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PROGRAMME AND REQUIREMENTS FOR PRODUCTION OF BIOLOGICALS DEVELOPING COUNTRIES

UC/GLO/84/118

Technical report: The Production of Biologicals in Venezuela*

Prepared for the Government of Venezuela
by the United Nations Industrial Development Organization,
acting as executing agency for the United Nations Development Programme

Based on the work of Aron Jakabos and Lajos Aradi
Experts in Vaccine Production

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EXECUTIVE SUMMARY

The Expanded Programme on Immunization (EPI) is an essential element of the strategy to achieve health for all by the year 2000 with the goal of reducing morbidity and mortality from diphteria, pertussis, tetanus, measles, poliomyelitis and tuberculosis by 1990.

Immunization coverage of infants in the country as a whole is rising. By 1985 about 20 % of infants were fully immunized with BCG, DPT, polio (OPV) or measles vaccines. Raising immunization coverage of the EPI vaccines, to the point where significant reductions in morbidity and mortality can be achieved is the main objective of EPI. The plan of action gives details on the objectives, strategies, and activities to meet the goal of EPI by 1990.

The goal can only be achieved by or before 1990 with the full support of all relevant ministries and with the partnership of international and bilateral organizations.

One of the key elements includes programme acceleration by domestic production of vaccines.

The method used to estimate the vaccine demand for EPI takes the size of target population, the immunization schedule, number of wasted doses, coverage of the target populations, etc. into consideration.

Estimated demand for EPI vaccines in Venezuela per year is as follows:

DPT	3,0 - 3,2	million doses
TT	2,2 - 2,4	million doses
BCG	1,2 - 1,3	million doses
OPV	3,2 - 3,3	million doses
Measles	0,5 - 1,0	million doses
Rabies	0,3 - 0,35	million doses (Human)

At present DPT, TT and rabies vaccines are produced in the INSTITUTO NACIONAL DE HIGIENE "Rafael Rangel" (INH). BCG has been produced in the DIVISION ENFERMEDADES CRONICAS DEPARTAMENTO TUBERCULOSIS Y ENFERMEDADES PULMONARES.

The built in (nominal) capacity of INH meets the present domestic demand. Although the INH is working in a University setting, it has significant production activities and it requires an independent production organization. All aspects of production, such as financial planning, production planning, costing, maintenance, etc. should be carried out as if the unit were an independent company. To stabilize production and to reach the nominal capacity the following action is suggested to be taken:

a) to provide two experts (through UNIDO) (one for management, one for maintenance for 3 months each);
b) to provide the required amounts of raw and auxiliary materials;
c) to develop trained staff with high motivation.

Because the Government policy is aimed at reducing the foreign exchange requirement of the economy and at creating export as "reserved" for national investment, in accordance with Andean Pact principles, it is advisable to increase INH capacity to sell the vaccines to the mentioned countries.

The production in INH could be increased per year up to

DPT	10 - 11	million doses
TT	6 - 7	million doses
rabies	0.5 - 0.6	million doses (Human)

by means of the following steps:

A provision of four international experts (management, maintenance, distribution, technology for 13 months each, total cost is about 350 000 USD);

B acquisition of a few new machines, total cost is 550 000 USD;

C development of trained staff with high motivation;

D providing raw and auxiliary materials, spare-parts and
E good maintenance.

With this vaccine production approximately 950 thousand USD gross income could be earned annualy from export.

For BCG production, one technological expert is needed for three months.

The quality control of vaccines plays a dominant role both in export and domestic use. In addition to ensuring that the quality meets WHO requirement, quality control is important both from the technical and economic aspects of vaccine production.

To start the production for export, a decision should be made in order to establish a multiline plant to produce the required amounts of vaccines in Venezuela to meet the demand of the countries in the region/subregion showing interest in buying them. Otherwise, the question of where to set up this kind of plant remains open in the region.
It has to be added that a significant number of munfacturers in industrialized countries have withdrawn completely or partially from the conventional vaccinefield. The increasing demand and the decreasing number of suppliers causes concern that the availability of vaccines in SELA countries might become critical during the forthcoming years.

One of the alternatives to ensure the availability of vaccines is the expansion of INH. The establishment of a new multiline vaccine production plant can be considered as a second option. There are also strong arguments for the above development from the aspects of promoting industrialization, greater self-sufficiency and self-reliancy and of export economy, because the direct material costs and hard-currency content of other fixed and variable costs are only 25 %.

The few Member States of SELA who took interest in a regional vaccine production at the time of writing this report - are Bolivia, Chile, Cuba, Ecuador, Mexico, Nicaragua, Panama, Venezuela.

Due to the fact that out of these 8 states, Chile, Cuba, Ecuador, Mexico, Venezuela already produce vaccines and the situation might be the same as in Venezuela, it would be advisable to carry out a study about the nominal and real capacities of the vaccine production plants. On the basis of a techno-economic survey, the Member States of SELA will be able to take further interest in the subject.

The total estimated demand of the mentioned countries is:

Total demand of EPI vaccines
in thousand doses

	1990	2000
DPT	15000	17000
TT	5000	6000
BCG	5000	5500
Measles	5000	5000
OPV	15000	15500

Refering to the programme of co-operation between UNIDO and SELA signed on 10 April 1986, SELA officially asked UNIDO Secretariat to carry out an analysis on the present situation of vaccine production in the mentioned region.

The importance of this kind of analysis is underlined by the situation in Venezuela where with a few experts and with a few new machines production could be improved saving and earning 950 000 USD foreign exchange annually.

It has to be mentioned that should a totally new plant be built, and if it should produce annually

DPT	17.0	million doses
TT	6.0	million doses
BCG	5.5	million doses
OPV	15.5	million doses
Measles	5.0	million doses

with a 12.5 million USD investment. This kind of plant has been included in the Governmental plans.
The main parameters of this plant:

A Bacterial vaccine production (BCG, DPT and separate TT plant)

space	450 m^2
equipment	1.5 million USD
staff	15 persons

B Live virus vaccines (measles)

space	450 m^2
equipment	1.3 million USD
staff	15 persons

C Inactivated virus vaccine production (polio, rabies)

space	550 m^2
equipment	2.0 million USD
staff	17 persons

D Central Kitchen

space	450 m^2
equipment	1.4 million USD
staff	19 persons

E Laboratories (microbiological, virological, potency testing)

space	800 m^2
equipment	1.8 million USD
staff	30 persons

F Packaging production line

space	950 m^2
equipment	3.5 million USD
staff	21 persons

TOTAL *

space	3550 m^2
equipment	11.5 million USD
staff	117 persons

(* Based on UNIDO Model Programme for the production of Vaccines in Developing Countries)

In addition to the great potential of social benefits for Venezuela, a regional project for vaccine production could play an illustrative role in the industrialization strategy based on a more self-reliant and export orientated economy. In light of the importance of the subject and with a view to assisting Venezuela in the expansion of the biological subsector pharmaceutical industry, the experts thoroughly support the setting up of a multiline vaccine production unit after the extension of INH capacity.

The research and development of new vaccines for the prevention and treatment of diseases which is already in progress could be carried out on a larger scale at the proposed multiline vaccines production unit. This can also help to justify the investment in the development of new products for which health service demand is large. To be self-sufficient in vaccine production is an important goal in public health, so is the availability of high- technology (fermentation) which should also be considered in the decision making process, otherwise, the gap between the industrialized and developing countries in this important field of biological industry will widen.

I. INTRODUCTION

1. The requirements for biologicals have recently gained great urgency as one of the basic elements of health for all by the year 2000 is the Expanded Programme of Immunization which was laid down by the United Nations. At present there are worldwide some forty producers of DPT vaccines and seventy that produce tetanus toxoid. In order to achieve the goal of EPI, that is providing immunization services for nearly every child by 1990, 3 - 4 times more vaccines would be required.
The programme needs continuous supply of biologicals which can be produced at national, subregional and regional level.
A number manufacturers in industrialized countries have withdrawn completely or partially from the conventional vaccine field. The increasing demand and the decreasing number of suppliers causes concern that the availability of vaccines in Venezuela, in SELA countries might become critical during the forthcoming years.

2. UNIDO has already prepared a model programme for projects for the industrial production of vaccines in developing countries which includes technical and economic details for the implementation of such projects at different stages.

3. An international team was formed for the purpose of preparing a comprehensive technical report including:

- review of the national immunization programme;
- demand and consumption of vaccines and biologicals in Venezuela;
- production of vaccines and biologicals;
- assessment of the existing manufacturing facilities;

- requirement for establishing industrial production of biologicals.

4. In this study, we accepted the FDA definition that biological product means: any virus, therapeutic serum, toxin, anti-toxin or analogous product applicable for the prevention, treatment or cure of diseases or injuries of man. There are six classes:

Classification on Biological Products

- active immunization;
- passive immunization;
- human blood derivatives;
- diagnostic agents (specific);
- allergens (specific);
- miscellaneous (venomes, pyrogens).

5. The WHO list of Essential Drugs contains 21 biological products, of which 5 vaccines are included in EPI:

- BCG vaccine;
- Diphtheria and Tetanus Toxoids and Pertussis vaccine adsorbed;
- Tetanus toxoid;
- Measles virus vaccine live;
- Poliomyelitis vaccine.

6. Venezuela adopted the Good Manufacturing Pratice (GMP) in 1983 (Norma Venezolano 1700-83 at CONVENIN was approved on 11.10.1983). Since then production, quality control, distribution and utilization of drugs have been under unified legislative and administrative control.

7. The Government of Venezuela adopted a Developmental Plan including population control and immunization programme under the overall objective of "Health for ALL by the year 2000".

8. Consequently, the present survey is dealing:

- with assessing the country's basic socio-economic data and existing national plans, policies and objectives regarding the health sector in general and utilization of vaccines and biologicals in particular, in order to define the framwork in which short, medium and long-term programmes are to be considered;

- with analysing the present conditions of production, import, distribution of vaccines and biologicals;

- with analysing the present quality assurance system for protecting the public by detecting sub-standard vaccines;

- with identifying those categories potentially most suitable for local production.

Note: During the project period a considerable amount of information was collected from many sources and by personal interviews. However, in the report only those data and information have been presented which are particularly relevant. The list of references is enclosed.

II. GENERAL INTRODUCTION OF VENEZUELA

1. Health services play an important role in raising the efficiency and effectiveness of society. Health is one of the basic requirements to improve the quality of life. The Government of Venezuela established a health care system based on the principle, that health is an inalienable right of all individuals and therefore it is the responsibility of the state.
   For some years the Government has been pursuing a policy for providing essential health care. Health plans have emphasized primary health care as the key approach to improve the health status of the people.

2. The WHO and PAHO global strategy of "Health for All by the Year 2000" has been accepted by the Government as a national objective. A significant programme has been made in the Health sector in the past years but the real goal of providing comprehensive health care covering all the people is still to be achieved.

3. There are two sectors providing health care in Venezuela: the public (Ministry of Health and Social Assistance and Intitute of Social Security) and the private one. The main care for the poor is provided in the public sector, but this has limited resources.

A---General data

1. Venezuela has a total area of 915490 sqkm and a population of 17.8 million (1986). The urban population is predominant (76.4 %).

2. Two important factors influence the topography of Venezuela: the continuation of the Andean mountains and the Orinoco. There are a number of important islands.

Venezuela is a country of varied scenary: mountains, valleys, plains, high plateaux, rivers, beaches, desert, forest and jungles.

3. The Gross Domestic Production at constant (1968) factory prices is Bs. 71089 million in 1985. The annual growth of GDP was high during the 1973-1978 period but in 1979-1986 there was economic stagnation. Since 1979 the per capita GDP has shown a decreasing trend. The per capita GDP is approximately 4000 bolivars.

4. During the last few years, the balance of payment came under serious strain due to increasingly difficult international trade and aid conditions. The real growth rate in export earning is around 3 % which is reasonable. The main export items are iron ore, oil, coffee,cocoa, bauxite, etc. Venezuela is an "export economy" country relying on the proceeds from its major export items to finance the imports of food and medicine, raw materials for consumer goods and industry as well as much of the capital goods, equipment and spare parts needed for the development of its own production capacity, particularly with a high domestic value added.

B---Health

1. The Government accepted the "Health for All by the Year 2000" WHO, PAHO programme. In 1979 only 60 % of the population was covered by essential health service. Small pox was eradicted and cholera was brought under control. The infrastructure developed greatly, there are 464 hospitals with a total number of 43546 beds. Venezuela is the largest tropical area in the world which is practically free of malaria.

2. Under the objective of "Health for All" major efforts were made to control diseases through immunization. The immunization programme reached 20 % of the population in the target age groups. A drug policy was introduced to make drug supply cheaper. A plan was drawn up for setting up plants for the manufacture of basic drugs.

3. The two major institutions of health care are the Ministry of Health and Social Assistance (MOHASA) and the Institute of Social Security (IVSS) an autonomous body under the Ministry of Labour. The Government has been committed to the creation of a new national health care system which would bring all the country's existing institutions together.

4. The MOHASA provides health care free of charges at governmental health care establishments. The Simplified Medicine Programme provides basic health care in remote regions.

C - Analysis of the demographical statistics

1. The fast growing population affects the socio-economic progress therefore the population control and family planning programme received great interest. The growth rate of the population is around 3.1 %, crude birth rate 3.56 %.

2. One of the key parameters of the demand for pharmaceuticals, vaccines is the size of population. The main demographical data were as follows:

Population (million)	17.8 (1986)
Birth rate (per 1.000 per year)	35.6
Death rate (per 1.000 per year)	5.5
Infant mortality per 1.000 live birth	33.1
Annual average population growth rate (%)	3.1

Population aged 0 - 15 (%)	42.1
Population aged 65+ (%)	3.1
Life expectancy, male (years)	64.9
Life expectancy, female (years)	68.4
Urban population (% of total)	76.4
Number of doctors	17.565 (1983)
Population per doctor	347 (1983)
Number of hospitals	464 (1983)
Number of hospital beds	43.546 (1983)
Number of pharmacies	2.897 (1985)
Number of pharmaceutical wholesalers	83 (1985)
Number of Representatives	72 (1985)
Pharmaceutical market valuation	2.000 - 2.500 million Bs (300 million USD)
Private Sector	60 %
Public Sector	40 %

3. Leading diseases: Dysentery, Amoebiasis, Helminthiasis, Mycosis, Cardiovasular diseases, Venereal diseases, Cancer.

B---Health-Expenditures

1. Public expenditure is in general directly linked to the size of the population of a country. This is even more so in Venezuela than in most other countries. The expenditure on social services has accounted for about 6.7 % of the GDP. Since the ordinary budget hardly covers the cost of current health expenses, it is assumed that a sizeable contribution from state governments and municipalities will be made available.

2. The public health expenditures were in 1986: 7.465 million Bolivares.

3. The last few years' expenditures were as follows:

	1984	1985	1986	1987
Total budget (million Bs)	103.546	113.320	125.558	129.076
Health expenditures (million Bs)	4.977	6.598	7.465	8.696
Health expenditure as % of the total budget	4.8	5.8	5.9	6.7

4. Most health care costs are met by the federal and state governments with small payments from some municipalities. Individual communities make some small contribution to their own facilities, such as maintaining buildings and constracting and equipping dispensaries.

E---Government-strategy-for-health-development

1. The major objectives of the present year are:

- reduction of population growth;
- expansion of productive employment;
- universal primary education;
- development of the technological base for bringing about a long term structural change;
- self-sufficiency in food;
- satisfaction of minimum basic needs of people;
- acceleration of economic growth;
- promotion of self-reliance.

2. The health sector objectives are:

- to improve the quality and to increase coverage of health care delivery system;
- to consolidate and strenghten existing primary health care;
- to prevent, control and treat major communicable and non-communicable disease;

- to foster facilitate health manpower development and its optimum utilization;
- to mobilize resources to support expanding health care services;
- to promote adequate production, supply and distribution of essential drugs, vaccines, etc.;
- to develop a network of health information system;
- and to promote and provide facilities for bio--medical and health system research.

3. The present survey is dealing with immunization so we consider only this side of the health sector. The strategies of the plan in the fields of vaccination is:

- to control communicable diseases effectively, the immunization and other related programmes such as establishment of health laboratory , health information and education have to expand towards achieving universal immunization, the target of DPT, OPV and measles immunization to cover children below 1 years of age has been set at 90 % and for BCG immunization for children under 15 years of age* at 95 %;
- supply of essential drugs, vaccines, sera, chemicals and reagents, rehydration fluids, etc. by increasing their production through establishment, extension of the manufacturing plants in the country.

4. The increasing coverage under the so called expanded programme on immunization against tetanus, diphtheria, measles, tuberculosis, pertussis and poliomyelitis will be a major concern.

III. PRINCIPLES OF IMMUNIZATION ACTIVITIES

1. The vaccine-preventable target diseases of the EPI account for the death of at least 20.000 children each year.

* Tuberculin negative children receive BCG up to 15 years of age.

The main target of the EPI is to provide immunization for all children, referred to as universal child immunization, by the year 1990, raising the coverage of vaccination to the point where significant reductions in morbidity and mortality can be achieved with intensive mobilization and development of new immunization delivery. There is a joint Government PAHO plan of EPI.

2. Project Document for the EPI covering the next few years details the objectives, strategies, immunization policy, activities and plan of action designed to meet the goal of Universal Child Immunization (UCI) in Venezuela. Key elements include programme acceleration by:

   - carefully designing and phasing social mobilization techniques to generate both support and demand;
   - involving all relevant sectors and departments of Government;
   - improving immunization services in existing Health Complexes;
   - intensifying rural outreach services in health complexes in a phased manner and
   - intensifying immunization activities in "high access" areas (major metropolitan cities and district towns) in a phased manner.

The Government of Venezuela is committed to meeting the goal of Universal Child Immunization (UCI) through these accelerated EPI activities within the context of the primary health care structure and as a leading element of maternal and child health services. This goal can only be achieved by or before 1990 and sustained beyond 1990 with the full support of national and community leaders, all relevant Ministries and with the partnership of International, Bilateral and Non-governmental Organizations.

A - Present status of immunizations

1. About 40.000 children under five years of age die every year. The vaccine preventable diseases included in Expanded Programme on Immunization account for at least 50 percent of these deaths.

2. To reduce the morbidity, disability and mortality associated with these vaccine-preventable diseases the Expanded Programme on Immunization (EPI) was formally launched in Venezuela in 7 April 1982.

   There has been a steady increase in the number of centres offering immunization and it is now estimated that 62 % of the population has access to immunization services. Immunization coverage of infants for the country as a whole, however, although rising, remains low. Approximately 23, 21, 44 and 19 % of infants are fully immunized with BCG, DPT, Polio (OPV) or Measles vaccine, respectively.*

B - The new strategy of EPI

1. The joint Government PAHO plan of action was accepted to accelerate the EPI programme.

   The objectives of the EPI are:

   (1) to reduce morbidity, disability and mortality from the EPI target diseases (and other diseases for which potent, safe and cost-effective vaccines become available) to a level where these diseases cease to be major public health problems ano

   (2) to promote self-reliance in the delivery of immunization services within the context of the primary health care structure.

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* The immunization coverage (percentage) of children less than 1 year of age for BCG, DPT, Polio and Measles as of February 1987 is 92,49,59 and 56, respectively (EPI, WHO, April 1987).

The target population for BCG, DPT, OPV and measles immunization is children under 1 year of age. (But upto 2 years of age the immunization services will be provided). Women of childbearing age also belong to the target population for TT/Tetanus toxoid. Routine immunization of pregnant women will be also provided and BCG for school children under 15 years of age (if they are tuberculin negative).

6---Immunization-policy

1. The highlights of the immunization policy are to improve immunization coverage and the effectiveness of the vaccines using all possible ways, i.e. Health Complexes, rural outreach services.
   The carefully designed and phased programme applies social mobilization techniques to generate health support and demand. The programme involves all relevant sectors and departments of Government and consequently improves the delivery of immunization services from existing Health Complexes. EPI has been accelerated by intensification of rural outreach services in health centres and by immunization activities in "high access" areas in a phased manner.

2. The main principle of the immunization schedule is to protect children as early age as possible.

Immunization-schedule

Birth (or first contact)	BCG (OPV)*
6 weeks	DPT, OPV
10 weeks	DPT, OPV
14 weeks	DPT, OPV
9 months	Measles

* Within six weeks it represents an extra dose of OPV.

All children born should receive BCG and OPV. Children, not coming into contact with health facilities during their first six weeks of life can begin their immunization at that first contact with the health services and receive BCG and OPV.

3. All women in the childbearing age should receive two doses of tetanus toxoid. These doses should be given at first pregnancy. Additional doses are necessary at subsequent pregnancies.

B - Financial and human resources

1. For the rapidly accelerated programme of universal immunization it will be necessary to markedly increase the funding for the EPI. As more donors become involved with supporting EPI activities it will become increasingly important that mechanisms are developed to assist in coordinating donor agencies' contributions and to rationalize their support.

   Government as well as International and Non-governmental Organizations have already begun to respond to the needs of the EPI.

2. Invest adequate human resources in EPI:

   The major components of this activity are: ensuring that needed positions are sanctioned, ensuring that sanctioned positions are filled and ensuring that health workers and supervisory staff involved in EPI activities receive proper initial and refresher training and receive effective supervision. Major activities are as follows:

   Staffing: Strenthening the management and service delivery capability of the EPI involves the complete staffing and activation of all managerial, support and service delivery functions at all levels.

Training: All of managers, health inspectors and supervisors, technical support staff, and vaccinators must be trained and motivated to support the EPI.

3. The technical problems (cold chain, central cold store, etc.) will be solved and controlled.

IV. DETERMINATION OF DEMAND

1. The demand of biologicals i.e. vaccines for the immunization programme depends on some influencing factors.
   The most important of them are as follows:
   - national immunization programme / immunization schedule;
   - social acceptance, education, information, etc.;
   - availability of vaccines;
   - availability of infrastructure (cold chain, delivery system, logistics, etc.);
   - epidemic / endemic situation;
   - size of target populations;
   - birth rate.

2. The target population for UCI are the newborns, pregnant women and women of childbearing age.

3. Based on these influencing factors, the estimated annual demand of vaccines for UCI programme is as follows:

DPT	3.0 - 3.2	million doses
TT	2.2 - 2.4	million doses
BCG	1.2-1.3	million doses
OPV	3.2 - 3.3	million doses
Measles	0.5 - 1.0	million doses
Rabies	0.3 - 0.35	million doses

For the calculations:

- the number of births in one year;
- the number of shots of EPI vaccines
  (3 shots of DPT and OPV,
    1 shot of BCG and measles,
    2 shots of TT for pregnant women);
- the increasing immunization coverage;
- the wastage of vaccines;

should be taken into account. Out of the above vaccine-preventable diseases, tetanus, mainly neonatal tetanus has great importance. Vaccines are important life-saving products that should not be carelessly handled or needlessly wasted. Proper planning of immunization sessions will help to maximize the use of vaccines. However, the loss of vaccine because a vial has been opened to protect even only one child is not considered to be a needless waste. On the contrary, it is better to open the vial and to waste the vaccine than to "waste" (leave unprotected) the child.

4. The above requirements only include vaccines for UCI but there are demands from outside of the target population. In practice in addition to the UCI programme approximately 2 % of the population requires TT vaccination.

5. Pursuance of research efforts as part of programme operations: The objectives of operational research should be to improve the effectiveness of immunization services. Specific concerns include the development of approaches for delivery services which engage the full support of the community, the improvement of methods and materials relating to sterilization of immunization equipment and the cold chain, the acquisition of additional knowledge concerning the epidemiology of the target diseases and further development of appropriate management information systems.

Specific operational research that has already been identified should be instituted as soon as feasible.

V. THE EXISTING PRODUCTION OF VACCINES AND BIOLOGICALS

1. There are about 78 licensed pharmaceutical laboratories in the country but local production is dominated by twenty.

2. The pharmaceutical companies are mainly engaged in formulation and they procure their raw materials by import.

A---Background-of-the-local-vaccine-production

1. From the 1920's the vaccine production were carried out in different laboratories. BCG vaccine has been produced since 1926 until a few years ago but it has not met the quality requirements. The Instituto Nacional de Higiene "Rafael Rangel" has been producing vaccines since 1938.

History of Manufacture of Biological Products in "Rafael Rangel" National Institute of Hygiene (INH)

Before the foundation of I.N.H. "R.R." in 1938, there has already been a Laboratory for Bacteriology and Parasitology in Venezuela, which belonged to the Direction of Public Health of the Ministry of Health, Agriculture and Animal Management. In this Laboratory, smallpox and typhoid vaccines has already been produced but production registers are available only since 1940, after the foundation of I.N.H.

That time smallpox and typhoid vaccines, anticrotalic sera and Kahn and Wassermann antigens were produced.
The Table enclosed below summarizes the manufacture of biological products in the last 45 years, with special regard to the years of important changes and the last 7 years. The Table well illustrates that the production of smallpox vaccine had been started in Venezuela far before the foundation of the Institute, the output was as much as 3.000.000 doses in 1940, it reached a maximum of 4.312.620 doses in 1955, and showed an ever decreasing trend until 1979 when the last batch of 139.500 doses was produced, mainly for the vaccination of travellers. Smallpox vaccines has not been in use, and, thus, has not been produced in this country since 1980.
Similarly to the smallpox vaccine, the typhoid vaccine had already been produced before the foundation of the Institute. The production was 75.788 doses in 1940, it grew up to about 1.000.000 doses in 1970. Then the production started to trend downward until 1985 when the last batch of 92.000 doses was produced. The Institute has not produced typhoid vaccine since 1986.
The production of Triple Vaccine (diphtheria, pertussis , tetanus) was started in 1956. One million doses were produced in 1970, but the increase of vaccine production can be regarded significant only since 1980 when the consistent use of Caracas fermentors was introduced. That time 2,532,340 doses were produced. By 1985, the production had reached 3,000,000 doses, the highest production quantity in the history of the Institute. The national demand is about 4 million doses from this produc , out of which the Ministry of Public Health and Social Welfare requires about 3,000,000 doses.
The production of rabies vaccines for canine and human use was started in 1955.

PRODUCCION DE BIOLOGICOS, POR AÑOS ESPECIFICOS DONDE SE REALIZARON CAMBIOS IMPORTANTES EN LA PRODUCCION Y ULTIMO QUINQUENIO. INSTITUTO NACIONAL DE HIGIENE "RAFAEL RANGEL" - VENEZUELA - [illegible]

PRODUCTOS BIOLOGICOS	AÑOS: [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] (1)	REQUERIMIENTO DEL PAIS EN [illegible]
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VACUNA DOBLE (D.T)	—	—	—	—	—	—	—	[illegible] "	—	—	
VACUNA ANTIRRABICA CANINA	—	—	—	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible]
VACUNA ANTIRRABICA HUMANA	—	[illegible] "	—	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible]
VACUNA ANTICOLERICA (4)	—	—	—	—	[illegible] "	[illegible] "	[illegible] "	[illegible] "	—	[illegible] "	[illegible]
TOXOIDE TETANICO	—	—	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible] "	[illegible]
SUERO ANTICROTALICO	[illegible] amp	—	—	—	—	—	—	—	—	—	
ANTIGENO DE [illegible]	[illegible] "	[illegible] fcos.	—	—	—	—	—	—	—	—	
ANTIGENO DE [illegible]	[illegible] "	—	—	—	—	—	—	—	—	—	
ANTIGENO DE [illegible]	—	[illegible] "	—	—	—	—	—	—	—	—	
ANTIGENOS FEBRILES	—	[illegible]	[illegible] equipos	[illegible] equipos	[illegible] equipos	[illegible] equipos	[illegible] equipos	—	[illegible] equipos	[illegible] equipos	
COMPLEMENTO DE COBAYO	—	—	—	—	—	—	[illegible] fcos	[illegible] fcos	[illegible] fcos	[illegible] fcos	
HEMOLISINA (5)	—	—	—	—	—	—	[illegible] "	[illegible] "	[illegible] "	—	

FUENTE DE INFORMACION: Archivos División de Elaboración de Productos Biológicos Instituto Nacional de Higiene "Rafael Rangel"

(1) Estimado al 31-12-83.
(2) No se aplica en el país.
(3) No se aplica en el país.
(4) Sólo para los servicios de vacunación internacional.
(5) Existencia suficiente en depósito.

In 1985, the Institute was able to satisfy the human rabies vaccine requirement of the Ministry of Public Health and Social Assistance by an annual production of 135.000 doses.
As to rabies vaccines for dogs, an annual volume of about 400.000 doses was produced during the last five years. This quantity covers only 25 % of the annual demand. It is to be mentioned that a total of 1.500.000 doses are required for the Antirabic Program of the Ministry of Public Health and Social Assistance.
The production of tetanus vaccines was started in 1956, and the average annual volume was about 2 million doses in the last five years. The national demand for this product is about 2.4 million doses. The production of biological products in the Institute cannot be increased significantly by the present methods, therefore, the gap between the production output of the Institute and the national demand will be widened, parallel to the increasing demands raised by the population growth.

2. For active immunization against BCG, diphtheria, and pertussis, and tetanus the Government undertook a project for the establishment of manufacturing units.

3. Short-term consultants gave assistance to overcome the main problems and accomplished the large-scale production of vaccines 10 years ago.

4. In Venezuela only DPT, TT, rabies and cholera vaccines were produced in 1986. BCG production was stopped a few years ago.

8 - Present vaccine production

1. The existence of facilities for the production and quality control of vaccines will contribute to a number of interrelated social and economic objectives such as reduction of dependance on outside supplies, increase of domestic stocks of technical know-how and human capital in many disciplines involved in the development of biologicals and creation of employment.

2. In its Expanded Programme on Immunization (EPI), PAHO-WHO has set as target the complete immunization of all children in the world against the major childhood infectious diseases by the year 1990. Until now, only 20 % of the child population has been immunized against these diseases. Local production of the required vaccines will certainly improve the coverage because it will reduce the costs on long term and in particular the requirement for hard currency to buy the vaccines from abroad. In addition, it will generate more knowledge on the control and application of vaccines in general.

   In the following, the general aspects of vaccine production technology will be discussed with particular reference to vaccines against the target diseases of the EPI.

3. Vaccines are prepared for active immunization of man against infectious diseases. They should contain the antigen(s) by which a protective immune response against the target disease is elicited. For certain vaccines the required microbial component is well defined such as diphtheria and tetanus toxins or meningococcal polysaccharides. In many cases the protective antigens are not exactly known and whole inactivated bacterial cells (pertussis, cholera, typhoid) or viruses (rabies, polio, influenza) are used as vaccine while in some cases live attenuated microorganisms are required for protection (BCG, measles, rubella).

Chemically fullydefined vaccines are preferable as in general risks of adverse reactions are lower than for whole cell or live vaccines.

4. Highly purified inactivated vaccines have the advantage that they can be applied at high concentrations. In this way, the number of immunizations may be reduced as has recently been demonstrated for diphtheria and tetanus vaccines. Further, they can be mixed to form one cobined vaccine.

5. For the preparation of vaccines, the various micro-organisms responsible for the infectious diseases have to be cultivated in order to obtain the basic material. The required culture volume per total human dose depends strongly on the type of vaccine.

6. In comparison with other biotechnological processess, the required culture volumes are relatively small. Also in other respects, the preparation of the different vaccines has a number of characteristics in common regarding the cultivation processes and processing to a final product. In homogeneous culture the micro-organisms are propagated in stirred fermentors.

   This culture technique has the advantage that the environmental culture conditions such as temperature, pH and oxygen can be continuously measured and controlled. In this way, more consistent products may be obtained while in addition, scaling up of the production process is facilitated and in comparison to stationary cultivation systems in small scale cultivation units, the risks of losses by contamination are reduced. Initially, the homogeneous culture system could only be used for the cultivation of bacteria.

7. In order to avoid conflicts with Good Manufacture Practices (GMP), the production facilities should be used for production of different vaccines on the basis of time sharing.

This means, that after a well documented cleaning of the facilities, another vaccine can be produced in the same unit by the same personnel. In this way, it becomes economically feasible to establish relatively large scale production units for rather small amounts of vaccines.

The tetanus and BCG vaccines have been excluded from the above scheme in view of the WHO requirements that the production of these vaccines should be performed in separated units. The major advantage of using the same production unit for different vaccines is not only a reduction in investments in premises and equipment, but as automatically larger batches will be produced, also the required time and personnel for production and control will decrease.

In the next few paragraphs production methods for each of the EPI vaccines will be presented.

a) Tetanus-Toxoid-vaccine-production

- Flow diagram of the TT production

Process	Controls
Culture medium	Sterility
Seed culture	Bacterial purity
Inoculum	Bacterial purity
Cultivation	Potency of toxin /Lf/ml; L+/ml;MLD/ml/
Filtration	pH
Detoxification	Sterility, innocuity, pH
Concentration and Purification	pH
Filtration	Sterility, innocuity

Final bulk	Antigen content, purity, sterility, concentration of gel, pH, residuel free formaldehyde
Final lot	Sterility, innocuity, potency, pH

The culture medium is the modificated Muller-Miller medium. Cl. tetanus Harvard strain stored at a temperature of 40°C in liofilized form is used. For the production "static culture method" is used. The cultivation is carried out in glass bottles of 15 litres, at temperature of 35 °C for 7 days. After cultivation, the average Lf value is 40 Lf/ml. Seitz apparatus is used for sterile filtration. After filtration, 0.5 % v/v. of a 40 % w/v formaldehyde solution is added. In the sterile glass containers at a temperature of 35 °C detoxification will be completed in 4 weeks. Trichloroacetic acid is used for concentration and purification. The average BU value is between 1000 - 2000 BU/ml. 1 % Thiomersal is used for preservation. The AL/OH/3 gel content in the final product is 3 mg/ml.

Comments on the present TT production in the "Rafael Rangel" Institute

1. The demandfor Tetanus Toxoid and Diphtheria-Pertussis-Tetanus Vaccine is expected to rise as the Government intensifies the natural Expanded programme for immunization.

2. The Tetanus toxoid production laboratory according to the WHO regulations has to function as a physically separated and self-contained unit. The laboratory has central air-conditioning. The vaccine was certified by WHO to be of standard quality. The Institute is supplying Tetanus Toxoid regularly to Government organizationsparticularly for EPI.

3. The TT vaccine production meets the most essential specifications. According to the calculations the full production of the TT block under present conditions can approximately reach

7 million TT doses (10 Lf) and
11 million T doses (5 Lf) for DPT

in one year. Hence this quantity is more than what is required for the UCI programme in Venezuela, large quantities could be exported.

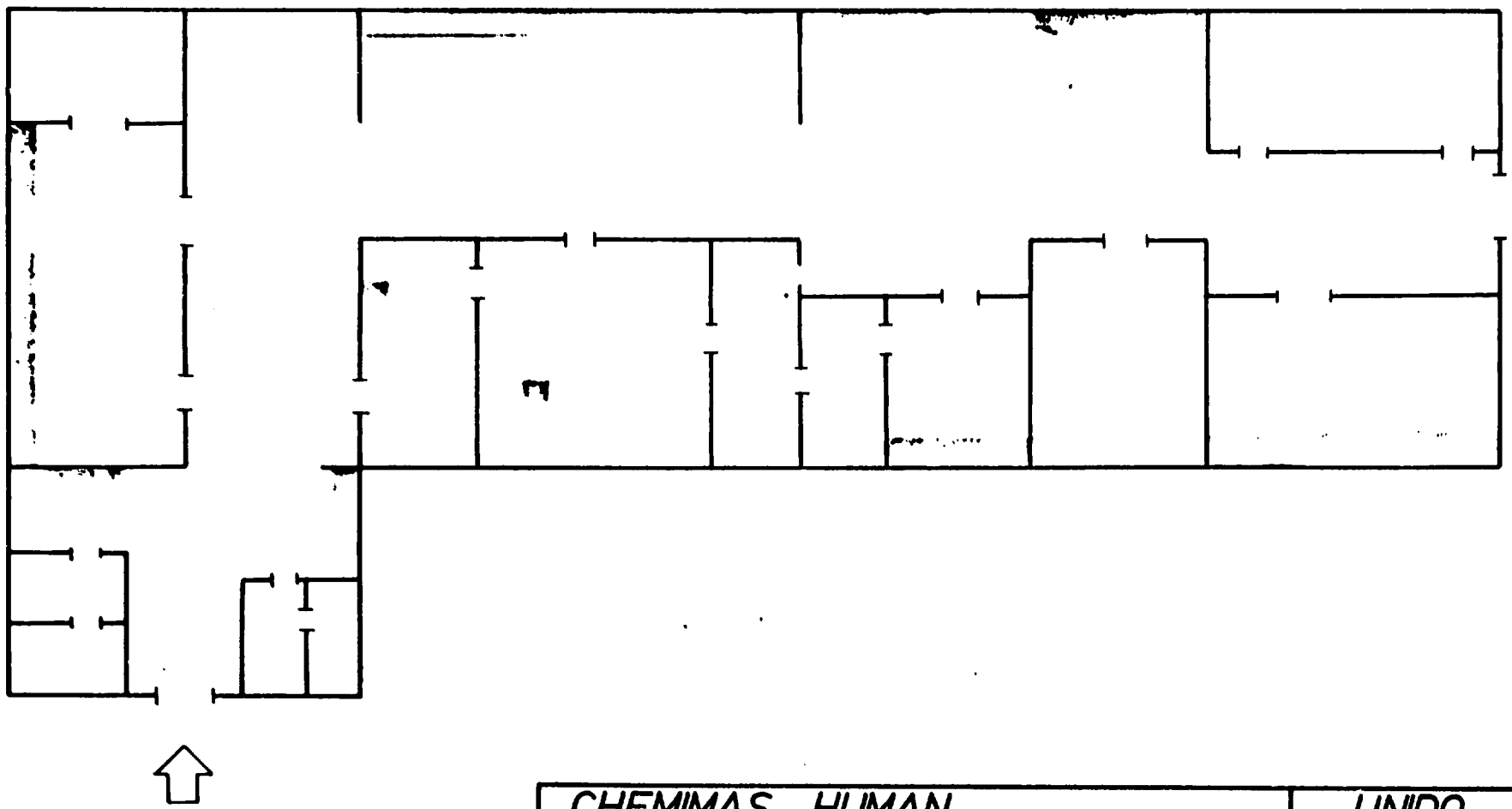
4. According to the calculation (see Annex II.) the capacity of the plant is sufficient. Another calculation was also carried out to determine what are the necessary requirements to increase even further the existing capacity. In this calculation, it was assumed that during the actual production, some batches would go wrong, the facilities and the raw materials may not always be available. In this case, only the glass bottle has to be changed into a 100 litre Tetano-Paljas S.S. fermentor. The capacity will be 35 x 10^6 Lf per year (see Annex III.).

5. Critical comments and recommendations:-
(these can also apply to the DPT and rabies production)

- a stable, well paid and well qualified staff of high motivation is a prerequisite for the improvement of the present situation;
- the assurance of the continuous training of the staff;
- the TT production unit should remain separated from other production units;
- the lack of equipment causes no difficulties in the production;
- the animal house meets the requirements;
- for concentration of tetanus toxoid, the ultrafiltration method can be used;

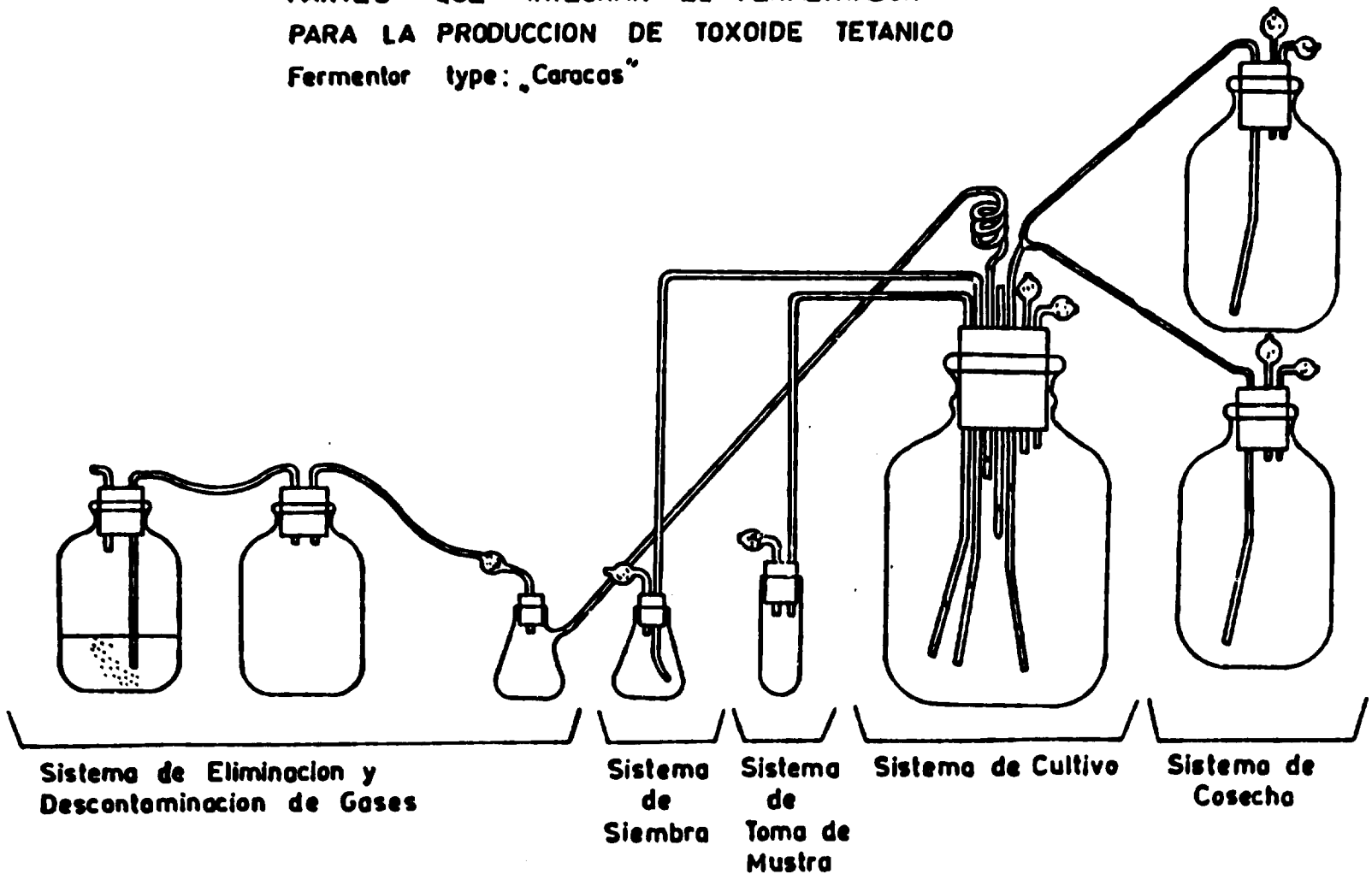
- establishing a maintenance programme;
- determining the maintenance methods and time of interventions;
- preventive maintenance following the maintenance programme of each machine;
- reception of reports on faulty machinery and other maintenance;
- determining priority order of interventions;
- recruitment of qualified personnel;
- running a store for spare parts for the machines;
- performance of direct and indirect workers should be supervised;
- material flow and time norms for production should be established;
- the real cost of the products should be determined;
- comparing actual production output to planned output;
- all aspects of production, such as financial planning, production planning, costing should be carried out as if the unit were an independent company;
- production organization should be set up based on the use of personal computers which has been proven to be a successful approach in small scale production units;
- to provide raw and auxiliary materials;
- to hire two experts (through UNIDO)(one for management, one for maintenance for 3 months each) to carry out and train the people in the above mentioned duites;
- the use of the UNIDO's document (Model Programme for the Production of Vaccines in Developing Countries) is highly recommended.

6. The lay-out of the TT plant and present fermentation processes can be seen on the following pages:



CHEMIMAS HUMAN	UNIDO
Instituto Nacional De Higiene "Rafael Rangel" TT production unit	
LAY - OUT	

PARTES QUE INTEGRAN EL FERMENTADOR
PARA LA PRODUCCION DE TOXOIDE TETANICO
Fermentor type: „Caracas"



b) DPT Vaccine production

1. DPT production is going on in the Instituto Nacional De Higiene "Rafael Rangel". The plan of the DPT block on the second floor can be seen on page 39.

2. DPT production consists of four units:

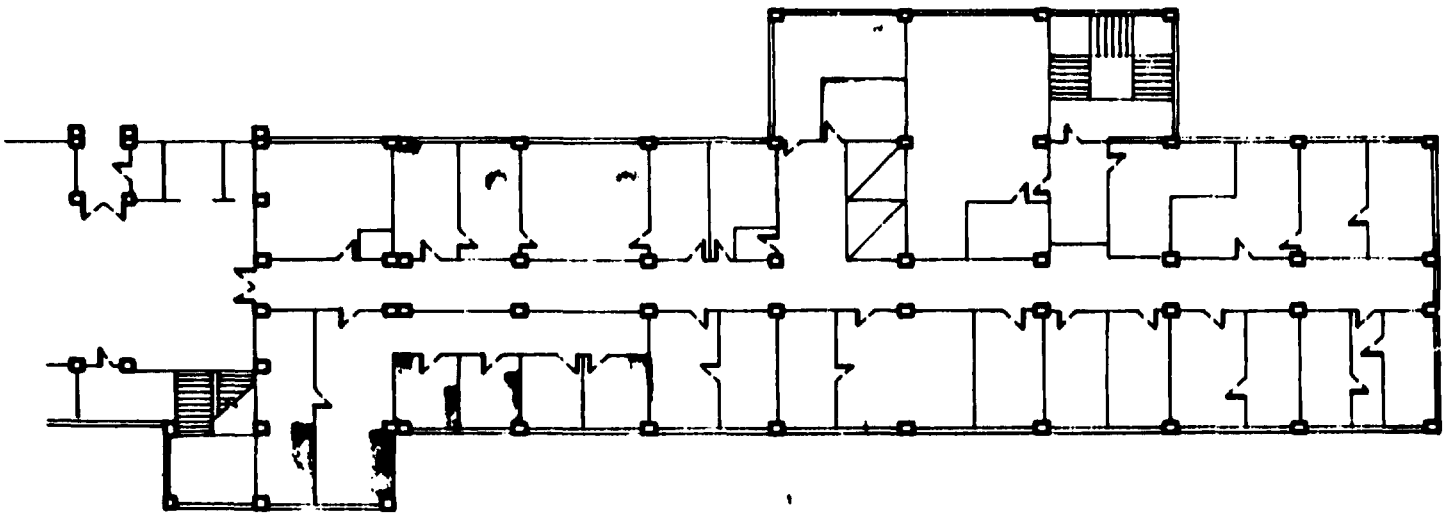
   - diphtheria toxoid unit (second floor)
   - pertussis unit (second floor)
   - filling unit (second floor)
   - washing unit (ground floor)

3. Diphtheria toxoid is produced using a fermentation method.

- Flow diagramme of Diphtheria toxoid production

Process	Controls
Culture medium	Sterility
Cultivation	Bacterial purity, pH, Lf
Single harvest	Purity, pH, Lf
Detoxification	
Concentration Standarization	
Purification Filtration	
Bulk	Sterility, toxicity, purity, antigen content
Final bulk	Sterility, toxicity, potency pH, stability, residual free formaldehyde
Final lot	Identity, sterility, potency, innocuity, adjuvant and preservative content

Diphtheria toxin is prepared in homogeneous culture in the fermentor "Caracas". Toxin synthesis is inhibited by iron and dissolved oxygen concentration in the medium. After the cultivation an average toxin titer of 200 Lf/ml is obtained. The culture is then clarified. After filtration the filtrate is detoxified. Batches of diphtheria toxoid are combined for ultrafiltration, fractionation anc filtration.



Second floor

CHEMIMAS - HUMAN	UNIDO
Instituto Nacional De Higiene "Rafael Rangel" Deporte - Petrussis production	
LAY - OUT	

--Comments-on-the current-Diphtheria-toxoid-production

Diphtheria toxoid production is going on according to the WHO regulations. Production meets the most essential requirements. According to the calculations, the production output of Diphtheria toxoid under the proposed conditions can approximate reach 11 million doses (15 Lf) per year. This quantity is more than what is necessary for the the UCI programme in Venezuela. Therefore large quantities could be exported. According to the calculation (see Annex IV.), the capacity of the plant is sufficient. In this calculation we took into consideration a new fermentor and a few refrigerated centrifuges.

Critical-comments and-recommendations:-

- a stable, well paid and well qualified staff;
- the assurance of continuous training of the staff;
- good maintenance (see TT production);
- to provide raw and auxiliary materials;
- to hire two experts (see TT production);
- to set up a production organization.

4. Production of pertussis is carried out using the fermentation method

- Flow-diagramme of pertussis production

Process	Controls
Culture medium	Sterility
Cultivation	
Separation Resuspension	
Single harvest	Purity, opacity

Combination Standarization	
Inactivation	
Final bulk	Sterility, toxicity, potency stability
Bulk	Identity, sterility, potency innocuity, adjuvant and preservative content

The homogeneous cultivation method is used. Harvesting is done by centrifugation. Detoxification is carried out by heat-treatment.

--Comment-on-the-present-pertussis-production

Pertussis production is going on according to the WHO regulations. The production meets the most essential requirements. According to the calculation the production output of the pertussis vaccine under the proposed conditions can approximately reach

11 million doses

per year. This quantity is more than what is necessary for the UCI programme. Therefore a large quantity should be exported. According the calculation (see Annex V.) the capacity of the plant is sufficient.

Critical comments and recommendations:

- stable, well paid and qualified staff;
- good maintenance;
- continuous training of the staff;
- provide raw and auxiliary materials;
- set up a production organization;
- hire two experts (see TT production).

5. The filling and packaging unit

The unit has the necessary equipment for the adsorption and combining of the DPT vaccine (400 litres Bilthoven "mixo-paljas" but it is out of use because of inexperience).
Bosch unit is used for filling. The closing unit is King type.
Filling is done according to the WHO regulations.
The production meets the most essential requirements.
The filling unit - with the following recommendation - has enough capacity to fill and package 11 million doses of DPT and 7 million TT doses a year.
The lay-out of this unit can be seen on the next page.

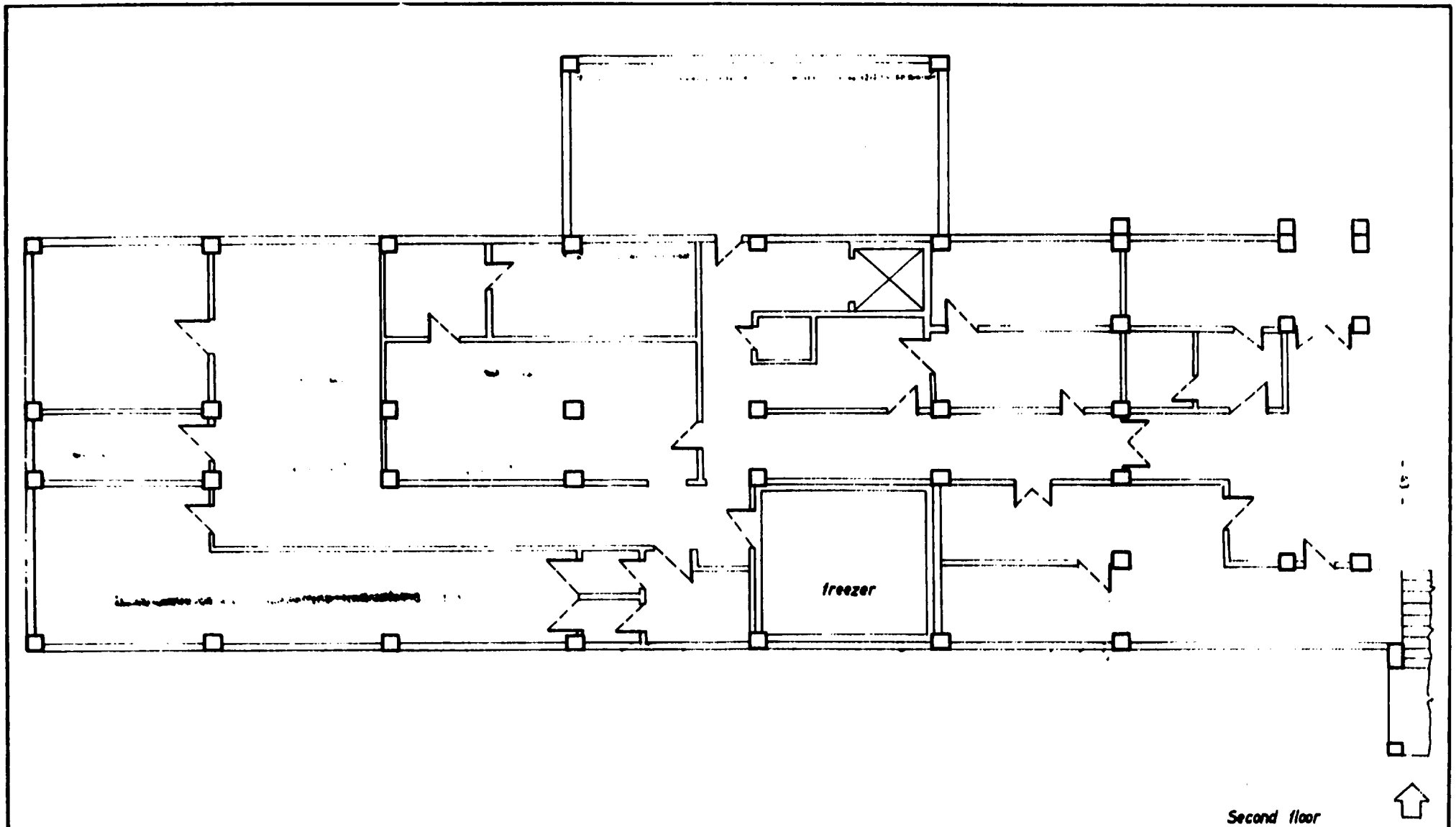
Critical comments and recommendations:

- stable, well paid and qualified staff;
- packaging materials asn spare parts;
- good maintenance;
- to set up a production organization;
- two experts (see previous chapter).

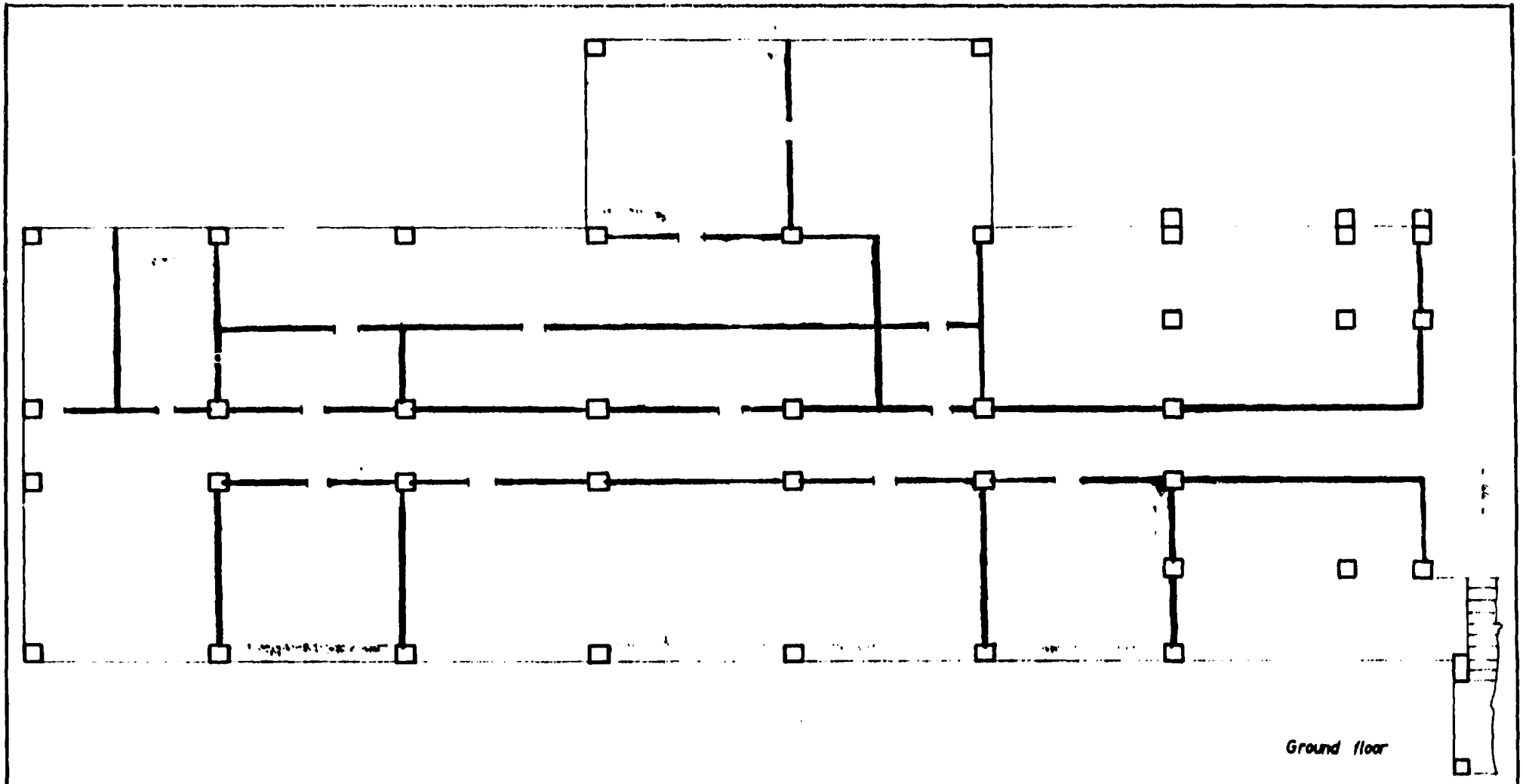
c) Rabies vaccine production

- flow diagramme of rabies vaccine production -

Process	Controls
Seed cells	Sterility, mycoplasma, viability, extraneous agents, identity, tumorigenicity
Cell bank	Sterility, mycoplasma, viability, extraneous agents, identity, tumorigenicity



CHEMIMAS - HUMAN	UNIDO
Institute Nacional De Higiene "Rafael Rangel" Filling unit	
LAY OUT	



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Instituto Nacional De Higiene "Rafael Rangel" Working unit	
LAY - OUT	

Production cell	Sterility, mycoplasma, cell growth, extraneous agents, identity
Virus culture	Sterility, extraneous agents, virustitre, ELISA
Harvest	Sterility, virus titre and identity, ELISA
Bulk vaccine	Residual live virus, protein N_2 content, Bovine serum proteins, residual cellular DNA content, ELISA/NIH sterility
Lyophilization	Sterility, potency (NIH) ELISA, innocuity, pyrogenicity, stability BPL-content, residual moisture

The production cell cultures are inoculated with seed virus. Virus is injected into mice. Cells are removed from the carriers. The lay-out of the plant can be seen on the next page.

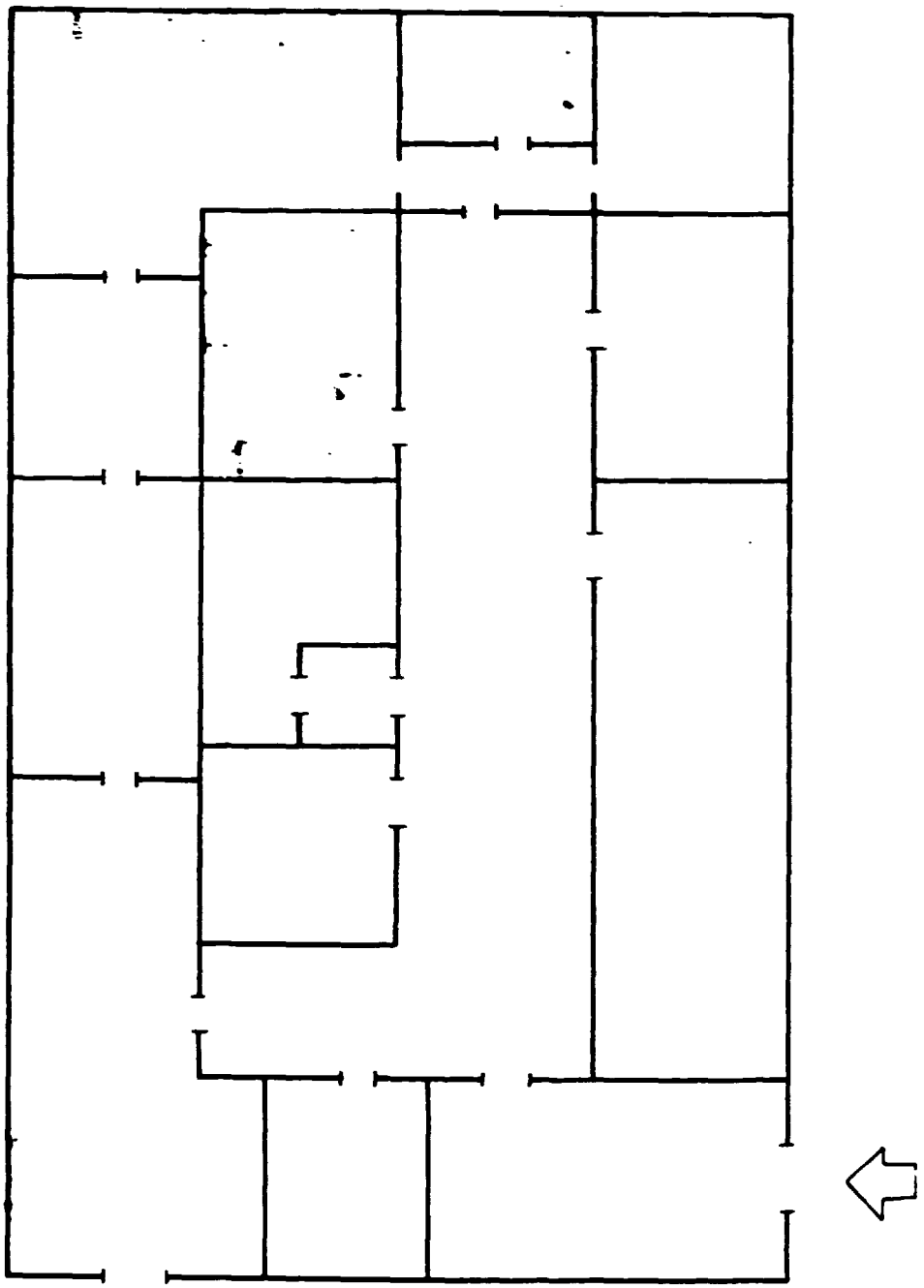
--Comments on the present rabies production

1. The demand for rabies vaccine (both human and veterinary) is expected to be stable. The rabies vaccine production laboratory works according to the WHO regulations. It is functioning is a physically separated and self-contained unit.

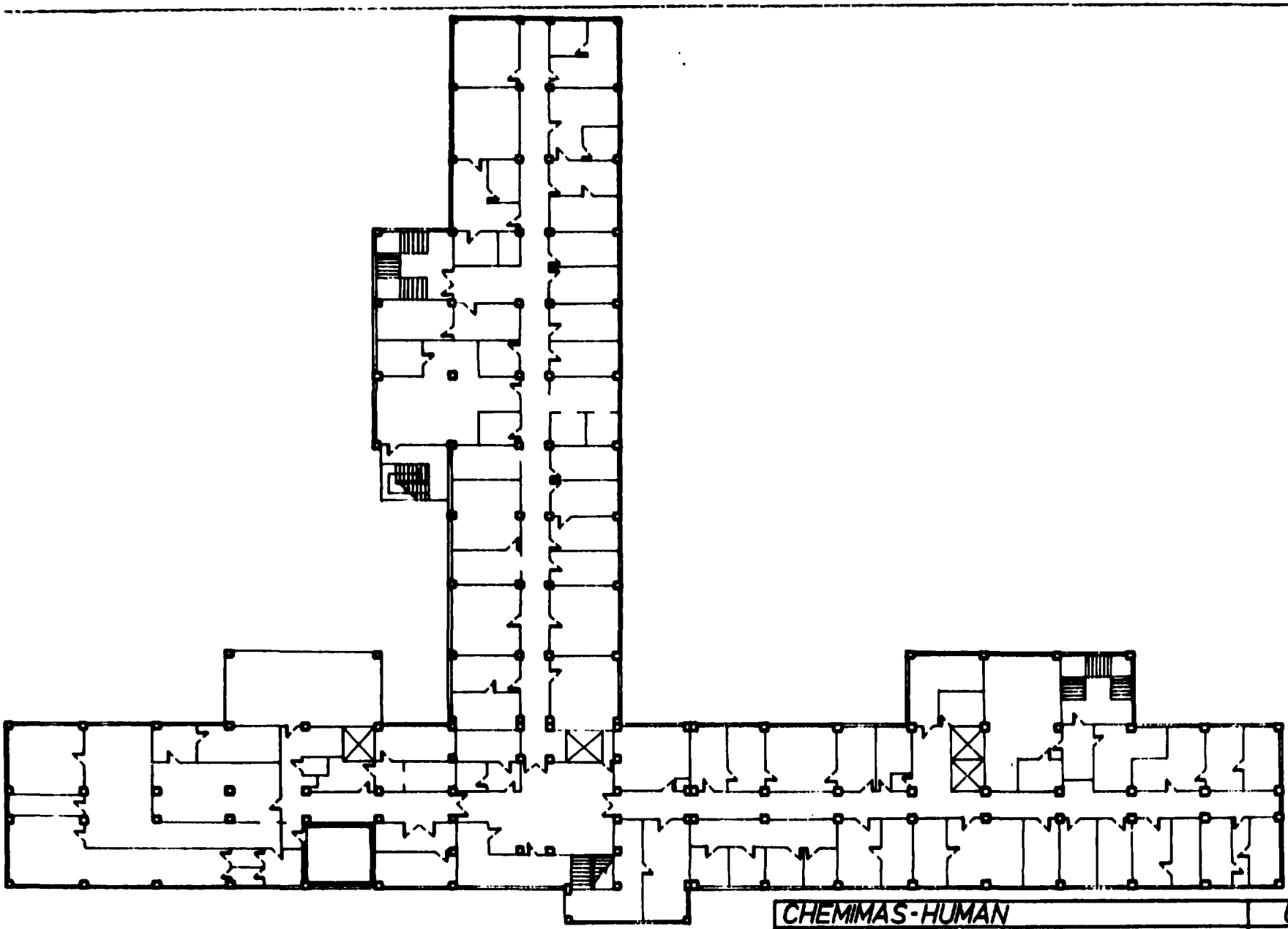
2. The rabies vaccine production meets the most essential requirements. According the calculation full production of the rabies vaccine block under present calculations can approximate reach

   0.5 - 0.6 million doses (Human)

   per year. This quantity is more than what is necessary for Venezuela.



CHEMIMAS HUMAN	UNIDO
Instituto Nacional De Higiene "Rafael Rangel" Rabies vaccine production	
LAY - OUT	



Second floor

CHEMIMAS-HUMAN	UNIDO
Instituto Nacional De Higiene "Rafael Rangel" Vaccine production	
GENERAL LAY-OUT	

3. Critical comments and recommendations:

- stable, well paid and well qualified staff;
- establishing of a good maintenance system;
- provide raw and auxiliary materials;
- set up production organization.

d) Critical comments and recommendation for the vaccines production in "Rafael Rangel"-Institute

1. Resulting from the analysis of information detailed above, the first fact to be mentioned is that the vaccine production of the INH cannot cover the national demand, either in the selection of products inevitable for the various public health programs of the Ministry of Public Health and Social Welfare, or in the volume of products in our days.

   Analysing of which factors inhibit the expansion of the production of very important vaccines, such as against measles, rubella and yellow fever, as well as of other biological products, such as equine hyperimmune sera (e.g. against snake venoms, etc.), and those produced in the Institute, it has to focus our attention on two specific causes. The first is that the present physical environment and equipment are not fully suitable for the production of various biological products. The second is that new generations of methods and techniques for production of biological products are not accepted or introduced.

   It is important to mention that the INH was established in terms of an Order of September 18, 1938 (Official Gazette, No.19.700), and moved into its present building in 1952. Biological products have been produced - with minimal modifications - under the same conditions for 35 years, and, originally, this environment was not planned specifically for this purpose, and, thus, various technological requirements of production of biologicals were not considered, either.

   On the other hand, again due to the lack of proper technological environment, the present production basis is actualiy the same as it used to be in the initial phase of production.

Practically, the fact is that the production of biologicals would be insignificant as to the national demands if the technical staff and personnel had not made efforts to modify the basic system of cultivation (Caracas fermentor) and to introduce technical innovations highly improving the effectivity of the traditional methods. This problem could be solved only through management decisions and efforts, as well as through strategical decisions. The former is connected with the national plans of the Institute Plan the Development of Venezuela, according to which, the country has to become self-sufficient producing biological products; this is important also strategically, with the aim to satisfy not only the national demands, but also to cover with these products the foreign market of the area under the geo-commercial influence of Venezuela (the Andean Pact, Central America, the Caribbean Area). The latter is related to the introduction and realization of more effective production methods and techniques of mass production.

In this order of ideas, there are existing alternatives for the realization of these political plans. The first would be the redimensionating of INH by constructing a new, modern centre. This would be started by the construction of a new Office Building and various laboratories producing biologicals at the first stage, then, at the later stages, also buildings required by other areas belonging to the scope of the Institute would be establishes. As to the production of biologicals, the transfer of suitable technologies should be ensured by specific contracts and agreements, which would involve the expansion of the product structure, the rise of production volume, all in rentable form and in harmony with the technological development of the area.

An other alternative would be the realization of a joint venture with a foreign company highly recognized in the field of production of biologicals: this would ensure the achievement of the above objectives.

1. The built in (nominal) capacity of INH is more than the present domestic demand in DPT, TT, rabies (Human) and cholera vaccines. There are, however, problems with the continuous training, payment of staff, maintenance and production organization.

2. There are quite a few expensive pieces of equipment out of use due to inexperience (mixing unit, freeze-dryer, fermentor, etc.).

3. The built in capacity is not yet fully utilized and at the same time there are export possibilities to neighbouring countries.

4. To stabilize production and to reach the stable nominal capacity the following action should be taken:

   - stable well paid and trained staff
     (supervision of the performance of workers, recruitment of qualified personnel, one worker should have only one full time job);
   - provide raw, auxiliary materials and spare parts;
   - hire two experts (through UNIDO)
     (one for management, duties:
     supervision of performance of workers,
     establish material flow and time norms,
     determine the real costs of products,
     set up production organization,
     financial planning,
     production planning;

one for maintenance, duties:
supervision of the performance of maintenance,
establish maintenance programmes,
establish preventive maintenance,
running a store for spare parts).

5. The Government policy is aimed at reducing the foreign exchange requirements of the economy and tp create exports. It is advisable, in the light of this, to increase the capacity of Instituto Nacional De Higiene "Rafael Rangel" at a minimal cost.
To stabilize annual production at

DPT 10-11 million doses
TT 6-7 million doses
Rabies 0.5-0.6 million doses (human)

and to keep the quality at a level meeting WHO requirements the following steps should be taken:

- a few new machines to be provided, total cost is 550.000 USD (a detailed study has to be carried out by the previous mentioned experts);
- stable well paid and trained staff;
- provide raw, auxiliary materials and spare parts;
- hire four experts 13 months each(through UNIDO)
(one for management, duties:
supervise the performance of workers,
set up production organization,
financial planning,
production planning;

one for technological tasks, duties:
establish material flow and time norms,
improve the technologies using the idle machines,
determine the real costs of products,
train the staff;

one for maintenance, duties:
supervise the performance of maintenance staff,
establish maintenance programmes,
establish preventive maintenance,
running a store for spare parts,
put into operation all the old and new machines;

one for distribution, duties:
set up a distribution network,
supervise the distribution,
distribution planning,
establish export,
export planning).

With this vaccine production, about 900-950 USD gross income could be earned annualy.

The quality control of vaccines plays a dominant role both is exports and domestic use. Quality control is an important requirement from both technical and economic points of view in vaccine production, therefore, independent quality control has to be established.

e) BCG-vaccine-production

- Flow diagramme of BCG-vaccine production

Process	Controls
Seed	Identity, virulent mycobacteria, contaminating microorganisms
Culture medium	Contaminating microorganisms
Cultivation	Contaminating microorganisms
Harvest	Opacity, total bacterial content, viability, contaminating microorganisms
Centrifuging Resuspension	
Bulk	Total bacterial content, virulent mycobacteria, viable count, contaminating microorganisms
Filling	
Freeze-drying	
Final product	Viable count, total bacterial content, identity, stability, Jensen test, contaminating microorganisms

Homogeneous culture system is developed for BCG production

Cultivation is performed in a bioreactor. The culture is harvested at the end of the logarithmic growth phase. After centrifuging and resuspension at the desired concentration, the suspension is filled in vials and lyophilized.

-Comments on BCG production

1. BCG production is performed in División de Enfermedades Crónicas - Departamento de Tuberculosis y Enfermedades Pulmonares . BCG vaccine production has been performed since 1926 but it was stopped from time to time. At present, there is no production. The new facilities will be ready and production will be started by the end of 1987.

2. To start the production and then to stabilize it, one expert may be hired (through UNIDO) for at least 3 months.

   The expert's duties:

   - supervise the performance of workers,
   - production planning,
   - financial planning,
   - set up production organization,
   - establish material flow and time norms,
   - technological transfer.

Summary

The DPT, TT, rabies vaccines production INH and BCG production in DEC correspond to the goals of the Government to reduce the foreign exchange requirements and to create export possibilities. The main factors, influencing the realization are as follows:

- stable, well paid and trained staff,
- a few new machines,
- short and long term consultants (experts).

f) Conventional Vaccines excluded from EPI

1. There are other vaccines exclusive from UCI.
   These are: Typhoid vaccine
   TAB vaccine (Typhoid and Paratyphoid A and B)
   Cholera vaccine

Out of these, only Cholera vaccine is produced in INH

g) Evaluation of UNIDO's Model programme

This programme is aimed at the promotion of the development of vaccines manufacture in developing countries. It contains a short description of the technology of all vaccines included in the EPI programme and of rabies vaccine. It describes in detail all the conditions necessary for the manufacture of vaccines taking into strict consideration the relevant WHO and GMP regulations. It contains detailed plans for the laboratories where the vaccines are to be manufactured, the quality control laboratory, the animal house, etc. listing also all the necessary equipment, machines, instruments, chemicals etc., number and qualification of the personnel required etc. It also includes the "cost-benefit" as well as the "risk-benefit" analyses taking into consideration various conditions.

The population of Venezuela is about 17.8 million. The analyses of the programmes related to a region of 200 million inhabitants (by 2000) are of fundamental importance for the realization of local vaccine manufacture, taking also into account of course, local peculiarities.
Present local manufacture seems to be realistic not only for domestic use but for export,too. And because the Government policy is aimed at reducing the foreign exchange requirement of the economy and at creating export as "reserved" national

investment, in accordance with Andean Pact principles it is advisable not only to increase INH capacity to sell the vaccines to the mentioned countries but on the basis of the export a new plant has to be set up as well.
To start the production for export, a decision should be made in order to establish a multiline plant to produce the required amounts of vaccines in Venezuela to meet the demand of the countries in the region/subregion showing interest in buying them. Otherwise, the question of where to set up this kind of plant remains open in the region.

It has to be added that a significant number of manufacturers in industrialized countries have withdrawn completely or partially from the conventional vaccine field. The increasing demand and the decreasing number of suppliers causes concern that the availability of vaccines in SELA countries might become critical during the forthcoming years.

One of the alternatives to ensure the availability of vaccines is the expansion of INH. The establishment of a new multiline vaccines production plant can be considered as a second option. There are also strong arguments for the above development from the aspects of promoting industrialization, greater self-sufficiency and self-reliance and of export economy, because the direct material costs and hard-currency content of other fixed and variable costs are only 25 %.

A few Member States of SELA that took interest in a regional vaccine production at the time of writing this report - were Bolivia, Chile, Cuba, Ecuador, Mexico, Nicaragua, Panama, Venezuela.

The Population
in millions

	1990	2000
Mexico	92.0	116.0
Cuba	11.0	12.0
Chile	13.0	15.0
Ecuador	11.0	15.0
Panama	2.0	3.0
Nicaragua	4.0	5.0
Bolivia	7.0	10.0
Venezuela	21.0	27.0
Total	161.0	203.0

Number of birth
in thousands

	1990	2000
Mexico	2900	3000
Cuba	200	200
Chile	300	300
Ecuador	300	500
Panama	100	100
Nicaragua	100	200
Bolivia	300	400
Venezuela	600	700
Total	4800	5400

Due to the fact that out of the 8 states Chile, Cuba, Ecuador, Mexico, Venezuela already produce vaccines and the situation might be the same as in Venezuela, it would be advisable to carry out a study the nominal and real capacities of the vaccine production plants. On the basis of a techno-economic survey, the Member States of SELA will be able to take further interest in the subject. Further valuable data in the field should be obtained from PAHO/WHO which had introduced the EPI programme in SELA countries.

The total estimated demand of the mentioned countries is: (has to be reconfirmed by PAHO)

Total demand of EPI vaccines
in thousand doses

	1990	2000
DPT	15000	17000
TT	5000	6000
BCG	5000	5500
Measles	5000	5000
OPV	15000	15500

Referring to the programme of co-operation between UNIDO and SELA signed on 10 April 1986, SELA officially asked UNIDO Secretariat to carry out an analysis on the present situation of vaccine production in the region.

Emphasizing the importance of this kind of analysis is shown by the situation in Venezuela where with a few experts and with a few new machines the production could be improved saving and earning a total of 950,000 USD foreign exchange annually.

It has to be mentioned that should a totally new plant be built and if it should produce annually

DPT	17.0 million doses
TT	6.0 million doses
BCG	5.5 million doses
OPV	15.5 million doses
Measles	5.0 million doses

with a 12.5 million USD investment. This kind of plant is included in the Government plans.

The main parameters of this plant are as follows:

A Bacterial vaccine production (BCG, DPT and separate TT plant)

space	450 m^2
equipment	1.5 million USD
staff	15 persons

B Live virus vaccines (measles)

space	450 m^2
equipment	1.3 million USD
staff	15 persons

C Inactivated virus vaccines production (polio, rabies)

space	550 m^2
equipment	2.0 million USD
staff	17 persons

D Central Kitchen

space	450 m^2
equipment	1.4 million USD
staff	19 persons

E Laboratories (microbiological, virological, potency testing)

space	950 m^2
equipment	1.8 million USD
staff	30 persons

F Formulation and packaging

space	950 m^2
equipment	3.5 million USD
staff	21 persons

TOTAL*

space	3550 m^2
equipment	11.5 million USD
staff	117 persons

(* Based on UNIDO Model Programme for the Production of Vaccines in Developing Countries)

In addition to the great potential of social benefits for Venezuela,a regional project for vaccine production could play an illustrative role in the industrialization strategy based on a more self-reliant and export orientated economy. In light of the importance of the subject and with a view to assisting Venezuela in the expansion of the biological subsector of its pharmaceutical industry the experts thoroughly support the setting up of a multiline vaccines production unit after the extension of INH capacity.

The research and development of new vaccines for the prevention and treatment of diseases which is already in progress could be carried out on a larger scale at the proposed multiline vaccines production unit. This can also help to justify the

investment in the development of new products for which the health demand is large. To be self-sufficient in the vaccine production is an important goal in public health so is the availability of high-technology (fermentation) which should also be considered in the decision process, otherwise the gap between the industrial and developing countries in this important field of biological industry will widen.

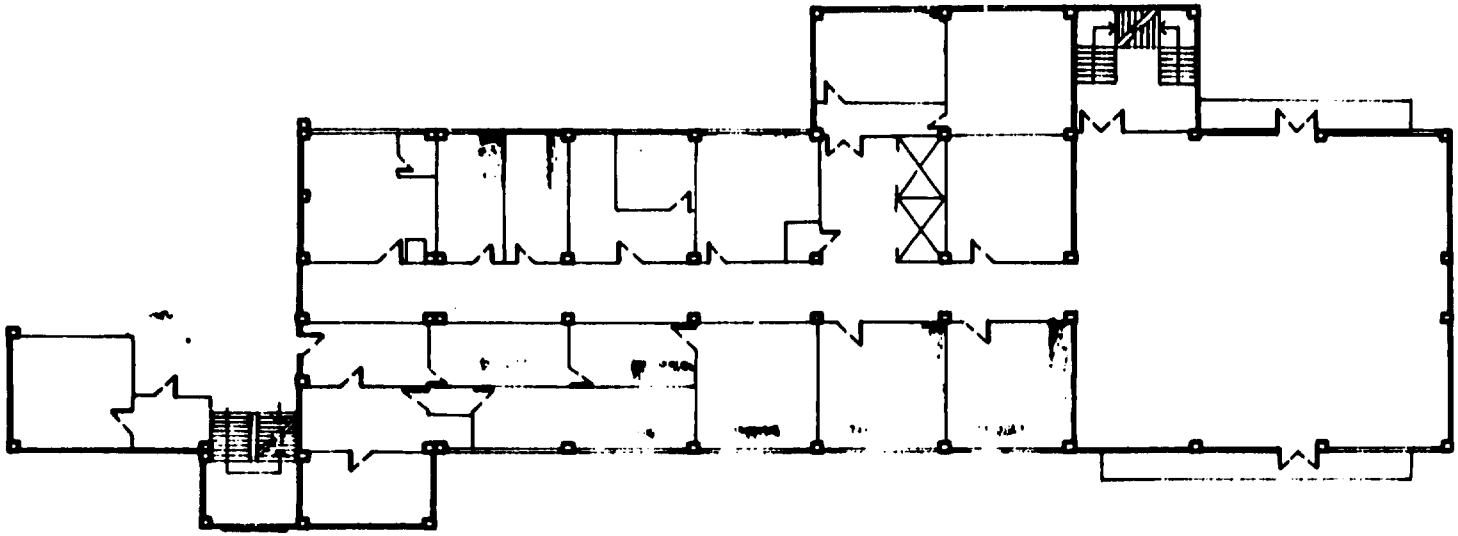
This idea is supported by the Government therefore the programme of setting up a new plant is included in the developmental plan.

h) Virus-Vaccines

Virus vaccines, included in EPI (OPV, Measles) are imported. Local production is planned in the proposed multiline unit.

i) Biologicals

The collection of blood is not regular. For transfusion blood is collected and used at hospital level. The establishment of the plasmafractionation capacity (for production of albumin and gamma globulin, etc.) is included in the developmental plan of the Government. Specific antigens are prepared in small volume in the INH for diagnosis of some enteral diseases (salmonella, shigella, etc.).



Third floor

CHEMIMAS - HUMAN	UNIDO
Instituto Nacional De Higiene "Rafael Rangel" Cholera production	
LAY-OUT	

VI. FINANCIAL AND ECONOMIC EVALUATION

There are two important aspects which should not be overlooked: the political and financial commitments to such an investment project and the marketability of the products manufactured locally. Politically, it can be demonstrated from start to finish that it is useful to the country. As far as financing is concerned, the governments accept that these are long term projects. The locally manufactured products must be competitive. As the previous chapters show, they are of comparable quality, safety and efficacy to the imported products with which health care personnel have become familiar over the years. The locally made products must always be available in the required qualities, at the right time, and in good condition if national immunization campaigns are to be conducted efficiently and effectively.

1. The Government of Venezuela has recently felt the need for arriving at some agreed general criteria for testing the cost differential arising out of the diversity of type and source of external assistance for development projects. As a general guideline the UNIDO form was taken as in the Manual for the Preparation of Industrial Feasibility Studies, and in the cost-benefit analysis.

2. This report does not deal with all of the principal components of costs of immunization like the wages of immunizators, travel cost, tests for monitoring the efficiency of immunization, only with the cost of production. The cost of the locally produced vaccines can not be calculated in the ususal way because the value of the machines, building and its depreciation, the factory overhead costs, administrative, sales and distribution costs are born by the Government or other organization as donation.

The direct materials and inputs, direct manpower cost are as below:

TT vaccine	0.14 Bs/dose
DPT vaccine	0.19 Bs/dose

The vaccines price for the UCI programme are:.

TT vaccine	1 Bs/ dose
DPT vaccine	1 Bs/dose

Because the whole UCI programme is donated by Government and they pay to the INH less than the actual cost, therefore financial and economic evaluation can not be determined in case of a single dose type form.

At present one vial contains 20 or 50 doses of vaccines. If the UCI programme will use only 50 doses per dosage form then the ex factory cost will be

DPT vaccine	0.20 Bs/dose (in form of 50 doses/vial)
TT vaccine	0.16 Bs/dose (in form of 50 doses/vial)

which includes the direct material, manpower and input costs.

3. A cost-benefit analysis for the UCI programme can be made. The main categories of benefits are:

- averted treatment costs,
- avoided production loss as a result of illness,
- avoided production loss as a result of premature death,
- improved health,
- positive external effects.

Although it is difficult to determine these benefits exactly quantitatively, but some examples are given below:

Tetanus

The treatment of tetanus is as follows:

Treatment cost:

The period of cure is 3 - 4 weeks in hospital, special and expensive medicines are needed, special equipment: artificial breathing unit, all of it costs around 400,000 - 600,000 Bs (20,000 - 30,000 US$) and the survival rate is only 20-50 %.

Production-loss:

There is no exact calculation method for loss determination. The working population is 5.1 million people and their production is annually 71,089 million Bs which means 13939 Bs/capita/year. One month loss is 1162 Bs.
The total annual cost of UCI is around 27,0 million Bs.
Taking all of the above factors into consideration one gets a rough idea that if there are over 1000 cases a year, then the UCI programme is worthwhile.

4. As long as the incidence of the mention diseases is very high, the effects in its victims are severe, and there is no effective treatment, vaccination generates social benefits exceeding its costs.

5. It should be mentioned that the risks of vaccination are closely related to the adverse reactions, which in turn depend on the purity (quality) and type of the biological product applied. Therefore in this study, good quality is considered a prerequisite for UCI and a product is considered to be of good quality if it complies with the WHO requirements. Since social benefits outweigh social costs, moreover international benefits are enjoyed, the participation of the health

authorities and public sector in the production is necessary in order to promote the idea that primary health care should be provided according to the needs and not according to the propensity to purchase.

VII. CONCLUSIONS AND RECOMMENDATIONS

1. The features of the production of biological materials are influenced by three variables. The first is connected to the production level, i.e. producers make efforts for mass production. The second is related to the expansion of the production structure, i.e. producers do their best to produce as many biological product types as only possible. The aim of this variable is to produce combined vaccines which partly help to reduce the operative costs of health programs, and partly simplify actual vaccination systems. The third variable is related to the realization of research programmes. The aim of these programmes is to improve the present methods by using new production technologies and to develop new biological product generations for the prevention and treatment of diseases.

   In the developed countries companies producting biological products often become united, mainly in order to gain technological advantages, thereby keeping up their production levels affected by market competition, and utilizing maximal effectivity. Transfer of technologies is of crucial importance for the Latin-American countries producing competitive biological products: this allows them to rise the production level and to expand their product mix.

2. The method used to estimate the vaccine demand for EPI takes the size of target population, the immunization schedule, number of wasted doses , coverage of the target population, etc. into consideration. Estimated annual demand for EPI vaccines in Venezuela is as follows:

DPT	3.0 - 3.2	million doses
TT	2.2 - 2.4	million doses
BCG	1.2 - 1.3	million doses
OPV	3.2 - 3.3	million doses
Measles	0.5 - 1.0	million doses
Rabies	0.3 - 0.35	million doses (Human)

3. At present DPT, TT and rabies vaccines are produced in the INSTITUTO NACIONAL DE HIGIENE "Rafael Rangel" (INH). The BCG have been produced in the DIVISION DE ENFERMEDADES CRONICAS - DEPARTAMENTO DE TUBERCULOSIS Y ENFERMEDADES PULMONARES. The built in (nominal) capacity of INH meets the present domestic demand. Although the INH is working within University Circle it has significant production activities and it requires an independent production organization. All aspects of production, such as financial planning, production planning, costing, maintenance, etc. should be carried out as if the unit were an independent company. To stabilize the production and reaching the nominal capacity the following action is suggested to be taken:

- to develop trained staff with high motivation (supervision of the performance of workers, recruitment of qualified personnel, one worker should have only one full time job);

- to provide the required amounts of raw, auxiliary materials and spare parts;

- to provide two experts (through UNIDO)
  one for management, duties:
  supervision of the performance of workers,
  establish material flow and time norms,
  determine the real costs of products,
  set up production organization,
  financial planning,
  production planning,

  one for maintenance, duties:
  supervision of the performance of maintenance,
  establish maintenance programmes,
  establish preventive maintenance,
  running a store of spare parts.

4. The Government policy is aimed at reducing the foreign exchange requirement of the economy and to create exports as "reserved" for national investment, in accordance with Andean Pact principles. To achieve the above it is advisable to increase INH capacity to sell the vaccines to the mentioned countries. The annual production in INH could be increased up to

DPT	10 - 11	million doses
TT	6 - 7	million doses
rabies	0.5 - 0.6	million doses (Human)

with the following steps:

- a few new machines to be provided, total cost is 550,000 USD (detailed study has to be carried out by the previously mentioned experts);

- development of trained staff with high motivation,

- providing raw, auxiliary materials and spare parts,

- provision of four international experts 13 months each (through UNIDO);

one for management, duties:
supervise the performance of workers,
set up production organization,
financial planning,
production planning;

one for technological tasks:
establish material flow and time norms,
improve the technologies using the idle machines,
determine the real costs of products,
train the staff;

one for maintenance, duties:
supervise the performance of maintenance staff,
establish maintenance programmes,
establish preventive maintenance,
running a store for spare parts,
put into operation all the old and new machines,

one for distribution, duties:
supervise the distribution,
distribution planning,
establish export,
export planning.

With this vaccine production, approximately 950 USD gross income could be earned annually.

The quality control of vaccines plays a dominant role both in export and domestic use. Quality control is an important requirement from both technical and economic points of view, therefore, an independent quality control has to be established.

Increasing BCG production will depend on the first year experiences, therefore, further advice can be given only after this period of time.

5. To start the production for export, a decision should be made in order to establish a multiline plant to produce the required amounts of vaccine in Venezuela to meet the demand of the countries in the region/subregion showing interest in buying them.
   Otherwise the question where to set up this kind of plant remains open in the region.
   It has to be added that a significant number of manufacturers in industrialized countries have withdrawn completely or partially from the conventional vaccine field. The increasing demand and the reducing number of suppliers causes concern that the availability of vaccines in SELA countries might become critical during the forthcoming years.
   One of the alternatives to ensure the availability of vaccines is the expansion of INH. The establishment of a new mulitiline vaccines production plant can be considered as a second option. There are also strong arguments for the above development from the aspects of promoting industrialization, greater self-sufficiency and self-reliance and of export economy, because the direct material costs and hard-currency content of other fixed and variable costs are only 25 %.

6. The few Member States of SELA that took interest in a regional vaccines production at the time this report was written are Bolivia, Chile, Cuba, Ecuador, Mexico, Nicaragua, Panama, Venezuela.

   Due to the fact that out of the 8 States Chile, Cuba, Ecuador, Mexico, Venezuela already produce vaccines and the situation might be the same as in Venezuela, it would be advisable to carry out a study about the nominal and real capacities of vaccines production plants. On the basis of a techno-economic survey, the Member States of SELA will be able to take further interest in the subject.

   The total estimated demand of mentioned States is:

Total demand of EPI vaccines
in thousand doses

	1990	2000
DPT	15000	17000
TT	5000	6000
BCG	5000	5000
Measles	5000	5000
OPV	15000	15500

In order to intensify the efforts made to set in motion the specific activities of Technical Co-operation among the Member Countries of the SELA, and within the context of the mandate of Decision No.226 of the XII. Regular Meeting of the Latin American Council (SELA), which in its articles 3 and 5 defines the priority areas for action and instructs the Permanent Secretariat, on the basis of the experience accumulated, to back the Member States in formulating Specific Projects, the Permanent Secretariat of SELA submits to the Ad-Hoc Group for its consideration this proposal for multilateral TCDC action as a Latin American option towards self-sufficiency in the production of human vaccines, a subject which is part of the field of biotechnology. Vaccination against immuno-preventivable diseases is considered to be the cheapest and most efficient way of preventing morbidity and mortality from a group of diseases that could well be erradicated from society by active immunization. The need for biologicals to be produced in developing countries with high rates of incidence and prevalence of infectious-contagious diseases that can be prevented by vaccination - such as diphtheria, whooping cough(pertussis), tetanus, poliomyelitis,measles, tuberculosis and rabies - has recently become imperative.

With backing from the PAHO, WHO and UNICEF , from its outset, the programme has noticeably assisted to improve vaccination coverage for the children of Latin America, managing to reduce morbidity and mortality from those diseases considerably. Despite those achievements, diseases such as measles, poliomyelitis, neonatal tetanus, whooping cough and tuberculosis are still the cause of high morbidity and mortality levels of children in many countries of the region. (See Annex No. VI. "Cases of Diseases Notified through the EPI".)

In order to meet the rising demand for vaccines, current SELA' countries production capacities must be increased in the midst of somewhat uncertain conditions for the biologicals industry, which many consider to be a high risk and low return venture. On the other hand, the need to increase vaccine production capacities may in all probability lead to higher costs and force organizations to take another possible option and to ensure the supply of vaccines to the EPI in Latin America by manufacture them at national, subregional and regional level. Annex VII. taken from the PAHO Director's Report of July 1985. on the progress made in the Expanded Programme on Immunization in the Americas shows that 11 countries of the Americas can produce bacterial vaccines such as DPT, DT and BCG. Those countries have a production capacity of some 60 million doses, but the majority of them do not operate at their maximum installed capacity.

Immunization programmes have been implemented systematically in the last 30 years in the majority of countries in Latin America. A review of vaccine consumption in recent years indicates a significant, constant increase in the demand for this item, partly due to the growth of the population, and partly to the increased coverage of programmes in the region.

The project to manufacture vaccines on an industrial scale in Latin America takes into account a broader market that ideally includes all the countries of the subregion. The programme would also consider an integrated production system characterized by the maximum utilization of human resources and infrastructure existing in the countries participating in the manufacturing process.

Ten Latin American currently produce bacterial vaccines (Triple, BCG), and 3 countries produce viral vaccines (polio, measles), but the fact remains that a few countries' production volume allows it to be self-sufficient. An important aspect as regards the quality of the vaccines produced in some Latin American countries, is that some products distributed do not comply with all the WHO requirements and consumers in the producing country itself tend to prefer to buy vaccines from industrialized countries.

The goal is to achieve uniformity in manufacture and quality control processes, optimum use of raw materials and equipping of the different production units, which would facilitate the transfer of technology, cut the cost of acquiring raw material and equipment, and improve servicing, maintenance and distribution of the final product.

The programme of producing biologicals, includes transfer and exchange of technology, and the acquisition of raw materials and equipment from the different countries. The integrated programme will lead to a cost reduction in the different budget items involved in production, at the same time will stimulate the economy in areas related to the sector that produces biologicals as such. It will also help create employment and develop advanced technologies that will serve as a back-up to research and development activities.

It is thought that the development of activities in this field, responding to a programme of different stages, each of them of growing complexity, have to be included in the future UNIDO report:

- Exchange of information, technology, human resources and equipment.

- Standarization of selected manufacturing procedures, quality control, equipment and raw materials.

- Agreements for production, and distribution areas and for the regulation of the biologicals market.

- Lastly it would be advisable in the short term to prepare a detailed study and later on a feasibility study of a project of this nature.

7. Referring to the programme of co-operation that UNIDO and SELA signed at 10 April 1986, SELA officially requested UNIDO Secretariat to carry out an analysis of the present situation of the vaccines production in the region as described in the previous para No. 9.
Emphasizing the importence of this kind of analysis is shown by the situation in Venezuela where with a few experts and with a few new machines the production could be improved saving and earning a total of 950.00 USD foreign exchange annually.

8. It has to be mentioned that should a totally new plant to be built it should produce annually

DPT	17.0	million doses
TT	6.0	million doses
BCG	5.5	million doses

OPV	15.5	million doses
Measles	5.0	million doses

vaccines, with a 12.5 million USD investment. This kind of plant is included in the developmental plan of the Government.
The main caracteristics of this plant are as follows:

A Bacterial vaccine production (BCG,DPT and separate TT plant)

space	450 m^2
equipment	1.5 million USD
staff	15 persons

B Live virus vaccines (measles)

space	450 m^2
equipment	1.3 million USD
staff	15 persons

C Inactivated virus vaccines production (polio, rabies)

space	550 m^2
equipment	2.0 million USD
staff	17 persons

D Central Kitchen

space	450 m^2
equipment	1.4 million USD
staff	19 persons

E Laboratories (microbiological, virological, potency testing)

space	800 m^2
equipment	1.8 million USD
staff	30 persons

F Formulation and packaging

space	950 m^2
equipment	3.5 million USD
staff	21 persons

TOTAL *

space	3550 m^2
equipment	11.5 million USD
staff	117 persons

(* Based on UNIDO Model Programme for the production of Vaccines in Developing Countries.)

9. In addition to the great potential of social benefits for Venezuela , a regional project for vaccine production could play an illustrative role in to industrialization strategy based on a more self-reliant and export orientated economy. In light of the importance of the subject and with a view of assisting "enezuela in the expansion of the biological subsector of its pharmaceutical industry the experts throughly support the setting up a multiline vaccines production unit after the extension of INH capacity.

10. The research and development of new vaccines for the prevention and treatment of diseases,which in IVIC is already in progress could be carried out in a larger scale at the proposed multiline vaccines production unit.
This can also help to justify the investment in the development of new products for which the health demand is large.

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SYMBOLS /EXPLANATORY NOTES/

WHO	World Health Organization
PAHO	Organización Panamericana de la Salud
IVSS	Institute of Social Security
MOHASA	Ministry of Health and Social Assistance
Bs	Venezuelan currency Bolívares present rate on the free market 1 USD = 22.8 Bs, for medicine 7.7 Bs and all other items 14.8 Bs.
USD	United State Dollar
EPI	Expanded Programme of Immunization
UCI	Universal Child Immunization
GMP	Good Manufacturing Practice
ELISA	Enzyme Linked Immuno Sorbent Assay
DEC	División Enfermedades Crónicas Departamento de Tuberculosis y Enfermedades Pulmonares
INH	Instituto Nacional de Higiene "Rafael Rangel"
IVIC	Instituto Venezolano de Investigaciones Científicas
GNP	Gross National Product
GDP	Gross Domestic Product
FDA	Bureau of Biologics of the Food and Drug Administration (USA)
UNICEF	United Nations Children's Fund
DPT	Diphtheria and Tetanus Toxoids and Pertussis Vaccine
BCG	Bacillus Calmette-Guerin Vaccine

ANNEXES

ANNEX I.

GOVERNMENT OFFICIALS, INSTITUTIONS CONTACTED BY THE MISSION

UNDP Office, Caracas

Mr. Alfredo Jefferson, Deputy Resident Representative
Mr. Hermann von Gersdorff, SPO
Ms. Sandra Dobelis de Medina, Coordinator

Ministry of Health and Social Assistance

Dr. Pablo Salcedo Nadal, Director General
Dr. Rafael Travieso, Director
Ms. Helena Michailas, Director

Calier Internacional

Mr. Víctor Morales Oliver, Vice President
Mr. Carlos E. Oropesa, Director
Mr. Ovidio A. Guerara M., Director

UNIDO, Vienna

Dr. A. Tcheknavorian-Asenbauer, Head of the Chemical Industries Branch
Dr. Jean Lanet, Chief of Pharmaceutical Industries Unit
Dr. Zoltan Csizer, Backstopping Officer

Instituto Venezolano de Investigaciones Científicas (IVIC)

Dr. Boris D. Drujan, General Director
Dr. José Azócar S.,
Dr. Paul Walder, Director of Technology

Instituto Nacional De Higiene "Rafael Rangel" (INH)

Dr. Felipe Bello Gonzalez, President
Dr. Jose Casanova, Vice President
Dr. Tomas Goldstein, Director
Dr. David Diaz, Personnel Director
Dr. Luisa Obregen der Aue, Manager

Sistema Económico Latinamericano (SELA)

Mr. Jayr Oezolt, Director
Mr. Ruber Garcia Lbaguno, Director
Mr. Braulio Boris Castillo, Manager

Organización Panamericana de la Salud (PAHO)

Dr. Barry Whalley, Resident Representative

División de Enfermedades Crónicas

Dr. Manuel Adrianza, Director

Shulton S.A.

Mr. Karoly Adam K.

Lummins Engine Co.

Mr. Miguel Tellez H., Manager
Mr. Gilbert S. Hodge, Director

ANNEX II.

Capacity of the local TT vaccine production

At present situation

Method of the production	Static culture
Volume of the glass bottles	15 litres
Volume of the culture in one week	100 litres
Cultivation cycle	7 days
Toxin concentration at the harvest	40 Lf/ml
Recovery efficiency	70 %
Yield from one cultivation	2.8×10^6 Lf
Doses/5Lf/ in one week/ 10 % loss is included	5×10^5
Doses/5Lf/ in one year/ 10 % loss is included	25×10^6
Capacity of TT production/10 Lf/	7×10^6 doses/year
Capacity of DPT production/5 Lf/	11×10^6 doses/year

ANNEX III.

Capacity of the TT-vaccine production using fermentor

Method of production	fermentation
Type of the fermentor	Tetano-Paljas
Fermentor size	100 litres
Operating volume	80 litres
Cultivation cycle	7 days
Number of cultivations in one week	1
Toxin concentration at harvest	60 Lf/ml
Recovery efficiency	70 %
Tetanus toxin produced in one fermentation	$3.36 - 10^6$ Lf
Doses /5Lf/ in one week/10 % loss is included	6×10^5
Doses/5Lf/in one year 10 % loss is included	30×10^6
Capacity of TT production/10 Lf/	7.5×10^6 doses/year
Capacity of DPT production/5 Lf/	15×10^6 doses/year

(Using a 200 litre fermentor the capacity could even be twice as high)

ANNEX IV.

Capacity of the local Diphtheria toxoid production

Method of production	fermentation
Type of fermentor	Ce ;
Fermentor size	3 ۷ ۰ litres
Toxin concentration at harvest	100 Lf/ml
Cultivation cycle	2 days
Number of cultivation in one week	2
Recovery efficiency	70 %
Diphtheria toxin produced in one fermentation	3.15×10^6 Lf
Doses/15 Lf/in one week 10 % loss is included	1.2×10^5
Doses/15 Lf/in one year/10 % loss is included	6×10^6

ANNEX V.

Capacity of the Pertussis Vaccine production

Method of production	fermentation
Type of the fermentor	Caracas
Fermentor size	6 x 15 litres
Cultivation cycle	2 days
Number of cultivation in one week	2
Bacterium count at harvest	3×10^{10} bacterium/ml
Recovery efficiency	70 %
Bacterium suspension in one week	3.78×10^{15}
Doses/1.5×10^{10}/in one week/ 10 % loss is included/	2.3×10^{5}
Doses/1.5×10^{10} / in one year/ 10 % loss is included	11.5×10^{6}

ANNEX VI.

CASES OF DISEASES NOTIFIED UNDER THE EPI

Number of cases of measles, poliomyelitis, tetanus, diphtheria and whooping cough notified between 1 January, 1985 and the date of the last report, and for the same epidemiological period of 1984, classified by country.

Subregion and Country	Date of last report	Measles '85	Measles '84	Polio '85	Polio '84	Tetanus Non Neonatorum '85	Tetanus Non Neonatorum '84	Tetanus Neonatorum '85	Tetanus Neonatorum '84	Diphtheria '85	Diphtheria '84	Whooping cough '85	Whooping cough '84
NORTH AMERICA													
Canadá	7 Sep.	2.031	...	—	...	2°°	...	...	...	5	...	1.036	...
Estados Unidos	5 Oct.	2.496	...	5	3	50°°	...	...	...	1	...	2.177	...
CARIBBEAN													
Antigua y Barbuda	10 Ago.	1	...	—	—	—	...	1	...	—	...	—	...
Bahamas	5 Oct.	21	...	—	—	5	...	—	...	—	...	1	...
Barbados	5 Oct.	2	4	—	—	—	3	—	—	—	—	—	—
Cuba	20 Abr.	1.277	1.552	...	—	...	1	...	—	...	—	18	39
Dominica	7 Sep.	60	8	—	—	—	—	—	—	—	—	—	1
Granada	5 Oct.	7	...	—	—	—	...	—	...	—	...	—	...
Haití	•	...	...	...	...	...	...	...	...	...	...	...	...
Jamaica	10 Ago.	46	220	...	—	...	2	...	1	...	5	1	26
República Dominicana	•	...	...	...	—	...	...	...	...	...	...	...	...
San Cristóbal-Nieves	18 Mayo	22	1	—	—	—	—	—	—	—	—	—	—
San Vicente y Granadinas	23 Feb.	1	1	...	—	...	—	...	—	...	...	1	—
Santa Lucía	10 Ago.	7	...	—	—	—	...	—	...	—	...	—	...
Trinidad y Tabago	7 Sep.	3.158	3.303	—	—	8	12	—	—	—	—	—	—
CONT'L. CTRL. AMERICA													
Belice	5 Oct.	5	...	...	—	2	...	...	...	...	...	35	...
Costa Rica	23 Feb.	—	—	—	—	—	—	—	—	—	—	20	54
El Salvador	20 Abr.	1.046	934	2	17	17	26	9	8	3	8	66	126
Guatemala	18 Mayo	945	...	13	14	22	...	2	...	8	...	477	...
Honduras	7 Sep.	5.539	1.272	...	...	14	11	3	13	—	—	168	368
México	5 Oct.	17.065	3.515	108	116	240°°	278°°	...	...	4	8	1.790	1.341
Nicaragua	•	...	...	...	—	...	...	...	...	...	...	...	...
Panamá	13 Jul.	583	243	—	—	1	3	6	3	—	—	80	112
SO. AMER. TROP. ZONE													
Bolivia	22 Mar.	73	615	...	...	5°°	8°°	...	...	8	6	311	318
Brasil	23 Feb.	8.562	7.915	113	109	316	352	75	85	313	451	3.610	3.192
Colombia	•	...	...	4	16	...	...	...	...	...	...	...	...
Ecuador	23 Mar.	597	2.863	—	—	15	16	19	14	7	13	191	127
Guyana	20 Abr.	43	45	...	—	2	4	...	...	43	—	1	—
Paraguay	10 Ago.	284	314	3	1	40	42	47	54	13	7	238	285
Perú	4 Nov.	...	...	31	102	...	...	...	...	...	...	...	...
Suriname	18 Mayo	65	16	—	—	—	2°°	...	...	—	—	—	—
Venezuela	13 Jul.	16.628	5.329	6	8	—	...	—	...	4	1	1.908	682
SO. AMER. TEMP. ZONE													
Argentina	13 Jul.	6.438	6.563	—	1	68°°	185°°	...	...	7	8	3.882	6.988
Chile	5 Oct.	6.764	2.900	—	—	20°°	19°°	...	...	141	181	602	809
Uruguay	23 Feb.	7	—	—	—	—	1	—	—	—	—	6	20

• no information received for 1985
°° Total No. of cases of tetanus; country does not notify cases of neonatorum tetanus separately.
§ Data for poliomyelitis up to week 43 (ending 26 Oct.)

— Zero
... No data available

Cuadro 1

Casos Notificados de Enfermedades del PAI *

Número de casos de sarampión, poliomielitis, tétanos, difteria y tos ferina notificados desde el 1 de enero de 1985 hasta la fecha del último informe, y para el mismo período epidemiológico de 1984, por país

Subregión y país	Fecha del último informe	Sarampión		Poliomielitis§		Tétanos				Difteria		Tos Ferina	
						No Neonatorum		Neonatorum					
		1985	1984	1985	1984	1985	1984	1985	1984	1985	1984	1985	1984
AMERICA DEL NORTE													
Canadá	7 Sep.	2.031	...	—	...	2**	...	...	...	5	...	1.036	...
Estados Unidos	5 Oct.	2.495	...	5	3	50**	...	...	...	1	...	2.177	...
CARIBE													
Antigua y Barbuda	10 Ago.	1	...	—	—	—	...	1	...	—	...	—	...
Bahamas	5 Oct.	21	...	—	—	5	...	—	...	—	...	1	...
Barbados	5 Oct.	2	4	—	—	—	3	—	—	—	—	—	—
Cuba	20 Abr.	1.277	1.552	...	—	...	1	...	—	...	—	18	39
Dominica	7 Sep.	60	8	—	—	—	—	—	—	—	—	—	1
Grenada	5 Oct.	7	...	—	—	—	...	—	...	—	...	—	...
Haití	•	...	...	...	...	...	...	...	...	...	...	...	...
Jamaica	10 Ago.	46	220	...	—	...	2	...	1	...	5	1	26
República Dominicana	•	...	...	...	—	...	...	...	...	...	...	...	...
San Cristóbal-Nieves	18 Mayo	22	1	—	—	—	—	—	—	—	—	—	—
San Vicente y Granadinas	23 Feb	1	1	...	—	...	—	...	—	...	...	1	—
Santa Lucía	10 Ago	7	...	—	—	—	...	—	...	—	...	—	...
Trinidad y Tabago	7 Sep.	3.158	3.303	—	—	8	12	—	—	—	—	—	—
MESOAMERICA CONTINENTAL													
Belice	5 Oct.	5	...	...	—	2	...	...	...	...	...	35	...
Costa Rica	23 Feb.	—	—	—	—	—	—	—	—	—	—	20	54
El Salvador	20 Abr.	1.046	934	2	17	17	26	9	8	3	8	66	126
Guatemala	18 Mayo	945	...	13	14	22	...	2	...	8	...	477	...
Honduras	7 Sep.	5.539	1.272	...	...	14	11	3	13	—	—	180	368
México	5 Oct.	17.065	3.515	108	116	240**	278**	...	...	4	0	1.790	1.341
Nicaragua	•	...	...	...	—	...	...	...	...	...	...	...	...
Panamá	13 Jul.	583	243	—	—	1	3	6	3	—	—	80	112
SUDAMERICA ZONA TROPICAL													
Bolivia	23 Mar.	73	615	...	...	5**	8**	...	...	8	6	311	318
Brasil	23 Feb	8.562	7.915	113	109	316	352	75	85	313	451	3 410	3 192
Colombia	•	...	...	4	16	...	...	...	...	...	...	...	...
Ecuador	23 Mar.	597	2.863	—	—	15	16	19	14	7	13	191	127
Guyana	20 Abr.	43	45	...	—	2	4	...	...	43	—	1	—
Paraguay	10 Ago.	284	314	3	1	40	42	47	54	13	7	238	285
Perú	4 Nov.	...	...	31	102	...	...	...	...	...	...	...	...
Suriname	18 Mayo	65	16	—	—	—	2**	...	...	—	—	—	—
Venezuela	13 Jul.	16.628	5.329	2	8	—	...	—	...	4	1	1.508	682
SUDAMERICA ZONA TEMPLADA													
Argentina	13 Jul.	4.438	4.563	—	2	48**	105**	...	...	7	8	3.082	6.988
Chile	5 Oct.	6.764	2.900	—	—	20**	19**	...	...	141	101	602	589
Uruguay	23 Feb.	7	—	—	—	—	1	—	—	—	—	6	20

* No se ha recibido información de 1985.

** Número total de casos de tétanos; país no notifica por separado casos de tétanos neonatorum.

§ Datos para poliomielitis hasta semana 43 (terminada 26 de octubre).

— Cero.

... No se dispone de datos.

Tomado de Ref. 2

ANNEX VII.

Table-2

Countries producing bacterial vaccines in Latin America, 1984

Vaccine	Type	Country	Laboratory	Strain
BCG	Freeze dried	Argentina	Córdoba	Paris,1173
		Brazil	A.Paiva	Moreau
		Cuba	C.Finlay	Moreau
		Mexico	Inst.Nacional de Higiene	Copen.1331
	Liquid	Ecuador	Inst.Nacional de Higiene Guayaquil	Gottemburg
		Uruguay	Lab.Calmette	Paris 1173
DPT	Submerged culture	Brazil	Butantan	
		Venezuela	Instituto Nacional de Higiene	
		Mexico	Instituto Nacional de Higiene	
		Chile	Instituto de la Salud Pública	
Tetanus	Submerged culture	Brazil	Butantan	
		Mexico	Instituto Nacional de Higiene	
DPT	Conventional	Argentina	Instituto Malbran	
		Ecuador	Instituto Nacional de Higiene	
		Peru	Instituto Nacional de la Salud	
		Cuba	Carlos Finlay	
		Brazil	Butantan, Fiocruz	
		Chile	Instituto de Salud Pública	
		Colombia	Instituto Nacional de Salud	
		Venezuela	Instituto Nacional de Higiene	

Countries producing viral vaccines in Latin America, 1984

Vaccine	Country	Laboratory	Strain	Type	Annual Production*
Polio (oral)	Mexico	Inst.Nacional de Virología	Sabin	1	6
Measles	Brazil	Bio Manguinhos	CAM-70	16	9
	Cuba	C. Finlay	Leningrad		being developed
	Mexico	Inst.Nacional de Virología	Edmonston-Zagreb		5

* Millions of doses

ANNEX VIII

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