tetanus (DPT) vaccine (Annexes 8, 9)

The target for the production of this vaccine for 1988 was the delivery of 12.4×10^6 doses. However, due to a shortage of diphtheria and pertussis components 3.0×10^6 doses had to be imported in order to meet domestic demands of EPI for this vaccine.

In the preparation of this vaccine WHO recommendations are aimed at. For compliance with WHO requirements the crucial criteria for acceptance is the potency of each component, which must be tested by the WHO potency assay. DPT, as presently tested, falls short of this since the potency assays for diphtheria and tetanus components use antibody levels rather than lethal challenges for evaluation. An inspection of the flow diagrams of production processes and quality control tests shows that there are other shortcomings in

the testing of all three vaccine components. In order to comply with WHO recommendations all these points should be rectified.

The capacity of NIH for the production of this vaccine is said to be ca. 12.5 x 10^6 doses p.a. However, due to a very high rate of wastage of pertussis (ca. 70%,) and a high rate of wastage of tetanus component (ca. 55%,) this capacity has not been fully achieved. Additionally there are a variety of constraints on production including inefficient production technology, a shortage of 2-8°C storage space and a shortage of incubation capacity at 37°C for detoxification.

The elimination of these wastages and constraints by the introduction of a variety of measures and some investment could increase the present production capacity by ca. 50%.

This would require, with respect to:

a) Diphtheria component

1. use of the results of development work, carried out in the department, in deep culture technology for the production of diphtheria cultures,
2. installation of one of two 750L fermenters on site (neither has ever been used) as a blending vessel,
3. redeployment of a 350L fermenter (presently used as a blending vessel) for the production of diphtheria cultures,
4. purchase and installation of ultrafiltration equipment.

b) Pertussis component

1. research and development work to resolve toxicity/potency problems with this DPT component.

c) Tetanus component

1. development work to adjust present method of detoxification suspected of causing significant losses,
2. completing installation of the second of two 750L fermenters for the production of tetanus cultures,
3. redeployment of the 360L fermenter presently used for the production of some of the tetanus cultures (in addition to glass bottles) for detoxification of tetanus cultures,
4. limited use of the 750L fermenter for detoxification of tetanus cultures produced in it.

d) Blending/filling DPT

1. purchase and installation of a filling line,
2. engagement of additional staff (50%) to carry out visual inspection of finished products.

Successful resolution of the technical problems of pertussis production and the use of a fermenter for the production of diphtheria cultures together with the suggested purchases and redeployment of some of the equipment should lead to the production of ca. 18.0 x 10^6 million doses of DPT and 10.0 x 10^6

doses of tetanus toxoid. These quantities would not only meet domestic demands for these two products but would also provide considerable surpluses (ca. 5.0 x 10^6 doses of DPT vaccine).

II. Tetanus toxoid vaccine (Annex 10)

Production target for this vaccine in 1988 (9.2 x 10^6 doses) was successfully met. The toxoid content of this vaccine is much higher than recommended by WHO for adult immunisation: this is thought to be necessary due to the method of purification of the toxoid. In order to meet WHO requirements for this product additional QC tests will have to be carried out. The method of potency assay should be changed in favour of toxin challenge of immunised animals.

III. BCG vaccine (Annex 11)

Formulation, production and testing of this vaccine meet WHO recommendations for this product. The delivery of ca. 8.0 x 10^6 doses in 1988 satisfied domestic demands. Maximum capacity is said to be 12.0 x 10^6 doses which could be achieved without any capital investment.

IV. Typhoid vaccine (Annex 12)

This product is not used in the EPI. However, the domestic demand for it in 1988 was 2.8 x 10^6 doses which was met. Its production may be doubled on demand without any capital expenditure.

Quality Assurance, Good Manufacturing Practice, Quality Control at the National Institute of Hygiene

Introduction of the guidelines of GMP at NIH began in 1985/86 and there is significant progress in a number of areas. Following training courses in GMP for the staff an inspectorate was established reporting to the head of QA/QC. The team of six inspectors, (graduates either in engineering, biology, biochemistry, pharmacy or microbiology) are responsible for inspection and validation of plant and equipment, sampling consumables and for testing environmental quality. They rely on a team of seven technicians in the chemical control laboratory to carry out the tests required.

Tests are carried out on most of the starting materials (exceptions are some of the chemicals) including media, media components, some of the chemicals, reagents, bottles and vials, rubber stoppers, aluminium closures, packaging materials, labels, pack-inserts, boxes as well as on intermediate, bulk and finished products. The results of inspection and testing are recorded and if possible shown on the inspected/tested materials.

The criteria for bulk and purified products are those of the WHO and for consumables, used in the manufacture, filling and packaging of products are those of USP XXI, Pharmacopoea Mexicana, Normas Para Materia and Index Mexico.

In addition to the work of the inspectorate, instructions and specifications, appropriate to the activities of staff members, are issued.

Description of quality control tests has been available for the past 10 years and there is a system of recording manufacturing processes and quality control tests. These were reviewed and in Sept. 1988 gradual introduction of Standard Operating Procedures (SOP) and Standard Operating Instructions

(SOI) began.

In compliance with GMP, release procedures for a batch of product include a review of results on starting materials, manufacturing documents, test results on intermediate bulk and finished products and test results of consumables associated with filling and packaging.

In addition to in-house quality control tests, the National Control Laboratory also carries out tests on each batch of product. Release of products for distribution and use requires satisfactory test results from both manufacturer and the National Control Laboratory.

NIH also operates a sample-retention and product-recall system.

For comments about compliance with WHO recommendations with respect to product formulation and testing, see Composition, Process Description and Quality Control for each product.

Although there have been significant achievements in the introduction of GMP at NIH with respect to the control of raw materials, other consumables, testing of in-process and finished products as well as in the system of documentation, not much improvement may be anticipated in respect of manufacturing premises, flow of materials and activities, nor in storage and warehousing. The premises were built for different purposes and have been adapted over many years for their present functions. The cost of their conversion to comply with GMP is likely to be prohibitive.

It is also understood that the community around NIH has protested about the location of the vaccine (and serum) production facilities which are regarded as being incompatible with a residential area.

Supply of Animals/Animal Testing Facility
(National Institute of Hygiene)

The National Institute of Hygiene (NIH) has breeding colonies of mice and guinea-pigs, supplying its own requirements for product testing. In addition it also purchases some 400 rabbits p.a. from an outside breeder. Quality of these rabbits is not certified, but they are quarantined for 15 days before use.

Mice, guinea-pigs and rabbits are accommodated in separate animal houses, or wings of a building, where temperature is regulated by a combination of hot-cold air supplied to the premises. Foot baths are installed at the entrance to each unit of animal accommodation. There are staff changing rooms and only authorised staff may enter these premises. Within each unit there are provisions for segregation of breeding stock from those available for, and from those under, test. Cages and breeding pens are suitably labelled. There is a high degree of hygiene in each of these units.

Animals are routinely monitored for pathogenic bacteria and internal parasites but not for pathogenic viral agents or for mycoplasmae. Weight gain of mice is also monitored at monthly intervals. Guinea-pigs and rabbits are said to be of normal health but some of the mice appear to be affected by disease, which is currently under investigation. Unfortunately, clincially affected mice have not been separated from the rest of the stock.

Diets for these animals are purchased from external suppliers (Purina). An inspection of the packages show that although dietary components are clearly shown, only a few of these are defined quantitatively. Clearly this is not adequate since there is no guarantee of a standard product which may

explain the variable performance (weight gain) of some of the mice.

There are 900 guinea-pigs and 120,000 mice bred p.a. Output of the breeding colony of guinea-pigs could be doubled but that of mice only slightly increased. Due to the age and design of the buildings, housing of animals does not meet GMP requirements.

Viral vaccines - National Institute of Virology

V. Trivalent Oral (Sabin) Poliomyelitis Vaccine (Annex 13)

This live, liquid vaccine was registered in 1974 and has been manufactured and tested to WHO requirements.

The present nominal production capacity of NIV for this vaccine is ca. 25.0 x 10^6 trivalent doses, a little over one half of the national demand. Until the end of October 1988 ca. 14.0 x 10^6 doses were produced and delivery of an extra 2-3 x 10^6 doses may be anticipated till the end of the year. The balance, ca. 25.0 x 10^6 doses, is imported.

By far the most significant constraint on production is the availability of patas monkeys whose primary kidney cells are employed for virus propagation. Work in progress aims to establish breeding conditions for patas monkeys in captivity and the acceptability of kidney cells of infant animals for virus propagation. Although breeding of these animals in captivity has not been satisfactorily achieved, early results with the use of monolayers derived from the kidneys of very young animals, show that these are significantly more productive than cells of adult animals.

Using existing production technology, output of the present unit could be doubled, provided certain requirements are met. These include, apart from the supply of monkeys, capital investment in filling and labelling as well as provision of extra space for visual inspection, packaging and storage.

Contemplating investment for the expansion of production capacity, it is pertinent to consider that eradication of poliomyelitis from Mexico, and possibly from the region, is anticipated by the early years of the 1990s. This would cause domestic demand to drop to ca. 20-25% of the present demand, i.e., to 10-12 x 10^6 trivalent doses, which is one half of the present nominal capacity. However, since the NIV is the sole producer of polio vaccine in the region it would be of regional interest to expand production beyond the needs of the domestic market, all the more since the product enjoys WHO approval.

VI. Measles Vaccine (Annex 14)

This attenuated, live, lyophilised vaccine was registered in 1978 and has been manufactured and tested to WHO requirements.

The nominal production capacity of this vaccine is 20.0 x 10^6 bulk doses. In 1988 13.0 x 10^6 doses (in bulk) were produced from which ca. 5.0 x 10^6 doses were filled in order to meet the demands of the domestic market for the product.

Although the present freeze-drying capacity is sufficient to lyophilise enough vaccine for the domestic market, it is the most important constraint

on converting all the bulk vaccine into finished product. To freeze dry all vaccine produced capital investment is needed also for expanding cold storage (2-8 °C) and deep-freeze capacity as well as engagement of extra staff.

Considering an expansion of finished measles vaccine production it is pertinent to bear in mind that field trials have been in progress with a liquid measles vaccine to be given by inhalation. Should liquid vaccine be adopted for use the need for the lyophilised product would decrease pro-rata. However, there would still be a need for a lyophilised product for the injection of children under six months of age.

Mexico's present requirement for measles vaccine is likely to remain, or even slightly increase, for the next 10 years or so Thus any surplus would be available for export. Although the liquid vaccine has been manufactured and tested to WHO requirements approval of WHO/PAHO would be advisable before offering the product for export, because of the novel method of administration.

VII. Rabies Vaccine (Annex 15)

This inactivated (UV light), Fuenzalida type rabies vaccine, derived from suckling mouse brain tissue, was registered in 1974 and has been produced and tested to WHO requirements.

The 1988 production of 150,000 human treatments and 2.1×10^6 canine doses of this vaccine is commensurate with both present production capacity as well as domestic demand.

Using present production technology an expansion of production is not contemplated. However, development of Vero-cell-derived rabies vaccine, under consideration, should lead not only to a technically superior product but also a very much greater production capacity, highly significant from the regional point of view.

Quality Assurance, Good Manufacturing Practice and Quality Control
(National Institute of Virology)

Introduction of the guidelines of Good Manufacturing Practice at NIV began in 1984/85. Steady progress has been made since.

Following training courses for the staff, a GMP inspectorate of three was established. They are responsible for the inspection and validation of premises, plant and equipment as well as sampling and testing of consumables. Each of them relies on the technical assistance of 2-3 staff who carry out not only the tests associated with quality control of a particular product but also all the other tests in connection with quality assurance.

Tests are carried out on tissue culture media (growth support), glassware, rubber stoppers (toxicity), plastic bottles used for tissue culture (toxicity, growth pattern), aluminium closures, labels (lot numbers, expiry date), package inserts (text), and boxes (dimensions). Testing of fine chemicals is very limited (5-10%) due to a lack of resources and a shortage of staff. Shortage of staff is also regarded as a general constraint in the monitoring of GMP and for that reason inspection is carried out once in every 2-3 weeks. The results of inspection are documentated and displayed on the items inspected/tested. Similarly, the results of tests on in-process and

finished products is recorded and they are suitably labelled, using a colour code. In cold rooms in-process materials and released products are adequately segregated.

Descriptions of Quality Control tests have been available for many years but their conversion into Standard Operating Procedures (SOP) and Instructions (SOI) are still in preparation for both production and quality control. Their issue is due in the first half of 1989.

In compliance with GMP, release procedures for a batch of product include a review of results on starting materials, manufacturing documents, test results on intermediate, bulk and finished products and test results on consumables associated with filling and packaging. The results of all of these tests are summarised in the form of a booklet which is cross-referenced with the original documents.

In addition to the in-house Quality Control tests, the National Control Laboratory also carries out the statutory tests on each batch of a product. Release of a product for general distribution requires satisfactory test results by both manufacturer and the National Control Laboratory. NIV also operates a sample retention and product recall system.

The achievements in the introduction of GMP with respect to the control of raw materials, other consumables, process and finished products as well as the system of documentation have been significant.

Introduction of the principles of GMP with respect to manufacturing premises and to plant and equipment has not been as successful as in other fields. This is due to the constraints on buildings, which were designed for different purposes and the shortage of investment for carrying out alterations.

Supply of Animals/Animal Testing Facility
(National Institute of Virology)

There are two breeding colonies of mice, a breeding colony of guinea-pigs and a small breeding colony of Erythrocebus patas monkeys. In addition there is a holding/testing facility of Macacca fasicularis monkeys used for polio vaccine testing.

One of the two breeding colonies of mice is accommodated on one floor of a building devoted to rabies vaccine production. The central area of the floor is divided into a number of mouse rooms which are surrounded with dirty (3 sides) and clean corridors. Entry of sterilized food and equipment and of personnel is strictly controlled via the clean corridor. Temperature of the mouse rooms is regulated by the introduction of filtered hot/cold air.

This colony of mice is subdivided into a master colony (1,000 breeding mice) and a production colony (6,000 breeding mice). The master colony, used for replenishing the stock in the production colony, is effectively segregated from the production colony. Parturient mice from the production colony are segregated in the delivery room. At one or three days of age infant mice are fostered onto a number of dams and segregated in another room where they are inoculated with rabies virus and kept there till sacrificed. Foster mothers are sacrificed whereas those which were deprived of their litters are returned for breeding.

Despite all the precautions and high degree of hygiene these colonies are affected with respiratory infection and need to be replaced.

In a separate building-complex are housed all other animal species with the exception of the breeding colony of E.patas monkeys.

One of the wings of this building houses the second colony of 38,000 breeding mice, serving, in the main, rabies vaccine production. These mice are kept and bred under conditions where segregation between the various sections is nominal. Standard of hygiene is good and disease problems are minimal in this colony.

The breeding colony of 400 Hartley strain guinea-pigs was recently established. Their accommodation is conventional and their care is good.

In another wing of the building complex are housed M.fasicularis monkeys used for polio vaccine testing. About 200 of them are imported p.a. There are five rooms in this section all opening to the same corridor. Temperature in the rooms is maintained at 25°C but ventilation is poor. Twenty animals per room are kept in small wire cages. One of the rooms is used for quarantining new purchases, the others for holding and testing respectively. Movement of personnel is controlled and changing of clothing and use of face masks is prescribed. Although devoted personnel care for the different rooms, the use of common corridors undermines the precautionary measures.

In yet another wing of the building are housed E.patas monkeys serving as kidney donors for polio vaccine production. There is a small surgery attached to this unit. Accommodation and care of these animals is essentially similar to that of the M.fasicularis monkeys.

In part of a separate building are housed the breeding colony of five male and twenty female E.patas monkeys and their offspring. There are two breeding cages per room (4 x 5m each) holding four females and one male. Pregnant animals and those with infants are kept in separate rooms in large wire cages. Temperature in this unit is controlled but ventilation, as in all other facilities holding monkeys, is poor. The mechanism for ventilation is apparently old and appears inadequately maintained. Movement of personnel, changing of clothing and use of face masks is controlled. Standard of hygiene in this section is higher than in the other sections holding monkeys.

An inspection of diet, supplied by Purina to the various units, showed that although there were 13 vitamins and 10 mineral supplements enumerated on the bags, none of them were quantified. This is clearly unsatisfactory since it does not assure a standard product.

Availability of Raw Materials and Other Consumables

There are no difficulties about the procurement of raw materials and other consumables for the production of biological products in the country. With respect to fine chemicals and reagents almost everything is available from within the country. There are a number of international companies, (Baker, Merck, Sigma) with manufacturing bases in Mexico, who either produce fine chemicals and reagents in the country or have them available from imported stocks. A few exceptions are thiomersal (Lilly, U.S.A.) and alhydrogel (Superfos, Denmark).

Dehydrated culture media and media components for bacteriological use are also available from a national producer (Bioxon). The only import is NZ-Case (Humko, U.S.A.) for tetanus toxin production, since the quality of the imported product is superior to that of the locally produced one.

As for viral vaccine production all tissue culture media, foetal calf serum, trypsin, gelatin and sorbitol are imported from the U.S. Plastic bottles for tissue culture are also imported either from the U.S. (Falcon) or from Denmark (Nunc).

Laboratory glassware, bottles, vials, stoppers, aluminium caps and rings, plasticware, other than tissure culture bottles, packaging materials, labels, package inserts and cardboard boxes are all manufactured locally. Some of the specialized laboratory glassware may be imported but other makes are available from a national supplier. Polycarbonate and metal cages are also produced locally.

No difficulties are anticipated in procurement of any of the consumables even if vaccine production increases substantially.

Manpower and Training at the National Institute of Hygiene and National Institute of Virology

Since administratively both of these Institutes belong to the Gerencia General de Biológicos y Reactivos (GGBR) who also set the training programme for them, it seems reasonable to discuss their staff and training programme together.

There are a total of 202 staff engaged in production, QA/QC, breeding and product testing at NIH. Their distribution, qualifications and experience is summarised in Table 1.

Table 1

Position	Departments			Qualification	Experience (yrs)
	Production	QA/QC	Animal Testing		
Director				University graduate	
Deputy Director	1	1	-	"	17
Product Manager	5	2	1	"	5-17
Chief Technician	12	4	4	"	5-16
Technicians	28	10	6	"	2-8
Ancillaries	89	15	23	School Certif.	3-25
TOTALS	135	32	34		

Bearing in mind the number of products and the quantities delivered per annum, the number of staff at NIH appears to be somewhat excessive, lowering productivity. Introduction of an incentive scheme for the reduction of wastage should be a priority. An improvement in salaries and career structure is also desirable in order to reduce staff turnover. Qualifications and experience of technical staff is favourable but the level of ancillary staff in production is high.

There are a total of 129 staff engaged in production, Q.A./Q.C., animal breeding and product testing at the National Institute of Virology. Their

distribution, qualifications and experience are summarised in Table 2.

Table 2

Position	Departments Production	QA/QC	Animal Testing	Qualification	Experience (yrs)
Director				University graduate	
Deputy Director	1	1	-	"	18
Managers	4	4	1	"	15-18
Technicians	9	11	2	"	5-18
Ancillaries	77	11	8	School Certif.	2-20
TOTALS	91	27	11		

The number of staff, at the present rates of production and production associated activities, is adequate. There is, however, substantial shortage in graduate and technical staff to undertake product-associated research and development work. The envisaged R and D work would aim to reduce dependence on importation of exotic animals for production of poliomyelitis vaccine and may also lead to an improvement in productivity. These are highly important objectives since, despite first class know-how and well qualified and experienced staff, the NIV cannot deliver half of the national requirement for this vaccine. Additionally the NIV alone produces polio and measles vaccines in the region and an extension of its production capacity would also have significant bearing for the region.

There is legislation in Mexico to assure further education (during working hours) of employees in industry. Management, developing its programme for further education, invites employees to indicate their interest in subject matters for the programme which, if possible, is incorporated.

A summary of internal and external courses and seminars as well as the number of employees attending and the number of working hours used between 1983-88 is appended (Annex VIII). These courses included full-time courses given (two weeks) by the Mexican Institute of Social Security (IMSS) on GMP for key personnel. In addition, courses on GMP have been organised for groups of employees, two hours per week for six months. These are short courses (2 hours per day for 3-5 days) on subjects like Production and control of bacterial vaccines, preventive maintenance, protein fractionation, sterilisation and disinfection, analytical methods, recombinant technology, basic immunology, microfiltration and ultrafiltration, evaluation, certification and validation of sterile areas, just to mention a few. Of great practical significance is the on-the-job training scheme, operated by both Institutes for employees in junior grades.

Standardisation, Registration/Licencing and Quality Control of Biological Products in Mexico at National Level

The first attempts at regulating pharmaceutical products in Mexico began in 1874. These regulations are regarded as forerunners of the Pharmacopoeia Mexicana which was first issued in 1930. Since that time it has been reviewed repeatedly, most recently in 1988.

The authors of Ph. Mexicana have drawn on the standards and recommendations of WHO, USP, BP and EP.

With respect to vaccines, antisera, haemoderivatives and diagnostic reagents, Ph. Mexicana deals with the composition of these products, describes the statutory quality control tests and defines the standards (Note: some confusion between WHO and NIH requirements) they must meet before they may be released for distribution and use.

For the administration of the rules and regulations of Ph. Mexicana, the Department of Standards and Quality Control is responsible. Execution of in-process and mandatory tests is the responsibility of the manufacturer in the first instance. However, the National Public Health Laboratory also takes samples of every batch of product and performs all the mandatory tests. Satisfactory test results by both parties enables release of products for use.

Registration and licencing of all biological products, whether produced in the country or imported, is required before distribution and use. Responsibility for this rests with the Department of Registration and Licencing. For registration and licencing the application needs to contain pharmaceutical form, composition, use(s), recommended dose and dose schedules in addition to particulars of production, quality control tests and the results of experimental and clinical trials. The licence is issued by the Ministry of Health.

The introduction of GMP in Mexico began in 1983. The second addition (1986) of the "Guía de Procedimentos Adecuados de Manufactura Farmacéutica" (GPAMF), provides the guidelines for both the National Inspectorate and for the personnel in the industry responsible for their execution. GPAMF deals with documentation and General Principles, organisation and personnel, system of Quality Control, installations, equipment, control of raw materials and consumables, control of packaging and distribution.

D. Venezuela

The following vaccines were produced in the country in 1988.

Bacterial vaccines

(1) Diphtheria-Pertussis-Tetanus (DPT, Annex 17)
(2) Tetanus toxoid

Viral vaccine

(1) Rabies (Annex 18)

Reagents

(1) Guinea-pig complement
(2 Haemolysin

Bacterial and viral vaccines, as well as reagents, are produced at the National Institute of Hygiene "Rafael Rangel" (NIH "RR"). The Institute was established in 1938 for the production of small pox and typhoid vaccines which ceased in 1980 and 1985 respectively. Production of the present range of vaccines began in 1956.

Bacterial Vaccines - National Institute of Hygiene "Rafael Rangel"

Diphtheria-Pertussis-Tetanus (DPT) Vaccine (Annex 17)

The national demand for this vaccine in 1988 was 4.0×10^6 doses which is the present production capacity of NIH-"RR". Production figures of individual components suggest that by the end of the year delivery of 4.0×10^6 doses is possible.

In the preparation of this vaccine NIH requirements are aimed at, thus to a degree precluding any claim of conformity with WHO requirements. For compliance with WHO-requirements the crucial criteria for acceptance is the testing to, and meeting of, quality by WHO standards.

An inspection of the flow diagrams of production processes and Quality Control tests shows that testing of diphtheria and tetanus components, as well as that of the bulk vaccine, was very inadequate, not only by WHO standards, but by any standards.

Production capacity of diphtheria and pertussis components is commensurate with present production of 4.0×10^6 doses whereas production of tetanus toxoid could be increased to 10.0×10^6 doses without capital investment.

Production-associated wastage of components is average, or below average and consistency of production of all three components is adequate to good.

Constraints on production include shortages of glassware used for production, inconsistency in media quality, delays in delivery of consumables and malfunctioning of autoclaves.

There is no research and development work in progress at the present time. However, with the delivery and installation of 2 x 450L fermenters, in the early months of 1989, development of deep culture technology for diphtheria and pertussis culture production is planned. Installation of these fermenters in newly converted premises form part of the plans for a 5-fold increase in DPT production from the present ca. 4.0×10^6 doses to 20.0×10^6 doses. Since 80% of the planned capacity is in excess of current domestic demand the aim is to export the surplus product.

These plans would also have to include careful consideration of the following:

1. current building conversion falls much short of GMP requirements for premises for the production of medical biologicals,
2. adoption of WHO requirements of product formulation and testing,
3. formal registration and licensing of the product,
4. enlargement of incubation capacity ($37^{\circ}C$) for detoxification of diphtheria and tetanus toxins,
5. purchase and installation of extra blending vessels,
6. capacity of media preparation,
7. supply of distilled water,
8. filling and labelling capacity,
9. capacity of visual inspection of finished products,
10. engagement of extra personnel,
11. measures to attract well qualified staff and reduce staff turnover.

These points for consideration are by no means complete but should be included in a feasibility study even if belatedly.

Tetanus Toxoid Vaccine

One vaccine dose of 0.5ml of this aluminium hydroxide adjuvanted vaccine contains 5Lf of formalin inactivated, ammonium sulphate purified toxoid of Cl.tetani, preserved with merthiolate (0.01%) and contained in 10-dose glass vials.

Formulation of the product is compatible with WHO recommendations but its testing falls much short of these recommendations at every stage of the production process. In order to produce a better tested and therefore safer product much stricter observation of WHO recommendations is called for.

The national demand of ca. 2.5 x 10^6 doses is well within the production capacity of NIH "RR".

Viral Vaccine - National Institute of Hygiene "Rafael Rangel"

Rabies Vaccine (Annex 18)

The 1988 production of 0.2 x 10^6 and 0.54 x 10^6 doses of rabies vaccine for human and animal use respectively met the domestic demand for human but only half of the demand for animal use. The present rate of production is not much short of nominal capacity therefore importation of ca. 0.5 x 10^6 doses of the canine vaccine is necessary p.a.

Production losses are, if anything, on the high side, and are due to cannibalism of infant mice and faulty glassware.

Constraints on production include a shortage of infant mice and breakdown of equipment.

Research and development aims to replace current production technology with the use of BHK-cell culture, but it is, as yet, at an early stage of development.

An increase of production is not contemplated beyond the utilisation of nominal production capacity until new production technology (BHK) becomes available.

Quality Assurance, Good Manufacturing Practice, Quality Control at the National Institute of Hygiene/Rafael Rangel

The NIH "RR" shares the building of the National Institute of Hygiene for the production of diphtheria and pertussis vaccines as well as for blending and filling of all products. This is an old building as are those where production of tetanus and rabies vaccines takes place. All NIH "RR" premises had been converted for their present use: the outlay, therefore, design and construction of production units, as well as the flow of materials and activities fall much short of even the basic demands of GMP. The cost of their conversion is likely to be prohibitively expensive.

Due to staff shortages, responsibility for both production and quality control rests with the same person. The section of quality control employs a single technician and two ancillary staff.

Documentation of production and quality control takes the form of handwritten notes in laboratory notebooks. These are summarised on printed forms and serve as the basis of batch release of products, together with satisfactory test results from the National Control Laboratory.

Staff at NIH "RR" have not been trained in the principles of GMP. A start has been made in describing manufacturing and quality control procedures in the form of standard operating procedures and their introduction is planned for 1989.

Methodology of quality control tests and their interpretation follow those of the Bureau of Biologies of NIH.

Supply of Animals/Animal Testing Facility
(NIH "RR")

Laboratory animals for product testing and for rabies vaccine production are supplied by the Technical Services Division of NIH, which maintains three buildings for the breeding of mice, rats, guinea-pigs and rabbits.

The mouse breeding colony consists of 6000 breeding mice supplying 45,000 per month, including those for rabies vaccine production (ca. 25,000) and product testing. The building which accommodates the mice is rather poor for the purpose and is heavily infested with rats. Conditions of general hygiene are not good.

There is a small breeding colony of ca. 250 Hartley strain guinea-pigs, which is said to be free of disease, supplying ca. 200 young animals per week.

The output of the breeding colony of 180 Wistar rats is about 300 young for testing.

The breeding colony of NZ-white rabbits consists of 80 females and 20 males producing ca. 160 rabbits per week for NIH and NIH "RR".

Health monitoring of these animals takes place at long intervals only (3-4 months) and is said to include tests for pathogenic bacterial, viral and protozoal agents. Mice suffer periodically from respiratory diseases and rabbits from infection with coccidia.

Diet for all the laboratory animals is supplied by a local manufacturer (Protina) and is of good quality. Minimal quantities of vitamins and trace elements, as well as other dietary components, are clearly shown. Unfortunately, diet for mice is in short supply at times.

For the purposes of product testing there are no problems with the supply of adequate number of animals, but for rabies vaccine production the weekly supply of infant mice is below optimal level.

Availability of Raw Materials and Other Consumables
(NIH "RR")

None of the fine chemicals, reagents, media components and dehydrated media employed in vaccine production and testing are manufactured in Venezuela. These are imported by local trading companies (from U.S.A., W. Germany, U.K., Holland) and supplied to NIH "RR".

Bottles for vaccine production are manufactured locally. However, rubber closures, aluminium caps and glassware for laboratory and production uses are all imported and supplied via trading companies. Packaging materials, cardboard boxes and labels are manufactured locally as are wire cages and concentrated feed for laboratory animals.

There are delays of 3-6 months in the supply of many of these consumables due to suppliers lack of stocks.

Manpower and Training
(NIH "RR")

The total number of staff at NIH "RR" is 43. This includes a staff of 23 in production, 4 of them university graduates; others attended technical college (some of the 7 technicians) or have school leaving certificates (most of the auxiliary staff).

The number of established posts in Q.C. is 5. Only 3 of these, however, are filled (one technician, two ancillary). Of the staff of 11 in blending/filling section, 3 are technicians and the others are ancillaries.

In the case of new entries, there is on-the-job training if required. Some staff members also received training at the National Control Laboratory. Apart from on-the-job training for technical and ancillary staff and a management course for graduates, no other further education is taking place.

There are 5 vacancies altogether, 3 of these in production and 2 in Q.C. Two of the 8 vacancies require university qualifications, the others, qualifications from technical colleges. None of these have been filled for some time due to lack of suitable candidates. Salaries at NIH "RR" are poor, one third of what is paid in private industry, and therefore fail to attract well qualified applicants. Indeed staff, having acquired some experience at NIH "RR", often leave for better pay and prospects. It appears that unless salaries and career structure are substantially increased, no improvement in motivation or performance may be anticipated.

Standardisation, Registration/Licencing and Quality Control of Biological Products at National Level

The principles of GMP in the production of pharmaceuticals were introduced in Venezuela 10 years ago and were last reviewed in 1987. Most private manufacturers have adopted them and have their own printed manuals, organised courses in GMP for the staff and their own GMP inspectorate. This is in addition to the National Inspectorate which also supervises compliance with GMP regulations by visiting manufacturing facilities, usually once a year.

Unfortunately, GMP has not been extended to include medical and veterinary biologicals in the country. The reason for this, and for the lack of registration of the products of NIH "RR", could not be ascertained from the relevant national authority.

Control of vaccines and of other biological products at the national level, is the responsibility of the National Control Laboratory (NCL), another of four divisions (NIH "RR" is also one of them) of NIH, and located in the same building.

Out of a total of ca. 200 staff at NIH, the National Control Laboratories only employ 4 graduates (all pharmacists), and 3 technicians for the testing of biological products. Graduate staff acquired specialised training either abroad (in France, Canada or Mexico) or during the last year of their undergraduate training. Work of the Laboratory includes performance of mandatory tests on every batch of the products manufactured by NIH "RR". Methodology of these tests and their interpretation is that of the Bureau of Biologies,

NIH. In addition, testing of imported products (vaccines, antisera, toxoids, haemo-derivatives) in conjunction with registration and licencing and that of returned products (consumer complaints) is also the responsibility of the National Control Laboratory.

IV. TECHNICAL REVIEW: EQUIPMENT FOR PRODUCTION OF BIOLOGICALS IN LATIN AMERICA (R.F. BERNEY)

A. Equipment at existing vaccine production centres

On this mission a number of Institutes were visited where vaccines were produced. This section details the major items of equipment found at these Institutes and the source of their supply. These lists should not be considered as complete equipment lists as complete lists were generally not available. Additionally, model numbers, quantities, capacities or age of equipment are not included even though this information was often available, because in this section the concern was with equipment type and source rather than with production capacities. Approximate quantities of each type of equipment at the Mexican Institutes may be obtained however from the table in Annex 18.

1a. National Institute of Virology (NIV) Mexico City

This Institute produces the full range of viral vaccines included in the Expanded Programme of Immunization (EPI). It is a well run Institute and produces good quality vaccines despite inadequate facilities, insufficient equipment, as well as neither a preventative maintenance programme nor adequate spare parts.

(a) Production Equipment

Typical production equipment at NIV is as follows:

Liofilization Machine	by	USIFROID, France
Liofilization Machine	by	HULL (out of service)
Labelling Machine	by	BOSCH, G.D.R.
Sealing Machine	by	MECCANICA ENOLOGICA, Italy
Sealing Machine	by	De VECCI, Mexico
Filling Machine	by	COZZOLI, Italy
Filling Machine	by	BREWER, W. Germany
Stainless Steel Tanks	by	AZTEKA, Mexico
St. Steel Pipes and Fittings	generally imported	
Vial Washing	by	MAXIFARMA, Spain
Stoppers are Mexican supply		
Disposable Plastic Bottles are imported from U.S.A.		
Autoclaves	by	AMSCO, Mexico and AMERICAN, U.S.A.
Glass Dryer	by	VECO, Mexico
Hepa Filters	by	VECO, Mexico
Laminar Flow Units	by	VECO, Mexico
Sterilizing Ovens	by	VECO, Mexico
Glassware	by	SELAS, Mexico
Centrifuges	by	I.E.C., U.S.A.; MISTRAL and BECKMAN
Oven	by	Blue 'M' Electric Co. U.S.A.
Laboratory Baths	by	GRANT, U.K.

Wide range of Laboratory Instruments by CONTINENTAL, FISHER, HERACUS, OLYMPUS, OHAUS, MOGUM, MICROTIPO, TAYLOR, ZEISS, BECKMAN, SARTORIUS, GELMAN, CHESSEL AND METTLER		
Air Filters	by	PALL, W. GERMANY

A typical detailed equipment list for the Final Processes Laboratory at NIV is included in Annex 21. It is important to note that by having viral and vacterial vaccine production in different locations in Mexico City much expensive production and service equipment is duplicated. Considerable economies could realise from adjacent facilities.

(b) Services Equipment

The NIV faculty consists of a number of separate buildings, some of which are quite old. Whilst the newer buildings were purpose built in the mid-1970s for the production of viral vaccines and are well served with water, drainage, barrier systems and cold rooms, the final processes are in cramped conditions and the air conditioning system is inadequate. Building construction and building services drawings are available for these new buildings but they are without order, have not been updated to show recent modifications, and no complete list is available. Drawings for the older buildings are not available and this makes the correct management of its services extremely difficult.

Typical service equipment at NIV is as follows:

Electrical switchgear	by	SQUARE D - Mexico
Reverse Osmosis Systems for Water Treatment	by	CONTINENTAL Water Treatment, U.S.A.
Refrigeration Compressors	by	GILBERT COPELAND, Mexico
Cold Rooms	by	REVCO, Mexico
Laminar Flow Units	by	VECO, Mexico
Incinerators	by	GOODRID Inter America Mexico
Steam Boilers	by	CLEAVER-BROOKS, Mexico
Reverse Osmosis Systems	by	MILLIPORE, U.S.A.
Water Distillator	by	FINN-AQUA, Finland
Vacuum Pumps	by	MILLIPORE
Freezers	by	REVCO, Mexico
Air Compressors	by	REMSA, Mexico
Telephone System	by	INDETEL, Mexico
Nitrogen Compressor	by	LINDE, W. Germany
Emergency Electricity Generator	by	SELMEC, Mexico
Hot Rooms	by	THELCO Mexico and ORTIZ, Mexico
Water Sterilizer	by	AMERICAN U.S.A. and AMSCO, Mexico

1b. National Institute of Hygiene (NIH) Mexico City

(a) Production Equipment

The NIH Mexico produces the full range of bacterial vaccines required for the EPI. It is located in a factory that was not purpose built for the production of vaccines and would be very difficult to adapt fully to conform with current G.M.P. requirements. Additionally, as can be seen from the site plan in Annex 26 it contains an area for horses (area 16) which is sandwiched between two areas of private property and which has been the subject of public complaints.

Even though small layout plans for each of the areas at NIH are available, proper engineering drawings showing building construction and services are not. This makes the task of planning layouts and improvements in the provision and running of services almost impossible, as well as acting as a severe constraint on developing plans for increasing production capacity.

At the NIH it is noticeable that many expensive items of equipment purchased in 1983 have not been connected up for service, (in particular: three 750 litre fermenters, one 150 litre vibromixer and one 350 HP Boiler). To avoid such inefficiencies in the future it is imperative that investment planning, purchasing and budgetary control of plant acquisition be assigned directly to the NIH and NIV Institutes themselves, rather than being handled by the more general Ministry of Health.

A typical equipment list for the fermentation laboratory is included in Annex 24.

Typical Equipment at the NIH is as follows:

Centrifuges	by	SHARPLIS and HEDKELL
Liofilization Machines	by	STOKES and New Brunswick
Laminar Flow Hoods & Covers	by	VECO, Mexico
Ovens	by	VECO, Mexico, BLUE M. U.S.A. and RIOS ROCHA
Autoclaves	by	AMSCO
Vibromixer	by	NATIONAL
Incubator Shaker	by	NEW BRUNSWICK
Fermenter	by	MARUBISHI, Japan
Fermatron Fermenter	by	NEW BRUNSWICK, U.S.A.
Fermenter System	by	BILTHOVEN, Holland
Fermenters	by	AZTECA, Mexico
Agitators	by	NEW BRUNSWICK
Agitator Seals	by	CHEMP AG., Switzerland
Centrifuges	by	I.E.C. DAMON
Purification Units	by	MILLIPORE, U.S.A.
St. Steel Casks	by	HERSTELLER, Holland
Glassware	by	KIMAX, Mexico
Sheet Filter	by	SEITZ
Refrigerated Centrifuge	by	I.E.C. DAMON
BCG Filling Machine	by	KUMABE, Japan
Freezer	by	WESTINGHOUSE, U.S.A.
Vortex mixer	by	SCIENTIFIC INDUSTRIES
Microscope	by	OLYMPUS, Japan

Laboratory Balance	by	SARTORIUS, Japan
Potentiometers	by	BECKMAN, U.S.A.
Tank Agitator	by	LIGHTIN, U.S.A.
Sterilizing Ovens	by	HOT PACK
Autoclaves	by	AMSCO
Autoclaves	by	FEHLMEX
Autoclaves	by	WILMOUT - CASTLE
Electric Ovens	by	CAISA and VECO, Mexico
Laminar Flow Cupboards	by	VECO, Mexico
Laminar Flow Cupboard	by	AIR CALIFORNIA
Refrigerators	by	TOLEDO
Extract Fan	by	VECO
Filling and Stoppering M/C	by	BREWER
Filling and Stoppering M/C	by	MAPISA
Filling and Stoppering M/C	by	COZZOLI
Glass Washing Machine	by	ROTA
Glass Washing Machine	by	MARXINFARMA
Stopper Washing Machine	by	BENDIX
Labelling Machine	by	EMPAC
Label Printing Machine	by	EMPAC
Capping machine	by	VECCHI
Vacuum Pumps	by	GELMAN, MILLIPORE and FELISA
Filling Machine	by	BOSCH

(b) Services Equipment

The NIH facility consists of many separate buildings of different ages, with the most recent buildings shown shaded in the site plan in Annex 26. No obvious rationalisation or improvement of engineering services was carried out when these later buildings were added. This, coupled with many recent undocumented repairs and alterations, means that it would prove both difficult and expensive to raise the standards of these services to the quality necessary for trouble-free servicing of a vaccine production facility. Additionally, many sections of steam and water pipes are over fifteen years old (often buried under concrete), and even badly corroded which makes their use undesirable. Electric wiring throughout is in poor condition and even though some has been replaced recently, the entire facility needs to be rewired.

The following is an incomplete list of the existing services supply equipment at the NIH.

Steam Raising Equipment	by	CLEAVER-BROOKS
H.T. Electrical Substation	by	MECCSA
H.T. Transformer	by	DEEMSA
Emergency Electricity Generator	by	Rolls-Royce
Emergency Electricity Generator	by	SELMEC
Incinerator	by	GOODRID INC. Mexico
Water Treatment - Ion Exchange	by	MILLIPORE, U.S.A.
Water Treatment - Reverse Osmosis	by	MILLIPORE, U.S.A.

Water Distillator	by	STOKES, U.S.A.
Air Compressor	by	ITSA, U.S.A.
Air Compressor	by	ATLAS COPCO, U.S.A.
Air Filters	by	HUNTER, U.K.
Compressors (Cold Rooms)	by	GILBERT COPELAND

Air conditioning is generally non-existent at NIH.

2. Carlos J. Finlay (CJF) Institute, Havana, Cuba

This Institute does not produce the full EPI range of either viral or bacterial vaccines. The only viral vaccine it produces is rabies vaccine. The bacterial vaccines it produces are tetanus toxoid, typhoid and BCG. The CJF Institute has developed a procedure for producing pertussis vaccine but it has no plans for its commercial production. Successful trials have been carried out on a DTP vaccine but there is as yet no general production.

(a) Production Equipment

Almost all equipment at the CJF was imported and is now quite old. It is important to note that even though the equipment is old, it has been well maintained and as far as can be expected is in good working order. A case in point is an eighteen year old Bilthoven/van Hemert glass fermentation system still in everyday use.

Because vaccine production is to move from CJF to the new BIOCEN facility in 1991 with completely new production and service equipment, the equipment existing at CJF has not been listed below in any great detail. A description of the envisaged BIOCEN facility including a part list of equipment was provided by the Cuban authorities and this is included in Annex 20. None of the equipment listed can presently be produced in Cuba so it will all have to be imported.

A sample list of typical equipment at the CJF Institute is as follows:

Air Conditioning Equipment	by	SANYO, Japan
Glass Fermenter	by	Van DOORN
Reactor	by	SEITZ
Laboratory Instruments	by	PHILLIPS
Centrifuge	by	HITACHI
Laboratory Instruments	by	PHARMACIA
Liophilization Machine	by	USIFROID
Autoclaves	by	SAKKURA - made under licence in Cuba
Filling Machine	by	BREWER

3. Raphael Rangel Institute, Caracas, Venezuela

The Raphael Rangel Institute (RRI) presently produces the following vaccines - tetanus, diphtheria, pertussis and rabies. The facility is located in hospital buildings adjacent to the National University in Caracas. It is a building wholly unsuited for the production of vaccine in terms of location, buildings and services.

The RRI has no maintenance personnel and relies on outside contractors for equipment servicing and repair. This has led to a proportionately high amount of the specialised equipment being incorrectly adjusted or completely out of service.

Due to plant breakdowns the RRI is presently totally dependent on a nearby media facility for distilled water and autoclave equipment. If either of these external services fail then vaccine production at the RRI will collapse.

(a) Production Equipment

Almost all of the equipment being used at RRI for vaccine production has been imported. A selection of the equipment at RRI is as follows:

Laminar Flow Cabinet	by	MICROFLOW (shortage of filters)
UV Light Unit	by	UNIVERSAL ELECTRIC
Mixers (Small)	by	SORVALL
Refrigerator	by	WESTINGHOUSE
Lyophilizer	by	VIRTIS (out of service since 1975)
Refrigerated Centrifuge	by	SORVALL, DU PONT (never installed)
Autoclave	by	ENVIRONMENTAL TECTONICS CORP. (faulty, unable to control temperature)
Freezers	by	REFCO
Centrifuges	by	SORVALL
Centrifuge	by	FANEM and IEC/Damon
Refrigerated Centrifuge	by	I.E.C.
Orbital Shaker	by	LAB-LINE
Laboratory Instruments	by	B & L, ORION, BECKMAN and SAUTER
Laboratory Bath	by	BLUE M Electric Company
Vacuum Pump	by	DOERR (out of service)
Magnetic Stirrers	by	COLE PARMER, and Jumbo/Fisher
Micro Fermentor	by	ACCO BRISTOL
Fermentor System	by	BILTHOVEN (purchased about 1980 not yet in operation)
Fermentor System	by	NEW BRUNSWICK (purchased about 1978, not yet in operation)
Filling and Stoppering Machine	by	BOSCH Gruppe
Labelling Machine	by	KING (out of service)
Liophilization Machine	by	USIFROID (out of service)
Autoclave	by	AMSCO (only Autoclave in working order in the whole Institute)
Centrifuge	by	INTERNATIONAL Centrifuge (out of service)
Sheet Filters	by	SEITZ
Fine Filters	by	MILLIPORE
Hollow Fibre Concentration Dialysis System	by	-

No complete equipment list was available from the RR Institute and there was a real absence of operation and maintenance manuals for even the most specialised equipment at the institute.

(b) Service Equipment

All steam, water and air services for the main production building at the RR institute are generated and distributed from the basement area. The pipe racks in the centre corridor of this area are too low and a hazard in themselves.

In general, the services might be considered as typical for the standard plumbing and heating of a hospital building. These installed services, however, cannot be considered to comply with the GMP standards required for a vaccine producing institute.

Electrical wiring at the institute is generally loose, uncovered and in many places in a dangerous condition. The air conditioning of areas in the central production building is non-existent and only a very small section of the animal facility has forced ventilation or air conditioning.

The electrical power system is limited in its capacity and restricts the use of equipment with large motors to one or two machines at any one time. This is totally unacceptable.

Finally, no back up service facilities were apparent for any of the services.

B. Availability of Equipment

1. Equipment Availability - Mexico

Following discussions held with Biomex and with Novum in Mexico, (refer Annex) I have developed the following outline of what equipment is generally available in Mexico and what must be imported.

This list is neither complete nor absolute because it was beyond the scope of this mission to make detailed evaluations of equipment manufacturing companies. It does, however, permit a rough overview of how developed the manufacturing sector is in Mexico.

Production Equipment

Equipment Type	Mexican Supplier	Remarks
Filling Machine	VECO, Mexico	Simple filling machines suitable for Pharmaceutical Ind. only
Fume Cupboards	"	High quality
Capping Machines	"	High quality
Laminar Flow Cabinets	"	High quality
Filters	"	High quality
Absolute Filters	VECO, Mexico & MILLIPORE, Mexico	High quality
Powder Mixers	VECO, Mexico	-
Filling Machine (non sterile area)	MAPISA	Factory in Mexico using technology from Italy
Incinerators	IVSA (Incin. Villarreal (S.A.) Incineradores EDA S.A. Incineradores Goodrid Interamericana S.A. de C.V.	Generally only with very simple controllers

Equipment Type	Mexican Supplier	Remarks
Centrifuges	SHARPLIS	Fabrication and assembly
	WESTFALIA	limited to small units in Mexico
	XOMOX	Part assembly in Mexico
	TRIALTO	Fab. and assembly in Mexico including large sizes in stainless steel
Freeze Dryers	None	Imported SHARPLIS or USIFROID
Liophilization Machines	None	Imported
Vacuum Dryers	Subsidiary of COLUMBIA, U.S.A.	
St. steel fermentors (304, 316 and 316L)	BEZAURY	Very promising. Attention to vessel standards and workmanship however could be improved.
	AZTEKA	
	T.E.I.S.A.	
	ASSESORES EQUIPMENT	
	BOMBEO	
	EILI - DICON	
Cold Room Equipment (-70 C, -30 C, +6C)	REVCO	Good manufacturing capabilities but weak on after sales service
Fridges/Freezers	FRILATIC	
	REFRITECHNICA INDUST. S.A.	
	CENTR. de REFRIG. S.A.	
	REVCO	
	ELIZONDO	
	RECOLD (Carrier)	
Glassware	KIMAZ	Up to 12 litres capacity
Agitators	LIGHTNIN	All with factories in Mexico
(St. Steel)	PHILADELPHIA GEAR	"
	NETTCO	"
Electric Ovens	IMPALAB	
	CAISA	
	IDEAL	
Autoclaves	AMSCO	Up to 90 x 90 cm in size Larger must be imported
Glass Washing	BENDIX	Factory in Mexico
Vial Washing	None	Imported BOSCH or CALUMATIC
Stopper Washing	None	Imported, NICOMAC
Final Process Equipment		Is generally imported from BREWER BOSCH, CALUMATIC or COZZOLI. Only quite basic equipment is manufactured in Mexico and available from REVCO and VECO
Glass Lined Equipment	PFAUDLER	Factory in Mexico
St. Steel Flask Dryers	AVANTE	Factory in Mexico
Labelling Machine	VECO	Mexican Fabricator

Service Equipment

Equipment Type	Mexican Supplier	Remarks
Air Conditioning Equipment	CARRIER YORK LUWA	All with factories in Mexico
Water Treatment - Double Distillation	None	Imported FINAQUA, ELGA or BARNSTEAD
Water Treatment - Reverse Osmosis	MILLIPORE	Assembly Plant only
Water Treatment - Ion Exchange	RHOON & HAAS, Mexico	Columns & Resins manufactured in Mexico
St. Steel Pipe	Greater than SCHEDULE 10 and up to 10 inch	Fabricated in Mexico
	Greater than SCHEDULE 10 and greater than 10 inch	Imported
	Less than SCHEDULE 10	Imported
St. Steel Pipe Fittings	None	Imported
St. Steel Sanitary Fittings	None	Imported
Carbon Steel Tanks		Many suppliers in Mexico
Rubber Lined Carbon Steel Tanks		Can be supplied in Mexico
Carbon Steel Pipe		Many suppliers in Mexico
Structural Steel		Many suppliers in Mexico
Instrumentation/ Control	TAYLOR	All with factories in Mexico
Discrete type	FISHER FOXBORO HONEYWELL	
Instrumentation/ Control Electronic	None	Imported
Pumps (non-specialist)	WORTHINGTON SENTINEL	Factories in Mexico
Pumps (Specialist)	EILI-DICON	Mexican Design & Fabrication
	DURCO	Part Fab. in Mexico
	VIKING	IMPORTED COMPONENTS
	MOHNO	IMPORTED COMPONENTS
	LUBOSA	IMPORTED COMPLETE
Standby Electricity Generator & change-over		Mexico can supply up to 750 KVA units SELMEC and IGXA
Switching		Greater than 750 KVA must be imported
Transformers	BIGGER3	Non specials can be manufactured in Mexico. Specials must be imported.

Equipment Type	Mexican Supplier	Remarks
Electrical sub-stations		Best to use local supplier with International Technology back-up, e.g. BBC, ALLSTROM, GEN. ELECTRIC
Steam Boilers	CLEAVER BROOKS SELMEC CERREY	Factory in Mexico
Air Compressors	JOY INGERSOL RAND ATLAS COPCO	All with factories in Mexico
Power Supply Regulators Inverters Peak Eliminators		Manufactured in Mexico
Effluent Treatment Equipment	INTEMA	Mexican specialist. Tanks etc. can be provided in Mexico, but very special equipment must be imported.
Refrigerant Compressors	YORK COPELAND MESA	All with production facilities in Mexico
Electrical Motor Control Centres	SQUARE D SIEMENS FEDERAL PACIFIC	All with factories in Mexico, capable of producing up to 500 KVA
Vacuum Pumps	None	Imported from NASH, USA, or EDWARDS HIGH VACUUM
Mechanical Seals	J. CRANE	Factory in Mexico
Valves Control		Generally Imported
Valves General Purpose	CRANE HATTERSLEY	Factories in Mexico
Valves Lined		Imported
Heat Exchangers	SWECO	Factory in Mexico
Pressure & Relief Valves, Safety Valves, etc.	CRANE	Factory in Mexico
Electric Motors		Many manufacturers but capacity limitations when large quantity orders needed

2. Equipment Availability - Cuba

In general, all production equipment and service equipment required for the production of vaccines in Cuba is imported. Some exceptions to this are small stainless steel tanks, refrigerators, non-specialised electrical power equipment, building materials and stainless steel wire cages. As a result of a drive by Cuba to develop and produce medical equipment for its national health programme, the recently set up "Union Enterprise for Medical Equipment Production" (UEPEM) will soon be able to supply Cuban built autoclaves from its new 51,000 sq. m. factory. Plans to produce Cuban heated water baths, incubators, shakers and laminar flow cabinets are well advanced but have not yet reached the commercial production stage.

Cuba has an additional problem in its efforts to import foreign technology and equipment in the form of an embargo operated by American owned companies. This prevents the sale of equipment to Cuba which contain more than 10% US components. This can often lead to Cubans having to pay higher prices from non-US suppliers.

3. Equipment Availability in Venezuela

My overall impression of the equipment supply situation in Venezuela is that a wider range of imported equipment is available than in either Mexico or Cuba due to Venezuela historically having been an oil rich economy. My impression also is that considerably less manufacture or even assembly of equipment is carried on in Venezuela than is the case in Mexico. In the past it has been far easier for Venezuela to import completely assembled equipment with oil profits rather than develop its industrial base or train technical personnel.

As a result the vaccine industry, like other industries in Venezuela, owns much highly sophisticated imported equipment that unfortunately lies idle due to lack of spares and inadequate training in its maintenance.

The following list gives an indication of the international manufacturers represented in Venezuela, but few comments can be made about whether these have production facilities or are just representative agents, as none of them were visited.

Pumps		FLYGT, SULZER, ABS, KSB, Sand-Piper, WADE, VIKING, GOULDS, BBC, etc.
Stainless Steel		Manufactured in Venezuela
Aluminium		Manufactured in Venezuela
Air Conditioning Equipment	by	Carrier, Airflow, TOMO, NORCOLD, TRANE and Honeywell
Air Conditioning Ductwork		Manufactured in Venezuela
Electrical Dist. Equip.		SIEMENS, NATIONAL, TELEMECANIQUE, BBC and GENERAL ELECTRIC
Filling Machines	by	INDUSTRIAS JESMI, Venezuela
Industrial & Process Filters		SEITZ, SARTORIUS and TEQUI
Special Gases	by	C.A. GASES Industriales de Venezuela
Mild Steel Tanks	by	GUACARA C.A. Venezuela TENAVAL. C.A. and others
St. Steel Tanks	by	Metalúrgica Guarenas, S.R.L. and others
Structural Steel	by	Metalúrgica Meridional CUA C.A. INPABICAVEN, C.A. ADAINOX, C.A. TALLER INDUSTRIAL SUIZO C.A.
Water Treatment Equip. (exclud. D. Distillation)	by	GACO Systems de Venezuela, NAL-VAN C.A. VENEAQUA C.A.

Pipework and Fittings	by	ACEVENCO de Venezuela Tubería Central Valencia MORINCA, C.A.
Valves	by	FUNDICION PACIFICO, C.A. SUMAR C.A. VALGRIF C.A. Ingeniera de MATERIALES, C.A.
Fans	by	FREDIVE C.A. METALAIRE, C.A. VINA VENTILADORES C.A. TALLERIES UMMON C.A.
Centrifuges	by	ALFA-LAVAL Venezuela SULZER de Venezuela
Laboratory Equip.	by	CENATEX C.A. Corporation BIOMED C.A. MICROTRIX VENEZOLANA
Glassware	by	MACIVID C.A.
Autoclaves	by	MASTER ELECTRIC, C.A.
Lab. Furniture	by	Medica Industrial C.A.

4. Other Latin American Sources of Equipment

Since this model programme for the Integrated Regional Production of Biologicals in Latin America has as one of its objectives "the promotion of self-reliance and self-sufficiency in the manufacture of production and control equipment", it is my belief that other member countries of SELA such as Argentina and Brazil should be examined as Latin American sources of sophisticated equipment. The following Argentinian suppliers are known to supply good quality equipment at prices far below European prices and should be considered.

Autoclaves, Freeze Dryers, Water Distillation Equipment, Vial Washing Machines and Clean Steam Generators	from HOGNER
Filling Machines	from DAUMAQ
Labelling Machines	from OLAGUER
Laminar Flow Cabinets	from FILTRAR
Stainless Steel Vessels	from METALURGICA VICTORIA
De-ionized Water Treatment Plant	from DEGREMONT

Additionally, even though I cannot supply typical names of Brazilian manufacturers of such equipment, I am sure there are some who should also be considered as suppliers of equipment for such regional production programmes.

C. Availability of Engineering Design Services

Mexico

There are many private engineering design companies based in Mexico City that would have sufficient basic expertise to design and project manage new facilities for the production of vaccines. Some specialist outside input might be required, however, to ensure that design conformed to GMP.

Typical companies are:

Bufete Industrial
Ingenería Civil Asociada
I.E.P.S.A. Eng. Electrical Projects
ATLAS FOSTER WHEELER
PROYECTOS MEXICANOS de Ingeniería Básica (PMIB)

Cuba

In Cuba all the engineering design for such facilities as CENPALAB, BIOCEN and the Genetic Engineering Institute (C.I.G.B.) was carried out by a division of EMPRESA MILITAR de PROYECTO & INVESTIGACIONES (EMPI). Judging by the superb result they achieved in the design and construction of the Genetic Engineering and Biotechnology Institute, there can be little doubt about their capabilities to plan and manage similar projects. EMPI, however, was only responsible for the design and construction of the buildings and the general services. They were not responsible for the detailed design of special services and production facilities in accordance with GMP. As will be outlined later in Section G (B) it is in this area of design, installation and verification of systems to GMP standards that some slight problems need to be remedied. No common standards for installation according to GMP appear to have been adopted in the facilities presently being built and this is unwise.

Venezuela

There are many general engineering design companies in Venezuela that would have sufficient expertise to design and build new facilities for the production of human vaccines in Venezuela. Again, some specialist input might be required to ensure that these designs conformed to current GMP.

D. Maintenance and Training at Existing Vaccine Production Centres

1a) National Institute of Virology (NIV), Mexico City

Equipment at NIV is repaired by an in-house team of ten technicians working in shifts to give twenty-four hour cover. Unfortunately, their work is hampered by poor workshop facilities, a total absence of spare parts even for critical imported machines, and no apparent training in the maintenance and repair of such specialised equipment.

According to the organisation chart of the Ministry of Health in Annex 27, the responsibility for equipment purchase, maintenance and the storage of spare parts for both the NIV and NIH is external to these institutes. This is unsatisfactory and might explain why some major items of plant in both institutes were purchased but not installed, whilst other items were out of service due to lack of spare parts (refer Equipment lists in Annexes 23, 24, 25.

In fact, the maintenance and storage of spares for both NIV and NIH is considered to be the direct responsibility of the engineering department of the NIH. In terms of manpower this is unrealistic as they have only marginally more personnel than NIV and are not in a position to do anything more than emergency repairs to equipment at their own premises. Furthermore, the stores and workshop facilities at NIH are inadequate even to

service their own facility let alone both.

A major cause for concern about the continued viability of the vaccine industry in Mexico is raised by the underfunding of capital projects and the lack of co-ordinated planning over the past four years. A more fundamental cause for concern is the absence of any complete working plant register, without which good planning is difficult and planned maintenance is impossible. The total lack of spare parts for specialised equipment at both NIV and NIH is a serious risk to the continued functioning of their equipment and must put in jeopardy their candidature for consideration as a regional production centre for vaccines.

With regard to training, even though the GGBR does include occasional courses related to the maintenance of industrial and laboratory equipment, these can have limited use in a vaccine production environment where neither spare parts are ordered in advance nor any planned maintenance is carried out.

Some indication was given by GGBR that repairs to specialised equipment could be carried out by another division of the Department of Health - "D.G. de Investigación Y Desarollo Tecnologia" (DGIDT). Unfortunately, the organogram in Annex 28 formally shows no such arrangement and, therefore, even a broad view of the vaccine production institutes must ignore this facility.

Furthermore, with a staff of about 120 in this department of "investigation and development" which caters for the whole Department of Health, it seems unlikely it could manage training, repairs and maintenance at vaccine institutes as well as serving all the hospitals in the country.

Following a visit to DGIDT, it was found that in the past 3 years, nine technical training manuals for hospital personnel had been produced as well as a detailed register of manuals for sophisticated equipment in use. The tremendous advances made by this department in information gathering and producing manuals demonstrates that the capabilities exist within the Department of Health to attack systematically the problem of untrained personnel and unco-ordinated policies of equipment purchase. Unfortunately, the present work only pertains to the hospital service.

The problem remains that maintenance personnel in both NIV and NIH are not trained in the servicing of the sophisticated equipment they are responsible for, and far too much reliance is placed on buying in technical service from outside at a very high cost.

Additionally, the lack of: a working plant register of equipment, manuals, spare parts lists and work control documentation prevents informed planning of facilities and the implementation of any maintenance programmes.

More so than in the general health sector, a highly qualified and technically proficient core group already exists in the vaccine institutes. Because of this inherent skill, and the sophistication but small scale of the equipment used for vaccine production, a strong basis exists for fully training the maintenance personnel in this sector. This specialist group could ensure the availability of vaccine production facilities to GMP standards as well as possibly becoming the vanguard group that could eventually develop technical expertise throughout the general health sector. Of course, the whole status of such personnel and indeed their pay levels would have to be raised if the trained group were to remain within the public sector and provide the development proposed.

With the average age of equipment at both Institutes generally greater than 10 years, and most of it poorly maintained, a major capital investment programme is essential if Mexico is to continue to manufacture good quality vaccines in the years to come.

1b) National Institute of Hygiene (NIH), Mexico City

It is worth repeating that the Engineering and Maintenance department of the NIH is officially responsible for all repairs, the storage of spares, and the maintenance of equipment at both the NIH and the NIV. IN NIH there are approximately 14 persons employed in maintenance out of a total staff of 280. At the NIV there are approximately 10 persons involved in plant repair out of a total staff of approximately 130. Obviously, since there is no substantial difference in the equipment that must be maintained at both institutes, it would seem on a pro-rata basis that present engineering staffing levels at NIH are less than at NIV and thus NIH cannot be in a position to carry out all maintenance functions.

From the equipment list in Section A, 1a, b it can be seen that BCG vaccine is filled and sealed using a KUMABE Japanese filling machine. Due to incomplete closure of some glass vials during this process as much as 30% of final product is being lost. A simple systematic test using recommended Japanese glass vials rather than the currently used Mexican glass vials might easily trace the cause of this incomplete closing to either glass or the machine. Unfortunately, this has not been carried out.

Results from tetanus production would seem to indicate a possible pick-up of contaminating particles somewhere in a clearly distinguishable part of the process. Even though the source of this pick-up is obviously in the production facility and is causing great losses of valuable product, the required methodical search to isolate the contaminating equipment has not been carried out.

Both the above examples appear to indicate a serious problem in the organisation of engineering and production at NIH preventing action to isolate and solve problems that are well within the Institute's capacity to solve.

2) Carlos J. Finlay Institute (CJF) Havana, Cuba

All equipment at the Carlos J. Finlay (CJF) Institute has an individually numbered tag permanently attached. This makes for the easy operation of the good preventative maintenance programme that exists at CJF.

The maintenance department at CJF consists of 20 men as follows: 1 Head of Department: 1 Electrician, 1 Machinist, 2 Mechanics, 2 Electricians, 1 Carpenter, 1 Welder, 2 Refrigeration Mechanics, 1 Lyophilization Machine Specialist, 1 Instrument Specialist, 1 Plumber, 3 General Helpers and 3 Administrators. There are physically separate workshops for each trade. This has instilled a sense of pride and responsibility in the workers which has resulted in well-organised functional work areas.

A preventative maintenance system, complete with hand-written documentation, was seen to be in operation at CJF. Typical standard forms in use are:

Lubrication Record Sheet
Electric Motor Service Sheet
Spare Parts Control Sheet
Work Order Sheet
Repairs Time-Log
Yearly Man Hour Plan for Preventative Maintenance Programme
Repairs Description Sheet
Equipment Log of Preventative Maintenance carried out
Work Regulation Sheet
Hours - Log Sheet for Repairs done
Hours - Log Sheet for preventative maintenance done
Record Card for Each Item of Equipment
Stores Control Sheet for Spare Parts
Spare Part Stock Level Sheets

The success of this well-run maintenance department was reflected in the absence of machines out of service, and the extended working life of sophisticated equipment. No other institute visited in Cuba appeared to have such a detailed and well organised maintenance department.

A serious flaw in the current operation of the planned maintenance system at CJF is, however, the inability to order spares at different times of the year. This makes for a very coarse matching of spares ordered, and spares required. A possible result of this inability to order new spares during the financial year is an excessive reliance on local service contractors with spares to carry out repairs on equipment such as steam boilers, refrigeration and water distillation equipment. A less serious difficulty is that the reference number now used for spare parts in the stores has no direct relationship to the machine for which it is a spare. Whilst this is not a problem on a small facility like CJF it would cause serious difficulties on a large facility such as BIOCEN.

Probably the key to the successful operation of the spares system at the CJF is that the maintenance department itself is responsible for the issuing and inventory of all spare parts.

It is imperative that a well thought out maintenance programme be developed for BIOCEN at the same time as equipment is being installed.

Additionally, the personnel who will eventually be responsible for the maintenance of imported sophisticated equipment should be trained by the foreign suppliers and involved in the installation of the equipment itself (as apparently was the policy when CIGB was being built). These personnel should also be involved in the preparation of the preventative maintenance programme. It is important to note that the correct servicing of equipment during its first years of operation will give the best returns in equipment service life.

Some assistance might be considered in the setting up of such a planned maintenance system for these new institutes, particularly when the task lends itself easily to a short intensive programme of work.

3) Raphael Rangel Institute (RRI), Caracas, Venezuela

Maintenance of services and production equipment as well as staff training is very poor at the RR Institute. Furthermore, the very large amount of expensive imported equipment that was purchased in the late 1970s and never put

into operation indicates a serious flaw in the overall planning and management at this institute.

It is my impression that with a concerted effort and a small amount of funding a lot of the idle equipment listed in Section 3 (a) could be put into service. It will take considerably more effort and funding to develop a satisfactory maintenance function and to bring the standard of existing services and buildings up to GMP standards. A more sensible alternative might be to consider building a new facility for the production of vaccines in Venezuela and returning the present buildings to the hospital.

From a visit to a private pharmaceutical facility in Caracas there is evidence that skilled maintenance personnel are available in Venezuela as well as competent Venezuelan personnel to design, install and run such facilities in line with GMP requirements. Detailed documentation was also available at this private facility and used for verification of procedures for production and maintenance. Similar documentation should be introduced into the public sector involved in vaccine production.

E. Cold Rooms Available for Final Products

1. Mexico

Finished vaccines are normally transported to the Gerencia General de Biológicos y Reactivos (GGBR) for storage prior to distribution to the field. Electrical supply to these cold rooms is ensured by an automatic standby electricity generator. The cold rooms for final vaccine products at the GGBR are as follows:

Room Tag	Stored Product	Temperature	Size
A	Products from NIH except DPT, BCG & TT	+ 2 to + 8 C	3 m x 3 m x 3 m
B	(as in Room A above)		
C	Products from NIV except Polio	+ 2 to + 5 C	3 m x 3 m x 3 m
D	Products from NIV except Polio	+ 2 to + 5 C	3 m x 3 m x 3 m
E	Auxiliary Room for Quarantined Products	+ 2 to + 8 C	3 m x 3 m x 3 m
F	Polio Vaccine from NIV	- 20 C	3 m x 3 m x 3 m
H	HAEMODERIVATIVES and Products from NIV	+ 2 to + 8 C	6 m x 6 m x 3 m

There are also 35 domestic size fridges for cooling "liquid ice" used in cold chain boxes.

At the NIH there are 7 cold rooms - (Tag Nos. 18, 19 and 21 to 25) for the storage of final product. Each of these cold rooms measures approximately 4 m x 4 m x 3 m.

At the NIV there are 5 main cold rooms available for the storage of finished product. Three stores measuring 4.5 m x 4.5 m x 3 m and at a temperature of + 4 C, and 2 other stores at - 20 C measuring 4.5 m x 4.5 m x 3.0 m and 6.0 m x 4.5 m x 3 m respectively.

As can be seen from the table in Annex 25, the GGBR conglomerate has a total of approximately 60 cold rooms in current use. A certain amount of rearrangement could probably release enough additional cold rooms to enable it to store the vaccine quantities required for regional supply - should the above 20 final process cold rooms be insufficient.

2. Cuba

According to the equipment list for BIOCEN included in Annex 20, the viral vaccine production facility will have a total of 13 x 20 cubic metres of + 4° cold room space. There is no indication however of how much of this will be used for the storage of final products. Considering the number of other cold rooms that will be constructed in the BIOCEN centre one can have little doubt that should it be so decided there would be more than adequate cold room storage space for the storage of the larger quantities of vaccine required for regional supply.

3. Venezuela

No cold rooms at the Raphael Rangel Institute in Caracas would be suitable for the large quantity of vaccines that would be needed for regional supply.

F. Buildings at Existing Vaccine Production Centres

As stated previously, the NIV Mexico City is located in premises where some buildings were purpose built for vaccine production, whilst others were only adapted to this purpose. Whilst the purpose built buildings of NIV reflect what was good practice at the time they were built, they would not satisfy current GMP standards. The adapted buildings are generally unsuitable for vaccine production and suffer severe congestion particularly in the water treatment and lyophilization equipment areas.

1. The NIH Mexico City operates in premises none of which was purpose built for the production of vaccines. It is unsuitable for the production of vaccines and contravenes GMP in many ways. Besides the obvious difficulty in trying to operate services when no up-to-date building service drawings are available, the absence of barrier systems (e.g. in vial washing area) and air conditioning is a serious drawback. Other problems such as corroded steam lines, a variable voltage power supply and a multitude of unrecorded system alterations over the years makes for continued difficulty in producing quality vaccines in these premises.

Furthermore, high quality distilled water produced at NIH has to be manually distributed in flasks because no piped distribution system exists.

2. The Carlos Finlay Institute, Havana, is located in a converted colonial style building totally unsuited for the production of vaccines. Process routings as a result are tortuous, building finishes do not conform to GMP, and there is a serious lack of space.

3. The main production area at the Raphael Rangel Institute, Caracas, is located in a four-storey building which was built as a general purpose hospital wing. In terms of building finish, layout, services and cleanliness it is totally unsuitable for use as a vaccine production centre. Whilst it is important to differentiate between the quality of production and the quality of the premises in which production takes place, the high quality production of tetanus toxoid at the RR Institute must in this instance be seen to be seriously threatened by the deplorable premises in which it is produced.

The animal facilities at the RR Institute are housed in buildings that also have been converted from other uses. They are unsecured against entry of rodents, lack suitable air conditioning and must generally be considered of poor standard. A further unacceptable problem with all buildings at the RR Institute is that they are rat infested.

G. Future Plans for the Production of Vaccines

(A) Mexico

In 1987 a plan was developed, and some basic engineering work carried out, for a new facility to produce blood derivative products, anti-snake serum and EPI vaccines in Mexico. An outline plan for this proposed facility is shown in Annex 22 (Plan XX-22-01).

Early in 1988, however, the plans to produce EPI vaccines at this new facility were deleted and the remaining plant plan was broken into 2 phases. Phase I was a plan to build a facility for producing blood derivatives. This portion of the overall plan was the only part being actively progressed at the time of our visit to Mexico. Phase II was for the later production of factors VIII and IX, hepatitis B and prothrombin, but plans for this were not being developed any further at present.

It is essential to note that the present plan is limited to a blood derivatives plant only. The site purchased is too small ever to support a vaccine production institute at a later date, and the buildings and services have been designed only to cope with the blood derivatives proposal. An outline site plan for this March 1988 proposal is shown in Annex 22 and dated June 10, 1988.

We must therefore conclude that Mexico has no plans at present to build a new vaccine production centre. We must also note that with capital investment budgets approaching zero at both NIH and NIV from 1985 to 1988 a programme of investment in the existing institutions to improve their running and attain current GMP standards must in fact be seen to have a low priority.

Without this investment not only will the institutions never meet the international standards that will be expected of a regional supplier of vaccines, but in fact their own national vaccine production must eventually collapse.

(B) Cuba

Of all the countries visited on the mission, Cuba has by far the most ambitious plans for vaccine production even if for only a limited range of vaccines. Furthermore, the planned BIOCEN facilities are at an advanced stage of construction and first production of vaccines at the new facility is

expected to commence in 1989 with full scale production by 1991.

According to studies carried out by the State Committee for Economic Collaboration (CESE), the body responsible for external economic co-operation, overall technical co-operation needs and priorities for the various branches and industries are as follows: (Ref. UNDP/CP/CUB/4 March 1986)

"To guarantee implementation of scientific and technical programmes linked to eccnomic development and those contained in the main social science and medical research programmes. To promote development of basic sciences and to give special attention to biology and its applications - for example, biotechnology and genetic engineering - taking into account the repercussions it may have on various branches of science and of the economy."

A visit to the well-designed, well-run and extremely well-equipped centre for Genetic Engineering and Biotechnology (CIGB) in Havana shows what high standards can be attained.

A visit to the site for the National Centre for Bioproducts (BIOCEN) which will produce (among other products) vaccines as well as a review of the engineering plans and construction programme for its 56,000 sq. metre development, shows that this new project obviously is receiving special attention and will most likely be producing large quantities of high quality tetanus toxoid, BCG and typhoid vaccines by 1991.

BIOCEN plans to produce the following vaccines: tetanus toxoid, DT (Diphtheria-tetanus), DTP (Diphtheria Tetanus Pertussis, oral antityphoid, injectable antityphoid, BCG, meningococcal (Groups B and C), meningococcal (Groups A and C), hepatitis B, yellow fever, rubella, Haemophilus influenzae b, parotitis, leptospirosis, measles and influenza.

The main buildings at BIOCEN will be for:

Production of bacterial vaccines
Production of culture media
Filling and lyophilization
Diagnostics
Production of viral vaccines
Quality control
Warehouse storage
Animal facilities
Pilot-scale plant
R & D
Administration

Another indication of the high priority being placed on the biotechnology sector in Cuba is the current capital investment and new buildings programme already at an advanced stage of construction at the Carlos J. Finlay Institute in Havana. This is all part of an integrated plan to move vaccine production out of unsatisfactory surroundings to BIOCEN and to improve production of the Carlos Finlay non-vaccine products by rearranging layout and expansion into 2200 sq. metres of new purpose built buildings at CJF.

The final indicator pointing to the likely success of an integrated and ambitious programme for the development of biotechnology and genetic engineering in Cuba is the building of a National Centre for the production of laboratory animals, (CENPALAB), Phase I of which is already completed and in use. Phase II, which will include facilities for non-conventional animals

as well as a facility for the production of concentrated animal food, will be completed by 1990.

The combination of all these new facilities in Cuba could enable Cuba to take the lead in the production of some vaccines in the Latin American region by 1991.

One caveat in the area of plant design and installation should be included however. After visiting all the above mentioned facilities, as well as the temporary production centre for meningococcal B vaccine, a number of installation details were seen that seriously contravened the spirit of GMP. Even though the actual items noticed were somewhat minor and could easily be remedied, they stood to jeopardize the correct functioning of systems critical to the whole facility.

A sufficient number of these minor deviations was observed in new installations for me to suspect the existence of a less than total understanding of the implications of GMP in plant design, installation and verification. Some help should be considered in this area. An area of concern hinted at by these incorrect installations is that insufficient planning is given to the purchase from abroad of sufficient ancillary items, not available in Cuba, such as stainless steel pipework, welding rods, valves, flanges, reducers and filters, etc. that are so essential for the correct installation of equipment to GMP standards. Many of the incorrect practices were obviously the result of unacceptable improvizations made because of a lack of such simple components.

(C) Venezuela

As far as could be discovered there are at present no plans to build a new vaccine production facility in Venezuela.

Some investment is already taking place in the refurbishment of an area in the basement of the existing production building at the RR Institute. This new work has not been carried out in conformity with GMP for a vaccine production area, and will also be subject to the same limitations inherent in the inadequate services available to this building.

Before further investment is made it might be wise to examine any long-term plans for vaccine production in Venezuela in the light of the following: the buildings and services at RRI, the equipment that could be easily returned to service, and the GMP requirements that must be met if the facilities producing vaccines are to meet world standards. This might afford a better overall solution than piecemeal efforts to improve the facility outside an overall integrated plan.

V. PROJECT ENGINEERING (A. JAKABOS)

Introduction

In recent years Latin American countries have learnt that some of the industries which they had established in the past, and which were appropriate for the golden age of development of the early 1970s, have turned out to be inappropriate for the conditions of the 1990s. Many countries, therefore, are searching for new ways of reducing their net dependence on the world economy. This too is the case in vaccine production. Therefore, in this chapter we consider production as of the 1980s' standard and not always following GMP recommendations. We accept the government view to keep the present vaccine production units in operation for the following reasons:

- to maintain present technologies which gives an opportunity to establish similar facilities (for example, formulation),
- to save foreign exchange,
- to offer job possibilities.

Certainly SELA and the governments concerned have to make the final decision in this field.

In this paragraph we will deal with the location taking into consideration three principles:

- public policies
- infrastructures
- general location considerations

The impact of public policies is different now from what it was when the existing facilities were built. Then there was no pressure for the decentralization of industries. Therefore, all of them were built either in the capital city or not far from big towns. This is an advantage for the vaccine industry to have access to universities and other institutions. But on the other hand most of them do not have any space for expansion.

It is more important that a vaccine production plant be near to the qualified labour force than to the material inputs and to the centres of consumption because a relatively small quantity of goods is involved.

A well-developed infrastructure is vital to the operation of vaccine production; therefore, the availability of energy, transport, water, communication and housing will be examined.

The socio-economic aspect will also be taken into consideration.

Location and Site

Venezuela

Instituto Nacional De Higiene "Rafael Rangel"

The institute is located inside the University of Caracas, in the centre of the city. The production facility and the Institute of Hygiene share the same building. The nearest building is a hospital.

The institute - the university - has good connections by road with no width, height or weight limitation. Air transport can be reached easily. There is also a good public passenger transport system.

The location of the institute is such that expansion is not possible on the present site. The present production methodology is of late 1970s' standard. For international acceptance much improvement is necessary.

If adequately repaired the same building could be used or, alternatively, a completely new facility should be built. An engineering and general contracting company is available. For design an expert should be consulted. Most of the equipment has to be imported. Electrical equipment can be obtained locally.

Conclusion: Existing facilities are of late 1970s' standard, and should be improved. To reach international standards complete reorganization and reconstruction is necessary.

Auxiliary

Venezuela

Water

There is a public water supply system. The institute receives its water from the University. Shortage of water is rare.

Electricity

Power is available. Interruption of high and low voltage, about twice per annum, is not a major inconvenience.

Gas, Oil

Both are available.

Steam, Hot Water

The institute does not have its own steam boiler or hot water supply, steam being supplied by the University.

Communication System

There are telephone and telex connections, but the service generally in the country is inadequate.

Sewage System

The tetanus toxoid department has an emergency storage tank in case of accident. Usually waste liquids are discharged directly into a nearby stream.

Manpower

All levels of skilled manpower are available. Post graduate training is necessary. Housing, food, recreation, schools, shopping facilities and medical services are available in Caracas.

VI. ECONOMIC REVIEW (L. HOLMSTROM)

Cuba

A. Supply and Demand of Vaccines

1. Supply of Vaccines

EPI vaccines for the Cuban market are supplied partly from local production at the Carlos J. Finlay Institute in Havana and partly from imports.

Three EPI vaccines were produced in 1988: BCG vaccine, tetanus toxoid and rabies vaccine. Production figures for 1987 and 1988 (estimate) were (million doses):

	1987	1988 (estimate)
BCG	-	0.150
TT	2.0	2.0
Rabies (human)	0.160	0.160

Rabies vaccine is the only viral vaccine being produced in Cuba. The output of 160,000 doses per year equals the present production capacity. According to information from the Carlos J. Finlay Institute, measles vaccine could be produced in a relatively short period of time if the authorities decided accordingly. Polio vaccine is being considered for production in the long-term perspective.

In bacterial vaccines, 2 million doses of tetanus toxoid are being produced, and this volume equals the present production capacity. Production of BCG vaccine was stopped in 1985-1987 because of quality inconsistencies. Production started again in 1988 with an expected output of 150,000 doses. About 1.5 million doses of diphtheria toxoid are also produced, but no DTP since there is no production of pertussis vaccine. The Carlos J. Finlay Institute claims that they are ready to start production of DT vaccine, while they are awaiting the production of pertussis vaccine.

According to the MoH, the following EPI vaccines were imported in 1987:

Measles	0.5 million doses
Polio	3.0 " "
BCG	1.0 " "
DPT	3.0 " "

The figures were hard to come by and should be treated with caution. These vaccines are being imported from the Soviet Union. The prices were not disclosed, but according to information from representatives of the MoH, the vaccines were valued at about UNICEF list prices of essential drugs in the annual trade agreements with the Soviet Union. This would constitute a total cost of about $US 500,000 over a year.

Apart from the EPI vaccines, about 1 million doses of triple viral vaccine (measles, mumps, German measles) are being imported each year from Belgium at a price of about $US 1 per dose.

2. Demand of EPI Vaccines

According to the MoH, the 1988 requirements of EPI vaccines in Cuba are as follows:

BCG	1.0	million doses
DPT	3.0	" "
TT	2.0	" "
Polio	3.0	" "
Rabies	0.2	" "
Measles	0.5	" "

We are not certain of the degree of reliability of these figures.

B. The Carlos J. Finlay Institute - Organization and Economy

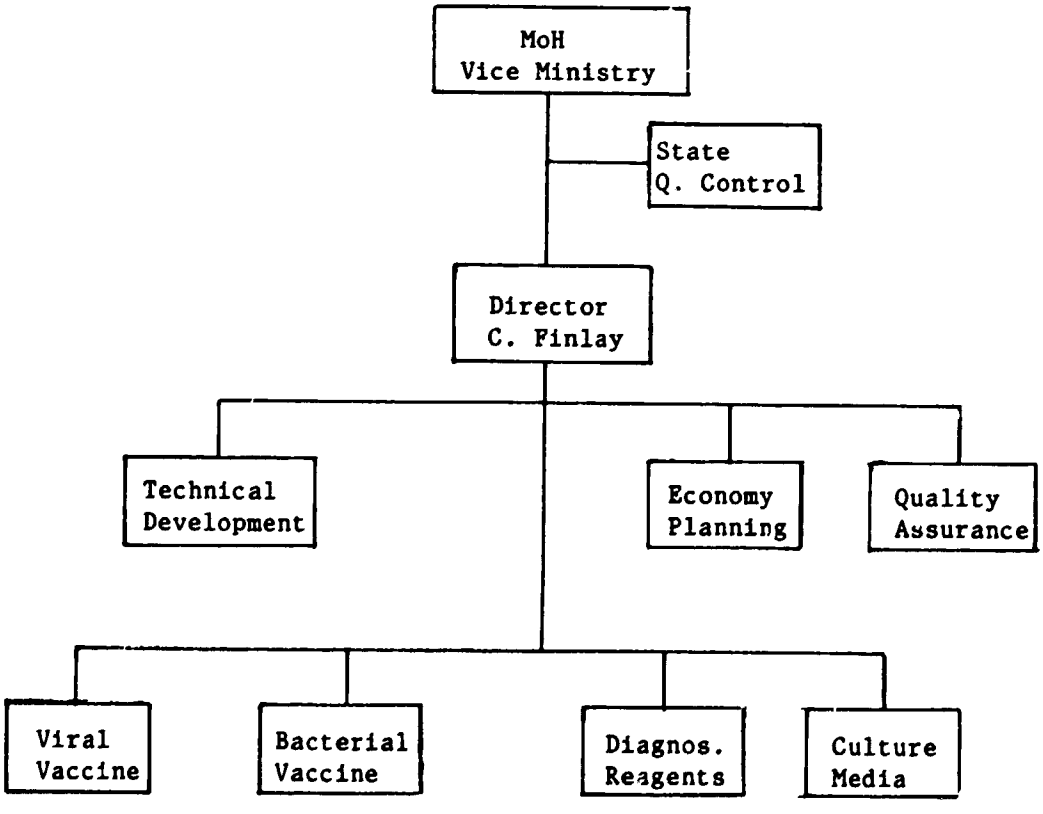
1. Organization

The local production of EPI vaccines is sustained by the Carlos J. Finlay Institute in Havana, organized as one of several federal institutions under the responsibility of the Ministry of Health.

The Institute started production in 1973 in facilities which were previously used as a school.

The primary function of the Institute is production, control and distribution of bacterial vaccines, viral vaccines, antisera and biological reagents. The Institute is also in charge of the importation of biological products required to meet the national requirements.

A simplified organization chart follows below:



The total number of employees is 350, including 53 graduates.

The organization will not be analyzed further since all present production of EPI vaccines will be moved from the Institute in the next 1-2 years to the National Centre of Bioproducts - Biocen - which is under construction. Production of diagnostic media will be left in the Institute together with a special area for R&D activities.

2. Financial Status and Performance

The Ministry of Health would not convey any information on total costs and financial performance of the present production of vaccines in the country.

Some information, however, pertaining to the costs and prices of vaccine production was disclosed in our discussions with the Accounting Department at the Institute. The following information was given on rabies, BCG and TT (pesos per dose):

	Rabies	BCG	TT
Sales price	0.53	0.060	0.056
Direct and indirect product cost	0.40	0.054	0.046
Gross margin	0.13	0.006	0.010
Gross margin, %	24%	10%	18%

With the official exchange rate of $US 1:0.76 Cuban pesos in November 1988, the corresponding costs in US dollars for vaccines would be 53 cents per dose for human rabies vaccine, 7 cents per dose for BCG vaccine and 6 cents per dose for tetanus toxoid.

The corresponding prices for the three vaccines are higher than the current prices charged by UNICEF. The product costs are also higher than the corresponding costs projected by WHO and noted by the consultants in Mexico. It is not possible for us, however, to say anything definite on the present performance of the EPI vaccine production in Cuba. The lack of information and the rate of uncertainty in the information given to us in Havana limits the use of such comparisons.

C. Biocen and Regional Production of Vaccines

As was mentioned previously in this report, all the present production of EPI vaccines at the Carlos J. Finlay Institute will be moved in the next 1-2 years to Biocen - the National Centre of Bioproducts - which is under construction.

In 1981, the Cuban Government formed the so-called Biology Front, a group of institutes working in the field of biology. Biocen is to play a key role in the Biology Front in research, development and production of vaccines and other biological products. It was stated in 1981 that Cuba should be an example of modern prophylactic medicine. The objectives of Biocen, quoting from a publicity brochure, are:

- to produce vaccines, diagnostic reagents and culture media required to attain the goal of making Cuba a world medical power,

- to obtain vaccines and diagnostic reagents needed for Latin American and Third World countries or any other country,
- to develop prophylactic medicine by protecting the population by means of immunoprophylaxis and early detection of disease,
- to integrate investigations and production with other institutions of the Biology Front.

These objectives are fully in line with the national development strategy to promote science and technology as an essential means of establishing the technical and material basis of socialism in Cuba, and to give special attention to the area of biology and its applications.

Biocen is being built at Bejucal outside Havana in an area of 9 hectares and with 56,000 m^2 of buildings. The main premises will be used for the production of bacterial vaccines, culture media, viral vaccines, diagnostics and for quality control, animal house, warehouses, research and administration.

Biocen began production in 1986 in temporary facilities in Havana producing, inter alia, meningococcal B vaccine.

The new institute is expected to be in operation during 1990-1992 and the following vaccines are to be produced:

Vaccines	Production start	Potential capacity (million doses)
TT	1990	40.0
BCG	1990	6.0
Pertussis	1991	15.0
Diphtheria	1991	30.0
Typhoid	1990	6.0
Meningococcal BC	1990	10.0
Rabies	1991	3.0
Measles	1991	6.0
Influenza	1991	4.0
Rubella	1992	6.0
Mumps	1992	6.0
Hepatitis B	1990	5.0

Production of polio vaccine is also being considered, but no formal decision is yet taken on this issue.

Total investment in Biocen is estimated at the equivalent of $US 57 million, including $US 31 million for machinery and equipment. About 80 per cent of the machinery and equipment is imported.

The consultant tried on several occasions to discuss the economic and financial background of the project. No substantial information, however, was given in the area of expected financial and economic rate of return on the investment. The reason for this might be that the MoH considered such information as classified but a more probable explanation, in our opinion, is that no comprehensive financial or economic analysis of the project is available. According to the MoH, the rate of return on this investment is inferior in significance to the overall objectives of the Biology Front. The two major factors influencing the creation of the project and the size of the investment area:

* The long-term strategy to make Cuba a world medical power and to use the biological sector as a comparative advantage in the development of the Cuban economy.

* The capacity of the project should be large enough to satisfy both local demand and the requirements of several other nations in order to save foreign exchange on import substitution and earn foreign exchange on exports of the vaccines and other biological products.

There is no doubt that the project is a logical part of the Cuban emphasis on the biological front and seeing the biological sector, the relatively well educated and trained staff and the relatively well developed R&D activities, as a comparative advantage in defining the most promising sectors in the long-term development of the Cuban economy.

The ambitious project could, however, turn out negatively for the Cubans since there is a definite risk that the substantial production volume which is planned for export will not be sold outside Cuba. As we understand, there has been no professional market research and no discussions with potential customers before the development of the project.

Customers are primarily intended to be Latin American and Third World countries with no vaccine production of their own. The competitive situation in many of these countries, at least in the EPI vaccine programme, is severe since the vaccine requirements are being met - either by donations or by rock bottom priced imported products produced in economically large quantities by international enterprises and purchased in similarly large quantities for distribution through organizations like UNICEF and PAHO.

Furthermore, potential customer countries may hesitate to buy biological products from Cuba, partly because of possible problems with product quality and delivery reliability, partly because of problems associated with the political situation in the region.

In discussing the market aspects of the project with MoH representatives, the suggested solution is to give away the vaccines at no charge if they cannot be sold. This would not constitute a sound long-term solution for Biocen.

We therefore recommend the MoH in Cuba to perform a professional, comprehensive, feasibility study of the Biocen project and to emphasize the market research aspects which should include discussions on possible trade agreements with potential customer countries and also a full financial and economic analysis of the whole project.

In the future, Cuba could play a key role in vaccine production and cooperation projects in the region. In order to do so, the Biocen project must be based on sound market and economic analyses, thereby increasing the possibility of Biocen being a reliable and trustworthy long-term partner.

Mexico

A. Supply and Demand of Vaccines

1. Supply of Vaccines

EPI vaccines for the Mexican market are supplied from two sources: Local production at the GGBR (Gerencia General de Biológicos y Reactivos), and imports.

Mexico is the only country in Latin America which produces the full range of EPI vaccines. Production figures (million doses) for 1987 and 1988 (estimate) were:

	1987	1988 (estimate)
BCG	7.6	8.2
DPT	10.5	12.4
TT	8.4	9.2
Polio	12.6	17.0
Rabies	1.9	2.2
Measles	5.0	6.0

To complete the national demand, two vaccines are being imported, polio and DPT. The Ministry of Health arranges two national polio vaccine days per year when about 16 million children are vaccinated each time. Total annual requirements are then about 32 million doses. These amounts were received in 1986, 1987 and 1988 as donations from the International Rotary Club. The strategy of the Ministry of Health is to balance the local production to suit only the normal needs during the year and import the amounts of vaccines required for the special campaigns.

DPT vaccine is also being imported and for the same reason. Government annual campaigns require about 2 million doses of DPT vaccine per year. UNICEF donated these amounts both in 1987 and in 1988.

Since all imports of EPI vaccines are donated, the Mexican Government does not need to make any outlays in foreign exchange. The donations of EPI vaccines are valued at about $US 2 million per year.

2. Demand of Vaccines

The GGBR is also in charge of distribution of vaccines within the country. The different agencies responsible for the immunization activities normally submit to the GGBR their requirements for vaccines needed during the upcoming year. The major agencies concerned are the Social Security Organization, the Employers Association, the Armed Forces and the private sector. The requirements of EPI vaccines for 1988 are:

BCG	6.8	million doses
DPT	13.6	" "
TT	12.4	" "
Polio	43.8	" "
Rabies	1.4	" "
Measles	4.2	" "

Of the figures for polio and DPT vaccines, 30.4 million and 2.4 million doses respectively are expected to be required for the two annual national campaigns.

The actual consumption of vaccines is less than the figures above. The estimated wastage is calculated at 15 per cent for polio, measles, rabies and DPT vaccines, 25 per cent for tetanus toxoid and as much as 50 per cent for BCG vaccine.

3. Future Vaccine Requirements

The major determinants to be considered for the calculation of future requirements of EPI vaccines are:

* Government health policy and national immunization programme;
* epidemic/endemic situation;
* birth rate;
* size of target population;
* coverage rates;
* wastage rates.

In 1986, the Ministry of Health made the following 5-year forecast of the national requirements of all the vaccines in the EPI programme except rabies:

EPI VACCINE REQUIREMENTS, 1987

Biologicals	Age Group Years	Target Group	Population to vaccinate Number	%	No. of shots	Total Number of Doses	Wastage Per-centage	Total Number of Doses
Polio	> 1	2,012,257	1,207,200	60	3	3,621,600	1.15	4,164,840
	1-4	8,917,220	2,675,166	30	1	2,675,166	1.15	3,076,441
Spec. campaigns	> 1	2,012,257	2,012,257	100	2	4,024,514	1.15	4,628,191
	1-4	8,917,220	8,917,220	100	2	17,834,440	1.15	20,509,606
Polio, total								32,379,078
DPT	> 1	2,012,257	1,207,354	60	3	3,622,063	1.15	4,165,372
	1-4	8,917,220	3,121,027	35	1	3,121,027	1.15	3,589,181
Spec. campaigns	> 1	2,012,257	804,903	40	2	1,609,806	1.15	1,851,276
	1-4	8,917,220	1,783,444	20	2	3,566,888	1.15	4,101,921
DPT, total								13,707,751
Measles	1	1,906,776	953,388	50	1	953,388	1.15	1,096,396
	2-4	7,010,444	350,522	10	1	350,522	1.15	403,101
Spec. campaigns	1	1,906,776	953,388	50	1	953,388	1.15	1,096,396
	2-4	7,010,444	1,402,089	20	1	1,402,089	1.15	1,612,402
Measles, total								4,208,295
BCG	> 1	2,012,257	2,012,257	100	1	2,012,257	2.00	4,024,514
	1-4	8,917,220	1,783,444	20	1	1,783,444	2.00	3,566,888
BCG, total								7,591,402
Tetanus toxoid	No. of pregnant women	2,434,182	1,217,091	50	2	2,434,182	1.15	3,042,728

EPI VACCINE REQUIREMENTS, 1988

Biologicals	Age Group Years	Target Group	Population to vaccinate Number	%	No. of shots	Total Number of Doses	Wastage Per-centage	Total Number of Doses
Polio	> 1	2,051,486	1,230,892	60	3	3,692,675	1.15	4,246,576
	1-4	9,091,062	909,106	10	1	909,106	1.15	1,045,472
Spec. campaigns	> 1	2,051,486	2,051,486	100	2	4,102,972	1.15	4,718,418
	1-4	9,091,062	9,091,062	100	2	18,182,124	1.15	20,909,443
Polio, total								30,919,909
DPT	> 1	2,051,486	1,230,892	60	3	3,692,675	1.15	4,246,576
	1-4	9,091,062	1,818,212	20	1	1,818,212	1.15	2,090,944
Spec. campaigns	> 1	2,051,486	820,594	40	2	1,641,189	1.15	1,887,367
	1-4	9,091,062	1,363,659	20	2	2,727,319	1.15	3,136,416
DPT, total								11,361,304
Measles	1	1,943,949	1,360,764	70	1	1,360,764	1.15	1,564,879
	2-4	7,147,113	1,072,067	15	1	1,072,067	1.15	1,232,877
Spec. campaigns	1	1,943,949	777,580	30	1	777,580	1.15	894,217
	2-4	7,147,113	714,711	10	1	714,711	1.15	821,918
Measles, total								4,513,890
BCG	> 1	2,051,486	2,051,486	100	1	2,051,486	2.00	4,102,972
	1-4	9,091,062	1,818,212	20	1	1,818,212	2.00	3,636,425
BCG, total								7,739,397
Tetanus toxoid	No. of pregnant women	2,481,637	620,409	25	2	1,240,819	1.15	1,551,023

EPI VACCINE REQUIREMENTS, 1989

Biologicals	Age Group Years	Target Group	Population to vaccinate Number	%	No. of shots	Total Number of Doses	Wastage Per-centage	Total Number of Doses
Polio	> 1	2,089,954	1,462,968	70	3	4,388,903	1.15	5,047,239
	1-4	9,261,531	926,153	10	1	926,153	1.15	1,065,076
Spec. campaigns	> 1	2,089,954	2,089,954	100	2	4,179,908	1.15	4,806,894
	1-4	9,261,531	9,261,531	100	2	18,523,062	1.15	21,301,521
Polio, total								32,220,730
DPT	> 1	2,089,954	1,462,968	70	3	4,388,903	1.15	5,047,239
	1-4	9,261,531	1,389,230	15	1	1,389,230	1.15	1,597,614
Spec. campaigns	> 1	2,089,954	626,986	30	2	1,253,972	1.15	1,442,068
	1-4	9,261,531	926,153	10	2	1,852,306	1.15	2,130,152
DPT, total								10,217,073
Measles	1	1,980,400	1,386,280	70	1	1,386,280	1.15	1,594,222
	2-4	7,281,131	1,092,170	15	1	1,092,170	1.15	1,255,995
Spec. campaigns	1	1,980,400	594,120	30	1	594,120	1.15	683,238
	2-4	7,281,131	728,113	10	1	728,113	1.15	837,330
Measles, total								4,370,785
BCG	> 1	2,089,954	2,089,954	100	1	2,089,954	2.00	4,179,908
	1-4	9,261,531	2,315,383	25	1	2,315,383	2.00	4,630,766
BCG, total								8,810,674
Tetanus toxoid	No. of pregnant women	2,528,170	632,043	25	2	1,264,085	1.15	1,580,106

EPI VACCINE REQUIREMENTS, 1990

B. gicals	Age Group Years	Target Group	Population to vaccinate Number	%	No. of shots	Total Number of Doses	Wastage Per-centage	Total Number of Doses
Polio	> 1	2,127,449	1,701,959	80	3	5,105,878	1.15	5,871,759
	1-4	9,427,686	471,384	5	1	471,384	1.15	542,092
Spec. campaigns	> 1	2,127,449	2,127,449	100	2	4,254,898	1.15	4,893,133
	1-4	9,427,686	9,427,686	100	2	18,855,372	1.15	21,683,678
Polio, total								32,990,662
DPT	> 1	2,127,449	1,701,959	80	3	5,105,878	1.15	5,871,759
	1-4	9,427,686	942,769	10	1	942,769	1.15	1,084,184
Spec. campaigns	> 1	2,127,929	425,490	20	2	850,980	1.15	978,627
	1-4	9,427,686	942,769	10	2	1,885,537	1.15	2,168,368
DPT, total								10,102,937
Measles	1	2,015,929	1,411,150	70	1	1,411,150	1.15	1,622,823
	2-4	7,411,757	1,111,764	15	1	1,111,764	1.15	1,278,528
Spec. campaigns	1	2,015,929	604,779	30	1	604,779	1.15	695,496
	2-4	7,411,757	741,176	10	1	741,176	1.15	852,352
Measles, total								4,449,198
BCG	> 1	2,127,449	2,127,449	100	1	2,127,449	2.00	4,254,898
	1-4	9,427,686	1,885,537	20	1	1,885,537	2.00	3,771,074
BCG, total								8,025,972
Tetanus toxoid	No. of pregnant women	2,573,527	900,734	35	2	1,801,469	1.15	2,251,836

EPI VACCINE REQUIREMENTS, 1991

Biologicals	Age Group Years	Target Group	Population to vaccinate Number	%	No. of shots	Total Number of Doses	Wastage Per-centage	Total Number of Doses
Polio	> 1	2,164,060	1,731,248	80	3	5,193,744	1.15	5,972,806
	1-4	9,589,928	479,496	5	1	479,496	1.15	551,421
Spec. campaigns	> 1	2,164,060	2,164,060	100	2	4,328,120	1.15	4,977,338
	1-4	9,589,928	9,589,928	100	2	19,179,856	1.15	22,056,834
Polio, total								33,558,399
DPT	> 1	2,164,060	1,514,842	70	3	4,544,526	1.15	5,226,205
	1-4	9,589,928	958,993	10	1	958,993	1.15	1,102,842
Spec. campaigns	> 1	2,164,060	649,218	30	2	1,298,436	1.15	1,493,201
	1-4	9,589,928	958,992	10	2	1,917,986	1.15	2,205,683
DPT, total								10,027,931
Measles	1	2,050,622	1,435,435	70	1	1,435,435	1.15	1,650,751
	2-4	7,539,306	1,130,896	15	1	1,130,896	1.15	1,300,530
Spec. campaigns	1	2,050,622	615,187	30	1	615,187	1.15	707,465
	2-4	7,539,306	753,931	10	1	753,931	1.15	867,020
Measles, total								4,525,766
BCG	> 1	2,164,060	2,164,060	100	1	2,164,060	2.00	4,328,120
	1-4	9,589,928	1,917,986	20	1	1,917,986	2.00	3,835,971
BCG, total								8,164,091
Tetanus toxoid	No. of pregnant women	2,617,815	916,235	35	2	1,832,471	1.15	2,290,588

The major differences in this forecast compared with the total demand for 1988 calculated by the GGBR are the requirements for polio vaccine and tetanus toxoid. The MoH forecast for polio vaccine does not include requirements for people over 5 years of age. So the MoH figures for polio vaccine should be increased by about 35 per cent each year according to the GGBR in order to get the total annual requirements.

The MoH forecast for tetanus toxoid only includes the expected number of pregnant women as the target group. In order to get the total requirement of tetanus toxoid for the whole population, the MoH figures should be increased substantially to correspond to one shot of vaccine for 9 per cent of the whole population in Mexico plus two shots for every pregnant woman, e.g. about 12 million doses for 1988.

According to a long-term demand forecast by the GGBR up to the year 2010, the demand for polio vaccine and measles vaccine should be reduced by about 30 per cent from 1991 because of the increased coverage of immunization of children between 0 and 5 years of age. The continued development of demand for these two vaccines and the other EPI vaccines is then expected to increase slowly in accordance with the development of the net birth rate in the country.

B. The GGBR Organization and Economy

1. Organization

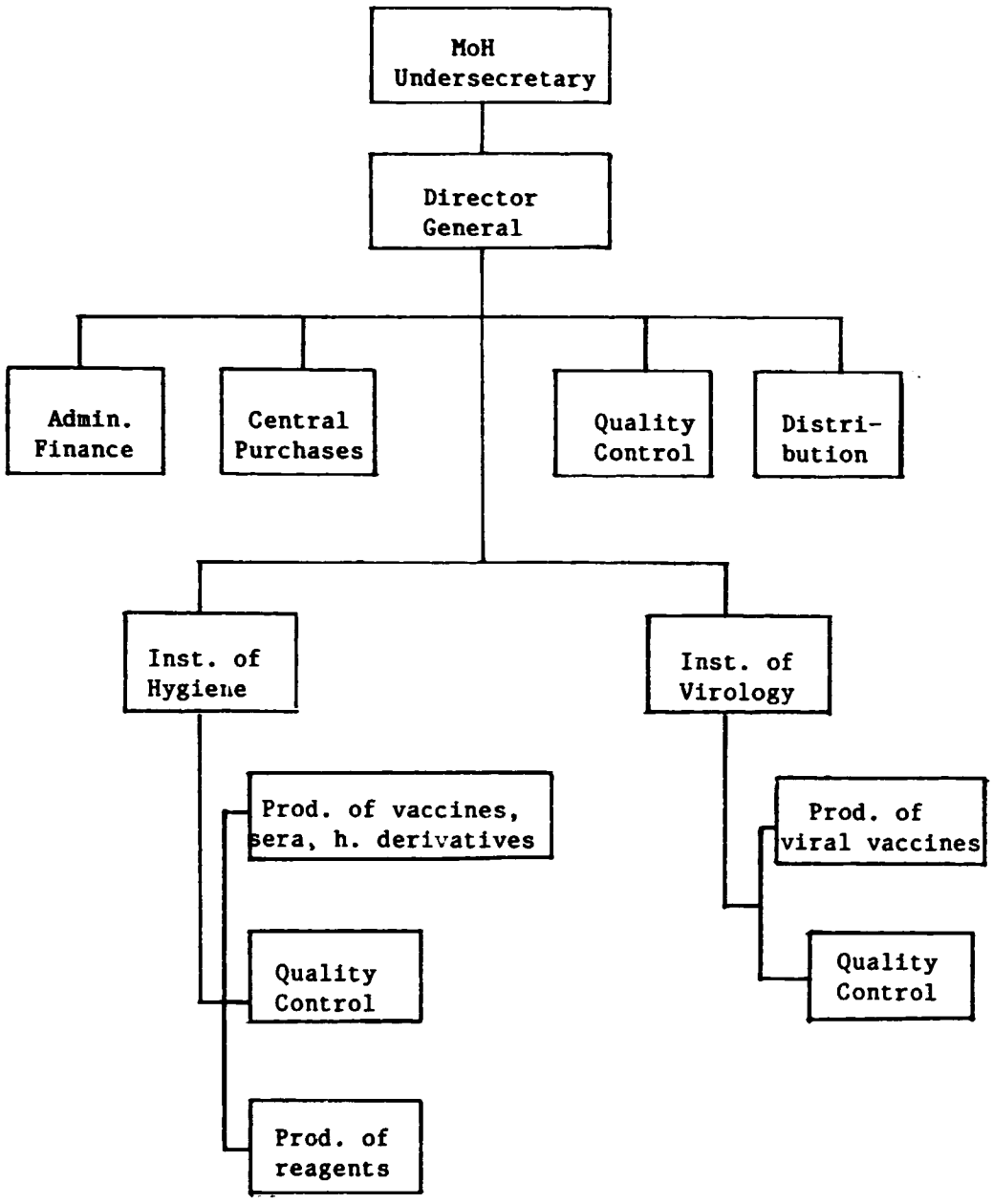
The national production of biological products for human health is sustained by the GGBR of the Ministry of Health through the National Institute of Hygiene and the National Institute of Virology. A small number of private, national and foreign companies complement the production in some areas, primarily hemoderivatives and heterological sera.

The production of vaccines in Mexico has been going on since 1888 when the first anti-rabies vaccine was elaborated by Dr Eduardo Leiceaga. The National Institute of Hygiene was first established in 1905 and the National Institute of Virology in 1960. The two institutes were put under the same administration when the GGBR was established in 1981.

The primary function of the GGBR is production, control and distribution of bacterial vaccines, antisera, hemoderivatives and biological reagents in the Institute of Hygiene and of viral vaccines in the Institute of Virology. GGBR is also in charge of imports of the biologicals and reagents required to complete the national requirements.

The GGBR is since 1979 the regional reference centre for PAHO (Panamerican Health Organization). In this capacity, GGBR functions as an external control organization for 12 Latin American countries and evaluates production samples of biologicals from these countries.

A simplified organization chart of GGBR follows:



The total number of employees is 708 with 291 in the Institute of Hygiene (218 technical staff and 73 for administration and maintenance), 183 in the Institute of Virology (126 technical staff and 57 for administration and maintenance), 35 people in a special reagents laboratory and 199 people in the central administration.

2. Financial Status and Performance

The GGBR is a public institution in the federal administration. It is not an enterprise and therefore it does not have a capital structure of its own. It is not engaged in any sales activities and is not able to claim any revenues.

The GGBR works within a cost budget stipulated each year by the MoH. Total costs for the past three years were (millions of pesos):

	1986	1987	1988 (estimates)
Wages	1,029	1,740	4,005
Material	1,614	3,380	7,173
Services	198	742	1,410
Machinery, equipment	300	-	-
Total	3,141	5,862	12,588

There has been no increase in real resources for the GGBR during this period of time, since nominal budget increases in wages and materials have been more than offset by corresponding changes in consumer prices. Inflation accelerated from 60 per cent in 1985 to 86 per cent in 1986 and 150 per cent in 1987. Estimated inflation rate for 1988 is 50 per cent.

One of the striking features of the budget is the fact that there has been no acquisition of machinery and equipment in the past three years, the only exception being a small investment for administrative purposes in 1986. Actually there have been only marginal new investments in the productive areas of GGBR in the past six years.

An attempt was made in early 1988 to calculate the cost of production in the GGBR. The analysis is not quite adequate as a basis for a correct profitability analysis, mainly because of the lack of data on capital costs, distribution costs and taxes. The consultant has, however, put together a rough estimate of the operating income of the institution, based on the prices charged by the MoH at the beginning of 1988 (millions of pesos):

Total revenues		20,071
Costs of goods sold		
Raw material	6,002	
Direct labour	1,434	
Indirect costs	4,105	11,541
Gross operating income		+ 8,530

It is also possible to show estimates of profitability for the EPI vaccines produced by the GGBR (pesos per dose):

	Polio	Measles	Rabies	BCG	DPT	TT
Sales price (public sales)	111	[illegible]	1700	118	180	120
Sales price (private sales)	168	1400	2540	178	270	180
Direct material	48	228	140	14	62	49
Direct labour	10	36	72	20	10	9
Indirect costs	31	123	250	59	18	17
Variable gross margin	88	387	462	93	90	75
- public sales	23(20%)	446(53%)	1238(73%)	25(21%)	90(50%)	45(37%)
- private sales	80(47%)	1013(72%)	2078(82%)	85(48%)	180(67%)	105(58%)

Sales prices are set by the MoH. The prices for the public sector seem to be in the same range as the prices charged by PAHO for the vaccines purchased in the international market. The prices charged from the private sector are about 50 per cent higher. Sales to the private sector are, however, less than 10 per cent of total sales.

The marginal rates of contribution are high for rabies, measles and DTP vaccines compared to international standards and more normal for TT, polio and BCG. All in all, based on the available data, production of the EPI vaccines in the GGBR shows an acceptable profitability.

C. Recommendations

Organizational Status

The profitability for GGBR shown above is not in itself a sign of high efficiency, but more the effect of a very strict overall cost budget with relatively low wage levels and low budgets for maintenance, training, research and development.

One area which should be considered for the future operations of vaccine production in Mexico is the organizational status of the operations. GGBR is an organism of the Federal Public Administration. The administrative system is bureaucratic with very slow and complicated procedures, especially for purchasing and staffing. GGBR is generally overstaffed and the personnel are not well paid, a fact which results in a high staff turnover. There are no incentives to increase productivity.

The GGBR should, in our opinion, be converted into an independent enterprise with professional management, preferably with complete or partial ownership by the private sector or as a decentralized company within the MoH. In the new organization the assets of GGBR should be transferred to the new company as well as the sales revenues of the GGBR products.

We recommend the Government to contact the private sector on this issue. The representatives of the private sector who were contacted during the mission all showed a generally positive attitude toward co-operation with the Government.

A New Plant and Regional Cooperation

For several years there have been discussions in the MoH concerning the limitations of the GGBR regarding production facilities and infrastructure and possible solutions of these. A study was performed in 1986 to identify the options that would guarantee the continued availability of biological products in Mexico. The study recommended construction of a new plant based on a reconstruction of the existing facilities of the GGBR and located outside the metropolitan area. In the study the rates of return on investment in vaccines and sera were lower than the corresponding rates for hemoderivatives. Discussions with the private sector of a joint project resulted in an indefinite postponement of the original project which included a new plant for the production of all GGBR products and instead priority was given to a smaller project, the production of hemoderivatives on a joint basis between the MoH and the private sector.

The question whether or not a new plant is needed for the future production of vaccines must be based on an analysis of the following factors:

* The possibility of continuing production in the present premises with the necessary modifications in investment and infrastructure.
* The future local demand of vaccines.
* The Government policy on the number and types of vaccines to be distributed and the relation between domestic production and imports.
* The Government policy on the export of vaccines with or without a regional agreement on production and cooperation.

The first issue has been analyzed by our technical consultants. The future local demand of EPI vaccines has been discussed previously in this report. There is no doubt that the development of demand for the foreseeable future is not per se a factor which necessitates a new plant. The two policy issues have to be addressed by the new Mexican administration, since it seems that the MoH at this stage does not have a comprehensive policy on the future development of vaccine production in the country.

If the Government's policy is to emphasize a new concentration on high-quality production, research and development of local vaccines and is to include exports of vaccines as a part of that strategy, then there is no doubt that a new plant will have to be constructed, partly on the need to meet GMP requirements and partly because the higher production capacities cannot be accommodated in the existing premises.

On the question of regional cooperation, there is no doubt that Mexico would be able to play a leading role not only in production and exports of vaccines but also in research, development and training. In our opinion, however, the question of regional cooperation must be secondary at this stage to the more imminent question of the policy issues regarding the development of the local production of vaccines. If these issues are resolved, if a new organizational status of the GGBR can be conceived and if a study can show that a new plant is feasible based on production, market, economic and financial criteria, and that such a project can also be financed, then new discussions on regional cooperation should be started, but not before then.

Venezuela

A. Supply and Demand of Vaccines

1. Supply of Vaccines

EPI vaccines for the Venezuelan market are supplied primarily through imports and also from local production at the National Institute of Hygiene, Rafael Rangel, in Caracas. This Institute produces three EPI vaccines - DPT, tetanus toxoid and rabies for humans.

Production figures for 1986, 1987 and 1988 were (millions of doses):

	1986	1987	1988 budget	1988 estim.
DPT	3.0	4.0	4.4	2.0
TT	1.8	3.8	4.0	3.0
Rabies	0.1	0.1	0.2	0.05

The official data on 1987 production seems high in comparison with the 1986 figures. The planned output figures for 1988 will be difficult to reach, since the accumulated production up to the end of September was 1.2 million doses of DTP and 2.0 million doses of TT. On the basis of the output figures after 9 months, a more realistic estimate for 1988 would therefore be 2 million doses of DTP and 3 million doses of TT.

The accumulated output of rabies vaccine is also lower than budget for the first 9 months of 1988. A more realistic production estimate would be about 50,000 doses for 1988.

BCG vaccine was previously produced in Venezuela, but production was stopped in 1981 following concern about the quality of the product. There are no plans to take up production again.

According to the MoH, the following EPI vaccines were imported in 1988:

DPT	3.1	million doses
TT	2.0	" "
BCG	0.6	" "
Polio	12.4	" "
Measles	2.0	" "

To the above list should be added 1.9 million doses of pertussis vaccine, which is imported directly by the Institute of Hygiene. Apparently, the Institute has problems with the production of the pertussis component of the DTP and therefore it had to be imported at least in 1987 and 1988.

The vaccines are imported from the traditional international suppliers. Normally, the import business is transacted directly with the suppliers and not through PAHO. According to the MoH, the Venezuelan Government has succeeded in getting better conditions when dealing directly with the suppliers than they previously did when using PAHO.

The 1988 prices for the imported EPI vaccines were:

DPT	$US 0.07	per	dose
Pertussis	" 0.04	"	"
TT	" 0.05	"	"
BCG	" 0.04	"	"
Polio	" 0.03	"	"
Measles	" 0.33	"	"

The prices for the imported vaccines are apparently very competitive. Imports of medicines, including vaccines, are valued at the most preferential rate of exchange which is 7.50 bolivares to the $US, while the normal exchange rate for imports is 14.50 to the dollar and the free rate 37.1 bolivares to the dollar in November 1988.

Total costs for the imports of EPI vaccines would be about $US 900,000 in 1988.

2. Demand of EPI Vaccines

According to the consultant's estimate, the 1988 requirements of EPI vaccines are as follows:

DPT	5	million	doses
TT	5	"	"
BCG	1.7	"	"
Polio	12.4	"	"
Rabies	0.2	"	"
Measles	1.2	"	"

There is quite a bit of uncertainty in the above estimates. There were no official data available on the present demand of EPI vaccines at least not to my knowledge. The only cross reference that I have is the Jacabos' report from 1987 which indicates substantially lower figures, particularly for polio, but also for DTP and TT. One explanation for the differences could be that the above figures for polio and DTP also include the requirements for the special immunization campaigns, and that the figure for TT would include the requirements not only for pregnant women but for the child population.

The actual consumption of vaccines is less than the figures above because of wastage. The estimated wastage is calculated at 15-20 per cent for all EPI vaccines, except for BCG which has a wastage of 25-50 per cent.

B. The National Institute of Hygiene, Organization and Economy

1. Organization

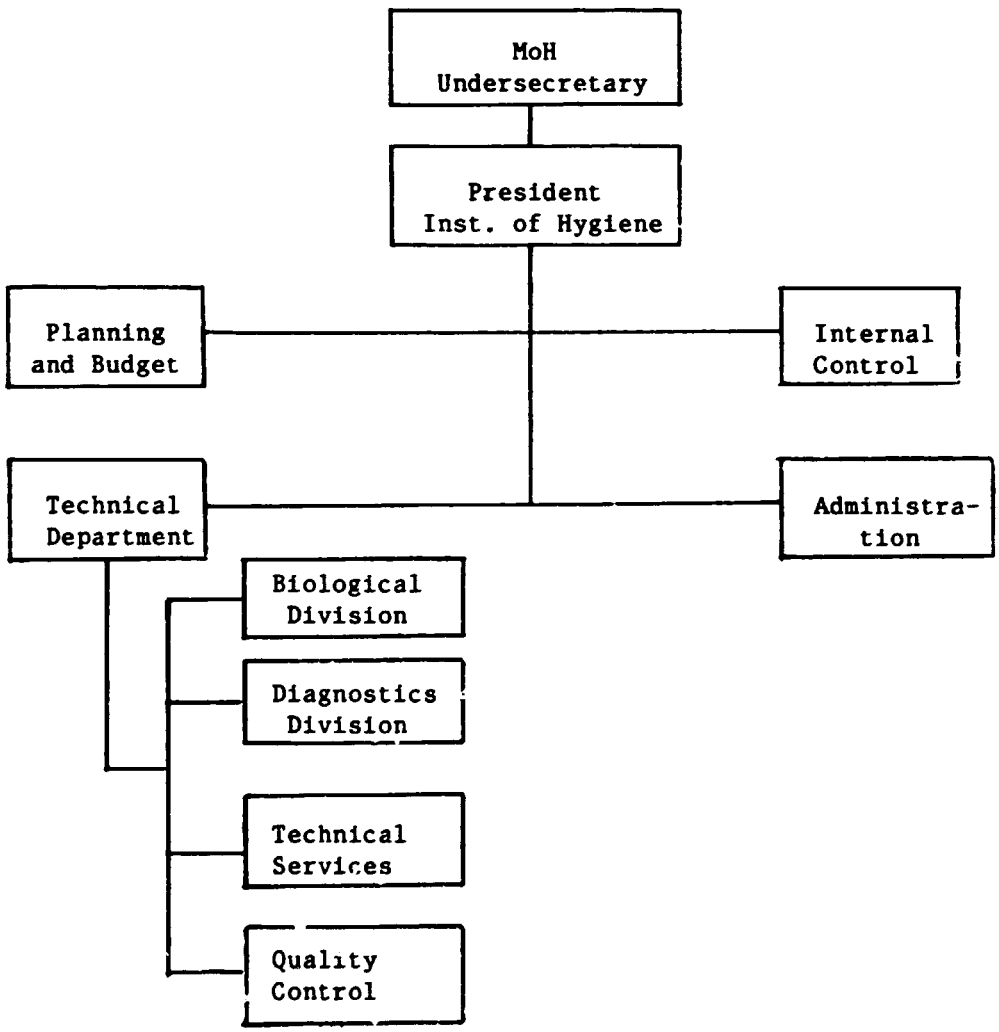
The domestic production of biological products for human health is carried out at the Institute of Hygiene, Rafael Rangel, organized under the responsibility of the Ministry of Health.

The Institute started production in 1938 and concentrated on smallpox and typhoid vaccine. The production of these two vaccines ceased in 1980 and 1986 respectively.

Today, the primary functions of the Institute are:

* Production of vaccines, including the three EPI vaccines DTP, TT and rabies for human use, and also about 500,000 doses annually of rabies vaccine for dogs and a small quantity of cholera vaccine.
* Analysis of samples for the diagnosis of possible endemic/epidemic diseases.
* Analysis and certification of the physical, chemical and micro-biological composition of drugs, foodstuff, cosmetics and natural products.

A simplified organization chart of the Rafael Rangel is shown below:



The total number of employees at the Institute is 477. Of this number, 55 people are working in the Biologicals Division. This Division has four departments: bacterial vaccine production, viral vaccine production, quality

control and final processing. The Biologicals Division thus constitutes only a small part of the total activities in the Institute.

2. Economy

Total costs for the Institute of Hygiene were 33 million bolivares in 1987 and 76 million in 1988.

Total costs for the Biologicals Division were 7.4 million bolivares in 1987 and estimated total costs for 1988 were 17.0 million. A rough cost distribution for these two years follows below (millions of Bs):

	1987	1988 (estim.)
Staff	3.6	3.1
Materials and services	3.8	3.8
Machinery and equipment	-	10.1
	7.4	17.0

The major cost difference between 1987 and 1988 is the item for machinery and equipment, where an acquisition of a new fermentor for the production of DPT and TT vaccines has been debited against the 1988 cost account. This investment was decided in 1987 in order to meet the national requirements for these two vaccines up to the year 2000 and furthermore to initiate exports to countries like the Dominican Republic, Peru, Bolivia and other Central American countries.

The other two major cost items, salaries and materials, are about the same over the 1987-1988 period. This is in reality a cost reduction since inflation, which had been about 11-12 per cent in 1984-1986, increased to 40 per cent in 1987 and to 33 per cent in 1988.

No analysis has been made of the profitability of the products in the Biologicals Division, and the present system of accounts does not permit such calculations. We can, however, obtain an indication of the profitability of the total activities performed in the Biologicals Division by comparing the prices and quantities of produced vaccines (also including rabies vaccine for dogs) to the total costs of the Division. The prices charged by the HoH for the three EPI vaccines in 1987 were:

DPT	0.60 Bs per dose
TT	0.40 " " "
Rabies (human)	1.00 " " "

These prices correspond to $US equivalents of 8, 5 and 13 cents respectively, using the $US 1 = Bs 7.50 exchange rate.

The consultant has made an estimate of the operating income of the Biologicals Division based on the produced quantities, including rabies vaccines for dogs, in 1987 and the above prices (millions of bolivares):

Total revenues		5.9
Cost of goods sold		
Labour	3.6	
Materials	3.8	
Indirect costs	0.8	8.2
Gross operating income ./.		2.3

This estimate shows a rather negative picture of the conceived profitability of the Division. The result in 1988 is probably even worse, since the prices and the costs have been about the same as in 1987, but the quantities produced have been substantially reduced.

Prices of the three EPI vaccines are expected to be increased in 1989 to 2 Bs per dose for DTP and TT and to 2.50 Bs for rabies vaccine. This will improve the profitability of the operations. On the other hand, the prices of the locally produced vaccines will then be substantially higher than the corresponding prices for the same vaccines which are purchased in the international market by the MoH or via UNICEF or PAHO.

C. Recommendations

The provision of EPI vaccines in Venezuela is primarily through imports, seemingly handled efficiently by MoH, and from local production of three vaccines, DTP, TT and rabies.

One of the problems with local production is the apparent low rate of efficiency of the operation. According to the technical consultants, the production process is characterized by insufficient production planning with a substantial part of the equipment and machinery being idle for long periods of time. Furthermore, the premises and the work routines do not comply with the generally accepted standards for vaccine production, GMP.

The low rate of profitability of the Biologicals Division is also a result of a bureaucratic administrative system, an inadequate accounting plan and a strict cost budget with relatively low wage levels and low disbursements for maintenance, training, research and development.

It seems that the Division is not managed in a professional way. One of the reasons for this is undoubtedly the apparent lack of clear objectives and policies on the part of the Government for the production of biologicals in the country.

In our discussions with representatives of the Moh and the Institute of Hygiene, there seemed to be a poor comprehension of the future provision of vaccines, the question of local production versus imports, the standards required for local production and the long-term resources required for production of vaccines in Venezuela.

Our recommendation is therefore that the new administration in the Government make a thorough analysis of the provision of biologicals, including EPI vaccines, for the country and clearly state objectives and policies for the future development of the sector. In this work, the Government should consider the organizational status and the need of professional management of the local operations. Today, there are no incentives to improve productivity.

One alternative is to convert the biologicals production - and possibly other activities as well in the Institute of Hygiene - into an independent enterprise, preferably with complete or partial ownership by the private sector or as a decentralized company with the MoH. The main advantage would be to improve productivity through new professional management and to improve the quality of production by working according to international standards to which several local private pharmaceutical companies are accustomed. A new organizational status and production in new GMP-approved premises are also prerequisites for exporting some of the locally produced vaccines.

We therefore recommend to the Government that they contact the private sector and other organizations or institutions in the biologicals and pharmaceuticals sector in Venezuela. The representatives of this sector who were contacted during the mission all showed a generally positive attitude towards cooperation with the Government and a willingness to try to find creative solutions to the issue of ownership and to the issue of creating a mix of products, quantities and prices to allow a reasonable return on the investment.

The question of regional cooperation and production of EPI vaccines does not seem to be of immediate interest to the Venezuelan authorities. The major reason is probably that the policy issues regarding the future provision of biologicals including the possible development of local production of vaccines have to be resolved first. When the policy framework is clear, new discussions on possible regional cooperation and production of EPI vaccines - and the role of Venezuela - should be started, but not before then.

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Annex 1

Morbilidad de las enfermedades inmunoprevenibles por años
Bolivia 1988

Enfermedades	Año 1985		Año 1986		Año 1987	
	Morbilidad < 5 años	Morbilidad > de 5 años	Morbilidad < 5 años	Morbilidad > de 5 años	Morbilidad < 5 años	Morbilidad > de 5 años
Difteria	1	29	3	12	4	12
Tosferina*	989		536		520	
Tétanos*	54		42		56	
Tétanos neonatal	3		33		48	
Poliomielitis	No hubo casos	No hubo casos	4	0	5	3
Sarampión*	221		439		975	
Rabia humana** (No se sabe grupo etáreo)		2325		2174		4569
Fiebre amarilla*	54		27		23	
Tuberculosis*	4584		4765		6666	

Fuente: Dirección Nacional de Epidemiología
Unidad de Estadística y Computación

Nota: * No se sabe el grupo etáreo.
** Corresponde a personas que recibieron tratamiento con vacuna antirrábica.

Morbilidad de las enfermedades inmunoprevenibles por años
Bolivia 1988

Enfermedades	Año 1985 Morbilidad	Año 1986 Morbilidad	Año 1987 Morbilidad
Difteria	30	15	16
Tosferina	989	536	520
Tétanos	54	42	56
Tétanos neonatal	3	33	48
Poliomielitis	No hubo casos	4	8
Sarampión	221	439	975
Rabia humana**	2325	2325	2174
Fiebre amarilla	54	27	23
Tuberculosis	4584	4765	6666

Fuente: Dirección Nacional de Epidemiología
Unidad de Estadística y Computación

Nota: ** Corresponde a personas que recibieron tratamiento con vacuna antirrábica.

Mortalidad de las enfermedades inmunoprevenibles por años
Bolivia 1988

Enfermedades	Año 1985		Año 1986		Año 1987	
	Mortalidad <5 años	Mortalidad > de 5 años	Mortalidad < 5 años	Mortalidad > de 5 años	Mortalidad < 5 años	Mortalidad > de 5 años
Difteria	0	3	0	2	0	1
Tosferina*	-	-	-	-	-	-
Tétanos*	-	-	-	-	-	-
Tétanos neonatal*	-	-	-	-	-	-
Poliomielitis	No hubo casos	No hubo casos	0	0	0	1
Sarampión*	-	-	-	-	-	-
Rabia humana		7		9		15
Rabia canina		1990		2061		3191
Fiebre amarilla		38		17		18
Tuberculosis*	-	-	-	-	-	-

Fuente: Dirección Nacional de Epidemiología
Unidad de Estadística y Computación

Nota: * No se conoce la mortalidad en estos males.

Población total estimada 1985	6.429.408	Niños nacidos	282.894
Población total estimada 1986	6.611.383	Niños nacidos	290.901
Población total estimada 1987	6.733.637	Niños nacidos	296.280

- En BCG los niños recién nacidos son vacunados en el esquema regular del PAI.

- Las movilizaciones nacionales son adicionales al esquema del PAI Regular y son 3 (tres) anualmente.

- Los requerimientos anuales son de conocimiento de la OMS/OPS.

- La procedencia de los biológicos durante los tres años, corresponde a los siguientes países:

  Bélgica, Canadá, Yugoslavia, Italia, Rusia, Brasil.

Establecimientos informantes y que informaron por años

Años	Establecimientos informantes	Establecimientos que informaron	Porcentaje
1985	1353	624	46,12
1986	1231	673	54,67
1987	1153	589	51,90

Nota: La disminución en los establecimientos informantes se debe a las acefalias especialmente en el área rural.

Dosis de vacuna remitidas y utilizadas en 3 años (1985-1987) en 11 unidades sanitarias de Bolivia

Tipo de vacuna	Año 1985			Año 1986			Año 1987		
	Dosis remitidas	Dosis aplicadas	% pérdida	Dosis remitidas	Dosis aplicadas	% pérdida	Dosis remitidas	Dosis aplicadas	% pérdida
Polio	1.188.800	742.994	37,50	1.904.000	1.273.393	33,12	2.007.160	1.148.458	42,78
D.P.T.	1.036.435	668.668	35,48	1.967.144	1.045.890	46,83	1.779.980	1.024.994	42,42
Sarampión	371.530	247.687	33,33	1.030.640	292.751	71,60	1.008.480	421.549	58,20
B.C.G.	193.909	133.731	31,03	127.510	85.004	33,34	409.580	193.229	52,82
Antiamarílica	90.550	56.593	37,50	253.030	121.102	52,14	174.950	58.956	66.30
Rabia humana	16.275	16.275	0,00	15.218	15.218	0,00	31.983	31.983	0,00

Annex 2

Necesidades y presupuesto de vacuna BCG. Ecuador 1987 - 1990

Año	Grupo de edad	Población	% Meta	Niños a vacunar	Total niños a vacunar	X 2,0 # dosis	Costo dosis + % 6 ADM	Costo Total
1987	Menor 1 año	305.404	100	305.404	429.868	860.000	0,0973	83.678
	De 1 a 4 años	1.244.638	10	124.464				
1988	Menor 1 año	312.353	100	312.353	439.649	880.000	0,0973	85.556
	De 1 a 4 años	1.272.961	10	127.296				
1989	Menor 1 año	319.201	100	319.201	319.201	640.000	0,0973	62.117
	De 1 a 4 años	1.300.869	-	-				
1990	Menor 1 año	325.846	100	325.846	325.846	652.000	0,0973	63.410
	De 1 a 4 años	1.327.946	-	-				
1991	Menor 1 año	323.336	100	-	332.336	665.000	0,0973	64.705
	De 1 a 4 años	1.354.396	-	-				
							US $ Total	359.466

Necesidades y presupuesto de vacuna D.P.T. Ecuador 1987 - 1990

Año	Grupo de edad	Población	% Meta	Niños a vacunar	Total niños a vacunar	X 3 Y X 1,3 ∮ dosis	Costo dosis + % 6 ADM	Costo total
1987	Menor 1 año	305.404	100	305.404	429.891	1.700.000	0,0326	54.230
	De 1 a 4 años	1.244.678	10	124.467				
1988	Menor 1 año	312.353	100	312.353	439.649	1.720.000	0,0326	56.072
	De 1 a 4 años	1.272.961	10	127.296				
1989	Menor 1 año	319.200	100	319.200	449.288	1.800.000	0,0326	58.680
	De 1 a 4 años	1.300.869	10	130.087				
1990	Menor 1 año	325.846	100	325.846	458.641	1.800.000	0,0326	58.680
	De 1 a 4 años	1.327.946	10	132.795				
1991	Menor 1 año	332.336	100	332.336	467.776	1.820.000	0,0326	59.332
	De 1 a 4 años	1.354.396	10	135.440				
							US $ Total	286.994

Necesidades y presupuesto de vacuna antipoliomielítica. Ecuador 1987 - 1989

Año	Grupo de edad	Población	% Meta	Niños a vacunar	Total niños a vacunar	X 3 Y X 1,3 # dosis	Costo c/dosis más % Admin	Costo total
1987	Menor 1 año	305.404	100	305.404	554.332	2.200.000	0,0384	84.480
	De 1 a 4 años*	1.244.678	20	248.928				
1988	Menor 1 año	312.353	100	312.353	566.945	2.200.000	0,0384	84.480
	De 1 a 4 años*	1.272.961	20	254.592				
1989	Menor 1 año	319.201	100	319.201	579.375	2.200.000	0,0384	84.480
	De 1 a 4 años*	1.300.869	20	260.174				
1990	Menor 1 año	325.846	100	325.846	458.641	1.800.000	0,0384	69.120
	De 1 a 4 años*	1.327.946	10	132.795				
1991	Menor 1 año	332.336	100	332.336	467.776	1.800.000	0,0384	69.120
	De 1 a 4 años*	1.354.396	10	135.440				
							US $ Total	391.680

(*) Incluye refuerzos.

Necesidades y presupuesto de vacuna antisarampionosa. Ecuador 1987 - 1989

Año	Grupo de edad	Población	% Meta	Niños a vacunar	Total niños a vacunar	X 1,3 # dosis	Costo dosis + % 6 ADM	Costo total
1987	Menor 1 año	305.404	100	305.404	554.332	721.000	0,128	92.288
	De 1 a 4 años	1.244.638	20	248.928				
1988	Menor 1 año	312.353	100	312.353	566.945	737.000	0,128	94.340
	De 1 a 4 años	1.272.961	20	254.592				
1989	Menor 1 año	319.201	100	319.201	449.288	584.000	0,128	74.760
	De 1 a 4 años	1.300.869	10	130.087				
1990	Menor 1 año	325.846	100	325.846	458.641	596.000	0,128	76.288
	De 1 a 4 años	1.327.946	10	132.795				
1991	Menor 1 año	332.336	100	332.336	467.776	608.000	0,128	77.824
	De 1 a 4 años	1.354.396	10	135.440				
							US $ Total	415.500

Necesidades y presupuesto de toxoide tetánico. Ecuador 1987 - 1990

Año	Grupo de edad fértil		Población proporcional embarazada	% Meta	Embar. a vacunar	Total embar. a vacunar	X.2 Y XI.3 # dosis	Costo dosis + % 6 ADM	Costo total
1987	2.182.953	1	173.027	100	173.027	214.142	557.000	0,0157	8.746
		2	205.577	20	41.115				
1988	2.244.819	1	177.861	100	177.861	219.742	571.000	0,0157	8.965
		2	209.403	20	41.881				
1989	2.307.855	1	182.610	100	182.610	225.244	586.000	0,0157	9.200
		2	213.169	20	42.634				
1990	2.371.955	1	187.167	100	187.167	230.338	599.000	0,0157	9.404
		2	215.857	20	43.171				
1991	2.437.247	1	191.846	100	191.846	235.555	612.000	0,0157	9.608
		2	218.545	20	43.709				

Nota: (1) En riesgo (2) Resto de provincias.

US $ Total 45.922

Annex 3

Producción de biológicos por años transcurridos de la actual década
Instituto Nacional de Higiene "Rafael Rangel" - Venezuela 1987

Orden	Producto biológico	Años							
		1980	1981	1982	1983	1984	1985	1986	1987 (1)
1	Vacuna antitífica (dosis) (2)	150.640	282.600	105.820	75.000	-	-	-	-
2	Vacuna triple (dosis)	2.532.340	2.546.450	1.366.340	2.534.360	619.520	2.926.240	3.000.000	3.500.000
3	Vacuna antirrábica canina	666.697	216.025	544.345	543.925	465.285	352.550	300.000	550.000
4	Vacuna antirrábica humana	146.752	77.720	22.456	102.752	113.512	138.358	150.000	150.000
5	Toxoide tetánico	2.067.360	1.680.386	1.680.000	1.656.190	2.249.030	1.804.800	2.000.000	2.500.000
6	Complemento de cobayo (FCOS)	-	-	400	790	1.018	957	900	900
7	Hemolisina (FCOS)	-	-	82	135	254	250	250	250

(1) Producción esperada.
(2) No se produce más.

Utilización de biológicos en programas nacionales de salud, demanda nacional, capacidad máxima de producción, importación
Instituto Nacional de Higiene "Rafael Rangel" - 1987

Orden	Producto biológico	1987			
		Demanda nacional	Capacidad máxima de producción	Producción nacional esperada (1)	Importación
1	Vacuna triple	4.000.000	4.000.000	3.500.000	-
2	Vacuna antirrábica humana	160.000	160.000	160.000	-
3	Vacuna antirrábica canina	1.200.000	600.000	500.000	700.000
4	Toxoide tetánico	2.500.000	3.500.000	2.500.000	-
5	Vacuna antirubeola	300.000	-0-	-0-	300.000
6	Vacuna antisarampión	1.200.000	-0-	-0-	1.200.000
7	Vacuna antiamarílica	900.000	-0-	-0-	900.000
8	Vacuna antihepatitis	-	-0-	-0-	1.000
9	Vacuna antipolio trivalente	3.550.000	-0-	-0-	3.550.000
10	Vacuna BCG	600.000	-0-	-0-	600.000

(1) Es aproximadamente la producción de los 2 últimos años (1985-1986)

Fuente de información: Div. Elaboración Prod. Biológ.

Vacunación canina y cobertura en Venezuela 1984 - 1988

Años	Población canina total (1)	Vacunaciones	Cobertura %
1984	2.022.144	468.362	23,2
1985	2.078.009	388.864	18,7
1986	2.134.969	571.465	26,8
1987	2.192.659	644.717	29,4
1988	2.250.887	729.290	32,4

Fuente: Departamento de Zoonosis División de Enfermedades Transmisibles MSAS.

(1) La población canina del país se estimó en un 12%.

Vacunación canina en áreas de riesgo - Venezuela 1984 - 1988

Años	Población canina en áreas de riesgo*	Vacunaciones	Cobertura %
1984	699.171	468.362	67,0
1985	724.631	388.864	53,6
1986	745.320	571.465	76,7
1987	766.398	644.717	84,1
1988	787.621	729.290	92,6

* Población canina en los Estados Aragua, Barinas, Carabobo, Guárico, Táchira y Zulia.

Fuente: La misma.

Cobertura por biológico (3ª dosis) en niños menores de un año (1982 - 1987)

Años	Población	VOP	Coberturas DPT	Sarampión
1982	504.111	76%	53%	45%
1983	515.190	77%	57%	42%
1984	525.349	66%	36%	43%
1985	534.801	61%	59%	57%
1986	543.645	57%	54%	45%

Fuente: PAI/MSAS.

Población total y población menor de 5 años - Venezuela
1984 - 1988

Años	Población total	Población 0 - 5 años
1984	16.851.198	2.513.382
1985	17.316.741	2.558.511
1986	17.791.411	2.600.721
1987	18.272.159	2.639.835
1988	18.757.389	2.675.932

Vacunación. Cobertura. Porcentajes. Terceras dosis menores de un año - Venezuela 1984 - 1987

Años	Población	Coberturas		
		VOP	DPT	Sarampión
1984	503.973	67,27%	37,98%	44,36
1985	502.329	65,06	62,46	61,14
1986	504.278	64,12	60,88	49,34
1987	510.834	62,06	57,88	60,15

Fuente: División de Enfermedades Transmisibles y Accidentes.
Departamento de Enfermedades Prevenibles por Vacunas (PAI).

Toxoide tetánico
Vacunación en niños de 3 años y más y embarazadas rurales - Venezuela
1984 - 1987

Años	3 años y más	Embarazadas rurales	Total vacunados
1984	373.614	50.726	424.340
1985	378.242	51.112	429.354
1986	682.416	300.680	983.096
1987	392.513	85.648	478.161

MSAS no llevó estadísticas sobre el número de embarazadas.

Población de mayor importancia para el PAI - Venezuela 1987

< 1 año	551.839
1 año	535.342
2 años	544.600
< 5 años	2.639.835

Mujeres de 14-44 años: 4.134.764

Sarampión

Nombre de la vacuna: ANTISARAMPIONOSA "RIMEVAX"
Laboratorio: SMITH KLINE - RIT
Costo: 0,3285 $

Polio

Nombre de la vacuna: ANTIPOLIOMIELITICA "SABIN"
Costo: 0,60 $ x frasco; el frasco contiene 20 dosis
Laboratorio: SMITH KLINE

Tétanos

Nombre de la vacuna: TOXOIDE TETANICO
Costo: 2 Bs x dosis; el frasco contiene 10 dosis
Laboratorio: Instituto Nacional de Higiene

Rabia

Nombre de la vacuna: ANTIRRABICA HUMANA
Costo: 2,50 Bs por dosis; el frasco contiene 2 dosis

Nombre de la vacuna: ANTIRRABICA CANINA
Costo: 3,50 Bs por dosis; el frasco contiene 10 dosis
Laboratorio: Instituto Nacional de Higiene

D.P.T.

Nombre de la vacuna: TRIPLE (Nacional)
Costo: 2 Bs por dosis
Laboratorio: Instituto Nacional de Higiene

Nombre de la vacuna: TRIPLE (Importada)
Costo: 0,84 $ por dosis
La vacuna viene en frascos de 10 ó 20 dosis

Annex 4

TETANUS TOXOID (TT)

Composition/Pharmaceutical form

One vaccine dose of 0.5ml contains not less than 10Lf of purified toxoid (metaphosphoric acid) from formalin inactivated culture of Clostridium tetani (Mueller 4) adsorbed onto aluminium hydroxide, preserved with thiomersal (0.01%) and presented in 10 dose glass vials.

1. Process description and quality control

In the preparation of this product WHO recommendations are aimed at. Tetanus toxoid is prepared in a devoted facility to the point of purification of the sterile crude toxoid. Although the facility does not meet GMP requirements, steps are taken to contain the live organisms within the facility.

The Mueller 4 strain of Cl.tetani was obtained from the USA (Massachusetts). For the preparation of master and working seeds the seed lot system is used. Seed lots are kept as lyophilised cultures.

Production cultures are grown statically in ca. 7.0L volumes of Mueller-Miller medium in glass bottles, one batch representing 50-60L culture. Toxin yield varies between 30 and 40Lf/ml.

Following coarse and sterile filtration, the culture supernatant is detoxified with 0.3% formalin at 35°C. After satisfactory sterility and toxicity tests the crude toxoid is removed from the devoted facility for purification with metaphosphoric acid precipitation in borate buffer, followed by dialysis, filter sterilisation and storage pending tests. Satisfactory purified toxoid is adsorbed onto aluminium hydroxide (Superfos) gel and the bulk vaccine is stored, pending tests before its release for filling.

Inspection of the flow diagram of production processes and quality control tests shows that with few exceptions these are compatible with WHO recommendations.

For conformity the following tests should also be carried out; single harvest: total combining power (TCP), minimum lethal dose (MLD); purified concentrated toxoid: irreversibility, potency, pyrogenicity; bulk vaccine: specific toxicity; final product: identity.

2. Production capacity, wastage, consistency of production

Nominal production capacity at CFI is ca. 5.0×10^6 doses p.a. Batch failure rate at CFI is under 5% and reproducibility of product is good.

3. Constraints on production

Not applicable at CFI any longer.

4. Research and development

None at the present time.

5. Considerations for increasing production

Projected annual production capacity at BIOCEN is 20.0×10^6 doses. This may be increased to a maximum of 40×10^6 doses p.a. by the installation of an additional 250L fermenter. Provision for downstream processing is deemed to be adequate for the extra production.

Annex 5

BCG VACCINE

Pharmaceutical form

Lyophilised live culture of Bacillus Calmette-Guerin (BCG) in 5% sodium glutamate, 10 doses in glass ampoules. Diluent: injectable Sauton medium.

Composition

One dose of 0.1ml contains not less than one million viable lyophilised colony-forming units of BCG and 0.05 mg of sodium glutamate.

1. Process description and quality control

This vaccine is produced in a devoted facility. In the preparation of the vaccine WHO recommendations are aimed at. The production strain, M.tuberculosis MC078, was obtained from Denmark. The seed lot system has not been adopted, instead the original seed lot from Denmark being used as working seed.

The rehydrated original seed is serially propagated on Sauton potato slopes before inoculation of Sauton liquid medium, 100ml in 250ml Erlenmeyer flasks. One batch represents 7-8 flasks.

Following incubation (7 days), harvest and centrifugation, wet cell mass is determined and a cell suspension is prepared in 5% sodium glutamate solution, to give in excess of 1×10^7 viable particles per 1ml. The suspension is stored pending tests before it is released for filling into glass ampoules for lyophilisation.

An inspection of the flow diagram of the production process/quality control tests showed that these are compatible with WHO recommendations.

2. Production capacity, wastage, consistency of production

Production capacity at CFI is about 1 million doses p.a. Inspection of production documentation and quality control showed that wastage was minimal (contamination) and consistency of production was good.

3. Constraints on production

Due to transfer of production this is not applicable.

4. Research and development

None

5. Considerations for increasing production

Projected annual output at BIOCEN is $3\text{-}6 \times 10^6$ doses p.a.

Annex 6

RABIES VACCINE

Pharmaceutical form/composition

For human use: 0.5ml of 14 treatment doses contains 10000 LD_{50} of ultra-violet light inactivated rabies virus (CVS) in 1% suspension of suckling mouse brain tissue in 5% dextrose preserved with phenol (0.1%) and thiomersal (0.01%) and presented in two dose glass vials.

1. Process description and quality control

This vaccine is produced in a devoted facility and in its preparation WHO recommendations are aimed at.

The original virus strain (CVS) was obtained from the Pan American Zoonoses Centre, and for its use the seed lot system is used. The working seed is thawed out and dilutions are made for the intracerebral inoculation of day-old suckling mice. Brain tissues are harvested 3 days post-inoculation and stored at -70°C pending tests. Satisfactory brain tissues are thawed out, homogenised, then centrifuged, and a 10% suspension is prepared and stored (-70°C) pending tests. From satisfactory 10% suspensions a 5% suspension is prepared and irradiated with ultraviolet-light then stored. From satisfactory 5% suspensions 1% suspensions are made in 5% dextrose, phenol (0.1%) and merthiolate (0.01%) added and stored (2-8°C) pending tests. Satisfactory bulk vaccine is released for filling.

Quality control of in-process, bulk and finished products is carried out according to WHO recommendations.

Samples of one or two lots per annum are sent to the Pan American Zoonoses Centre for testing and so far have been approved.

At the CFI production capacity was 0.2×10^6 doses for human use and 0.5×10^6 doses for veterinary use.

2. Research and development

Work with tissue culture grown rabies virus (CVS) is in an advanced stage of development. Eight production batches have been produced in BHK-cells in Roux-flasks, inactivated with bromethyamin and suspended in saccharose/glycin solution, a liquid vaccine.

Experimental challenge trials in dogs were in progress in 1988. Field trials, in preparation, are expected to complete by the end of 1990.

Future development work with this and other strains (Fuenzalida 57 and 97) includes use of either human diploid or Vero-cells for virus propagation; lyophilised products will be formulated for both medical and veterinary use.

Annex 7

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Difteria-Pertussis y tétano
NOMBRE PROPIO:	Toxoides diftérico y tetánico combinados con vacuna Pertussis
TIPO:	Líquido
FORMULA:	Cada D.H.S. de 0,5 ml contiene: 25 Lf. toxoide diftérico (no $<$ 2 U.A./ml) 7,5 Lf. toxoide tetánico (no $<$ 2 U.A./ml) 4 U.P. de vacuna Pertussis 0,68 mg de fosfato de aluminio equivalentes a 0,1505 mg de aluminio
METODO DE INACTIVACION:	Vacuna Pertussis: Thimerosal + refrigeración ($4-8^{\circ}C$) Toxoides diftérico y tetánico: Formol + calor
PRESERVATIVO:	Thimerosal (1:10000)
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	20 ml (40 ds.)
EMBALAJE:	Cajas de 55 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: ($4-8^{\circ}C$): (sin refrigeración):	18 meses No se acepta
TIEMPO DE ENTREGA:	Programadas por el Ministerio de Salud Pública
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los comités de Expertos de la OMS en patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano"

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Difteria y tétano
NOMBRE PROPIO:	Toxoides diftérico y tetánico combinados (Uso adulto)
TIPO:	Líquido
FORMULA:	Cada D.H.S. de 0,5 ml contiene: 5 Lf. toxoide diftérico (no < 2 U.A./ml) 5 Lf. toxoide tetánico (no < 2 U.A./ml) 2,04 mg fosfato Al. equivalentes a 0,4515 mg Al.
METODO DE INACTIVACION:	Formol + calor
PRESERVATIVO:	Thimerosal (1:10000)
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	20 ml (40 ds.)
EMBALAJE:	Cajas de 55 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Programadas por el Ministerio de Salud Pública
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: F.D. A. (USA)

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil- Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Tifoidea
NOMBRE PROPIO:	Vacuna tifoidea
TIPO:	Líquido
FORMULA :	1 dosis (1 ml) contiene 10^9 organismos salmonella tífica Ty2
METODO DE INACTIVACION:	Calor + thimerosal
PRESERVATIVO:	Thimerosal (1:10000)
RECIPIENTE:	Frascos de vidrio neutro tipo X U.S.P.
TAMAÑO:	20 ml (20 ds.)
EMBALAJE:	Cajas de 55 frascos
DILUYENTE:	Solución salina Büffer
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Programadas por el Ministerio de Salud Pública
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección o exposición previa a S. tífica
NOMBRE PROPIO:	Antígeno tifoideo H (flagelar) (Ensayo de aglutinación en placa o tubo)
TIPO:	Liquido
FORMULA:	Reacción en placa: 1 ml contiene 3 x 10^9 org. salmonella tífica H-901 Reacción en tubo: 1 ml contiene 1 x 10^9 org. salmonella tífica H-901
METODO DE INACTIVACION:	Formol + t.a./72 h
PRESERVATIVO:	Formol 0,5%
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	Frascos de 5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección ó exposición previa a S. tífica
NOMBRE PROPIO:	Antígeno tifoideo O (somático) (Ensayo de aglutinación en placa o tubo)
TIPO:	Líquido
FORMULA:	Reacción en placa: 1 ml contiene 3 x 10^9 org. salmonella tífica 0-901 Reacción en tubo: 1 ml contiene 1 x 10^9 org. salmonella tífica 0-901
METODO DE INACTIVACION:	Calor
PRESERVATIVO:	Fenol 0,5%
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE;	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección ó exposición previa a S. paratífica A
NOMBRE PROPIO:	Antígeno paratifoideo A (flagelar) (Ensayo de aglutinación en placa o tubo)
TIPO:	Líquido
FORMULA:	Reacción en placa: 1 ml contiene 3 x 10^9 org. salmonella paratífica A Reacción en tubo : 1 ml contiene 1 x 10^9 org. salmonella paratífica A
METODO DE INACTIVACION:	Formol + t.a./72 h
PRESERVATIVO:	Formol 0,5%
RECIPIENTE	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional :

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección o exposición previa a S. paratífica B.
NOMBRE PROPIO:	Antígeno paratifoideo B (flagelar) (Ensayo de aglutinación en placa o tubo)
TIPO:	Líquido
FORMULA:	Reacción en placa: 1 ml contiene 3 x 10^9 org. salmonella paratífica B Reacción en tubo : 1 ml contiene 1 x 10^9 org. salmonella paratífica B
METODO DE INACTIVACION:	Formol + t.a./72 h
PRESERVATIVO:	Formol 0,5%
RECIPIENTE:	Frascos de vidrio neutro tipo I I.S.P.
TAMAÑO:	5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS;	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección o exposición previa a rickettsias
NOMBRE PROPIO:	Antígeno proteus OX2 (somático) (Ensayo de aglutinación en placa)
TIPO:	Líquido
FORMULA:	1 ml contiene 3 x 10^9 org. proteus vulgaris OX
METODO DE INACTIVACION:	Calor
PRESERVATIVO:	Fenol 0,5%
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Antígeno febril para detectar anticuerpos bacterianos (aglutininas) asociados con infección o exposición previa a rickettsias
NOMBRE PROPIO:	Antígeno proteus OX19 (somático) (Ensayo de aglutinación en placa)
TIPO:	Líquido
FORMULA:	1 ml contiene 3 x 10^9 org. proteus vulgaris OX19
METODO DE INACTIVACION:	Calor
PRESERVATIVO:	Fenol 0,5%
RECIPIENTE:	Frascos de vidrio neutro tipo I U.S.P.
TAMAÑO:	5 ml
EMBALAJE:	Cajas de 50 frascos
DILUYENTE:	Solución salina fosfatada
ESTABILIDAD: (4-8°C):	18 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Entrega inmediata con pedidos de hasta 200 frascos. Con pedidos de hasta 400 frascos, después de 60 días
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional:

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Toxoide tetánico
NOMBRE PROPIO:	Toxoide tetánico
TIPO:	Líquida
FORMULA:	Cada dosis humana simple de 0,5 ml contiene 7,5 Lf de toxoide tetánico (no menos de 2 U.A./ml)
METODO DE INACTIVACION:	Formoldehido
PRESERVATIVO:	Thimerosal (1:10000)
RECIPIENTE:	Frasco de vidrio neutro tipo I U.S.P.
TAMAÑO:	20 ml (40 dosis)
EMBALAJE:	Caja de 55 frascos
DILUYENTE:	Büffer salina
ESTABILIDAD: (4-8°C):	24 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Programada por el Ministerio de Salud Pública
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: F.O.A.

PAIS:	Ecuador
FABRICANTE:	Instituto Nacionalde Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	Vacuna antirrábica uso humano CRL
NOMBRE PROPIO:	Vacuna antirrábica Fuenzalida Palacios uso humano
TIPO:	Líquida
FORMULA:	Una dosis (1 ml) contiene 20 mg de cerebro de ratón lactante, inoculado con virus fijo, cepas CVS, 51 i 91
METODO DE INACTIVACION:	Luz ultravioleta
PRESERVATIVO:	Fenol 1 por 1000 - Thimerosal 1 por 10000
RECIPIENTE:	Frascos de vidrio 20 ml tipo I U.S.P.
TAMAÑO:	20 ml (14 dosis, 1 ml por dosis)
EMBALAJE:	Entrega según órdenes
DILUYENTE:	Solución glucosada al 5%
ESTABILIDAD; (4-8°C):	12 meses
(sin refrigeración):	No se acepta
TIEMPO DE ENTREGA:	Programada por el Ministerio de Salud
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: Centro Panamericano de Zoonosis (CEPANZO)

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-[illegible]3334 INHMTE-ED
VACUNA:	Antituberculosa
NOMBRE PROPIO:	Vacuna B.C.G.
TIPO:	Líquida
FORMULA:	1 ml contiene 0,5 mg de masa bacilar 10-15 UFC/ml/x10^6
METODO DE INACTIVACION:	---
PRESERVATIVO:	---
RECIPIENTE:	Ampollas de vidrio ámbar
TAMAÑO:	20 dosis
EMBALAJE:	Caja de 10 ampollas
DILUYENTE:	Sautón 1,4
ESTABILIDAD: (4-8^{o}C):	30 días
(sin refrigeración):	No
TIEMPO DE ENTREGA:	Cada 15 días 20000 dosis
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: Centro Panamericano de Zoonosis (CEPANZO) 10 sublotes como promedio por año

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	ONCO B.C.G.
NOMBRE PROPIO:	Onco-BCG
TIPO:	Líquida
FORMULA:	1 ml contiene 40 mg de masa bacilar 620 -902 UFC/ml/x10^6
METODO DE INACTIVACION:	---
PRESERVATIVO:	---
RECIPIENTE:	Ampollas de vidrio blanco
TAMAÑO:	3,5 ml de suspensión
EMBALAJE:	Cajas de 10 ampollas conteniendo cada ampolla 3,5 ml de suspensión
DILUYENTE:	Sautón 1,4
ESTABILIDAD: (4-8^{o}C):	30 días
(sin refrigeración):	No
TIEMPO DE ENTREGA:	Cada 15 días 50 ampollas
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: Centro Panamericano de Zoonosis (CEPANZO) 5 lotes como promedio por año

PAIS:	Ecuador
FABRICANTE:	Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez"
LOCAL:	Julián Coronel 905 y Esmeraldas Guayaquil-Ecuador
TELEX:	04-03334 INHMTE-ED
VACUNA:	
NOMBRE PROPIO:	Solución tuberculina - PPD(RT 23)
TIPO:	Líquida
FORMULA:	1 dosis de 0,1 ml contiene 2 unidades de tuberculina
METODO DE INACTIVACION:	---
PRESERVATIVO:	---
RECIPIENTE:	Frascos de vidrio neutro
TAMAÑO:	70 dosis
EMBALAJE:	Cajas de 10 frascos
DILUYENTE:	Solución Büffer
ESTABILIDAD: (4-8^{o}C):	Por 6 meses
(sin refrigeración):	No
TIEMPO DE ENTREGA:	Cada 3 meses 20000 dosis
OTROS COMENTARIOS:	Los biológicos se fabrican siguiendo las recomendaciones de los Comités de Expertos de la OMS en Patrones Biológicos y las "Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano" Control internacional: Centro Panamericano de Zoonosis (CEPANZO)

Metas propuestas por el Ministerio de Salud - Producción del I.N.H.M.T.

Biológico	1984		1985		1986		1987		1988 (1)	
	Metas M. de S.	Producción	Metas M. de S.	Producción	Metas M. de S.	Producción	Metas M. de S.	Producción	Metas M. de S.	Producción
Vacuna B.C.G. líquida	1.000.000	836.115	300.000	845.265	300.000	743.625	859.736	1.096.590	360.000	1.303.155
Vacuna triple (DPT)	1.200.000	1.336.400	1.600.000	1.144.900	2.400.000	1.370.080	1.923.679	985.000	1.720.000	-
Vacuna mixta (D.T.)	600.000	1.708.440	600.000	508.440	1.000.000	160.640	727.349	450.850	900.000	-
Toxoide tetánico	400.000	450.000	400.000	400.080	360.000	400.000	466.796	400.000	200.000	200.000
Vacuna antirrábica humana	255.000	255.010	204.000	237.860	280.000	280.000	306.000	176.708	243.000	256.938

(1) Cortado a 30 de noviembre.
Las cantidades están dadas en dosis.

8 de diciembre de 1988

DE: División de Producción de Biológicos de Uso Humano.

PARA: Dr. Enrique Granizo M. Subsecretario General de Salud.

ASUNTO: Informe sobre datos solicitados en télex 22677 MINSAL-ED # 0486 de fecha 88-11-30.
Por disposición del Dr. Gualberto Avalos Z., Director I.N.H.M.T.

Atentamente,

Dra. Gladys A. de González

1.- Producción de vacunas en el Ecuador

Justificación

La necesidad nacional y la importancia estratégica que tiene para el país la producción de biológicos, justifica la razón del interés manifestado por las autoridades del Ministerio de Salud Pública, a través del tiempo, a los diferentes Asesores OPS/OMS que han visitado el país, de continuar e incrementar la producción de biológicos en el Instituto Nacional de Higiene y Medicina Tropical "Leopoldo Izquieta Pérez", como un verdadero apoyo a los programas nacionales de vacunación, entre ellos el Programa Ampliado de Inmunizaciones (PAI), que fué iniciado por la Organización Mundial de la Salud en 1974 y que actualmente ha pasado a ser un elemento esencial de la estrategia para lograr salud para todos en el año 2000. El objetivo de esta estrategia es el de reducir la morbilidad y mortalidad causada por difteria, tosferina, tétano, sarampión, poliomielitis y tuberculosis, suministrando inmunización contra estas enfermedades para cada niño en el mundo en 1990.

Por otro lado, el abastecimiento internacional a través de importaciones realizadas por el Estado, se vuelve cada vez más difícil por factores tales como las dificultades de compra con efectivas seguridades sobre la calidad de biológicos, la disponibilidad oportuna de los mismos en el mercado internacional y la disponibilidad oportuna de divisas para su contratación.

De este modo, contar con una fuente técnica y económicamente viable de abastecimiento local, que facilite la disponibilidad oportuna de las vacunas esenciales, propicie el desarrollo técnico-científico, reduzca la dependencia tecnológica y de abastecimiento del exterior, representan una estrategia que cuenta con el respaldo de organismos internacionales, tales como la Organización Mundial de la Salud, Convenio Hipólito Unanue, etc., así como de sectores nacionales relacionados.

Todas estas consideraciones justifican la razón del interés siempre demostrado por el I.N.H.M.T. de lograr cooperación técnica, transferencia de tecnología, abastecimiento de equipos e insumos por parte de organismos y países con mayor desarrollo que el nuestro, para reforzar así las estructuras existentes y aprovechar al máximo nuestras capacidades operativas en producción de biológicos.

Antecedentes

La producción de biológicos inmunizantes de uso humano en el país, se inicia en el año 1941, con la creación del Instituto Nacional de Higiene "Leopoldo Izquieta Pérez", que para ese año adquirió el compromiso de continuar con la elaboración de la vacuna antivariólica (actualmente ya no se produce por erradicación de la enfermedad), la misma que hasta ese momento se encontraba a cargo del Instituto de Vacunas de Guayaquil.

En el año 1942 se inicia la elaboración de vacuna BCG líquida.

Entre 1943-1956 se elaboraron los siguientes biológicos: vacuna Pertussis fluida, vacuna tifoidea precipitada por alumbre, vacuna antirrábica tipo Semple y antígenos febriles.

Entre 1956-1987 se elaboraron los siguientes biológicos y se emprendieron las siguientes acciones:

- Vacuna tifoidea fluida utilizando cepa Ty2.

- Toxoide diftérico simple precipitado con fosfato de aluminio (actualmente ya no se produce por falta de demanda).

- Toxoide diftérico + vacuna Pertussis, precipitados con fosfato de aluminio (actualmente fuera de producción).

- Toxoide tetánico simple precipitado con fosfato de aluminio.

- Toxoide diftérico y tetánico precipitados con fosfato de aluminio (vacuna D.T. tipo adulto).

- Toxoide diftérico + vacuna Pertussis + toxoide tetánico, precipitados con fosfato de aluminio (vacuna triple).

- Vacuna antirrábica humana tipo CRL (cerebro ratón lactante).

- Se hicieron ensayos para la obtención de vacuna B.C.G. liofilizada.

- Preparación de sueros hiper-inmunes para control de antígenos febriles.

- Introducción de la técnica de concentración de toxoides diftérico y tetánico utilizando el concentrador y dializador AMICON.

- Realización de etapa experimental de producción de vacuna Pertussis en cultivo agitado.

- Establecimiento de buenas prácticas de manufactura y un más amplio control de calidad a cada uno de los biológicos producidos en el I.N.H.M.T., con cuyo propósito se han efectuado modificaciones en las técnicas de fabricación, se han implementado nuevas pruebas de control en los productos elaborados y se ha normatizado a nivel interno la metodología, estandarizándose la elaboración de flujogramas para cada tipo de biológico.

- Implementación de técnicas de bioseguridad en los laboratorios.

- Elaboración de normas técnicas de fabricación y control de calidad de los biológicos de uso humano, las que fueron previamente revisadas en Washington por expertos OMS/OPS y han brindado la oportunidad al país de cumplir con el requisito básico de poseer Normas Nacionales de Fabricación y Control de Inmunizantes de Uso Humano.

Situación actual de la producción de biológicos

El Instituto Nacional de Higiene y Medicina Tropical es la Institución del Ministerio de Salud Pública dedicada a actividades de laboratorio en el campo de servicios de salud pública, entre las que se encuentra la producción de biológicos para inmunoprofilaxis. Para atender estas actividades cuenta con una División de Producción de Biológicos para Uso Humano que tradicionalmente se ha dedicado a esta tarea y la experiencia acumulada en muchos años ha permitido que los productos elaborados alcancen los niveles de calidad establecidos por la OPS/OMS, como lo demuestran los resultados tanto del control

interno como del control internacional a que son sometidos. Además, tiene personal técnico calificado y estable en las diferentes áreas de producción.

La planta productora de biológicos tiene una superficie aproximada de 1.743 metros cuadrados, perfectamente planificada y funcional para la época en que se construyó, esto es, en 1966, habiéndose efectuado remodelaciones y ampliaciones.

En la División de Producción Salud Humana se producen cuatro de los productos biológicos para inmunización activa que utiliza el Programa Ampliado de Inmunizaciones, esto es, vacuna BCG líquida, toxoides diftérico y tetánico y vacuna Pertussis adsorbidos (vacuna DPT), toxoides diftérico y tetánico adsorbidos (vacuna D.T. tipo adulto), toxoide tetánico adsorbido (T.T.); además se produce la vacuna antirrábida humana tipo CRL.

Los siguientes son los departamentos que conforman la División de Producción, con funciones específicas para cada uno:

- Departamento de B.C.G. y P.P.D.

- Producción de vacuna BCG líquida.

- Preparación de diluciones de PPD; 2 TU y 10 TU.

- Control de calidad interno de la vacuna BCG líquida y de las diluciones de PPD.

- Departamento de Pertussis

- Producción de vacuna Pertussis concentrada.

- Control de calidad interno de vacuna Pertussis concentrada.

- Producción de vacuna tifoidea concentrada.

- Control de calidad interno de vacuna tifoidea concentrada.

- Producción, envase, acondicionamiento y control de calidad interno de los siguientes antígenos febriles: tifoideo O, tifoideo H, paratifoideo A, paratifoideo B, Proteus OX2 y Proteus OX19.

- Mezcla, envase y acondicionamiento de productos finales: vacuna triple (DPT), vacuna mixta (DT), toxoide tetánico (TT), vacuna tifoidea.

- Control de calidad interno de las vacunas: triple, mixta, toxoide tetánico y tifoidea.

- Preparación y esterilización de medios de cultivo, soluciones Büffer y otros.

- Liofilización de cepas bacterianas utilizadas en producción como "lote de semilla".

- Preparación y control de calidad de sueros hiper-inmunes utilizados en el control de antígenos febriles.

- Departamento de toxoide tetánico

- Producción de toxoide tetánico concentrado y purificado al granel.

- Control de calidad interno de toxoide tetánico concentrado y purificado al granel.

- Departamento de toxoide diftérico

- Producción de toxoide diftérico concentrado y purificado, como producto al granel.

- Control de calidad interno de toxoide diftérico concentrado y purificado al granel.

- Departamento de vacuna antirrábica uso humano

- Producción de vacuna antirrábica para uso humano tipo CRL.

- Control de calidad interno de vacuna antirrábica humana CRL.

Almacén de vacunas

Lugar donde se almacenan los productos terminados y aprobados para su distribución dentro del país. El almacenamiento se lleva a cabo bajo condiciones tales que permiten mantener la estabilidad de los productos dentro de los límites de vigencia.

El I.N.H.M.T. se hace cargo de la distribución de sus productos para entregarlos al Banco Nacional de Vacunas, al Banco Regional de Vacunas, a otras entidades del sector salud, así como también al sector privado. Los precios de venta son autorizados por el Ministerio de Salud Pública, tanto para el sector público como para el sector privado.

Bioterios

A nivel central: Existe un área física para este departamento en la sede central del I.N.H.M.T., que se encarga de producir animales de laboratorios(conejos y cobayos) para pruebas de diagnóstico, pruebas de control biológico de las vacunas e investigación en general.

Los requerimientos de ratones utilizados en la preparación de vacuna antirrábica de uso humano así como en las pruebas de control de los biológicos, son atendidos por los Laboratorios Veterinarios del I.N.H.M.T. que tiene un área física independiente técnica y administrativamente.

A nivel departamental: Cada departamento de la División de Producción cuenta con su correspondiente bioterio para alojar y mantener los animales de laboratorios utilizados en la ejecución de las pruebas de control en los biológicos que elaboran.

Producción anual de cada biológico

Capacidad operativa actual. La producción de biológicos humanos se realiza en base a lo solicitado por el Ministerio de Salud Pública para sus campañas de vacunación.

En el cuadro siguiente se resume la demanda nacional de biológicos utilizados tanto por el P.A.I. como por la División Nacional de Zoonosis y la producción de los mismos en el I.N.H.M.T., en el último quinquenio.

Como el país no cuenta con tecnología propia para la fabricación de sustancias químicas utilizadas en la preparación de medios de cultivo, reactivos químicos, vidriería especializada y disponibilidad de equipos y repuestos, estamos obligados a importarlos de países industrializados, pero como las importaciones son lentas y los recursos económicos escasos, hay necesidad de adquirirlos en el mercado local, lo que trae como consecuencia, en algunas ocasiones, atrasos e insuficiencia de la producción, así como encarecimiento del producto.

Cuando se dispone de todos los insumos necesarios, la capacidad de producción satisface las metas propuestas por el Ministeriode Salud para los programas de inmunización del país.

Capacidad operativa máxima. Con la infraestructura que se dispone, los métodos de producción utilizados y teniendo a disposición los insumos necesarios, las siguientes serían las capacidades operativas máximas de producción de biológicos anuales:

Vacuna B.C.G. líquida: 1.500.000 dosis
Vacuna Pertussis concentrada: 2.000.000 dosis
Toxoide tetánico concentrado y purificado: 3.500.000 - 4.000.000 dosis
Toxoide diftérico concentrado y purificado:
Vacuna triple (D.P.T.): 2.000.000 dosis
Vacuna mixta (D.T.): 1.000.000 dosis
Toxoide tetánico (T.T.): 800.000 - 1.000.000 dosis
Vacuna antirrábica uso humano: 1.000.000 dosis

Es necesario hacer notar lo siguiente: la capacidad operativa máxima de producción de vacuna D.P.T. ha sido determinada tomando como base la capacidad operativa máxima de producción de vacuna Pertussis concentrada, que junto con los toxoides diftérico y tetánico son los componentes de la mencionada vacuna. Entre la capacidad operativa máxima de producción de vacuna D.P.T. y la demanda nacional de este biológico por parte del P.A.I. para 1989, hay solamente una diferencia de 200.000 dosis.

Métodos de producción empleados

Vacunas:

B.C.G.: Vacuna bacteriana viva, líquida, elaborada con la cepa Paris 1173-p2A.

Triple (D.P.T.): Mezcla de vacuna antipertussis obtenida por proceso de cultivo estacionario en medio sólido de Cohen y Wheeler, y de toxoide tetánico y toxoide diftérico purificados, obtenidos por procesos de cultivo estático en superficie.

Mixta (D.T.): (adulto) Mezcla de toxoide tetánico y toxoide diftérico purificados, obtenidos por procesos de cultivo estático en superficie.

Tetánica (T.T.): Toxoide tetánico purificado, obtenido por procesos de cultivo estático en superficie.

Tifoidea: Salmonella Typhi Ty2 muerta, obtenida por cultivo estático en superficie.

Antirrábica uso humano: Virus rábico fijo multiplicado en cerebro de ratón lactante e inactivado por luz ultravioleta.

Antígenos:

P.P.D.: A partir del antígeno concentrado se preparan las siluciones de 2 TU y 10 TU, utilizando solución Büffer.

Febriles: Se producen por cultivo estático los siguientes antígenos febriles: tifoideo H, tifoideo O, paratifoideo A, paratifoideo B, Proteus OX2 y OX19.

Sistema de trabajo. En la producción de biológicos se usa el sistema de lote de semilla que es obtenido a partir de cepas liofilizadas enviadas por OPS/OMS, manteniendo sus mismas características (pureza, identidad, etc.).

Controles. Las prácticas de manufactura que se utilizan siguen estrictamente las recomendaciones de los Comités de Expertos de la Organización Mundial de la Salud en Patrones Biológicos y las Normas Internas de Producción Nacional. Se efectúa un riguroso control de calidad interno a lo largo de todo el proceso de producción y un periódico control internacional, lo cual permite liberar al consumo productos de probada calidad.

Mantenimiento de instalaciones y equipos

Para asegurar la continuidad de la producción de biológicos, es indispensable contar con un rápido y eficiente mantenimiento de equipos. Los instrumentos de mediciones, los equipos para producción, los equipos que mantienen los ambientes controlados, requieren un constante mantenimiento preventivo y un muy oportuno mantenimiento correctivo. Los actuales controles electrónicos aumentan los requisitos de preparación y conocimiento del personal que está a cargo de estas acciones y normalmente obligan a contratar externamente estos servicios.

Recursos

Los recursos administrativos, financieros, materiales y de personal necesarios para la producción son aportados por el Ministerio de Salud Pública del país.

Los recursos financieros resultan cada vez más insuficientes para la producción de biológicos; se hace necesario el crecimiento de la inversión global destinada a este menester, ya que actualmente representa un porcentaje muy bajo del presupuesto total del Instituto.

Es necesario recalcar que la producción de biológicos de uso humano es entregada totalmente al Ministerio de Salud en forma absolutamente gratuita, lo que para fines de presupuesto institucional representa una fuerte carga financiera.

Las cepas y patrones biológicos son aportados por la OPS/OMS.

Personal de producción

División y Departamentos	Profesionales	Auxiliares Microb.	Auxiliares de servicio
División producción	1		
Departamento B.C.G.	4	3	5
Departamento Pertussis	6	1	6
Departamento difteria	2	1	4
Departamento tétano	2	4	
Departamento vacuna antirrábica U.H.	2	6	
Almacén de vacunas		1	1
Total	17	16	16

2.- Abastecimiento y planificación futura para la producción de biológicos inmunizantes

Es un hecho indiscutible que la demanda de biológicos para prevención de las enfermedades, se incrementará a través del tiempo. La Organización Mundial de la Salud incentiva a los países en desarrollo a incrementar las coberturas de vacunación actuales al 100%, y la población en el mundo tiende a indicar un incremento de la población objeto. Ambos factores van a afectar principalmente la demanda de biológicos en los países en desarrollo.

Hasta ahora una parte significante de la producción corriente en países desarrollados es exportada a países en desarrollo a través de PAHO y UNICEF. Sin embargo, muchas de estas compañías se han retirado del campo de producción de vacunas en esta década.

Es razonable pensar que la buena cooperación internacional, particularmente en este importante campo de la salud pública, debe encaminarse a lograr los siguientes objetivos:

Un objetivo general, que es ayudar a los países en desarrollo a alcanzar la meta de "Salud para todos en el año 2000", como lo ha definido la Organización Mundial de la Salud.

Un objetivo industrial que consiste en a) asistir a los países en desarrollo a establecer y/o a ampliar la producción local de preparaciones biológicas a través de la identificación y análisis de la restricción económica y técnica que retrasa el desarrollo de la industria, y b) proponer soluciones para reducir el efecto de aquellos impedimentos.

En los países en desarrollo, a diferencia de los países desarrollados, el análisis del costo-beneficio social es el método internacionalmente aplicado para evaluar la inversión del sector público tanto en la producción de biológicos como en la implantación de programas de vacunación. Mientras la incidencia de la enfermedad es alta, los efectos de sus víctimas son severos y no hay tratamiento efectivo, la vacunación genera beneficios sociales que exceden a su costo.

Debido a que los beneficios sociales pesan más que los costos sociales, debe existir el compromiso directo de las autoridades de salud que, además de la implantación de programas de vacunación, debe el sector público participar también en la producción, teniendo presente la idea política de que la atención primaria de la salud debe ser suministrada como algo elemental por parte del Estado y no como un medio de compra de biológicos en el mercado internacional.

Como se ha manifestado en párrafos anteriores, las actividades de producción de biológicos en el Instituto Nacional de Higiene y Medicina Tropical se realizan de acuerdo a métodos de tipo pre-industrial, lo que conlleva a la utilización de métodos de trabajo manual intensivo, tales como: cultivos en botellas o en jarras de vidrio, cosechas en centrífugas de capacidad limitada, envase en equipo antiguo o a mano con baja capacidad de rendimiento, se carece de tanques de mezcla con capacidad suficiente para el tamaño de los lotes de vacunas DPT, DT y TT, lo que aumenta el riesgo de heterogeneidad en los lotes, etiquetado y acondicionamiento final a mano. Se produce actualmente la vacuna BCG en estado líquido con una caducidad de 14 días, lo que impide que

este biológico llegue con efectiva garantía de calidad a sitios alejados del país. Hay menor eficiencia y mayor riesgo de reacciones indeseables en el caso de la vacuna antirrábica de uso humano, preparada a partir de cerebros de ratones lactantes, etc.

Aunque se obtienen productos satisfactorios, en la mayoría de los casos, estos sistemas obligan a mantener al personal trabajando en producción prácticamente todo el año, con bajo rendimiento y con mayores riesgos para la calidad de los productos.

Es por esto que se deben de tomar acciones para mejorar las condiciones de producción, aumentar su rendimiento e incrementar la capacidad de producción. Esto implica algunos cambios en los métodos de producción para lograr mayores cantidades de dosis de biológicos en tiempos más cortos de procesos.

A fin de mejorar la eficiencia de producción actual e incrementarla para alcanzar metas mayores, acordes con el crecimiento de la población del país, la proyección futura de la División de Producción de Biológicos se asienta sobre bases reales, programando metas posibles de alcanzar a corto y mediano plazo, aprovechando la infraestructura existente y reduciendo a lo estrictamente indispensable la implementación de equipos e insumos.

Vacuna DPT, vacuna DT y toxoide tetánico

Si se tiene la intención de incrementar la producción de estos productos finales, se debe tener en consideración que debe haber un incremento en la producción de los principios activos de las mencionadas vacunas, esto es, Pertussis, difteria y tétano, en cantidades suficientes y proporcionales entre los tres componentes para cubrir las necesidades del país, en primer lugar, y si hubiera excedente, poderlo comerciar e intercambiar con otros productos biológicos que no se fabriquen aquí.

Las acciones a emprender consideramos que deberían ser:

Elaboración de principios activos: Tanto en la producción de vacuna Pertussis como de toxoide diftérico y toxoide tetánico se debe cambiar el método de producción actual, que es el cultivo estático, a fermentación. Este cambio implica un período de adaptación y desarrollo industrial que se puede apoyar en otros laboratorios que ya lo han realizado.

Como es lógico, la introducción del método de cultivo por fermentación implica la adquisición de fermentadores de características apropiadas, que sean de fácil operación manual y mantenimiento. Además, la implantación de esta nueva técnica requiere adiestramiento del personal y asesoría externa de expertos internacionales.

El incremento de volúmenes de cultivo lleva aparejado un incremento en la capacidad de centrifugación para cosechar las bacterias en condiciones óptimas de tiempo y temperatura, por lo que será necesario contar con centrífugas refrigeradas de mayor capacidad. En fin, toda la infraestructura actual de los laboratorios involucrados deberá ser fomentada ya que se manejarán mayores cantidades de vacuna, aumentando los riesgos.

En cuanto a la vacuna Pertussis, actualmente se ha terminado una etapa experimental intermedia de conversión al método de cultivo en fermentadores, esto es, utilizando el cultivo agitado en medio líquido, con el fin de adquirir experiencia llevando a cabo un escalamiento del proceso y optimizarlo. Contando con esta infraestructura, se podría pensar en la asimilación de nueva tecnología para producción de vacuna Pertussis acelular que en algunos países latinoamericanos está en vías de desarrollo.

Elaboración de producto final: Se lleva a cabo en un área de envase y acondicionamiento de productos finales. Esta área requiere:

- Automatizar las labores de envase y sellado de recipientes que contienen las suspensiones inyectables.

- Automatizar las labores de etiquetado y acondicionamiento de las vacunas.

- Ampliar la capacidad de la máquina de lavado de viales y ampollas.

- Contar con tanque de acero inoxidable para la mezcla y homogenización de productos al granel, previo al envase.

- La esterilización de materiales es actualmente limitada, así como otros servicios básicos, como ser vapor, electricidad, suministro de agua bidestilada para inyectables, etc. Servicios que necesitan también ser incrementados.

Vacuna BCG

Es necesario cambiar el método de producción actual, al de producción de vacuna BCG liofilizada. El departamento cuenta con la infraestructura necesaria.

Emprendiendo esta acción se logra:

- Disponer de un biológico cuya caducidad es de 1 año en lugar de 14 días, que es lo que corresponde a la vacuna líquida.

- Contar con un biológico que tenga un control de calidad completo, dado que su vida media es de un año.

- Poder suministrarlo a los sitios más alejados del país, puesto que el BCG desecado puede tolerar por algunas horas la temperatura ambiente sin sufrir menoscabo en su calidad.

- Abastecer el consumo del país, primero, y el excedente ponerlo a disposición del Ministerio de Salud para su comercialización, beneficio que redundaría en el autofinanciamiento parcial de la producción de este tipo de vacuna.

- Fomentar el desarrollo tecnológico del país, al elaborar uno de los productos básicos, liberándonos de la dependencia tecnológica internacional.

Vacuna antirrábica uso humano

Producción de vacuna antirrábica utilizando sustrato celular.

Emprendiendo esta acción se logra:

- Producir un biológico cuya técnica de manufactura garantice un mayor rendimiento a la vez que probada eficacia, inocuidad y estabilidad. En el país, hay una gran demanda de este biológico debido a la alta incidencia de rabia urbana y de mortalidad humana.

- Abastecer al país para su consumo interno y posibilidad de exportación del excedente de producción.

- Impulsar el desarrollo de la tecnología nacional y reducir la dependencia tecnológica del exterior.

Bioterios para la producción de animales

Los requerimientos para mejoras son los siguientes:

- Renovar pié de cría de colonias de animales de laboratorio:

  a) conejos, se precisan 10 hembras y 5 machos de raza Nuevo Zelandés;

  b) cobayos, se precisan 30 hembras y 10 machos albinos;

  c) ratones.

- Tapones de caucho # 3 para bebederos (actualmente escasos en el mercado), aproximadamente 1000 unds.

- Cajas plásticas con rejillas para mantenimiento de animales de investigación (aproximadamente 100 grandes y 50 pequeñas).

- Material de hierro: varillas ángulos y planchas para construcción de castillos.

- Malla metálica cuadrada de 1/4 y de 1/2 pulgada (paredes y pisos de castillos).

- El Departamento de vacuna antirrábica humana precisaría de la creación de un bioterio de producción de ratones, posiblemente como servicio de ampliación del bioterio de la sede central. Con esto se conseguiría mejorar el volumen de producción de la mencionada vacuna, así como atender requerimientos de otros departamentos de la División de Producción de Biológicos de Uso Humano. Los actuales requerimientos son atendidos por los Laboratorios Veterinarios del Instituto, que funcionan en área física independiente.

Ampliación de la línea de producción

- Producción de antitoxina tetánica de origen equino.

- Producción de antitoxina diftérica de origen equino.

- Producción de suero antirrábico.

Estos productos se encuentran en el listado del Cuadro Básico de Medicamentos y Vacunas Esenciales del país.

- Producción de reactivos de diagnóstico, de acuerdo a necesidades básicas del país, en el sector de salud humana.

Mecanismos para cumplimiento de estas metas

1 - Adquisición de equipos y suministros.

2 - Transferencia de ciencia y tecnología:
Asistencia de personal técnico nacional a centros internacionales con mayor desarrollo para el área específica.

Asistencia de expertos internacionales a los laboratorios nacionales de producción, por períodos de tiempo necesarios para cada caso en particular.

3 - Preparación de personal nacional para dar mantenimiento a los equipos utilizados.

4 - Otorgar becas a los profesionales responsables de cada área de la División de Producción, a fin de que se actualicen en ciencias básicas necesarias para la asimilación de nueva biotecnología en la producción de vacunas y otros.

5 - Otorgar a la División de Producción una organización especial, considerándola como una fábrica de biológicos.

6 - Actualización de libros y publicaciones periódicas, relacionados con la industria de producción y control de biológicos.

Asimilación de nueva biotecnología

Actualmente algunos institutos de diferentes países de América Latina están iniciando la asimilación de nueva biotecnología para el desarrollo de nuevas vacunas: DNA recombinante, hibridomas, expresión de antígenos en procariotes y eucariotes. Y es interesante observar que en estos casos los gobiernos nacionales han dado apoyo mediante inversiones para edificios, adiestramiento de científicos y fondo para gastos de investigación.

Es necesario notar que el campo de producción de biológicos para inmunoprofilaxis forma parte del de biotecnología y es importante que ambas actividades se desarrollen armónicamente ya que van asociadas. De hecho, cualquier desarrollo de investigación en biotecnología conlleva una acción simultánea y coordinada en el campo industrial.

Es deseable buscar formas de coordinación que contribuyan a avanzar en la obtención de mejores productos para ofrecer mejor servicio en el campo de la inmunización.

No es probable que la tecnología de producción de vacunas en escala comercial, en los países en desarrollo, vaya a ser afectada por la ingeniería genética, que actualmente está en todo su auge en países desarrollados. Esto es debido a que esta clase de tecnología nueva puede probablemente ser fácilmente transferida porque los microorganismos manipulados genéticamente pueden ser cultivados en los mismos fermentadores y con el mismo estándar técnico. De aquí que una planta de producción de vacunas debe ser vista como una inversión para la transferencia de nuevas biotecnologías y como una fuente de producción de elementos considerados en todos los países del mundo como "productos estratégicos".

3.- Tipo de servicios de apoyo que existen para la producción de vacunas y biológicos

Cooperación técnica:

- Otorgamiento de becas para estudios en el exterior.
- Financiar la participación de funcionarios nacionales en reuniones internacionales.
- Colaboración en el desarrollo de cursos y seminarios.
- Apoyo a investigaciones en salud.
- Control internacional de los biológicos producidos.
- Suministro de cepas y patrones de referencia.

Servicios de apoyo:

- Consultores y asesores OPS/OMS en campos técnicos.
- Capacitación de personal de todos los niveles, en particular a la actualización técnica.
- La oficina de compras facilita información sobre precios y fuentes de una amplia gama de productos y equipos, facilitando la importación a través de OPS/OMS.
- Difusión de información técnica.

Dra. Gladys A. de González
Jefe División Producción
Salud Humana

Diciembre 7 de 1988

Annex 8

DIPHTHERIA-TETANUS-PERTUSSIS (DTP) VACCINE

Pharmaceutical form

Inactivated cells of Bordetella pertussis combined with toxoids of Corynebacterium diphtheria and of Clostridium tetani adsorbed on aluminium hydroxide. Preservative: merthiolate (1/10000), presentation: 10 doses of 0.5ml each in glass ampoules.

Composition

One vaccine dose of 0.5ml contains not less than 15Lf of ammonium sulphate precipitated toxoid of C.diphtheriae (PW-8) combined with 13 IOU of heat inactivated cells of B.pertussis (strains 134 and 509) and 20Lf of purified toxoid of Cl. tetani (strain Harvard) adsorbed on aluminium hydroxide.

1. Diphtheria toxoid component

1.1 Process description and quality control

In the preparation of this toxoid WHO recommendations are aimed at. The Park-Williams 8 strain (PW-8) of C.diphtheriae was obtained from the USA and the seed lot system was correctly adopted for its use.

The production cultures are grown statically in a modified Mueller-Miller medium containing acid hydrolysate of casein. The average batch represents ca. 120 x 0.5L cultures in 5L Povitsky bottles. Following inoculation of the bottles they are incubated for 8 days at 35°C. The cultures are harvested and following a series of filtrations, the sterile culture supernatant is detoxified by the addition of formaldehyde (0.7%), incubated at 37°C for 30 days followed by holding it (2-8°C) for 12 additional days.

The crude toxoid is concentrated by ultrafiltration and precipitated with ammonium sulphate. Following dialysis, the purified toxoid is sterilised by filtration and stored (2-8°C) pending tests before its release for blending.

An inspection of the flow diagram of production processes/quality control tests (Annex I/A-Mexico) shows that although WHO recommendations were followed there were some notable omissions with respect to the testing of bulk purified toxoid.

For complete compliance with WHO recommendations the following tests also need to be carried out: irreversibility, potency, innocuity and purity (NDN).

1.2 Production capacity, wastage, consistency of production

In 1988, 35 batches of diphtheria toxoid were produced, yielding ca. 10 million doses. Maximum production capacity is said to be 12.5 million doses p.a. The discrepancy in 1988 was due to two months of loss of production (alterations to production facility).

The average yield of toxin is 80-100Lf/ml. Between 8 and 10% of production cultures are lost due to contamination. An additional 30% loss of Lf value occurs during purification. This later loss is inherent in the method of purification and may be regarded as "normal" loss.

Consistency of production is satisfactory.

1.3 Constraints on production

Using the static culture technique output can be increased only by utilising more culture bottles. Additionally the blending vessels are too old and difficult to maintain. A 350L fermenter, which had been withdrawn from pertussis production, has been used to meet blending demands.

In order to meet the demands of the EPI in the country, 3.0 million doses of DTP were purchased in 1988 due to the shortage of diphtheria toxoid component for the domestic production of this vaccine.

1.4 Research and development

In the course of 1988 work has been in progress to adopt fermentation technology for the production of diphtheria toxin. This work has shown encouraging results, and if successful, will permit replacement of the present static culture method of toxin production with deep culture technology.

1.5 Considerations for increasing production

There are two 750L fermenters which have been partly installed but never used. One of these may be deployed for blending and the other for tetanus toxin production (see later). Thus the 350L fermenter, presently used for blending, will be released for diphtheria toxin production. Using this fermenter 24 times p.a., yielding 100Lf/ml and an overall recovery of 60% of the toxin produced, will yield 18.0×10^6 doses p.a. (Annex I/D).

With respect to downstream processing, any shortage of incubation space for detoxification may be resolved by concentration of the crude toxin by ultrafiltration.

Utilisation of the resultant increase of diphtheria toxoid (ca. 50%) will require pro-rata increases in the production of both tetanus toxoid and pertussis culture (see later).

2. Pertussis components

2.1 Process description and quality control

In the preparation of this component of DTP vaccine WHO recommendations are aimed at.

The production strains of B.pertussis, strain 509 and 134, were obtained from R.I.V. Holland.

For the preparation of master and working seed lots, the seed lot system is correctly employed. The seed lots are lyophilised and stored at 2-8°C.

For the production of pertussis cultures a 1000L fermenter (working volume ca. 900L) is used.

The inoculum for the fermenter is prepared on Bordet-Gengou (petri dish -- slope) and glutamate-proline medium (shake flask --- 10L fermenter).

The 900L glutamate-proline production medium, complete with 1% yeast extract, is inoculated and incubated at 37°C for 40-44 hrs, yielding on average, 30 IOU. The culture is filled into glass bottles. Cells from the harvest culture are precipitated by the addition of citric acid (pH4.0) and overnight sedimentation. Culture supernatant is syphoned off, merthiolate added (1/10000) and stored (2-8°C) pending tests. The cells are inactivated with heat (56°C for 45 mins) and stored (2-8°C, pending tests) before blending the two strains. Blends of the two strains are stored (2-8°C, pending tests) before release for the preparation of final bulk of DTP vaccine.

An inspection of the flow diagram of production process/quality control tests shows that these are broadly compatible with WHO guidelines for this product.

For complete compliance with WHO requirements, serological identification of each of the two production strains in the inactivated and concentrated cell suspensions should be carried out.

2.2 Production capacity, wastage, consistency of production

In 1988 a total of 35 batches (over 31000L) of pertussis cultures were grown. This yielded 9.0 million doses of pertussis vaccine component (at 13 IOU per dose) for DTP vaccine. It is understood that about 30% of the batches pass all the tests. About 5-6% of failure was due to contamination and the rest (ca. 65%) was due either to failing potency or toxicity tests. Such a high rate of wastage is also a reflection on the consistency of production.

2.3 Constraints on production

A shortage of storage space at 2-8°C is said to be one of the constraints on production. However, the main constraint is undoubtedly the inconsistency of producing acceptable pertussis components for DTP vaccine. A reduction of loss of cultures would result not only in pro-rata release of storage space but increased pertussis components for DTP.

2.4 Research and development

These should be aimed at reducing toxicity of the pertussis component. It is understood, however, that mice, used as untreated controls in the toxicity test (weight gain), do not perform adequately at times. It is a prerequisite of any development work to resolve this problem.

Experiments aiming to reduce toxicity of the pertussis component should include 1) reduction of culture supernatant in acid precipitated cells, 2) inactivation with formaldehyde instead of heat.

2.5 Considerations for increasing production

An increase of production of the pertussis component of DTP is conditional on successful resolution of toxicity/potency of this component. Cutting present losses of ca. 70% by half would lead to a doubling of present production leading to ca. 18.0×10^6 doses p.a.

3. Tetanus toxoid component

3.1 Process descriptions and quality control

(Tetanus toxoid is prepared in a devoted facility. Although the facility does not meet GMP requirements, steps are taken to contain the live organisms within the facility.)

In the preparation of this toxoid WHO recommendations are aimed at. The Harvard (Boston) strain of Cl.tetani was obtained from Holland. For the preparation of master and working seeds the seed lot system is used. However, preparation of the working seed is not entirely correct in that part of the working seed lot is further than five subcultures removed from the master seed. Both seed lots are lyophilised and stored at 2-8°C.

Tetanus toxin is produced either in a 360L fermenter, or in static cultures in glass jars.

The inoculum for the production culture is grown in thio-glycolate and Latham media for the inoculation of 360L Latham medium either in the fermenter or in glass jars. After 6-7 days incubation (35°C) when most of the cells have lysed (yield 40-50Lf/ml), the culture from the fermenter is run out into large glass bottles (if not produced in them), formaldehyde added (0.8%) and incubated at 37°C for 21 days. The toxoid is clarified and sterilised by filtration before purification by ultrafiltration. The filter-sterilised, concentrated toxoid is stored (2-8°C) pending tests before its release for formulation.

An inspection of the flow diagram of production processes/quality control tests shows that production processes are compatible with WHO recommendations. Quality control tests, with notable exceptions, also follow WHO recommendations.

For complete compliance with WHO recommendations the following tests also should be carried out:

1) Single harvest: purity (of culture), TCP, MLD.
2) detoxification, sterilisation: sterility,
3) purification, sterilisation: purity (N.D.N.), sterility,
4) purified, concentrated bulk toxoid, ready for blending: irreversibility, Lf, pH, potency (by lethal challenge), pyrogenicity, innocuity.

3.2 Production capacity, wastage, consistency of production

The 1988 production of 21.0 million doses (20Lf/dose) of tetanus toxoid is said to be maximum production capacity.

An examination of production documentation of four batches of tetanus toxoid (batches 1700-1703) showed that there were variations in the Lf values of the concentrated, purified toxoid, ranging from 90 to 270Lf/ml. The reason(s) for the variation is not clear. It is suspected, however, that the use of a relatively high concentration (0.8%) of formaldehyde and perhaps adsorption of toxoid in the course of filtrations may account for, what appears to be, a high degree of wastage.

It should also be noted that to use both static and fermenter technology is not strictly in accord with a consistent production process.

3.3 Constraints on production

The principal constraint is the shortage of incubation capacity for detoxification. In 1988, a total of 22800L of toxin was detoxified, using 0.8% formaldehyde for 21 days per batch. Using a lower concentration of formaldehyde and six weeks for detoxification would reduce incubation capacity by one half.

3.4 Research and development

None is taking place at the present time. It is suggested that experiments be carried out to determine the optimum concentration of formaldehyde, commensurate with complete detoxification to 42 days at 35°C.

3.5 Consideration for increasing production

An increase of tetanus toxoid production will require complete installation of the 750L fermenter, partly installed alongside the 360L fermenter, which is presently used for toxin production. Using the larger fermenter 28 times p.a. will result in 16800L of culture requiring detoxification. Using six weeks for detoxification, this may be accomplished in the walk-in incubator (11500L p.a. in glass bottles), in the 360L fermenter (8 x 360L, ca. 2900L) and the 750L (3 x 600L p.a., ca. 1800L).

Adoption of these suggestions should lead to:

1) consistency of toxin production,
2) production of 10.0×10^6 doses of tetanus toxoid,
3) production of 18.0×10^6 doses of tetanus for DTP formulation.

4. Preparation of DTP vaccine

4.1 Process description and quality control

The final bulk of DTP vaccine is prepared by blending sufficient volumes of concentrated diphtheria and tetanus toxoids and inactivated pertussis cells to give 15Lf of diphtheria toxoid, 13IOU of pertussis cells and 20Lf of tetanus toxoid per 0.5ml dose. The vaccine components are adsorbed onto alhydrogel (Superfos, Denmark) and stored (2-8°C pending tests) before release for filling.

An inspection of the quality control test carried out on the final bulk vaccine and finished product shows that the bulk vaccine is tested to WHO standards. However, potency assays of the diphtheria and tetanus components are assessed by antibody responses rather than by lethal challenge as required by WHO. For complete compliance with WHO recommendations the following tests should also be carried out on the finished product: identity, adjuvant and preservative contents.

4.5 Considerations for increasing production

Increasing DTP production from the present 12.0 million to 18.00 million doses p.a. will require investment in the following:

1) installation of the two 750L fermenters,
2) purchase and installation of ultrafilters,

3) purchase and installation of new filling line,
4) a 50% increase in the cost of raw materials and other consumables,
5) engagement of extra personnel (50%) to carry out visual inspection of finished product.

Annex 9

DIPHTHERIA TOXOID/FLOW CHART OF PRODUCTION AND QUALITY CONTROL

PROCESS-STAGE	TESTS CARRIED OUT IN			
	CUBA	MEXICO	VENEZUELA	WHO RECOMMENDED
INOCULUM	Purity	Purity Lf	Smear/microsc.	Adjuvant content
MEDIUM	Sterility	Visual inspect. Iron content pH	Visual inspect.	Free formaldehyde content
CULTIVATION	Purity Lf pH	Purity Lf	Visual inspect. -	Identity Innocuity
SINGLE HARVEST	Purity Lf pH	Purity Lf pH	- Lf	Irreversibility pH
FILTRATION	Lf Sterility MLD	Lf Sterility	-	Potency Preservative content
DETOXIFICATION	Lf Spec. toxicity pH Sterility	Lf Spec. toxicity	- Spec. toxicity	Specific toxicity Sterility
PURIFICATION CONCENTRATION FILTER STERILIS.	Lf Purity (NDN) Sterility	Lf Purity (NDN) Sterility pH	- - Sterility	
BULK PURIFIED TOXOID (ready for blending)	Lf - Thiomersal Toxicity Sterility Irreversibility - Purity (NDN) - - Free formaldehyde	Lf pH Thiomersal Toxicity Sterility - - - - - Free formaldehyde Sulphur cont. Chloride	Lf - - - Sterility - Potency* Purity - Innocuity	

* antibody

PERTUSSIS/FLOW CHART OF PRODUCTION AND QUALITY CONTROL

PROCESS-STAGE	TESTS CARRIED OUT IN			
	CUBA	MEXICO	VENEZUELA	WHO RECOMMENDED
INOCULUM	Purity Opacity	Purity Opacity	Purity Opacity pH	Adjuvant content Free formaldehyde (if applicable)
	MEDIUM pH	Sterility pH	- pH	Identity Innocuity pH
SINGLE HARVEST	Purity Opacity	Purity Opacity pH	Purity Opacity pH	Potency Preservative content Specific (mouse) toxicity
INACTIVATION	Sterility Opacity	Sterility Opacity	Sterility Opacity	Sterility
CONCENTRATION	Mouse toxicity - Potency pH	Mouse toxicity - Potency pH	Mouse toxicity - Potency	

TETANUS TOXOID/FLOW CHART OF PRODUCTION AND QUALITY CONTROL

PROCESS-STAGE	TESTS CARRIED OUT IN			
	CUBA	MEXICO	VENEZUELA	WHO RECOMMENDED
INOCULUM	Purity	Purity Identity	Microscopy	Adjuvant content Free formaldehyde content
	MEDIUM pH	Sterility pH	Sterility pH	Identity Innocuity
SINGLE HARVEST	Lf Purity (NDN) - -	Lf - - - pH	Lf - - - Kf pH	Irreversibility pH Potency
DETOXIFICATION	Specific toxicity	Specific toxicity	Specific toxicity	Preservative content
STERILISATION	Sterility Lf	- Lf	- -	Specific toxicity Sterility
PURIFICATION	Lf Purity	Lf -	- -	
STERILISATION	Sterility Specific toxicity	- Specific toxicity	- -	
PURIFIED	-	-	-	
	Lf	-	-	
CONCENTRATED	pH	-	-	
	-	-	Potency*	
BULK	Purity (NDN)	Purity (NDN)	Purity (NDN)	
	-	-	-	
TOXOID	Sterility Specific toxicity Innocuity Thiomersal	Sterility Specific toxicity - not applicable Free formaldehyde	Sterility - Innocuity - Free formaldehyde	

* antibody

PROCESS-STAGE	TESTS CARRIED OUT IN			
	CUBA	MEXICO	VENEZUELA	WHO RECOMMENDED
BULK	Sterility	Sterility	Sterility	
	Potency+	Potency*	-	
TETANUS	-	Innocuity	-	
	Aluminium content	Aluminium content	-	
VACCINE	Preservative content	Preservative content	-	
	pH	pH	pH	
FINAL PRODUCT	Sterility	Sterility	Sterility	
	-	-	-	
	Innocuity	Innocuity	Innocuity	
	Aluminium content	-	Aluminium content	
	Preservative content	-	Preservative content	
	pH	pH	pH	

* antibody response
+ challenge

DIPHTHERIA TOXOID/PRODUCTION

Method of production	Deep-culture
Working volume of fermenter	360L
Toxin yield at harvest	100Lf/ml
Cultivation cycle	2 days
Number of cycles per week	1
Number of cycles per annum	24
Efficiency of recovery	60%
Dipheria toxoid produced in one week at 60% recovery	21.6×10^6 Lf
Doses (25L/dose) in one week (at 10% wastage)	0.75×10^6
Doses (25Lf/dose) in one year (at 10% wastage)	18.0×10^6

TETANUS TOXOID/PRODUCTION

Method of Production	Fermenter	Glass bottles
Volume of culture in one week	360L	124L
Cultivation cycle	7 days	7 days
Toxin yield per ml	40Lf	40Lf
Toxin yield per batch	14.4×10^6Lf	4.96×10^6Lf
Number of batches p.a.	22	120
Total Lf produced in 1988	$317.0 \times 10x^6$	595.0×10^6
Total Lf produced in 1988		972.0×10^6
Total number of doses (20Lf/ dose) produced in 1988		21.0×10^6
Toxoid needed for 21×10^6 doses at 20Lf/dose		420×10^6Lf
Efficacy of toxoid recovery		45.5%

TETANUS TOXOID PRODUCTION

Method of production	Fermenter
Working volume of fermenter	600L
Volume of culture	600L
Cultivation cycle	7 days
Number of cycles per annum	28
Total volume of culture per annum	16800L
Toxin yield at harvest	50Lf/ml
Efficacy of recovery	70%
Yield from one batch (cycle) (at 70% recovery)	21.0×10^6 Lf
Number of doses per batch (lot) (at 20Lf/dose and a loss of 10%)	1.0×10^6
Doses (20Lf/dose) per annum	28.0×10^6
Capacity of production (at 20Lf/dose)	10.0×10^6 doses
Capacity of DTP production	18.0×10^6 doses

TESTING OF DIPHTHERIA/PERTUSSIS/TETANUS BULK VACCINE, FINISHED PRODUCT

	TESTS CARRIED OUT IN		
	MEXICO	VENEZUELA	WHO RECOMMENDED
BULK	Aluminium content	-	Aluminium cont.
DPT	Innocuity	-	Inoccuity
VACCINE	Mouse toxicity	-	Mouse toxicity
	-	-	Osmolarity
	pH	pH	pH
	Potency: Diphtheria	-	Potency: Diphteria
	Tetanus	-	Tetanus
	Pertussis	-	Pertussis
	Preservative content	-	Preserv. cont.
	Sterility	Sterility	Sterility
FINISHED PRODUCT	-	-	Identity: Diphteria (Lf)
	-	-	Tetanus (Lf)
	-	-	Pertussis (Aggl.)
	Sterility	Sterility	Sterility
	-	Potency: Diphtheria*	Potency (if not
		Tetanus*	done on bulk)
		Pertussis	
	Inoccuity	Inoccuity	Inoccuity
	-	-	Adjuv. cont.
	-	Preservative content	Preserv. cont.
	pH	pH	pH

* antibody titration

Annex 10

TETANUS TOXOID

Pharmaceutical form Toxoid of Clostridium tetani adsorbed onto aluminium hydroxide. Preserved with merthiolate (0.01%), and presented in 10 x 0.5ml doses in glass vials.

Composition One vaccine dose of 0.5ml contains not less than 20Lf of purified toxoid (ultrafiltration) of Cl.tetani (Harvard strain) adsorbed onto aluminium hydroxide and preserved with merthiolate (0.01%).

Annex 11

BCG VACCINE

Pharmaceutical form Lyophilised live culture of Bacillus Calmette-Guerin (BCG), 5mg of Danish strain 1331 and 7.5mg of sodium glutamate, 50 doses in glass ampoule. Diluent is injectable sodium chloride solution.

Composition One dose of 0.1ml contains not less than 0.1mg lyophilised BCG bacteria (viability in excess of 1×10^6 colony forming units) and 0.15 mg of sodium glutamate.

1. Process description and quality control

This vaccine is produced in an isolated facility.

In the preparation of this vaccine, WHO recommendations are aimed at.

The original seed of BCG, Danish strain 1331, was obtained from Denmark.

For the preparation of master and working seeds, the seed lot system is correctly used. Seed lots are lyophilised and stored at 2-8°C.

The rehydrated working seed is serially propagated on Sauton potato slopes which are used for the inoculation of Sauton liquid medium in conical flasks. These are incubated for 6-7 days followed by harvesting and filtration. Following wet weight determination the culture is homogenised and by the addition of 1.5% solution of sodium glutamate the suspension is adjusted to give 10mg of bacteria per one ml. The culture is stored (2-8°C) pending tests before filling into glass ampoules for lyophilisation.

An inspection of the flow diagram of production processes/quality control tests shows that these are compatible with WHO recommendations for this product.

2. Production capacity, wastage, consistency of production

Maximum capacity is ca. 12.0×10^6 doses per annum. In 1988 a total of 8.0×10^6 doses was produced, with very little wastage (contamination). Consistency of production has been good.

3. Constraints on production

None.

4. Research and development

None.

5. Considerations for increasing production

Production may be increased, if so desired, by 50% without investment in extra staff or equipment.

Annex 12

TYPHOID VACCINE

(This is not an EPI vaccine and therefore it is only dealt with briefly)

Pharmaceutical form Chemically inactivated whole culture of Salmonella typhi type 2 in 10 dose glass vials.

Composition One vaccine dose of 0.5ml contains not less than 1000×10^6 phenol-inactivated cells of S.typhi type 2 in saline-diluted whole culture of the bacteria. Preservative is phenol (0.5%).

Four to five batches of ca. 70L each are produced in submerged cultures p.a. In 1988 2.8×10^6 doses were produced. Production of this vaccine may be readily doubled on demand without any capital expenditure.

Annex 13

TRIVALEN T ORAL (SABIN) POLIOMYELITIS VACCINE

Pharmaceutical form A suspension of live attenuated poliomyelitis virus types 1, 2 and 3 stabilised in magnesium chloride solution in 5 ml glass vials containing 25 doses for oral use.

Composition One dose of 0.2ml contains not less than 10^6 type 1, 10^5 type 2 and $10^{5.5}$ type 3 $TCID_{50}$ of attenuated live (Sabin) polio virus, propagated in primary, monkey kidney, monolayer cell culture, stabilised in a solution of 1M magnesium chloride.

Shelf life Two years at -25°C and up to six months at 2-8°C.

1. Process description and quality control

This product was registered in 1974 and has been manufactured to WHO requirements.

The three types of the vaccine strains of the virus are produced on a time-sharing (campaign) basis in a devoted facility.

The master seed cultures of the three types of the virus (poliovirus type 1 LSC2AB; type 2 P712CH2AB; type 3 Leon 12AB) were obtained from the WHO.

For the preparation of working seeds the seed lot system is used. Prior to the introduction of routine production of the strains the working seed lots were tested and subsequently approved by WHO. These are maintained at -70°C.

For the preparation of seed viruses static monolayers of primary kidney cells of adult Erythracebus patas monkeys are used. The trypsinised kidney cells from four monkeys yield ca. 6.0L of cell suspension which is distributed into 60 bottles and propagated in Eagle's, minimum, essential medium supplemented with antibiotics. Following establishment of monolayers (8 days at 37°C) the cell culture medium is removed and the monolayers inoculated with the seed virus in virus culture medium (medium 199). 25% of monolayers are used for control. The cell/virus cultures and controls are incubated at 33-43°C. The cultures are harvested when ca. 90% of the monolayers are destroyed (3 days post-inoculation).

Virus cell cultures, derived from the kidney cells of each of the monkeys, are pooled and stored pending tests. Following satisfactory tests, harvests of pairs of kidneys are pooled and separation of cell debris is carried out by coarse filtration. Pooled, monovalent bulk is tested before and after filtration whilst stored at -30°C pending on tests.

Following release of the monovalent bulk components of the vaccine these are blended in proportion to give 10^6, 10^5 and $10^{5.5}$ $TCID_{50}$ of types 1, 2 and 3 respectively per 0.2ml of the product. Following testing of the blended bulk vaccine it is released for filling.

An inspection of the flow diagram of production processes and quality control tests shows that these are compatible with WHO recommendations for this product.

2. Production capacity, wastage, consistency of production

Present annual production capacity of this vaccine is ca. 25.0 x 10^6 trivalent doses. Production cycle of a trivalent batch is approximately 15 months (sequential production, six months for type 1; four months for type 2 and 5 months for type 3 respectively). In an average year 200 monkeys are used. Approximately 40%, 15% and 30% of these are used for the production of types 1, 2 and 3 of the virus respectively and the remaining 15% for Q.C. tests.

Until the end of October 1988 ca. 14 million trivalent doses were delivered and delivery of an extra 2-3 million doses may be expected by the end of this year. Since the country's requirement is between 40 and 45 million doses p.a. the difference is imported (25 million doses this year from Smith, Klein-RIT).

Wastage is said to be around 20%. This arises from refusal of some of the kidneys for use on the basis of gross post-mortem observation of carcasses, extraneous viruses, in-process contamination and low virus titres ($10^{7.5}$/ml) at harvest.

The average yield per 1ml of culture fluid is $10^{8.25}$, $10^{7,95}$ and $10^{8.35}$, log 0.15, of types 1, 2 and 3 respectively.

3. Constraints on production

The only significant constraint on production is the availability of monkeys. They are imported from Chad. In the course of the last 15 years supply of these monkeys failed entirely in two years. At other times the requisite number may not be available and delays in delivery also occur. Although other species of monkeys would be suitable for use, their rate of wastage would be higher due to infection with unacceptable viruses.

4. Research and development

There are two lines of R and D work in progress at NIV. One of these is examining the possibility of breeding patas monkeys in captivity and using kidney cells of very young monkeys. Breeding has not been resolved satisfactorily, although early results with the use of monolayers derived from kidneys of very young monkeys show that these yield higher virus titres than those of adult animals.

The second line of research is to assess the value of monkey kidney monolayers in perfusion chambers. The results have been disappointing on account of neuro-virulence of virus cultures produced this way. This is thought to occur because viruses undergo more than 2-3 cycles of multiplication leading to reversion. Research is severely handicapped by a lack of R and D staff and facilities.

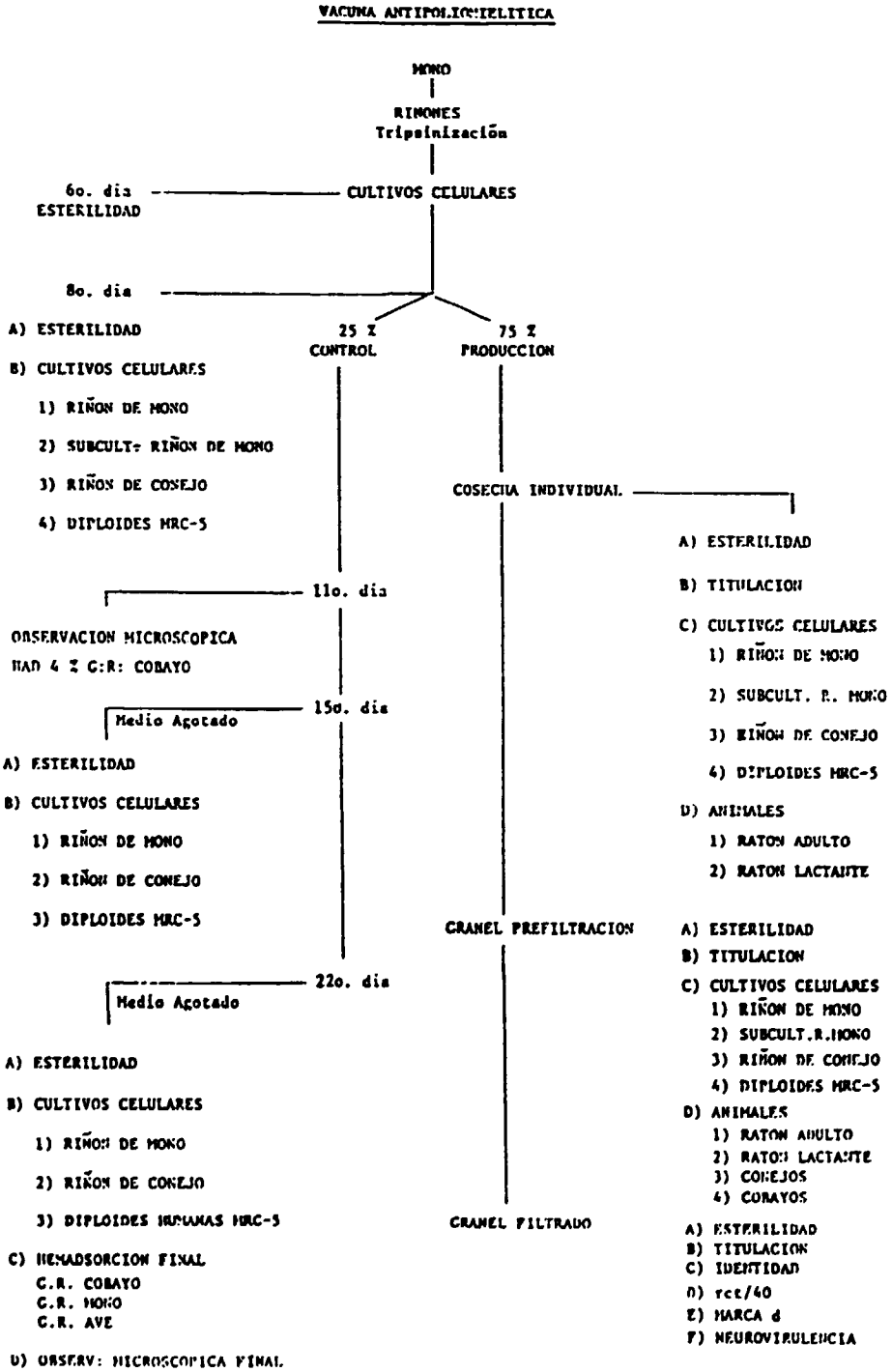
5. Considerations for expanding production

Using existing production technology output of the present unit may be doubled, providing the following requirements are met:

1) availability of twice as many patas monkeys,
2) doubling filling capacity (introduction of one more filling line),

3) trebling labelling capacity,
4) increasing space for visual inspection from ca. $20m^2$ to $60m^2$,
) increasing space for packaging from ca. $75m^2$ to ca. $200m^2$,
6) doubling storage capacity at -30^oC.

It is understood that sufficient lateral extension of the present site may be possible. Should all the aforementioned requirements be met, doubling the present output may be anticipated in 1990/91.



Annex 14

MEASLES VACCINE

Pharmaceutical form Attenuated live virus stabilised in gelatin-sorbitol phosphate and lyophilised in glass vials containing 3 doses. Before use reconstituted with 1.8ml of injectable water.

Composition One dose of 0.5ml contains not less than 10^3 $TCID_{50}$ of the live attenuated Edmonston (Zagreb) virus, propagated in human diploid cells (MRC-5), stabilised in gelatin-sorbitol phosphate buffer and lyophilised.

Dose and route of administration 0.5ml subcutaneously.

Shelf-life One year at 2-8°C (under review: may be extended to two years).

1. Process description and quality control

This product was registered in 1978 and is manufactured to WHO requirements.

The vaccine is produced in a devoted facility.

The original virus seed (Edmonston) was obtained from Zagreb and the human diploid cell line, MRC-5, for virus propagation from England.

For the preparation of master and working seeds the seed lot system was adopted. The virus seed is lyophilised and stored at -70°C and the MRC-5 cells in liquid nitrogen at -196°C.

The MRC-5 cells are thawed out and propagated by serial passage from generation G20 to G26. The cells are harvested and pooled. Following replacement of cell culture medium with virus culture medium, 10% of the cell suspension is used as uninoculated control culture and the remainder is inoculated with working seed virus. The cell/virus suspension is distributed into flat plastic bottles (Nunc, Denmark) for virus propagation of G27 of the MRC-5 cell culture. It takes ca. one month to get to this point. Three harvests are collected usually in days 3, 4 and 5 post-virus inoculation. Each of these harvests is tested and if satisfactory they are pooled and stored (-30°C) pending tests. Following satisfactory tests the cell-virus suspension is clarified by coarse filtration and stored at -30°C pending satisfactory tests before release for formulation, filling and lyophilisation. Virus yield in this system is close to 10^6 $TCID_{50}$/ml.

Inspection of the flow diagram of production processes and quality control tests shows that these are compatible with WHO recommendations for this product.

2. Production capacity, wastage, consistency of production

In 1988 13 million doses of bulk vaccine were prepared from which ca. 5 million doses were filled. The maximum production capacity, without investment, is 20 million doses of bulk vaccine p.a. Wastage is minimal (2/35 filling lost, 5-6%), and consistency of production is of a high order.

3. Constraints on production

The principal constraint is the shortage of freeze-drying capacity. Two lyophilisers, each with its own filling line, are in use, lyophilising ca. 5.0 million doses p.a. corresponding to the national demand for this product. A lesser constraint on production is the quality of imported gelatin and sorbitol which is not always satisfactory.

4. Research and development

Due to a lack of staff and facilities little can be accomplished by the production staff although improvement of the stabiliser for measles vaccine is called for. There are plans for the employment of 4-5 graduates and the same number of technical staff entirely engaged in R and D, relating to existing products. In the course of the EPI programme, coverage with measles vaccine has not been as good as required. This is attributed to the route of administration (subcutaneous injection) requiring skilled staff. Clinical trials have been conducted recently with 60,000 children, administering liquid measles vaccine by inhalation. Serological results are encouraging and vaccines, recalled from the field, are being titrated at the present time. No other collaborative work is in progress between NIV and other outside institutes or organisations.

5. Considerations for expanding production

In order to convert the 20 million doses of bulk measles vaccine into finished product, the following requirements will have to be met:

1) increasing capacity for lyophilisation by a factor of three,
2) expanding deep-freeze capacity,
3) expanding cold storage (2-8 ^{o}C) by 15-20m^{2},
4) employment of extra staff for filling, lyophilisation, visual inspection, labelling and packaging.

One of the two lyophilisers (which is old and outdated) should be replaced.

CONTROL DE VACUNA ANTISARAMPION

DESCONG. CELS. MRC-5

G-20
G-22 ——— MEDIOS AGOTADOS (M.A.)
G-24 ESTERILIDAD
G-26

M.A.
- A.- ESTERILIDAD
- B.- CULTIVOS CEL. DE:
  - RIÑON DE MONO
  - RIÑON DE CONEJO
  - DIPLOIDES MRC-5
  - DIPLOIDES Wi-38

CULTIVOS CONFLUENTES

G-27

S. VIABLES
BIOLOGIA
MORIGENICIDAD
S. NO VIABLES
- ESTERILIDAD
- INOC. EN ANIMALES
  - RATON ADULTO
  - RATON LACTANTE
  - COBAYOS
  - HUEVOS EMBRIONADOS

CULTIVOS CONTROL (10%)

MEDIO AGOTADO — 7 DIAS
- OBSERVACION MACRO Y MICROSCOPICA
- ESTERILIDAD
- INOCULACION EN CULTIVOS CEL. DE:
  - RIÑON DE MONO
  - RIÑON DE CONEJO
  - DIPLOIDES MRC-5
  - DIPLOIDES Wi-38

MEDIO AGOTADO — 15 DIAS
- OBSERVACION MACRO Y MICROSCOPICA
- HEMADSORCION
- INOC. EN CULTIVOS CEL. DE:
  - RIÑON DE MONO
  - RIÑON DE CONEJO
  - DIPLOIDES MRC-5
  - DIPLOIDES Wi-38

CULTIVOS DE PRODUCCION

COSECHAS DE VIRUS VACUNAL — A. ESTERILIDAD, B. POTENCIA

GRANEL
- A. ESTERILIDAD
- B. POTENCIA
- C. CULTIVOS CEL.
  - RIÑON DE MONO
  - RIÑON DE CONEJO
  - DIPLOIDES MRC-5
  - DIPLOIDES Wi-38
- D. INOC. EN ANIMALES
  - RATON ADULTO
  - RATON LACTANTE
  - COBAYO
  - H. EMBRIONADOS

FILTRADO
- A. ESTERILIDAD
- B. POTENCIA

LIOFILIZADO
- A. ESTERILIDAD
- B. IDENTIDAD
- C. POTENCIA
- D. INOCUIDAD
- E. HUMEDAD
- F. ESTABILIDAD

Annex 15

RABIES VACCINE

Pharmaceutical form For human use: ultraviolet-light inactivated rabies virus in 1% suspension of suckling mouse brain tissue in 1ml glass vials containing phenol (0.1%) and merthiolate (0.01%). For canine use: same inactivated virus in 2.5% suckling mouse brain tissue with same preservatives in 20ml (10 doses) glass vials.

Composition For human use: 14 treatment doses of 1ml of 1% suspension of inactivated rabies virus strains (Fuenzalida 57, 97 and CVS) in suckling mouse brain tissue preserved with phenol (0.1%) and thiomersal (0.01%). For canine use: every 2ml dose contains 0.025g of the same inactivated virus in brain tissue containing the same preservatives.

Shelf-life One year at 2-8°C.

1. Process description and quality control

This product was registered in 1974 and is manufactured to WHO requirements.

Rabies vaccine is produced in a devoted facility. The original virus strains (Fuenzalida 51 and 91 - isolated in Chile from dog and human respectively) and CVS were obtained from the Pan American Zoonoses Centre.

For the preparation of master and working seeds the seed lot system is used. A suspension of the master seed is lyophilised and kept at -20°C. The suspension of working seed is stored at -70°C.

The working seed is thawed out and dilutions prepared for the intracerebral inoculation of suckling mice. For the preparation of human vaccine, day old mice, and for the canine vaccine, 3-4 day old mice, are used. The inoculum is also injected intracerebrally into adult mice to determine viability of the virus. Sufficient suckling mice are inoculated to yield between 1.5 and 2.0kg brain tissue per strain of virus. Brain tissues are harvested 3 days post-inoculation and stored at -70°C pending tests. Satisfactory brain tissues are thawed out, homogenized then centrifuged and a 10% suspension prepared and stored pending tests. From a satisfactory 10% suspension a 5% suspension is prepared and irradiated with ultraviolet light. From the irradiated brain tissues dilutions are made, a 1% dilution for human and 2.5% dilution for use in dogs. To suspensions of bulk vaccines preservatives are added (phenol 0.1%, thiomersal 0.01%) and stored (2-8°C) pending tests. Satisfactory bulk vaccine is released for filling.

Inspection of the flow diagrams of production processes and quality control tests show that these are compatible with WHO recommendations for this product.

2. Production capacity, wastage, consistency of production

The 1988 production of 150,000 human treatment doses (14 treatment doses/vial) and 2.1 million canine doses are commensurate with production capacity.

There is little wastage in rabies vaccine production. On average one of sixteen lots (6.25%) is lost due to contamination and an additional 2.5% loss is due to the presence of live virus in the bulk vaccine, a total of ca. 9%.

Considering virus yield of the various lots of brain tissues, the variation between the lots is in the region of ± 10%.

3. Constraints on production

There is a respiratory problem in one of the two breeding colonies of mice, supplying suckling mice for virus propagation. Replacement of this colony is likely to cause serious loss of production.

4. Research and development

Under consideration is the development of virus production in Vero-cells. Since purchase of the patented virus is deemed to be too expensive development of a local strain is contemplated. This type of R & D work will mean employment of additional staff as well as capital investment.

5. Consideration for expanding production

Since present production capacity is sufficient to meet domestic demand, expansion of production, using the present production technology, is not contemplated. Any surplus product in the past had been exported to Central American countries via PAHO.

Annex 16

Cursos internos, externos y seminarios (1983 - 1988)

Actividades	1983	1984	1985	1986	1987	1988	Total
Cursos internos (promedio 6 h)	2	28	8	11	16	19	84
Núm. de personas	-	236	81	415	391	500	1.623
Núm. de horas capacitando	-	39.648	3.888	27.390	37.536	57.000	798.516
Cursos externos	-	22	4	25	42	28	121
Núm. de personas	-	58	11	51	211	220	551
Seminarios	15	31	14	23	28	14	125
Núm. de ponencias	-	31	14	23	28	47	143

Annex 17

DIPHTHERIA-TETANUS-PERTUSSIS (DPT) VACCINE

Pharmaceutical form Inactivated cells of Bordetella pertussis combined with toxoids of Corynebacterium diphtheriae and Clostridium tetani adsorbed onto aluminium hydroxide, preserved with merthiolate (0.01%) in 10-dose glass vials.

Composition One vaccine dose of 0.5ml contains not less than 15Lf of ammonium sulphate precipitated and purified toxoid of C.diphtheria (PW-8) combined with 16 NIH-UO of heat-inactivated cells of B.pertussis (strains 134 and 165) and 10Lf of purified (ammonium sulphate) toxoid of Cl.tetani (Harvard) adsorbed on aluminium hydroxide gel and preserved with merthiolate (0.01%).

1. Diphtheria toxoid component

1.1 Process description and quality control

In the preparation of this product NIH (USA) requirements are aimed at.

The production strain, PW-8, was obtained from PAHO and the seed lot system is used. Master and working seed lots are lyophilised and stored at 2-8°C.

Forty-five litres of Mueller-Miller medium is distributed into 100 conical flasks, inoculated with the production strain and incubated statically (34°C) for 8 days. Following visual inspection their contents are pooled, and cells are sedimented by the addition of filter aids. The supernatant is drawn off and filtered before 0.65% formalin is added (pH 7.2), then filtered again (0.22u). It is held at room temperature for 8 days, pH adjusted (pH 7.2) and incubated at 36°C for 6 weeks. Crude toxoid is stored at 2-8°C till 12-13 batches are available to form a pool of ca. 600L crude toxoid for purification. Following concentration by ultrafiltration, toxoid is precipated with ammonium sulphate, dialysed, diluted (3200Lf/ml), filter sterilised and stored (2-8°C) pending tests.

An inspection of the flow diagram of production processes and quality control tests shows that testing of this product is inadequate at every stage of production.

1.2 Production capacity, wastage, consistency of production

Maximum production capacity is ca. 4.5×10^6 doses p.a. In 1988 twenty-four batches (960L) were produced yielding 4.0×10^6 doses at 15Lf/dose. Losses included contamination (5-6%), harvesting/detoxification/purification (30%). The Lf value of the 24 batches ranged between 70 and 125Lf/ml.

1.3 Constraints on production

Lack of consistency of medium, shortage of culture bottles, inadequate supply of distilled water and malfunctioning of autoclave.

1.4 Research and development

Delivery of a 450L fermenter is expected in the early months of 1989. Development of deep culture technology for diphtheria toxin production is planned for 1989.

1.5 Considerations for increasing production

With the use of deep culture technology the production of 20.0×10^6 doses of diphtheria toxoid is aimed at. As yet no consideration has been given to commensurate downstream processing capacity which will require proportionately greater capacity processing equipment.

2. Pertussis component

2.1 Process description and quality control

In the preparation of this product NIH (USA) requirements were aimed at.

The production strains, B.pertussis, strain 134 (agglutinogens 1, 3 and 7) and strain 165 (agglutinogens not available) were obtained from the NIH (USA) and the seed lot system is correctly used. The cultures are lyophilised and stored at 2-8°C.

A production batch consists of 4 x 25L of culture in aerated Cohen and Wheeler medium in 50L glass jars. Following incubation (48 hr, 37°C, yield 35-40 IOU), the cells are precipitated with citric acid (pH 3.8-4.0) overnight at room temperature. The supernatant is drawn off and the sedimented cells from the four bottles are pooled, pH adjusted (pH 6.8) and centrifuged. The three litre cells are inactivated by heat (56°C, 0.5 hr), merthiolate added (0.01%) and the cells stored (2-8°C) pending tests.

An inspection of the flow diagram of production processes and quality control tests shows that these are in good agreement with WHO recommendations. For better compliance serological testing of inactivated/concentrated cell suspension prior to blending of two strains should be carried out.

2.2 Production capacity, wastage, consistency of production

The annual production capacity of ca. 4.0×10^6 doses is almost the same as the production of 3.8×10^6 doses in 1988. This originated from 5200L (52 batches) of culture at ca. 70% recovery of cells. Losses occur during concentration (ca. 25%) and filling (ca. 5%). Losses due to either toxicity or lack of potency are rare.

2.3 Constraints on production

Occasional breakdown of services (autoclave, distilled water).

2.4 Research and development

None in progress at present. Development of deep culture technology is planned for 1989.

2.5 Consideration for increasing production

Using a 450L fermenter, employed on a time-sharing basis with diphtheria culture production, manufacture of ca. 20.0×10^6 doses of pertussis component

is planned. This is an unrealistic aspiration on a time-sharing basis since production of that amount of pertussis would require 30 to 40 batches of culture (at 40 IOU) depending on wastage. A significant increase of production will also necessitate pro-rata increases in downstream processing capacity (blending, filling, visual inspection, storage) which in turn will require considerable additional capital investment.

3. Tetanus toxoid component

3.1 Process description and quality control

NIH (USA) requirements are aimed at. Tetanus toxoid is prepared in a devoted facility. This facility does not meet GMP requirements and although some steps are taken to contain the live organism within the facility, these are inadequate (no restriction on entry, no change of clothing, etc.).

The Harvard strain of Cl.tetani was obtained from Boston and for its use the seed lot system is used. Both master and working seed lots are lyophilised and stored at 2-8°C.

A production batch consists of 4 x 40L of culture of gently stirred Mueller-Miller medium in 50L glass bottles.

Following incubation (36°C for 6-7 days) 0.4% formalin is added to the cultures, which are divided into 20L aliquots and incubated (36°C) for four weeks. The supernatants of the toxoided cultures are drawn off, sterilised by sequential filtration; following decontamination of the outsides of the containers, the crude toxoid is transferred from the devoted facility for purification. Seven to eight batches are pooled (1000-1200L), concentrated by ultrafiltration (30-40L) and purified by ammonium sulphate precipitation. Following dialysis and filter sterilisation the purified and concentrated toxoid is stored for blending pending tests.

An inspection of the flow diagram of production processes and quality control tests shows that testing of this product is inadequate at every stage of the process. For example, toxoid is routinely released for purification without a sterility test.

3.2 Production capacity, wastage, consistency of production

Nominal production capacity is said to be over 10.0×10^6 doses p.a. The 1987 production of tetanus toxoid was 4.4×10^6 doses and in 1988 it is likely to be somewhat higher, ca. 5.3×10^6 doses.

Wastage at harvesting (10%), purification (25%) and filling (5%) is lower than average. Consistency of production, judged by the Lf values of harvest cultures (40-55Lf/ml) and purified concentrated toxoid, is good.

3.3 Constraints on production

Shortage of 20L glass bottles and delays with delivery of consumables.

3.4 Research and development

None.

3.5 Considerations for increasing production

Using the present production technology annual production could be increased by a factor of four to ca. 20.0 x 10^6 doses. This would require production of 40 batches instead of 10 currently produced. Such an increase would require careful consideration of downstream processing especially incubation capacity for detoxification. Such an increase is deemed desirable to match the planned increases in the production of diphtheria and pertussis components.

4. Preparation of DTP vaccine

4.1 Process description and quality control

The final bulk of DTP vaccine is prepared by blending sufficient volumes of concentrated diphtheria and tetanus toxoids and inactivated pertussis cells to give 15Lf, 10Lf and 16 NIH units of opacity respectively per 0.5 ml dose. The vaccine components are adsorbed on alhydrogel (Superfos, Denmark) and stored (2-8^{o}C) pending tests before release for filling.

An inspection of quality control tests carried out on the final bulk vaccine and finished product shows that the bulk vaccine is hardly tested at all.

4.5 Considerations for increasing production

Increasing DTP production from the present 4.0 x 10^6 doses p.a. would require investment as follows:-

1. expanding incubation capacity for detoxification of diphtheria and tetanus toxins,
2. purchase and installation of extra blending vessel,
3. engagement of extra personnel,
4. pro-rata increase in the cost of raw materials and other consumables.

In addition a review of the following capacities is also called for:

1. media preparation,
2. supply of distilled water,
3. filling/labelling,
4. visual inspection of finished products.

Annex 18

RABIES VACCINE

Pharmaceutical form For human use: ultraviolet-light inactivated rabies virus in 1% suspension of suckling mouse brain tissue, in 2-dose glass vials with phenol and merthiolate preservatives.

For veterinary use the vaccine contains the same inactivated virus in 2.5% suckling mouse brain tissue, with the same preservatives in 5-dose glass vials.

Composition One human dose of 2ml contains 1% suspension of inactivated rabies virus strains (Fuenzalida 51, 91 and CVS) in suckling mouse brain tissue in 1% glucose solution and preserved with phenol (0.1%) and merthiolate (0.01%).

For veterinary use the 2ml dose contains the same inactivated virus in 2.5% brain tissue in 5% glucose solution and preservatives.

Shelf life One year at 2-8°C.

1. Process description and quality control

This vaccine is produced in a devoted facility which falls far short of basic GMP requirements.

In the preparation of the vaccine WHO recommendations are aimed at.

The original virus strains, Fuenzalida 51, 91 and strain CVS were obtained from the Pan American Zoonoses Centre.

The seed lot system is correctly employed. The master and working seed lots of viruses are propagated in the brains of adult mice and 20% suspensions of infected brain tissue are lyophilised and stored.

The working seed is thawed out and 1/100 dilution is used for the intracerebral inoculation of one and four day old mice for the preparation of human and veterinary vaccines respectively. Four days after inoculation mice are sacrificed, brain tissues are harvested and pooled (one virus is handled at a time) and stored (-70°C) pending tests. Due to a shortage of infant mice 5-11 sub-lots are collected before being pooled to form a lot of ca. 600g tissue. This is homogenised, diluted (30%), centrifuged and the supernatant diluted sequentially to 10% and 5% and is stored at 2-8°C pending tests. Satisfactory brain tissue supernatant is irradiated in 5% suspension and stored (2-8°C) pending tests. Satisfactory suspensions are diluted to 1% in 1% glucose solution for human and to 2.5% in 5% glucose solution for veterinary use. These are stored (2-8°C) awaiting filling.

A discussion of production processes and quality control tests (in the absence of flow diagram) revealed the absence of the following tests:

1. master and working seed lots: extraneous agents, viability, identity,
2. inoculum: identity,
3. 5% suspension prior to inactivation: identity,
4. bulk vaccine: innocuity, sterility, potency (these tests are carried out on the irradiated 5% suspension of brain tissue),
5. filled vaccine: visual inspection, protein, phenol, thiomersal.

Annex 19

ANIMAL PRODUCTION

CENPALAB produces the following conventional (CV) species, lines and strains:

- Outbred mice
  * OF 1

- Inbred mice
  * Balb/cJ
  * A/J
  * AKR/J
  * C57BL/6
  * DBA/2
  * CBA/Ca
  * CBA/J
  * C3H/HeJ

- Hybrid mice (F1)
  * B6D2F1 (C57BL/6 x DBA/2)

- Mutagenic mice
  * nu/nu

- Outbred rats
  * Sprague Dawley
  * Long Evans
  * Wistar

- Inbred rats
  * Fischer (F-344)
  * Lewis
  * SHR (hypertensive)
  * WKY (normotensive)

- Outbred rabbits
  * New Zealand White
  * White Semigiant

- Hybrid rabbits (F1)
  * New Zealand White x White Semigiant

- Outbred Guinea pigs
  * Hartley

- Outbred dogs
  * Beagle

- Outbred Mongolian Gerbils

- South African clawed toad

- Minipigs and Micropigs

- Outbred hamsters
  * Syrian golden

- Non-human primates
  * Rhesus monkey
  * Green monkey
  * Chimpanzee

- Sheep
  * Pelibuey (Cuban)

Annex 20

PRODUCTION OF BIOLOGICALS IN CUBA

The National Centre for Bioproducts (Biocen) is under construction in Havana Province at around 30 km from the capital. The whole Biocen area is 9 hectares, where the following buildings will be erected:

- Bacterial vaccine production plant
- Viral vaccine production plant
- Diagnostic medium production plant
- Culture medium production plant
- Filling and Freeze drying central plant
- Quality control department
- Pilot Plant and research Lab.
- Animal housing
- Warehouse
- Social Administrative building
- Maintenance and Workshop
- A building for electric supply system, compressed air, vacuum etc.
- Laundry
- Theatre - conference room

The total electricity supply is determined by the expected maximum simultaneous load and supplemented with 3 diesel generators of 1000 KVA each. Air conditioning and ventilation systems are designed according to the GMP standards. All climatization facilities in sterile and other risky areas as well as refrigerator installations for cold rooms are duplicated in case of emergency. The same applies to the central steam station, which is provided with 2 boilers of 16 tons/n capacity at 16 ATM. Besides the central water supply system, each production unit will have its own distillator. Provisions of different sorts of gas such as O_2, OO_2, N_2 will be made by gas-bags, located at the required work place.

Annex 21

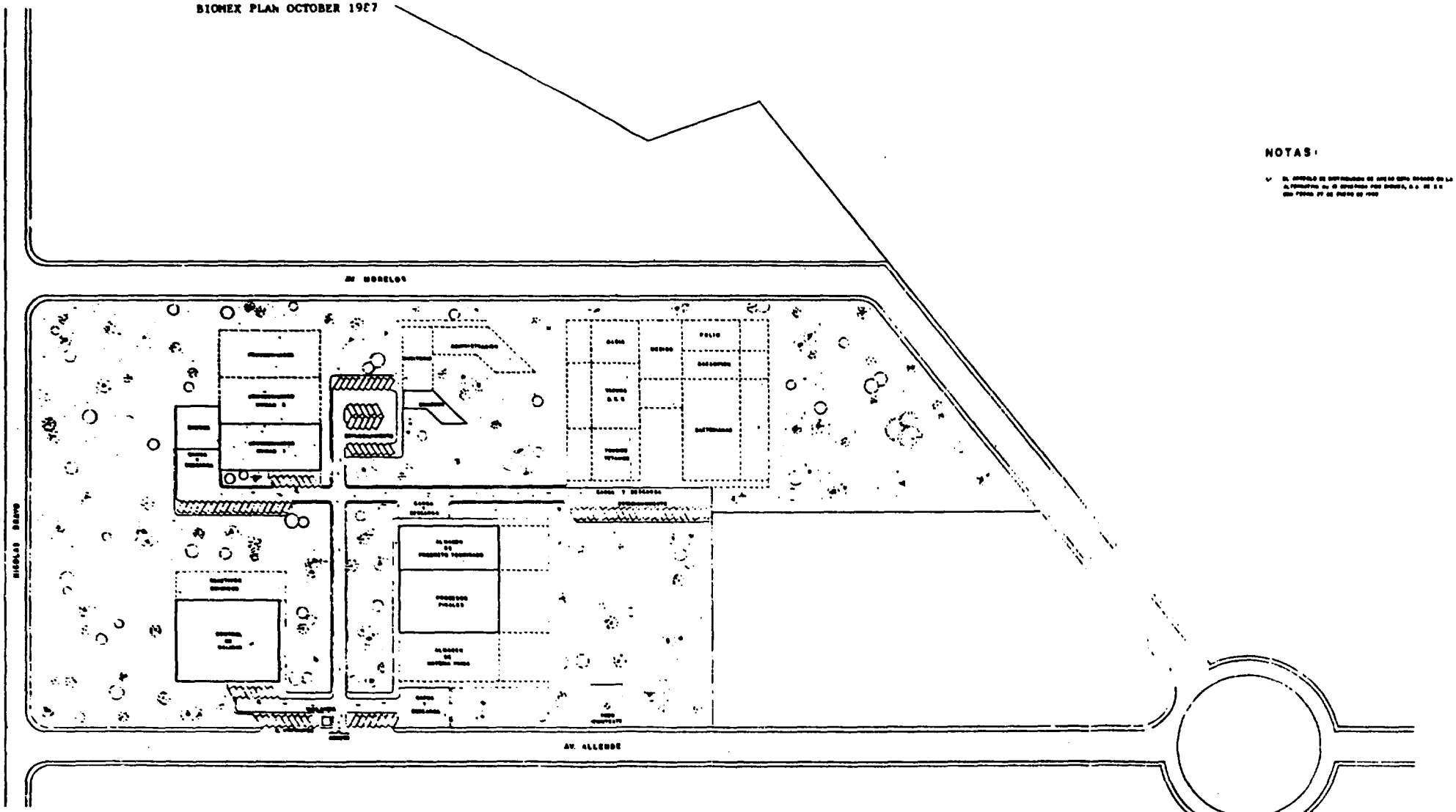
List of principal equipment installed at G.G.B.R. - Mexico

Principal equipo instalado en la Gerencia General de biológicos y reactivos

Equipo	INH	INV	LCR	Of.Cent.	Total
Plantas de emergencia	2	2	1	1	6
Equipo de inyección-extracción de aire	26	21	9	3	59
Calderas	3	3	1	0	7
Subestaciones eléctricas	1	1	0	1	3
Cámaras de congelación	0	4	0	1	5
Cámaras frías	28	24	0	8	60
Cámara fría para fraccionamiento	1	0	0	0	1
Autoclaves y hornos	23	18	3	0	44
Refrigeradores domésticos	15	9	6	5	35
Congeladores de baja temperatura	2	11	0	0	13
Refrigeradores congeladores	10	10	4	32	56
Congeladores Revco	8	15	0	0	23
Liofilizadoras	12	3	0	0	15
Fermentadores	10	0	0	0	10
Potenciómetros	20	15	2	0	37
Microscopios	17	26	3	0	46
Espectrofotómetros y colorímetros	10	8	4	0	22
Equipo purificador de agua	6	5	0	0	11
Gabinetes de flujo laminar	8	12	1	0	21
Llenadoras-taponadoras automáticas	4	2	0	0	6
Engargoladoras automáticas	3	2	1	0	6
Etiquetadoras-codificadoras automáticas	2	3	0	0	5
Lavadoras automáticas de frascos	3	1	0	0	4
Incineradores	2	1	0	0	3

Annex 22

BIOMEX PLAN OCTOBER 1987



NOTAS:

1. [illegible]

APROBADO PARA CONSTRUCCION

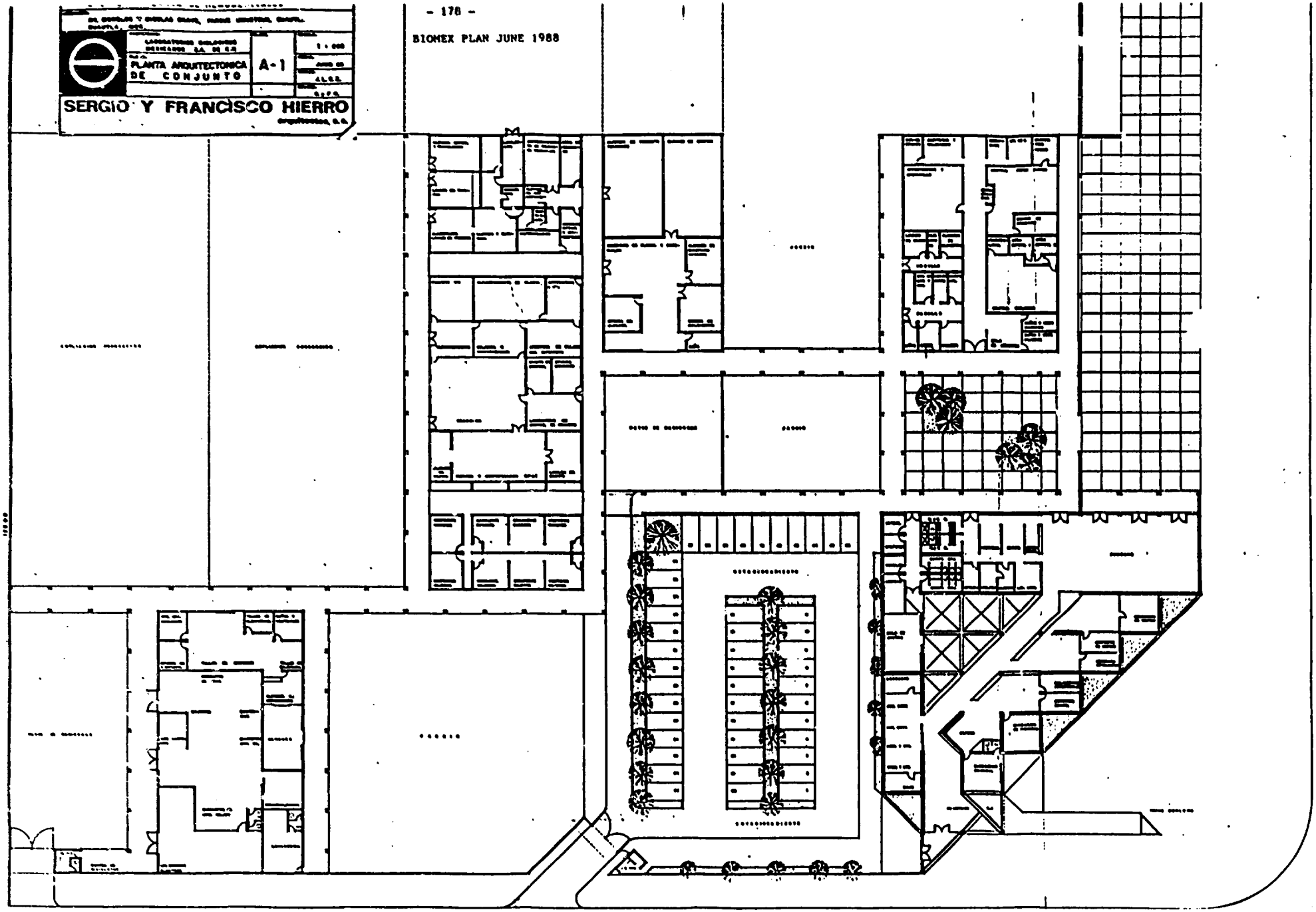
biomex
LABORATORIOS BIOLOGICOS MEXICANOS, S.A. DE C.V.

PROYECTOS MEXICANOS DE INGENIERIA BASICA, S.A.

PLANTA DE BIOLOGICOS Y REACTIVOS

XX-22-01

BIOMEX PLAN JUNE 1988



Annex 23

Final Processes Equipment List N.I.V.

SECRETARIA DE SALUBRIDAD Y ASISTENCIA
Dirección General de Administración
Departamento de Inventarios

RESGUARDO DE ACTIVO FIJO

Dependencia: Instituto Nacional de Virología
Empleo y nombre del responsable: Lab. Procesos Finales, QBP. Alberto Perales
Fecha de cargo inicial: Octubre 15 de 1987

Núm. de control	Artículos a su cuidado	Valor unitario Cargo	Valor unitario Abono	Saldo
P07-221277	Bomba de aire y vacío Mca. Gast Fab Usa. Cat. 211 P5			2.134,00
225364	Bomba de vacío y presión 2,5 CFH 1/6 HP 115 V. 60 C.			2.400,00
08-423241	Engargoladora aut. c/alimentador de retapas transportador de cadena de plástico equipada c/2 motores de 1/4 HP y uno de 1/7 HP de Cap. de 3.000 a 4.000 por hora			59.673,00
F07-599364	Engargoladora Autm. Mca. Talleres de Vecchi Mod. EA-16 p/trabajar retapas tipo antibiótico obteniendo una producción de 3 mil a 48 mil operaciones por hora aproximado c/accesorios			319.396,00
611613	Etiquetadora tipo Epra 01 Máquina etiquetadora Autm. c/transporte lineal trabajando los objetos en posición horizontal p/aplicar una etiqueta de cuerpo. Manuf. alemana c/acc.			1.314.846,53
P08-422856/57	Gabinete de Lám. Cold Roller con plato agitador de acero Inox. patas ajustables p/nivelar el mueble y la altura			36.022,00
P07 254252	Inyector de grasa DEF			280,00
P08-338517/23	Locker c/2 compartimientos c/chapa color gris Mod. 1567			462,00
F07-296090	Máquina Labbelete Etiquetadora Autom; en todos los aditamentos completos			15.500,00

Entregué	Conforme:	Recibí de conformidad:
El encargado del inventario	El Jefe de la Oficina	
Erasmo Ruiz López	C.P. Ma. Soledad Zamora	QBB. Alberto Perales García

SECRETARIA DE SALUBRIDAD Y ASISTENCIA
Dirección General de Administración
Departamento de Inventarios

RESGUARDO DE ACTIVO FIJO

Dependencia: Instituto Nacional de Virología
Empleo y nombre del responsable: Lab. Procesos Finales, QFB. Alberto Perales G.
Fecha de cargo inicial: Octubre 15 de 1987

Núm. de control	Artículos a su cuidado	Valor unitario Cargo	Valor unitario Abono	Saldo
P08-422807	Mesa fregadero 3,27x3,04 m c/cubierta y alambrín c/tarja izquierda en lámina acero con demás accesorios			3.188,25
246958	Perico			184,00
244261	Pinza electricista Klein # 9			199,95
F07-599367	Plato de alimentación gabinete de cold Roller plato giratorio de 70 cm de acero Inox. # 12 c/contraplato de hitto torneado y apoyado sobre beleros			69.610,20
599366	Plato de alimentación o acumulación gabinete de cold Roller plato giratorio de 70 cm de acero Inox. # 12 con contraplato de hietto torneado y apoyado sobre baleros			69.610,20
F08-762261	Ventilador de pedestal Mca. Birtman Mod. PL-16			18.975,00

Entregué:	Conforme:	Recibí de conformidad:
El encargado del inventario	El Jefe de la Oficina	
Erasmo Ruiz López	C.P. Ma. Soledad Zamora	QFB. Alberto Perales García

SECRETARIA DE SALUBRIDAD Y ASISTENCIA
Dirección General de Administración
Departamento de Inventarios

RESGUARDO DE ACTIVO FIJO

Dependencia: Instituto Nacional de Virología
Empleo y nombre del responsable: Lab. de Procesos Finales, QFB. Alberto Perales
Fecha de cargo inicial: Octubre 15 de 1987

Núm. de control	Artículos a su cuidado	Valor unitario Cargo	Valor unitario Abono	Saldo
F07-345140	Módulo de flujo laminar Mca. Veco Mod. MFL-C12 c/filtros HPA y Vecoflow c/una eficiencia del 99,97% Cap. de retención hasta 0,3 micras y mayores			36.950,00
369530/31	Módulo de flujo laminar especial Mca. Veco Mod. MFL-C24 d/2 equipos de filtros Hepa Vecoflow c/una eficiencia del 99,97% y Cap. de retención de partículas hasta 0,3 micras y mayores			72.000,00
633099/100	Máquina engargoladora Autm. Mca. Talleres de Vecchi Mod. EA-16. Este Mod. de máquina está preparado p/trabajar retapas tipo antibiótico, Diám. hasta 55 mm c/acc.			261.912,20
P08-422861	Máquina engargoladora Mca. Talleres de Vecchi Mod. EASA-50 equipada con cabezal tipo antibiótico p/una sola medida y base universal			27.125,00
F07-523239	Máquina etiquetadora Mca. Osea Mod. Nibbio Mignon completamente automática Man. alemana, producción p/envase por hora, motor de HP 60 C. trifásico, acero Inox. c/acc.			880.000,00
P08-422861	Máquina engargoladora Mca. Talleres de Vecchi Mod. EASA-50 equipada c/cabezal tipo antibiótico p/una sola medida y base universal			27.125,00
F07-630710	Máquina taponadora Cozzoli Autm. p/ máquina Cozzoli llenadora Mod. VR-526 943 p/trabajar c/tapones 20 mm de diám.			8.133.375,00

Entregué	Conforme:	Recibí de conformidad:
El encargado del inventario	El Jefe de la Oficina	
Erasmo Ruiz López	C.P. Ma. Soledad Zamora	QFB. Alberto Perales G.

SECRETARIA DE SALUBRIDAD Y ASISTENCIA
Dirección General de Administración
Departamento de Inventarios

RESGUARDO DE ACTIVO FIJO

Dependencia: Instituto Nacional de Virología
Empleo y nombre del responsable: Q.B.P. Alberto Perales G. Procesos Finales
Fecha de cargo inicial: Marzo 8 de 1988

	Artículos a su cuidado	Valor unitario Cargo	Valor unitario Abono	Saldo
1 Jgo.	Desarmadores planos de 1/4 a 7/8			39.103,00
1 "	Llaves españolas de 1/8 a 3/4 Std.			45.486,00
1 "	Llaves de estría de 1/8 a 3/4 Std.			75.715,00
1 Pza.	Pinza de presión de 3/8 a 2/8			34.737,00
1 "	Martillo de bola mediano			10.609,00
1 "	Perico # 12			33.665,00
1 "	Perico # 10			23.016,00
1 "	Piedra esmeril			11.846,00
24 "	Cascos de protección			35.880,00
1 "	Máquina etiquetadora Mca. Puttini, Mod. Rotatichet 1C/P1 para una velocidad de 4.000 pzas. por hora, con edificador para trabajar Fco. Vial con diám. 1,5x28 cm			23.361.539,00
2 "	Tamaños adicionales de envase			6.491.240,00
1 "	Teléfono Interfón # 586 Indetel de color marfil			
2 "	Tijeras de barrilito			14.856,00

Entregué	Conforme:	Recibí de conformidad:
El encargado del inventario	El Jefe de la Oficina	
C. Erasmo Ruiz L.	C.P. Ma:. Soledad Zamora	I.B.2. Alberto Perales G.

Annex 24

Fermentation Area Equipment List N.I.H.

Gerencia General de Biológicos y Reactivos
Instituto Nacional de Higiene
Departamento de Vacunas Bacterianas

Laboratorio de Fermentaciones

Equipo	Marca	Modelo	Capacidad	Antigüedad	Servicios	Estado	Fallas
Fermentador	Azteca	AZ-1000	1000 lts	1 año	E. Eléctrica Agua aire vapor	En servicio	
Fermentador	Azteca	AZ-750-1	750 lts	5 años	E. Eléctrica Agua aire vapor	Fuera de servicio	Sin instalar
Fermentador	Azteca	AZ-750-2	750 lts	5 años	E. Eléctrica Agua aire vapor	Fuera de servicio	Sin instalar
Fermentador	NBS	FM-250	250 lts	8 años	E. Eléctrica Agua vapor aire	En operación	
Fermentador	Marubishi	MF-300	300 lts	18 años	E. Eléctrica Agua aire vapor	En operación	
Fermentador	N.B.S.	IF-70-1	70 lts	8 años	E. Eléctrica vapor aire agua	En operación	
Fermentador	N.B.S.	IF-70-2	70 lts	8 años	E. Eléctrica vapor agua aire	En operación	
Fermentador	N.B.S.	IF-70-3	70 lts	8 años	E. Eléctrica aire agua vapor	Fuera de servicio	No se tiene mecánico
Tanque mezclador	Lightnin	NS-3VM	420 lts	3 años	E. Eléctrica	En operación	
Labroferm	N.B.S.	FS-314	33 lts 3 x 14 l	10 años	E. Eléctrica Agua aire	En operación	

Equipo	Marca	Modelo	Capacidad	Antigüedad	Servicios	Estado	Fallas
Filtro prensa	Seitz Original	1690	40x40 cm	16 años	E. Eléctrica	En operación	
Vibro fermentador	Nacional	Sin modelo	150 lts	2 años	E. Eléctrica vapor aire agua	Fuera de servicio	Sin instalar
Centrífuga	Damon/iec Division	B-20 A	1,5 lts	3 años	E. Eléctrica	En operación	
Centrífuga refrigerada	Damon/iec Division	DPR-6000	6 lts vol. operación 6000 RPM max.	2 años	E. Eléctrica	En operación	
Horno esterilizador	Hot Pack	Sepermatic Oven Z1 2032	0^{o} a $400^{o}C$ 100x80x60 cm	8 años	Energía Eléctrica	En operación	
Liofilizadora	NBS	B-63	20 entradas IHP para botellas (1 l)	8 años	Energía Eléctrica	En servicio	
Agitadora incubadora	NBS	G-25	15 matraces de 500 ml	8 años	Energía Eléctrica	Fuera de servicio	Quemado el motor ventilador
Labroferm	NBS	CFS-314	33 lts 3x14 l	12 años	Energía Eléctrica	En operación	
Agitadora	NBS	G-53	77 garrafones 4 l	12 años	Energía Eléctrica	En operación	
Autoclave AMSCO	AMSCO	UME3648C	0,336 m^3	5 años	Energía Eléctrica vapor	En operación	
Horno esterilizador	Sin marca	Sin modelo	0,216 m^3	3 años	Energía Eléctrica	En operación	
Agitadora incubadora	NBS	G-25	15 matraces 500 ml	8 años	Electricidad	En operación	

Equipo	Marca	Modelo	Capacidad	Antigüedad	Servicios	Estado	Fallas
Agitadora incubadora	NBS	R-25	15 matraces de 500 ml	8 años	Electricidad	En operación	
Agitadora	NBS	G-53	77 garrafones de 4 lts	8 años	Electricidad	Sin instalar	
Agitadora	NBS	G-53	77 garrafones de 4 lts	8 años	Electricidad	Sin instalar	
Tanque mezclador	Azteca	AZV-200	200 lts	3 años	E. Eléctrica Agua aire vapor	Fuera de servicio	No instalado
Potenciómetro o medidor de pH	Beckman	3500 digital	Rango 0-14 pH	9 años	Energía Eléctrica	Fuera de servicio	No da ajuste la lectura es inestable
Potenciómetro	Beckman	Zeromatic SS-3	0.-14 pH	13 años	Energía Eléctrica	En operación	
Placa calefactora	Corning	PC-35 1	20x15 cm	6 años	Energía Eléctrica	Fuera de servicio	Motor de agitación quemado

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Laboratorio de Fermentaciones

Equipo	Marca	Modelo	Capacidad	Antigüedad	Estado	Fallas
Compresora de aire	ITSA	1288014	20 HP 80 ft^3/min	8 años	En servicio	
Compresora de aire	Atlas Copco	BT-3	20 HP 5,1 m^3/min	8 años	En servicio	
Cuarto estufa			26,91 m^3	8 años	Fuera de operación	Falta control de temperatura
Cámara fría (4-8°C) C-20	Gilvert Copeland	A-200	26,89 m^3	8 años	En servicio	

Annex 25

Final Processes Equipment List N.I.H.

Procesos finales

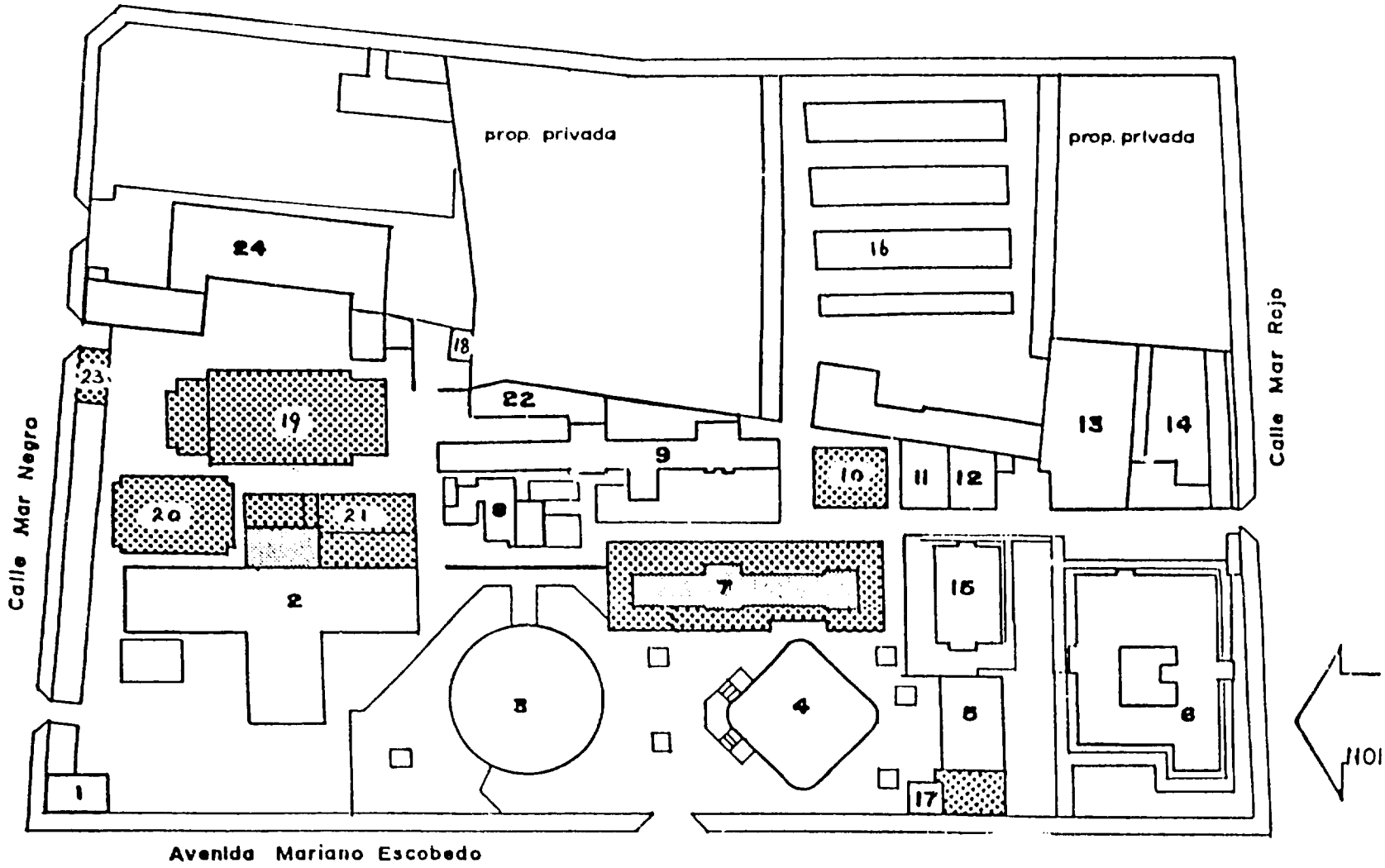
Nº	Equipo	Marca	Modelo	Capacidad	Antigüedad	Estado
	Autoclave	FEHLMEX (3)		3 m^3	6 años	
1	"	AMSCO (4)		5 m^3	15 años	Bueno
2	"	AMSCO (5)		1,7 m^3	6 años	Bueno
	"	AMSCO (6)		1,7 m^3	6 años	Bueno
	"	WILMOUT-CASTLE (1)		0,5 m^3	25 años	Bueno
	"	" " (2)		0,5 m^3	25 años	Bueno
	Horno eléctrico	CAISA	E-242-T	1,2 m^3	15 años	Bueno
	" "	CAISA	E-742-T	1,0 m^3	12 años	Fuera de servicio
	" "	VECCO	HE-2,80	1,5 m^3	12 años	Fuera de servicio
	" "	VECCO	HE-2,80	1,5 m^3	12 años	Fuera de servicio
	Estufa eléctrica			0,6 m^3	15 años	Fuera de servicio
	" "	FELISA (Mezclas)		0,6 m^3	15 años	Fuera de servicio
	Marmita	WANDERER			12 años	Fuera de servicio
	"	W. MAYER			12 años	Fuera de servicio
	"	THERMO	F-60 T		12 años	Fuera de servicio
13	Tanque mezclador	GARZAM (Mezclas)		450 lt	12 años	Regular
11	" "	"		450 lt	12 años	Regular
10	" "	"		450 lt	12 años	Regular

Nº	Equipo	Marca	Modelo	Capacidad	Antigüedad	Estado
8	Tanque mezclador	GARZAM		450 lt	12 años	Regular
2	" " (hidróxido)	"		350 lt	12 años	Regular
	Flujo laminar	VECCO	SHFL-A18	1,4 m^2	12 años	Bueno
	" "	"	SHFL-A18	1,4 m^2	12 años	Bueno
	" "	Air California		4,0 m^2	12 años	Bueno
	" "	Air California		4,0 m^2	12 años	Bueno
	" "	VECCO		1,4 m^2	12 años	Bueno
	" "	VECCO		1,4 m^2	12 años	Bueno
	Cámara fría (21) (Acond)	Gilvert-Copeland	A-300	3 HP (4x6x2)	10 años	Bueno
	" " (22) "	" " 4-8°C	A-200	2 HP (3x3x2)	10 años	Bueno
	" " (23) "	" " "	A-200	3 HP (3x3x2)	10 años	Bueno
	" " (24) "	" " "	A-150	1,5 HP (3x3x2)	10 años	Bueno
	" " (25) "	" " "	A-150	1,5 HP (3x3x2)	10 años	
41	Llenadora	BREWER	60453	1800 frascos/hora	15 años	Regular
42	"	"	60453	1800 frascos/hora	15 años	Regular
43	"	MAPISA	V-6	1800 frascos/hora	15 años	Regular
44	"	"	V-6	1800 frascos/hora	15 años	Regular
45	"	BREWER	60453	Fuera de servicio		Falta refactiones
46	"	COZZOLI				Funcionando
47	"	COZZOLI	FSU30			Funcionando
48	Lavadora de frasco	ROTA		750 frascos/hora	20 años	Funcionando
49	" "	MARXINFARMA	LV-715000	2500-3000 frascos/hora	6 años	Bueno

Nº	Equipo	Marca	Modelo	Capacidad	Antigüedad	Estado
50	Lavadora de tapones hule	BENDIX	2FD	Fuera de servicio		Falta refactiones
51	" " " "		2FD	Fuera de servicio		Falta refactiones
52	Etiquetadora	EMPAC (Acon)		Fuera de servicio	2 años	Bueno
53	Loteadora	EMPAC "	Stampee	1800 etiq./hora	2 años	Bueno
54	Engargoladora	VECCHI "	EA-16	900 frascos/hora	15 años	Bueno
55	"	" "	EA-50	900 frascos/hora	15 años	Bueno
56	"	" "	EA-50			No se usa
57	"	" "	EA-50			
58	"	" "				
59	Bomba de vacío	GELMAN (Mezclas)		50 litros/min	2 años	Bueno
60	" "	MILLIPORE "	YYSS-00000	50 litros/min		Bueno
61	" "	FELISA "	1400	50 litros/min	2 años	Bueno
	Refrigerador	MABE 4-8°C	RGAP 808	No se encuentra		
	"	TOLEDO 4-8°C	RC-700-C	3/4 HP (2x1,5x1,5)		Bueno
	Cámara fría (1) mezclas	COPELAND 4-8°C	300-TSR	3 HP (4x4x2)	20 años	Bueno
	" " (2) acond.	GILVERT 4-8°C	BA-500	5 HP (4x4x2)	20 años	Bueno
	" " (8) "	GILVERT-COPELAND	A-300	3 HP (4x4x2)	15 años	Bueno
	" " (18) "	GILVERT-COPELAND	A-500-18	5 HP (4x4x2)	1 año	Bueno
	" " (19) "	GILVERT	GA-500	5 HP (4x4x2)	14 años	Bueno
	Campana extrac. gases	VECCO				Bueno
	Llenadora	BREWER	60453	1800 frascos/hora		Bueno

Annex 26

PLAN OF N.I.H. MEXICO

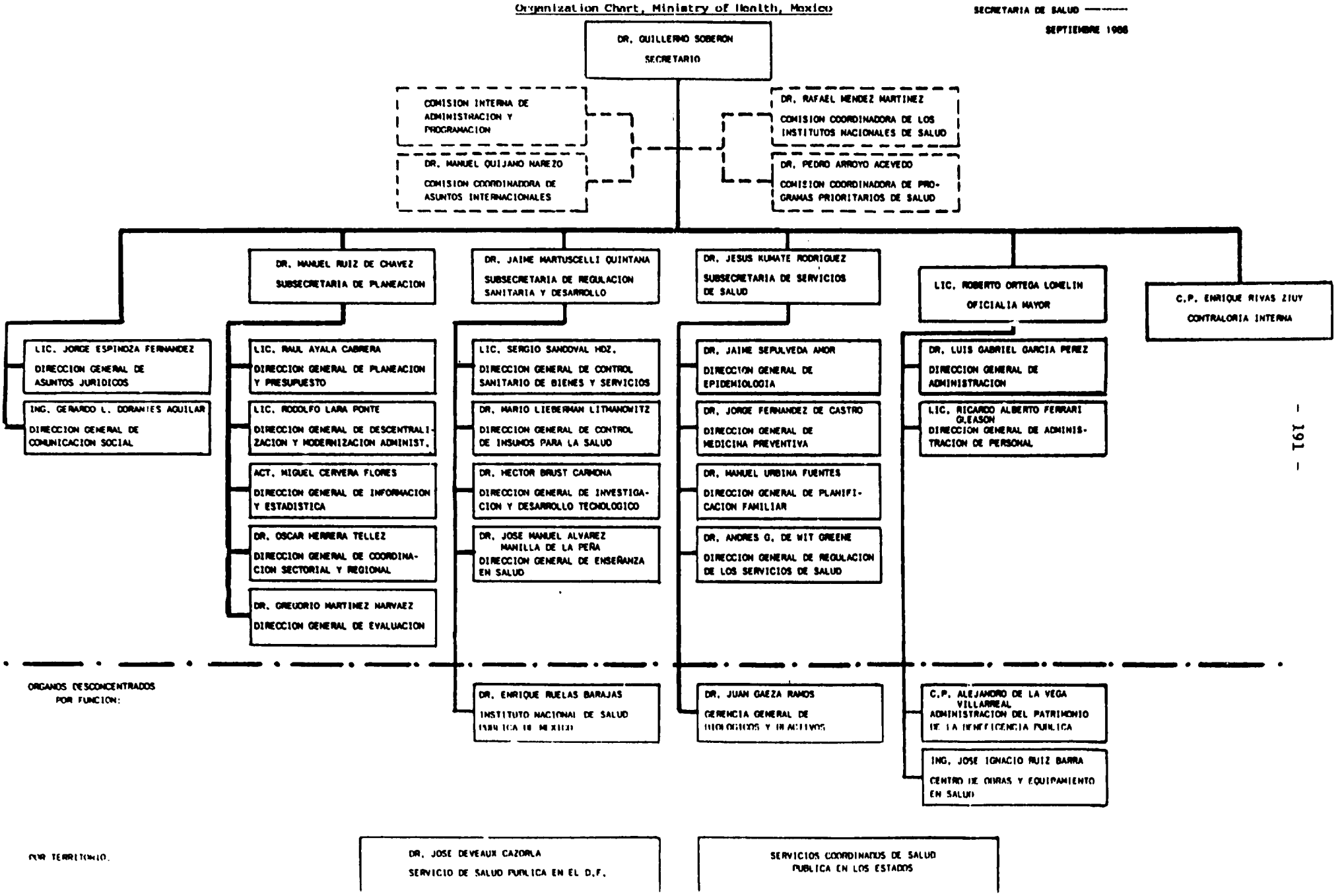


Secretaría de Salubridad y Asistencia Dirección Gral. de Producción de Biolog. y R. Inst. Nal. de Higiene	**PLANTA DE CONJUNTO** **INSTITUTO NACIONAL DE HIGIENE**
Dr. Jorge Fdez. de Castro Director Gral. de P.B y R	Dr. Hector Villalva P. Director del I.N.H.
Dib. J. Ramirez G.	Mayo / 1979

1._ Portería
2._ Laboratorios y Oficinas
3._ Lab de Hemoderivados
4._ Auditorio
5._ Lab de Anaerobios
6._ Lab. Produc. de vacuna BCG
7._ Oficinas y cafetería
8._ Caldera y dest de agua y planta eléctrica y subestación
9 Bioterio
10._ Lab. pruebas de Pirógenos
11._ Tanques de combustible
12._ Caldera
13._ Mantenimiento
14._ Corrales
15._ Bioterio
16._ Area de Caballerizas
17._ Of. sindical
18._ Incinerador
19._ Lab. [illegible]
20._ Lab. de fermentac
21._ Serpentarios
22._ Bioterio
23._ Caseta de control cuarto de bomba
24._ Almacen

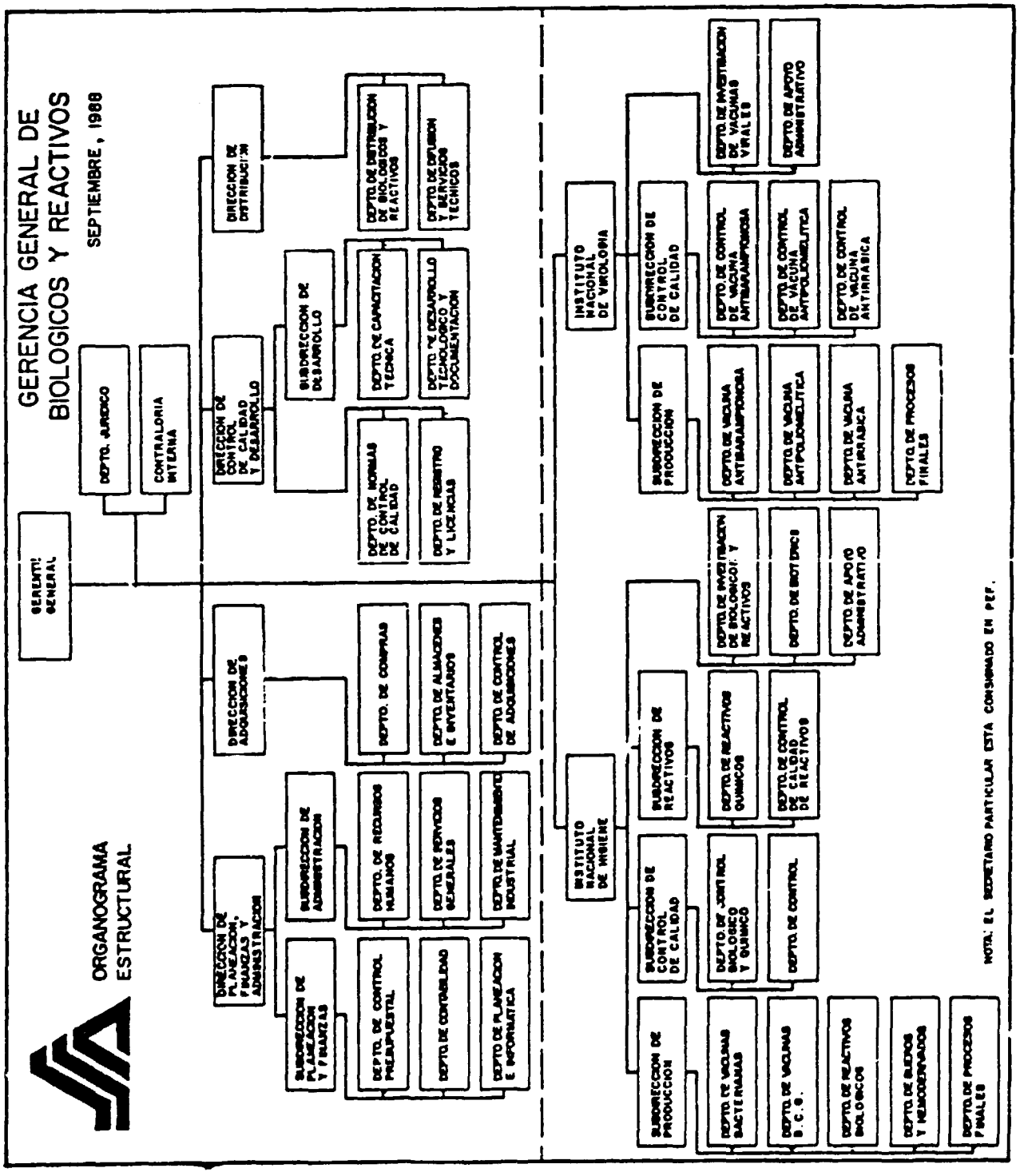
Annex 27

Organization Chart, Ministry of Health, Mexico



Annex 28

ORGANISATION CHART G.G.B.P. Mexico



Annex 29

SIGNIFICANCE OF DIFFERENT FORMS OF MAINTENANCE

The objectives of maintenance are:

To extend the useful life of equipment. This is particularly important where there is a lack of capital.

To ensure the optimum availability of installed equipment for production.

To ensure instant operational readiness of all equipment for emergency use.

To ensure the safety of personnel.

The first two objectives must obviously lead to a reduction in production costs. The maintenance problems requiring solutions are not primarily engineering or technical.

Of the various approaches and techniques employed to ensure adequate maintenance, the first and most important is maintenance prevention which starts at the design and purchase stages.

Maintenance that is not eliminated by maintenance prevention must be planned. Several approaches and techniques can be used: in-house preventive maintenance, corrective maintenance, predictive maintenance, etc.

Maintenance problems cannot be solved by concentrating solely on technical services, such as enlarging and improving repair facilities and training skilled labour, to the exclusion of other approaches. Such practices, particularly when maintenance management and organization are neglected, will lead only to an uneconomic use of capital and skill.

Long-term planning is as important as short-term planning as a means of overcoming maintenance difficulties and of avoiding emergency repairs. Maintenance planning ought to include maintenance prevention, preventive maintenance and predictive maintenance. The main concept of maintenance prevention is to eliminate maintenance work as much as possible and thus to reduce the strain on the two scarcest resources, skill and capital.

Preventive maintenance must receive increasing attention.

It is essential to understand the functioning of production equipment under local conditions and also the physical changes that take place in equipment and that lead, sooner or later, to the need for repair or replacement. The countries in question should purchase production equipment suitable for operation under local conditions. It is, therefore, important to build up experience and data that will help in the assessment of equipment functioning. In this connection predictive maintenance is a very powerful tool. Where the procurement of spare parts takes a long time, the failure of expensive parts should be anticipated long before it actually occurs so that replacements will be available when needed. Predictive maintenance helps the operator to avoid storing a greater number of expensive parts than necessary.

The question was raised as to which of the various maintenance techniques are the most suitable. Since conditions differ from country to country, the extent to which these various techniques will be used will differ even from one producer to another; all techniques, however, should be used as part of general maintenance planning. They support each other and are interdependent. The local personnel should be trained to understand the purpose, benefits and costs of each technique so that the optimum combination of techniques may be achieved.

To plan and implement the various maintenance techniques, adequate data and technical information must be supplied by the manufacturer. The present flow of such information is considerably below the required level. A flow of information from user to supplier on the performance of equipment under local conditions is also important. To maintain such a flow, local technical ability must be developed and experience and knowledge of the performance of equipment under local condition amassed. Such performance data transmitted to the manufacturers should enable them to improve equipment design and should help the users to formulate better specifications when they order equipment.

Although maintenance offers tremendous possibilities for savings in money and manpower, managers, engineers and scientists, oddly enough, are not greatly interested in this field. Managers are generally more concerned with production efficiency, sales engineers with design, and scientists with innovations.

Irrespective of the size and type of the enterprise, the management of maintenance can make all the difference between profit and loss. Proper management of maintenance activities is thus as important as the proper management of production. A maintenance and repair organization must be systematically planned and developed: it should not be allowed just to happen.

Considerable effort is usually expended hiring and training skilled labour and technicians and purchasing the equipment and tools necessary for maintenance. It is thus important to ensure that:

the time of such personnel is not wasted and that capital is effectively employed,

the labour force and equipment are adequate to cope with the maintenance and repair required to keep production equipment in operation and that they are used effectively; on the other hand, the enterprise should not overburden itself with superfluous labour and equipment, which would mean extra cost and less profit,

maintenance and repair work carried out is truly essential and planned for,

an adequate stock of spare parts is stored and a system established so that parts are transferred to where they are needed and the stock is replenished when necessary.

The planning, organizing, follow-up and control are the tasks of maintenance management.

Management responsibility should cover long-term planning and day-to-day work. Procedures on how to handle everyday problems should be well established, with authority and responsibility defined and those assigned to handle these tasks trained and qualified for them. Action should not be left to individual initiative or to procedures that are not co-ordinated.

Follow-up, inspection and cost control are three very powerful management tools. They help planning and provide data for improvement of maintenance performance. Maintenance usually becomes effective only after a long period of review in which improvements are achieved through data feedback. Flexibility, adaptability and a good follow-up system are necessary for efficient management and successful maintenance.

Many factors affect the choice of maintenance organization for each enterprise, such as the size of plant, availability of skills, etc. However, before an effective maintenance and repair organization can be established, top management must recognize the vital need for such an organization and understand its aims and objectives.

Preventive Maintenance

Few preventive maintenance programmes have been established in South American countries because the economic benefits of preventive maintenance are not well understood. These benefits include:

Avoidance of losses caused by unforeseen interruption in production or stoppage of equipment. The most important of these is the loss incurred by failure to meet stipulated delivery dates and the consequent loss of sales and profits.

Avoidance of cost of idle machine operators and valuable equipment.

More efficient organization of repair work, which results in better repair work and longer machine working time between repairs.

Lower consumption of spare parts and hence less drain on financial resources, particularly foreign currency.

The introduction of a programme of preventive maintenance should be preceded by a compilation of records on failures, down-time and cost of interruption of work and its effect on other machines. This information should be compiled for every machine. When these data are available, a preventive maintenance programme can be properly established.

Maintenance Organization and Planning

Only through an adequate maintenance organization and planning can maintenance requirements be met efficiently and economically. In the countries visited deficiencies in repair and maintenance arise more from lack of proper management than from lack of technical expertise.

With proper organization and management, not only will the volume of maintenance and repair work and spare parts consumption be materially reduced, but also it will be spread more evenly over the whole year, and peak loads avoided. Thus, the enterprise will be able to build up a maintenance force to cope increasingly with an average load rather than with peak loads. Unexpected stoppages will be greatly reduced.

No single pattern of organization can be recommended for all enterprises. The way maintenance is organized will vary from country to country, and even from enterprise to enterprise within an industrial sector. It is essential to give much thought to the choice of the organizational pattern most suitable for each enterprise. Over-organization can be as harmful as under-organization, since it may also increase the over-all cost of production.

Practical and efficient maintenance planning and management can usually be achieved only after several years of continuous planning and improvement based on facts and figures fed back from actual performance.

Contracting for maintenance services is a useful means of coping with peak loads and annual major overhauls and of obtaining specific skills and specialized equipment that individual enterprises cannot afford but it should be based mainly on economic grounds.

Maintenance Planning and Preventive Maintenance

All companies should give special attention to maintenance planning and programmes of preventive maintenance. Only in this way can maintenance problems be dealt with efficiently and economically. Maintenance planning reduces substantially the consumption of spare parts and makes it easier to predict when the major components will need to be changed. Thus it contributes significantly to the solution of the spare parts problem.

There is clearly an economically optimum level of maintenance activity and of equipment availability. Increasing maintenance activity and equipment availability beyond this level will result in a decrease in the net profit of the plant. The determination of this level requires systematic cost control and the availability of detailed technical information.

Experience shows that programmes should be introduced gradually. Starting with an elaborate programme may put a strain on the enterprise both organizationally and financially, and there is even a risk that management may eventually give up the idea of establishing maintenance programmes because of these initial difficulties.