



WORLD HEALTH ORGANIZATION
 ORGANISATION MONDIALE DE LA SANTE

DAP/85.11

ORIGINAL: ENGLISH

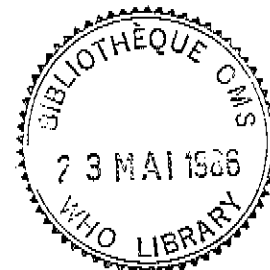
*WHO Doc. In vaccines, parenteral
 solutions*

3674

*no Fyol
 2.10.88*

GUIDELINES AND RECOMMENDATIONS FOR THE ESTABLISHMENT
 OF A LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT
 (L. V. P. S. P. P.) IN DEVELOPING COUNTRIES

by Dr Stefano Raffaelli



The issue of this document does not constitute formal publication. It should not be reviewed, abstracted, quoted or translated without the agreement of the World Health Organization. Authors alone are responsible for views expressed in signed articles.

Ce document ne constitue pas une publication. Il ne doit faire l'objet d'aucun compte rendu ou résumé ni d'aucune citation ou traduction sans l'autorisation de l'Organisation mondiale de la Santé. Les opinions exprimées dans les articles signés n'engagent que leurs auteurs.

TABLE OF CONTENTS

	<u>Page</u>
I. Introduction	2
II. Acknowledgements	3
III. Description of Large Volume Parenteral Solutions Types	4
IV. Importance of LVP Solutions in modern medicine	5
V. Aim of the Proposal (Scope of work)	5
VI. The LVP Solutions Production Plant (LVPSPP)	6
A. A rationale for local formulation	6
B. Selections of formulas and kind of packaging	6
C. Raw materials	9
D. Recommended criteria for the planning, design, construction, operation and maintenance of the proposed LVPSPP	9
E. Economic and feasibility considerations	9
Annex I. - The Hospital Size Plant (Model A)	15
Annex II. - The Industrial Plant (Model B)	17
Annex III. - Production equipment and Quality Control Instruments	32
Annex IV. - Personnel qualifications, training of personnel	37
Annex V. - WHO Drawings Schedule	41

I. INTRODUCTION

The concept of essential drugs and vaccines, conceived and developed in WHO over the last five years, forms one of the basic components of primary health care. The Declaration of Alma Ata highlights the importance of the availability of essential drugs and vaccines and the regular supply of a limited number of essential drugs is one of the indicators of the success of the Global Strategy for Health for All by the Year 2000. The WHO Seventh General Programme of Work clearly indicates the objectives and targets for the WHO Action Programme on Essential Drugs and Vaccines in support of the primary health care strategy.

Resolutions EB61.R17, EB63.R20, WHA31.32, WHA32.41 and WHA35.27 laid the basis for the establishment in 1981 of the WHO Action Programme on Essential Drugs and Vaccines. In the same year, the UNICEF/WHO Joint Committee on Health Policy adopted a joint WHO/UNICEF programme for support to the provision of essential drugs for primary health care in developing countries.

It is within the above resolutions and the spirit of the Action Programme on Essential Drugs and Vaccines that the following guidelines for the establishment of a Large Parenteral Solution Production Plant for the local production of the most widely used infusions, in developing countries is presented.

The guidelines for the establishment of Large Volume Parenteral Solution Production Plants (LVPSPP) in developing countries consists of: (a) buildings, (b) equipment, (c) instruments, (d) infrastructures, and (e) outline of training programmes for operative personnel. It also includes health and safety standards, GMP guidelines and ecological

considerations at the least possible investment cost and greatest reliability to enable manufacture, support and control of manufacture of essential infusions in developing countries.

The above LVPSPP attempts to provide alternative solutions for the problems faced by the developing countries in the field of local formulation of essential drugs. This model gives consideration to pre-fabricated materials to facilitate developing countries to overcome some local technical constraints. However, it is strongly recommended that during the feasibility studies, local availability of adequate building materials should be thoroughly investigated.

In addition, the LVPSPP includes considerations of manpower and adequately trained personnel requirements, the use of selected formulas and packaging.

Two alternative plants are presented: Hospital plant with an annual manufacturing capability of 250,000 infusions (500 ml cap. each), this model can be sufficient for a community of 2-3 million population; and a second one, with a yearly capacity of 1,350,000 litres infusions, which can supply the needs of a community of 10-15 million people.

Since these guidelines are a preliminary approach to the establishment of LVPSPP in developing countries, both models require a complete feasibility study, taking into account local climatic conditions, infrastructures, availability of qualified personnel, etc. before a decision is made about their establishment.

WHO should continue to provide assistance in obtaining the necessary technology for the operation of the plant, which includes master formulae, operating procedures, in-process control, etc. This specific feature would substantially accelerate the transfer of technology needed by the developing countries.

Training programmes for production and quality control personnel needs to be developed and WHO could provide the necessary input for implementing countries.

It is considered that those countries with a population of less than 10 million might like to consider joint projects to implement LVPSPP with neighbouring countries through the Technical Cooperation among Developing Countries (TCDC) approach.

Return of investment of plant can be scheduled in 4-5 years.

These guidelines are provided in order to allow Member States, interested in establishing production plants for Large Volume Parenteral Fluids to quickly appraise the magnitude of the project and adjust the basic guidelines to their national realities. It is also expected that these guidelines will assist in the preparation of concrete feasibility studies for local production of the most used parenteral fluids.

* * *

II. ACKNOWLEDGEMENTS

The author would like to express his gratitude for help received from various knowledgeable professionals who have contributed to the development of these guidelines. Special mention should be made to Dr E. Lauridsen, World Health Organization, Geneva, Switzerland; Dr F.S. Antezana, World Health Organization, Geneva, Switzerland; Mr J. Hedges, ASTRA, United States of America; Dr G. Battaglino, Ministry of Health, Rome, Italy and Mr A. Bertuzzi, OLSA, Milan, Italy for their valuable contribution. The content of this document remains the author's responsibility.

The author would also like to give recognition to WHO for its support and for providing the opportunity to develop these guidelines within the Action Programme on Essential Drugs.

III. DESCRIPTION OF THE LARGE VOLUME PARENTERAL SOLUTIONS TYPES

Even if well known, we take the opportunity to recapitulate in the following pages the description of parenteral solutions, their fields of use, and the importance in modern medicine.

The Large Volume Parenteral Solutions are fundamentally simple formulas: made up of salts or sugars, or mixtures of both, dissolved in water. However, the final product shall meet requirements of the highest standard of quality, due to its specific application and use.

In Table 1, briefly described below, the different types of parenteral solutions appear.

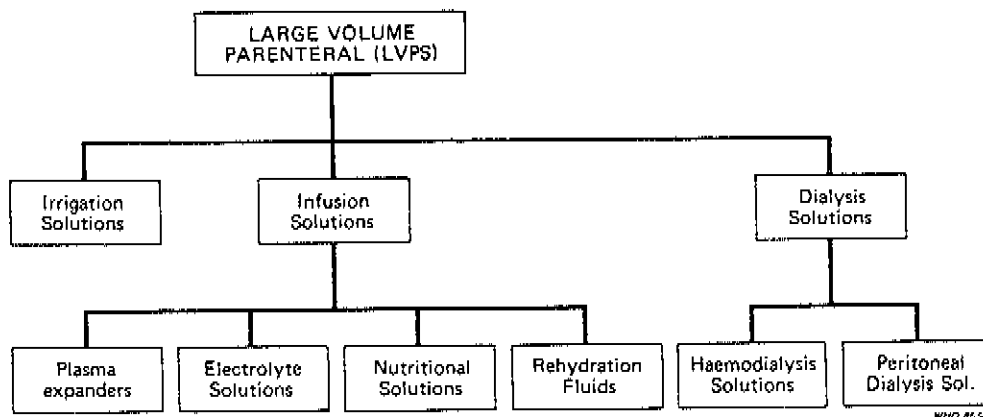


TABLE 1.

Irrigation fluids

They are used in surgical procedures, such as for rinsing of body cavities with antibiotic solutions.

Infusion solutions

They might be given either intravenously (most common) or subcutaneously. There are several types of such solutions depending on the medical needs, and their uses are varied.

1. Plasma expanders: This kind of solution, e.g., Dextran, substitutes the blood lost due to accident or during a surgical operation, etc.
2. Rehydration fluids: They are mainly used to restore severe loss of liquids in patients due to diarrhoea, when the general conditions of the patient are so bad that he cannot take rehydration fluids by mouth (e.g., NaCl solution).
3. Nutritional solutions: They are normally sugar solutions, given to patients not able to be fed normally, e.g., after serious abdominal surgery or when the patient is in coma (e.g. Dextrose solutions, aminoacid solutions).
4. Electrolyte solutions: These solutions serve to restore the proper electrolyte balance of the patient (e.g., Darrow solutions).

Dialysis solutions

These solutions are absolutely necessary when the kidney functions are diminished; and, as a consequence, they cannot eliminate the toxic waste products from the body.

1. Haemodialysis solutions: Normally, they are very concentrated salt solutions and are used with an artificial kidney, diluted with demineralized water.

2. Peritoneal dialysis solutions: These are similar solutions to the above, but sterile. Instead of the artificial kidney, it is possible to use the peritoneum of the patient as a membrane. Two litres of solution are given directly from the container into the peritoneum. After the necessary time in the body of the patient, the solution is drained off again into the container with the waste products, which have passed from the body through the peritoneum.

IV. IMPORTANCE OF PARENTERAL SOLUTIONS IN MODERN MEDICINE

The importance of the use of parenteral solutions in modern therapy is today very well known.

Not only in case of epidemic (e.g., cholera), but also in the daily hospital practice, the use of parenteral solutions is spreading more and more; and the need for them is growing every day.

Large volume intravenous fluids are vital in the treatment of traumatic shocks of burns with consequence of dehydration.

The use of parenteral solutions permits not only to correct organic disfunctions, such as the acid-base or saline balance in the organism, but also to administer some drugs to the patient and to feed him as well. This enables a considerable reduction of the hospitalization time of the patient.

It is estimated today that most developed countries' consumption of LVPS is about 500 ml to 1 litre per capita per year.

In some developing countries the consumption per capita is estimated at 100 ml; and in others, especially the less developed countries, the consumption is even lower than that. This seems to be directly related to the availability of health services.

Due to the importance of parenteral solutions for the delivery of health services, the WHO Expert Committee on the Selection of Essential Drugs had selected 8 types of parenteral solutions in the WHO model list of essential drugs (see TRS 722, 1985).

In addition the use of saline solutions for peritoneal dialysis and haemodialysis will increase enormously the pattern of consumption of parenteral solutions.

In fact, for peritoneal dialysis, each patient uses 2 lt. of sterile saline solution every 6 hours; and in case of extra body dialysis, the need is 5 lt. of saline solution 3 times per week per patient.

P. S. - Closely related to the production and use of parenteral solutions in today's health services, is the availability of ORS, therefore full consideration should be given to the possibility of producing ORS within the frame of this project. Furthermore the WHO publication "Guidelines and Recommendations for the Establishment of a Large Volume Parenteral Solutions Production Plant (L.V.P.S.P.P.) in Developing Countries" can serve as a basis for the above suggestion of producing jointly LVPS and ORS.

In addition the LVPS Plant could easily supply drinkable water for the ORS mixture.

V. AIM OF THE PROPOSAL

The aim of this guideline is: (i) to provide technical information for the establishment of a Production Unit for Parenteral Solutions (LVPSPP), (ii) to discuss the production programme and the selection of different kinds of materials for containers, and (iii) to give criteria for construction, economic feasibility, qualifications, and training of personnel required in the manufacturing and quality control of parenteral solutions.

In the following pages we will describe two models of manufacturing units, one hospital size and the other for industrial scale. This description includes estimated investment figures for the carrying out of the project.

Each specific project should take into consideration the actual conditions of the country concerned. Therefore, feasibility studies are recommended before further decisions are taken. This document provides the reader with enough technical and financial information, in a preliminary phase, to make some decision toward the possibility of undertaking production of LVPS.

VI. THE LVP SOLUTIONS PRODUCTION PLANT (LVPSPP)

The LVP solutions plant described in this document consists of: (a) buildings, (b) equipment, (c) instruments, (d) factory infrastructure, and (e) personnel, which all together fulfill the technical requirements, keeping in mind safety and WHO's GMP recommendations.

The following guiding principles should be taken into account in the actual establishment of the project:

- the lowest possible operation cost;
- the production programme planned according to the most suitable and economically feasible schedule;
- due to the nature of the LVPS, selection of its containers according to the local situation;
- when considering the feasibility of this project and health needs, the concept of self-reliance and strategical nature of LVPS.

A. A rationale for local formulation of LVPS

The establishment of local production generally will:

- (a) permit regular and sufficient availability of infusions (LVPS) of internationally-accepted quality;
- (b) allow flexibility of infusions supply, according to the local needs, especially in emergency conditions, such as epidemics and natural disasters;
- (c) save hard currency;
- (d) develop technical and other national capabilities;
- (e) promote the development of related industries;
- (f) acquire an advanced technology which could be the basis for a more diversified pharmaceutical industry.

B. Selection of formulas and containers

1. Selection of formulas:

In considering the feasibility of establishing a LVPS plant in developing countries, it is recommended that the planning be based on the estimated national requirements made by the Ministry of Health.

Although there is no statistical data available on the consumption of infusions in developing countries, it is estimated that within the population with access to health services, 300 ml per capita might be the average requirement compared to 500 ml to 1,000 ml in the developed countries per year. With the above assumption, it is easy to

calculate the quantity of infusions needed for an area, country, or region. In addition, solutions for peritoneal dialysis and haemodialysis can also be produced in the same unit.

The production of infusions has different levels of complexity. Therefore, the implementation of the production unit should be initiated step by step, taking into account the following factors:

- (i) technology,
- (ii) trained personnel,
- (iii) factory infrastructures.

The following stages of complexity have been identified:

Stage I - production of the simple LVPS as:

- . dextrose 5% and 10%
- . sodium chloride 0.9%
- . dextrose 5% in normal saline (sodium chloride 0.9%)

Stage II - production of more complicated solutions as:

- . Ringer solutions
- . Ringer lactate
- . Darrow solutions

Stage III - production of:

- . plasma expanders
- . aminoacid solutions
- . solutions for dialysis (peritoneal or extrabody).

Note - At the initial stage of production it is advisable to consider the importation of containers in order to reduce the technical problems connected with the local production of containers. In this case the use of imported printed PVC bags could be recommended.

Where local capabilities are available, consideration should be given to produce the containers locally.

TABLE 2 - Proposed Schedule to Set Up an Industrial Plant (Model B)

YEARS	OBJECTIVE
0)	approval of the feasibility study and final decision to realize the plant
1)	factory construction
2)	running test and start up of the production
3)	stage I completed
4)	starting stage II and local production of plastic containers
5)	
6)	starting stage III

2. Selection of containers

The selection of suitable containers for infusions requires serious analysis of the various factors to be taken into account:

- (i) cost of material,
- (ii) sources and availability,
- (iii) stability,
- (iv) transportation,
- (v) quality.

There are three different types of containers used for infusions:

- (i) glass bottles,
- (ii) rigid or semi-rigid plastic containers,
- (iii) collapsible plastic bags.

All three types have advantages and disadvantages. Glass bottles are fragile, heavy and bulky, and must be made of a special glass quality; but they prevent water evaporation, which can be a serious problem in hot climatic countries.

Plastic containers of polypropylene prevent evaporation, are transparent enough to allow visual inspection; but, on the other hand, they are brittle. Plastic containers of polythene are not very transparent and, thus, do not allow a good visual inspection. While polythene has problems withstanding sterilization temperatures, it does prevent evaporation. Both these types of plastic containers could be produced on the spot (importation implies the high cost of freight).

Plastic PVC bags have the advantage of not being fragile and, therefore, being easy to handle compared with glass bottles. PVC bags can also be imported flat, which saves freight costs. They withstand sterilization temperatures and allow easy visual inspection. Disadvantages of PVC bags include their allowance of water evaporation and their containing softening ingredient. The presence of traces of this softening ingredient in simple solutions containing salt and/or sugar does not represent a major problem; however, this could be a major problem for blood and fat emulsions. The table below summarizes the characteristics of the different containers:

	<u>Glass bottles</u>	<u>Polypropylene plastic bottles</u>	<u>Polythene plastic bottles</u>	<u>Plastic PVC bags</u>
1) Sterilization	+++	+++	+	++
2) Prevents evaporation	++	+	+	-
3) Allows visual inspection	+++	++	+	+++
4) Fragility	-	+	+	++
5) Bulkiness (when imported)	-	-	-	++

As a conclusion, the most suitable alternative in selecting containers for infusions should be decided considering technical input as shown in the above table, along with the national conditions and feasibility in each country.

Note - A new material has been recently introduced in the market; it is a combination of calendered PVC coupled with polyethylene or other polymers. Despite the expectation that these containers have created, it is considered too early to include them in the document, until they are sufficiently tested.

Introduction of 1,000 ml containers along with the ordinary 500 ml, might result in a reduction of production costs and increase the output in litres.

C. Raw Materials

The quality of a product is strongly related to and influenced by the raw materials used in the manufacture and processing of the final dosage form. Materials to be controlled are those raw materials that appear as a physical part of the final dosage form including the package. Thus, the drug substance, excipients and the primary packaging materials (such as, containers, closures or plastic resins) make up this group.

An adequate system should be established for the proper receipt, testing and storage of raw materials. Standard operating procedures must provide for proper segregation, and storage of all raw materials, and for their orderly and accurate transfer from one location to another. Provisions should be made for proper rotation of these materials (FIFO system), and a suitable quarantine procedure should exist for all raw materials that fail to conform to a given specification or standard.

The raw materials used in the manufacture and processing of drugs, regardless of whether they appear in the finished product, should be identified, stored, examined, tested, inventoried, and controlled as to their proper use. Appropriate records should be maintained as to their origin, receipt, testing, and disposition, and as to the assurance of their conformance to standards of identity, purity, quality, strength, potency, and freedom from contaminants at the time of use. A resample and retest date should be established for stored raw materials, especially active and inactive drug substances, to assure the desired quality after extended storage.

The product is affected by the presence of extraneous substances in the drug, contaminants in the excipients as purchased, and contaminants entering the product during manufacturing or packaging operations. The control of raw materials, active or inactive, begins before the purchase and is maintained by careful handling procedures throughout the manufacture of the packaged dosage form.

D. Recommended criteria for the planning, design, construction, operation and maintenance of the proposed Large Volume Parenteral Solution Production Plant

We have considered two sizes of plants:

1. The hospital size plant (Model A), is designed to enable the production of the most commonly used LVPS formulas. The production output, one shift based, is 500 litres of LVPS daily, equivalent to 1,000 units of 500 ml.

The capacity of the hospital size plant has been calculated to be suitable for countries with approximately 2-3 million people, and an extension can be easily made. (See drawings Nos. 1 and 2.)

2. The industrial plant (Model B) has a production capacity for a country with 10-15 million people, with the general technical characteristics described afterwards, but designed to combine efficiently semi-automatic and manual processes. The production output, one shift based, is 6,000 litres of LVPS equivalent to 6,000 units of 1,000 ml daily. (See drawings Nos. 3, 4, 5, 6 and 7.)

E. Economics and feasibility considerations

Consideration of the following matters is recommended to any interested country before the implementation of the proposed hospital size plant.

1. Feasibility estimates, for each project. A simplified method of a feasibility study is shown below. In this method only two criteria are required: the cost of investment and the estimated saving due to local production.

The plant necessary to support the needs of a community of 2-3 million people is based on the layout of a plant with a total area of 384 square metres (276 of them designed for LVPS production), utilizing Model A, the estimated investment for the proposed plant is shown below:

TABLE 3 - Estimated cost of investment for hospital size LVPS plant (Model A)

	in 1,000 US \$ from	in 1,000 US \$ to
Site work and surroundings	20	40
Buildings and structure (for production and quality control laboratories)	70	100
Services and auxiliary equipment	35	55
Production equipment and in line control	250	300
Installation and engineering	100	130
	<hr/>	<hr/>
Total cost	475	625

AVERAGE: Approximately US \$550,000.00 (1985 price)

Specific figures

Building cost including assembly, air conditioning, sanitary, electrical site work and surroundings (first three of the above list), average = US \$160,000.

Specific building cost: $\frac{\text{US } \$ 160,000}{276 \text{ sq. m}} = \text{US } \$580/\text{sq. m}$

This plant has an average capacity of:
250,000 (500 ml each) units per shift/year.

The building cost will vary from country to country, therefore adjustments are necessary to arrive at reasonable estimates of actual investments.

The estimate is based on providing complete infrastructure services and no provisions were made for duties, delivery charges, insurance and other associated expenses.

2. Availability of infrastructure such as energy, water, personnel, distribution network, etc.
3. Financial and technical support could be provided for national projects by UNDP, WHO, UNIDO, UNICEF, World Bank and others.
4. Increase of need for Large Volume Parenteral Solutions, resulting from the extension of any health care programmes, particularly PHC.
5. The possibility of Technical Cooperation among Developing Countries (TCDC), in order to improve the cost effectiveness in the operation of the plant.

In order to determine the feasibility of the project, the following basic information is required:

- (a) Projected forecast requirement in estimated quantity and value units for the next 5-10 years;

TABLE 4 - Production cost of 500 ml Dextrose 5% packed in PVC bag. hospital size plant (Model A)

Production per year, pcs.	100,000	250,000	300,000	500,000
<u>Incidence in US\$ per unit</u>				
PVC empty-printed bags	0.130	0.130	0.130	0.130
Injectable Dextrose	0.022	0.022	0.022	0.022
Depreciation in 10 years	0.550	0.220	0.183	0.110
Polyethylene sachet	0.013	0.013	0.013	0.013
Carton box, 1/20	0.030	0.030	0.030	0.030
Quality control	0.017	0.017	0.017	0.017
Salary and wages	0.170	0.068	0.082	0.049
General services (partly included in the G. E. of the hospital)	0.046	0.038	0.041	0.027
Total cost in US\$ per unit	0.978	0.538	0.518	0.398

N.B. - The inflation was not evaluated in the calculation, as well as the unavoidable increase of price for the LVPS imported.

TABLE 5 - Simplified estimated payback time period of the capital investment (Hospital size plant - Model A - LVPS 500 ml cap.)

Production year	Quantity of standard packs in 1000/year	Estimated cost in case of import in US \$1000/year	Estimated cost in case of local formulation in US \$1000/year	Saving due to local formulation in US \$1000/year	Total estimation of cumulative saving in US \$1000
1st year	100	85	98	- 13	- 13
2nd year	250	212	134	78	65
3rd year*	300	255	155	100	165
4th year**	500	425	199	226	391
5th year	500	425	199	226	617
6th year	500	425	199	226	843
7th year	500	425	199	226	1 069
8th year	500	425	199	226	1 295
9th year	500	425	199	226	1 521
10th year	500	425	199	226	1 747

* Start of the second shift which will attain the full production after two years.

** Payback time after five years.

TABLE 6 - Production cost of 500 ml Dextrose 5% packed in PVC bags
(Industrial plant - Model B)

Production per year, pcs.	600,000	1,200,000	1,800,000	2,500,000	3,600,000
Incidence in US\$ per unit					
PVC empty-printed bags	0.130	0.130	0.130	0.130	0.130
Injectable Dextrose	0.022	0.022	0.022	0.022	0.022
Depreciation in 10 years	0.666	0.333	0.222	0.160	0.111
Polyethylene sachet	0.013	0.013	0.013	0.013	0.013
Carton box, 1/20	0.030	0.030	0.030	0.030	0.030
Quality control	0.015	0.012	0.010	0.008	0.005
Salary and wages	0.216	0.108	0.072	0.063	0.044
General expenses	0.075	0.037	0.025	0.030	0.021
Total cost in US\$ per unit	1.167	0.685	0.524	0.456	0.376

N.B. - The inflation was not evaluated in the calculation, as well as the unavoidable increase of price for the LVPS imported.

TABLE 7 - Simplified estimated payback time period of the capital investment
(Industrial plant - Model B; LVPS 500 ml vol.)

Production year	Quantity of standard packs in 1000/year	Estimated cost in case of import in US \$1000/year	Estimated cost in case of local formulation in US \$1000/year	Saving due to local formulation in US \$1000/year	Total estimation of cumulative saving in US \$1000
1st year	600	510	700	- 190	- 190
2nd year	1.800	1.530	943	587	397
3rd year*	2.500	2.125	1.140	985	1.382
4th year**	3.600	3.060	1.354	1.706	3.088
5th year	3.600	3.060	1.354	1.706	4.794
6th year	3.600	3.060	1.354	1.706	6.500
7th year	3.600	3.060	1.354	1.706	8.206
8th year	3.600	3.060	1.354	1.706	9.912
9th year	3.600	3.060	1.354	1.706	11.618
10th year	3.600	3.060	1.354	1.706	13.324

* Start of the second shift which will attain the full production after two years.

** Payback time after four and half years.

TABLE 8 - Production cost of 1 litre Dextrose 5% packed in PVC bag
(Industrial Plant - Model B)

Production per year, pcs.	600,000	1,350,000	1,900,000	2,700,000
Incidence in US \$ per unit				
PVC empty-printed bags	0.148	0.148	0.148	0.148
Injectable Dextrose	0.044	0.044	0.044	0.044
Depreciation in 10 years	0.666	0.296	0.210	0.148
Polyethylene sachet	0.016	0.016	0.016	0.016
Carton box, 1/10	0.040	0.040	0.040	0.040
Quality control	0.015	0.010	0.008	0.005
Salary and wages	0.216	0.096	0.082	0.058
General expenses	0.075	0.033	0.039	0.028
Total cost in US\$ per unit	1.220	0.683	0.587	0.487

N.B. - The inflation was not evaluated in the calculation, as well as the unavoidable increase of price for the LVPS imported.

TABLE 9 - Simplified estimated payback time period of the capital investment
(Industrial Plant - Model B - LVPS 1,000 ml vol.)

Production year	Quantity of standard packs, in 1000/year	Estimated cost in case of import in US \$1000/year	Estimated cost in case of local formulation in US \$1000/year	Saving due to local formulation in US \$1000/year	Total estimation of cumulative saving in US \$1000
1st year	600	600	732	- 132	- 132
2nd year	1.350	1.350	922	428	296
3rd year*	1.900	1.900	1.115	785	1.081
4th year**	2.700	2.700	1.315	1.385	2.466
5th year	2.700	2.700	1.315	1.385	3.851
6th year	2.700	2.700	1.315	1.385	5.236
7th year	2.700	2.700	1.315	1.385	6.621
8th year	2.700	2.700	1.315	1.385	8.006
9th year	2.700	2.700	1.315	1.385	9.391
10th year	2.700	2.700	1.315	1.385	10.776

* Start of the second shift which will attain the full production after two years.

** Payback time: about five years.

ANNEX 1

HOSPITAL SIZE PLANT (Model A) (See drawings Nos. 1 and 2)

The production unit described in this paper is designed to serve the needs of a larger hospital (like a teaching hospital), as well as to supply infusions to smaller rural hospitals.

This approach is advisable when transportation is a problem in the area and there are long distances between the factory and the consumers.

There are other advantages of having a hospital size plant, such as utilizing existing infrastructure as well as services of the hospital, e.g.:

- technical services (steam, raw water, electricity, etc.)
- analytical control laboratories
- storage facilities for packaging, raw materials, and finished products.

The proposed hospital size plant will consist of one building, separated from the other hospital buildings, where all the production and in-process control facilities are accommodated as illustrated in the WHO drawing No. 1. This model plant could be attached to large hospitals with adequate facilities and where limited consumption of parenteral solutions are required. The necessary biological laboratory and animal house will be built far from the production premises to avoid any contamination. As described above, the proposed hospital size plant will have a production capacity of 1000 units of 500 ml per day for one shift (about 10-12 persons) and will require building space on a total area of 384 m² if ORS production is included, otherwise 276 m² are sufficient for the LVPS production.

The following production and quality control equipment will be needed:

PRODUCTION EQUIPMENT

- 1 (one) WATER DEMINERALIZER, mixed bed type, hourly output: 450 litres
- 1 (one) DEMINERALIZED WATER STORAGE TANK, made of stainless steel AISI 316: 500 litres cap.
- 1 (one) WATER DISTILLER, in st. st. AISI 316, hourly output: 100 litres (50 litres when heated by electricity)
- 1 (one) DISTILLED WATER COLLECTION AND STORAGE TANK, 500 litres cap., with electric resistor suitable to keep the temperature of water up to 80°C, made of stainless steel AISI 316
- 2 (two) ST. ST. CENTRIFUGAL PUMPS
- 1 (one) SCALE, counter type, cap. 20 kg
- 2 (two) MIXERS, in st. st., 250 litres useful cap.
- 2 (two) STERILE FILTRATION SYSTEM, by membranes
- 1 (one) SET OF PIPE FITTINGS
- 1 (one) HEAT EXCHANGER for cooling the distilled water before feeding the mixers
- 1 (one) FILLING AND SEALING machine, 2 st. st. syringes, 500 ml cap. each
- 1 (one) TANK for filtered solution, 50 litres useful cap.
- 1 (one) VERTICAL LAMINAR FLOW CABINET
- 1 (one) STEAM AUTOCLAVE, 1-door model, st. st. chamber, 1 cu.m cap., equipped with built-in electric steam generator, temperature chart recorder
- 3 (three) IRON UNDERCARRIAGES
- 3 (three) ST. ST. PLATFORMS with st. st. trays
- 1 (one) AIR COMPRESSOR, complete with 300 litres cap. tank, to compensate pressure during the cooling of the autoclave after sterilization
- 1 (one) LIQUID VIEWER, polarized light
- 1 (one) ELECTRIC WELDING MACHINE, for polyethylene outer sachets
- 1 (one) DEVICE for printing batch number on the bags

A) CHEMICAL LABORATORY

- 1 (one) WATER BATH, in st. st., complete with Vertex and relay
 - 1 (one) ANALYTICAL BALANCE
 - 1 (one) ELECTRIC STIRRER
 - 1 (one) POLARIMETER, complete with tubes and Sodium lamp
 - 1 (one) LABORATORY VACUUM-PUMP
 - 1 (one) pH-METER
- ASSORTED GLASSWARE, chemical reagents, etc.

B) MICROBIOLOGICAL LABORATORY*

- 1 (one) VORTEX-GENIE, for mixing reagents, etc.
 - 1 (one) TEMPERATURE-BLOCK MODULE HEATER, maintaining $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$
 - 1 (one) MICROSCOPE, monocular body; eyepiece X10 objectives 4-10-40 and illuminator with support
 - 1 (one) DUAL PENS TEMPERATURE CHART RECORDER
 - 2 (two) INCUBATOR, forced air circulation; Two temperature ranges - slightly above ambient to 60°C and 0°C to 60°C . Temperature uniformity $\pm 0.15^{\circ}\text{C}$. Audible or visual temperature alarms desired
 - 1 (one) DRY HEAT OVEN for glassware depyrogenation, capable of heating at 250°C or above. Should also have a temperature recording device.
 - 1 (one) LAMINAR FLOW CABINET, for sterility testings, 99.99% final filter efficiency, meeting class 100 conditions (Fed. Std. 209)
 - 4 (four) MEMBRANE FILTRATION ASSEMBLIES, for sterility tests
 - 1 (one) AUTOCLAVE, Lab. model, 80 lt. cap., electrical heating - complete with two st. st. baskets
- ASSORTED CULTURE MEDIA: glassware, test tubes, racks, and baskets, sterilizable gloves, etc.

Note: Membrane Filters may be purchased - Millipore, Sartorius, Gelman, Pall, etc.

C) BIOLOGICAL LABORATORY AND ANIMAL HOUSE

- 12 (twelve) CAGES, suitable for single rabbits, in st. st., each cage is complete with feeder compartment and drinking tube
 - 1 (one) RACK, made of iron, suitable for housing above-mentioned cages, having pan to collect droppings. Should be easy to clean and sanitize.
 - 8 (eight) RESTRAINING CAGES, with pan and light-fitting neck stocks for comfort.
 - 1 (one) ANIMAL BALANCE, with cage, for weighing rabbits
 - 1 (one) ANIMAL TEMPERATURE RECORDER, complete with rectal probes.
 - 1 (one) TEMPERATURE MEASURING DEVICE - needed to calibrate recorder and temperature measuring probes.
- Appropriate syringes, needles and glassware for test procedures

* Note: Even though the Pyrogen (Rabbit) test has been established for the Biological Laboratory it would be advisable to set up the L.A.L. Test capabilities in the Microbiological Laboratory. This would enable Bacterial Endotoxins tests to be performed in accordance with current US test procedures. Lysate may be purchased from Mallinckrodt, Cape Cod Associates, Microbiological Associates and others who might be licensed.

ANNEX II

THE INDUSTRIAL PLANT (Model B) (See drawings Nos. 3, 4, 5, 6 and 7.)

The general design of planning is made on the assumption that the plant will be set-up, in most cases, in developing countries, situated in the tropical area.

This design was always kept in mind for the selection of materials, technical planning and solutions.

1. Plant capacity
 - (a) Efficiency/flexibility
 - (b) Expansion possibility
2. Safety/security
3. GMP Consideration - the prevention of mix-up and contamination through:
 - (a) Segregated areas:
 - quarantine;
 - released area;
 - clean zones (heating - ventilation and air conditioning levels - HVAC).
 - (b) Flow: materials, personnel, visitors
 - (c) Cleanable surfaces:
 - floors;
 - walls;
 - ceiling;
 - counter top.
4. Ecology/climate
5. Infrastructure - as a function of available energy, water, transportation, sewage, etc.

1. Plant capacity

The author has considered a production capacity of 6000 litres per day of parenteral solutions, because this is the quantity which allows the combination of economic profitability and dimensions of the plant suitable for a country of 10-15 million people.

In this way it is possible to realize a very rational production plant which can solve the problem of LVPS in the majority of developing countries; as a single production centre, as a plant at the service of a pool of countries and as the first of several production centres for highly populated countries.

LVPS capacity

The plant can produce: 1,350,000 litres of parenteral solutions per year packed in containers of 1000 ml volume.

N.B. if we consider packing LVPS in 500 ml PVC bags, the production capacity will be: 6000 litres x 1.4 x 225 working days = 1,800,000 pcs, in fact the same volume of the autoclave chamber can contain 1000 LVPS of 1000 ml cap. or approx. 1400 pcs of 500 ml cap.

The guidelines are based on the following assumptions:

- 225 effective working days per year are available (5 days a week);
- 30 days for annual leave and general factory overhaul;
- 6 days for public holidays.

The working hours are 8 hours a day or 40 hours a week, i.e., a total of 1,800 hours a year (one shift): effective machine hour is calculated at 6 hours a day or 1,350 hours a year.

It is important to know that the plant capacity can be doubled by introducing a second shift.

The average batch size of solution is as follows:

- injectable solution: 2000 litres
- standard pack size: 1000 ml

This volume of manufacturing capacity may be accommodated in a plant of about 2600 square metres which may be broken down into the following areas:

	(area for offices, laboratories		
	(and services	sq. m	618.0
main building	(area for production		
	(and packaging	sq. m	338.0
	(area for warehousing	sq. m	1474.0
satellite building:	area for infrastructures	sq. m	168.0

The offices, quality control laboratory, canteen, reception, lockers and toilets, are located in the management services area of the main building.

The production and packaging area includes the quarantine area, manufacturing of solutions, packaging and supervision office.

The warehousing area includes areas for receipt and shipment, quarantine for incoming shipments and released goods, storage of raw materials, containers, labels and finished products.

The infrastructures would vary in composition from country to country, depending on the available services for energy, water, sewage, transportation and communication.

In our proposal the infrastructure units include energy plant, fuel storage, raw water reservoir and water treatment plant.

(a) Efficiency/feasibility

The general dimension of the building, including roof heights, ceiling heights, room sizes, construction design and materials, have been considered to provide flexibility and efficiency in the activity programmed for the plant.

(b) Expansion possibility (See drawing No. 6.) A very common problem which arises in plant operations is the need for expansion after the plant has been in operation for some time.

The expansion is easy to realize, as it is possible to see from the WHO drawing No. 6, in the east area simply dismantling the prefabricated walls and adding the required space.

These expansion plans can be implemented at any time without disrupting production activities or jeopardizing GMP guidelines in affected areas.

2. Safety/security considerations

The plant is designed to meet all safety standards including fire hazards, building strength, etc.

Fuel storage has been segregated from the main building: emergency exits, fire alarms and fire fighting equipment have been provided in different places of the buildings.

A first aid room has been provided.

A security fence and a gate are recommended for additional safety and security of personnel and operations.

3. GMP Considerations

In the realization of the building, we have essentially considered the GMP, to prevent mixing of products and contaminations, including the contamination from different products, from the operative personnel and from the environment.

Areas have been foreseen to keep the products not yet controlled as, for example, raw materials, labels, containers, semi-finished materials, finished products, separated from those controlled and ready for use or shipment.

The flow of materials is realized so that crossings are avoided and the possibility of mixing is eliminated.

The way of the operative staff in the production area is also realized so that contaminations introduced from staff to the product and vice versa are prevented.

Further precautions against the possibility of contaminations are foreseen for the visitors.

The building materials and the finishing have been chosen for their easiness to keep them clean and for their resistance to atmospheric agents of tropical countries.

4. Ecology/climate

The planner of a pharmaceutical industry, which is at the service of the country's health, must take into consideration the environmental contamination.

Even if a factory of infusional solutions does not produce toxic wastes, the problem of wastes has been thoroughly considered, so that the environmental pollution can be avoided as much as possible.

A line for industrial wastes has been foreseen (production department, laboratories and technical services) and another one for sanitary wastes (toilets, showers, sinks, kitchen, etc.).

Line A, which gathers the sanitary wastes, undergoes a treatment to coagulate and separate all solids for sedimentation.

Line B, which gathers the production wastes, is treated as line A, but previously the liquids undergo a neutralization, before passing to the biological treatment.

The two lines are connected far from the plant, with some precautions to avoid any returns.

To drain the solid refuse and the sediment picked up by the discharging plant, it is advisable to foresee the installation of an incinerator.

Since the climate conditions where the plant will be installed are generally heavy, the temperature and humidity are controlled through the air conditioning plant or by means of an efficient ventilation, according to the necessities.

5. Infrastructures

In the industrial plant presented, provisions are made for the following services:

- (i) Energy plant
- (ii) Fuel storage
- (iii) Raw water reservoir
- (iv) Waste water treatment plant
- (v) Incinerator
- (vi) Security

According to the specific case, the various problems will be analyzed in detail, considering the conditions of the site where the plant will be installed.

Description of Buildings, Installations, Air conditioning, Air filtering and Control Laboratories

1. BUILDINGS

The establishment is composed of a principal building (prefabricated) which contains:

(a) Production: (manufacturing and packing); in this area the production, the packaging and the storage of the products waiting for analysis are placed.

(b) Warehouse: in this area the raw materials are stored, as well as the packaging materials and the finished products; conventional storage with pallet racks, 4 pallets in height.

(c) Services: in this area there are offices, analysis laboratories, canteen, changing room and toilets;

and a satellite building where the technical services are installed as: power central panel, boiler house, water tank and treatment plant and animal house and biological laboratory.

The principal prefabricated* building proposed is fundamentally a steel structure, the walls are prefabricated elements where doors and windows are inserted. (See drawing No. 4.)

The insulating material of the roof and walls has passed through the most severe controls in many countries with extreme climate conditions.

The prefabricated construction proposed has many advantages in comparison with a traditional construction in masonry.

(i) Standardization of the building elements

- planning and time costs reduction;
- use of materials tested by qualified firms.

(ii) Light construction

- use of non-heavy means of lifting;
- more inner space available, keeping at minimum the thickness of the walls and division walls;
- lesser charge of the foundations.

(iii) Prefabricated construction

- dimension suitable to transport (container);
- only bolted and "put in place" connection during construction;
- the construction can be carried out by semi-skilled personnel;
- easiness in realizing internal divisions and of varying the dimensions of the rooms;
- local industries can carry out part of the works such as: foundations, flooring, fencing, etc.;
- extensions and alterations can be carried out without disturbing the production process;
- the steel structure can be used for fixing of pipes, ducts, installations and appliances of all kinds.

* The greater or lesser convenience in the use of a prefabricated building has to be examined according to the circumstances. It is evident that if locally it is possible to construct a building with traditional systems at a good level of finishing, it is preferable.

Since the construction costs change quite a lot from one country to the other, depending on the local availability and therefore on the costs of the construction materials, inner transport, etc., it is preferable, at the stage of preliminary study, to make a comparison of the different types of alternative construction, so that it is possible to choose the most economical and convenient solution.

BUILDING DESCRIPTIONS

1.1 GENERAL DESIGN CRITERIA

The design criteria of the plant have been conditioned in most of the architectural choices by the peculiar needs of the pharmaceutical industry.

A very high degree of cleanliness and hygiene, of the personnel and of the equipment and premises, and the absence of any contamination from outside, are factors of paramount importance.

Such factors have determined the choice of a very compact, blacked-out building, concentrating in a single block the production areas, the warehouses, the laboratories, the offices as well as the lockers and the personnel services. A secondary goal has also been achieved, that of reducing the outside perimeter and surfaces.

A satellite building has been designed, in order to group the technical services of the different utilities: electrical power, water, steam, as well as the emergency generator, the maintenance workshop; the animal house with the biological laboratory also will be separated from the main building.

As far as the design of the production area and warehouses is concerned, the plan has been studied with the aim of assuring an easy and one-way flow of raw materials and finished products.

An important role has also been played by the possibility of expansion in the future. For this reason the offices and the personnel services areas have been situated on the front of the building. This front will not be affected by future expansion which might interest the warehouses (expanding the east wall) or the production areas (expanding in the warehouse area).

1.2 PREFABRICATED MAIN BUILDING

	<u>m2</u>
- Distilled water	39.0
- Solutions preparation	37.0
- Clean area entry	11.5
- Bags filling and sealing	30.0
- Sterilization and packaging	<u>219.0</u>
Sub-total for production:	<u>336.5</u>
- Quality control labs	78.0
- Raw and packaging materials warehouse	192.0
- Finished products and shipping	987.0
- Quarantine	<u>294.0</u>
Sub-total for warehouses	<u>1,473.0</u>
- Offices	119.5
- Showers and toilets	110.0
- Canteen	79.0
- Lobby, reception, aisles	<u>184.0</u>
Sub-total for misc. areas	<u>492.5</u>
TOTAL FOR PREFAB. BUILDING	<u>2,380.0</u>

1.3 ARCHITECTURAL

1.3.1 MAIN BUILDING STRUCTURE (See drawing No.5.)

The main building frame is made in prefabricated steel components, hot zinc plated. The bolts are in steel galvanized electrolytically.

1.3.2 FOUNDATIONS

The foundations are in reinforced concrete with a perimetral socle of concrete 1.00 m in height.

1.3.3 ROOFING

A treated galvanized steel insulated sandwich deck is used for the roof. The external sheet is protected by acrylic paint.

In the roof some areas are made for natural lighting by means of sheets of translucent laminated plastic.

1.3.4 WALLS

The external walls are made from prefabricated galvanized steel panels with double metallic support and internal insulation. The external sheet is protected by acrylic paint.

1.3.5 FLOORS

The industrial floor makes a single slab, it consists of cast reinforced concrete, with wear resistant, dust-proof surface finish. Floors are normally smoothed. The floor finishing will be with epoxydic resins. This makes the surface resistant and washable.

1.3.6 WINDOWS AND DOORS

Two main doors, two-wing type, with iron frame and panels, as for the walls, are foreseen for the store.

All windows, doors and frames comply with high quality standards and assure a very good sealing.

Along the perimeters of the main prefabricated building are foreseen fixed frames with mosquito wire-nets and external sun-screen blades.

Inside the main prefabricated building there are the:

1.3.7 OFFICES - PRODUCTION DEPT. & QUALITY CONTROL LAB. prefabricated:

Walls

- framework in anodized aluminium - moulding 1.00 m height in plastic laminated sandwich panel - upper part with glass 5 mm thickness.

Windows and doors

- the external windows of the offices are made of iron frame with glass 4 mm thickness and mosquito wire-nets.
The internal windows and the door are in aluminium and laminated plastic.

Ceilings

- false ceiling in aluminium staves pre-painted, supported by a structure of galvanized iron sections.

1.3.8 SHOWERS AND TOILETS

Internal walls: made in galvanized steel sandwich and partitions with equipped walls.

Ceiling: with corrugated sheet iron and false ceiling in aluminium staves prepainted.

Doors: made in enamelled wood.

Floor: of cast reinforced concrete, ruttet down and painted with epoxy resins.

1.4 SECONDARY BUILDING

Satellite (200 m²)

This building includes:

- Animal house
- Rabbits breeding
- Biological laboratory
- Air compressor and air conditioning room - Raw water treatment plant - Boiler room
- Pumps room
- Maintenance workshop
- Electric room
- Electric generator (under shed)

It is connected to the main building through a pipe rack. This building will be constructed locally in masonry.

Janitor's lodge

The janitor's lodge is located close to the main gate, constructed locally in masonry.

1.5 SEWAGE

The toilets as well as the laboratories and production equipment discharges are executed in heavy PVC pipeline. Discharges are collected in a leaching trench properly designed for underground dispersion.

Toilets discharge will be previously clarified in a separate tank, while kitchen discharge will be defatted in a proper trench.

Production equipment discharge will get no treatment.

Laboratories, with the exception of the sterile ones, will have cast iron floor drains.

A PVC pipeline guarantees ventilation into the discharge branches. Ventilation columns have a PVC vent stack on the roof.

1.6 FENCING

The area of the factory will be fenced by reinforced concrete fence posts and wire-net.

The access to the factory area takes place through an iron gate.

Parking areas and roads within the factory area are paved with a surface layer of gravel and asphalt binder (thickness: 8 cm). The unpaved area is reserved for gardening.

1.7 RAIN UNDER DRAINAGE

The rain on paved and green areas is disposed of underground; the rain from the building roofs is conveyed to the main drain which carries the water to a dispersion pit.

2. INSTALLATION

2.1 ELECTRIC WORKS

A transformation cabin is necessary if it is not possible to have energy directly at low tension.

Main distribution board

The distribution of low tension will be at 380/220 V - 3 phase + neutral 50 Hz.

Every single phase will be connected in order to obtain the maximum balancing of the whole system.

Wiring

Cables with 4 copper wires, insulated in Sintenax and tested at 4 KW, every single wire insulated with thermoplastic material and tested at 3 KW will be installed.

The cables from the main board to the distribution panels will be in metal pipes.

The cables from the secondary panels to the utilization points will be in raceways or in PVC pipes.

Control boards

They will be completed with main switches and power switches.

Lighting

The following illumination levels will be guaranteed:

- production:	300 lux
- stores:	150 lux
- laboratories:	300 lux
- offices:	200 lux
- technical and auxiliary services:	150 lux

Fluorescent lamps 2 x 40 W (or 2 x 65 W) will be used.

The outside illumination will be effected with sodium lamps 400 W fixed in brackets projecting from the building.

Lights control

The illumination circuit will be controlled as follows: 1) Offices, locker rooms, with switches placed at the entry of the rooms. 2) Stores, working rooms and corridors, directly from the central distribution panel.

Light taps and energy

In the rooms will be installed groups complete with:

- three poles tap 3 x 16A + earth, complete with switch and fuses - two poles tap 2 x 16A + earth, complete as above - light tap.

Grounding system

A grounding system for the building is absolutely necessary.

Telephonic system

It is suggested with internal derivation and distribution lines to the different departments.

We recommend, as well, the installation of time clocks with electric stamping and factory hooters.

2.2 SANITARY SYSTEMS AND PIPELINES

The disposable water must be analyzed and, if necessary, treated before admitting it in the industrial water line.

In order to have a sufficient reserve of water for the fire pump network, the production and sanitation, a water reservoir of sufficient capacity will be built with a distribution system under pressure.

A false ceiling is planned to be constructed where necessary so that the piping can be brought in to position from above.

For the pipes we propose the use of the following materials:

- cold water	steel pipes, galvanized pipes, plastics
- warm water	galvanized pipes
- demineralized water	stainless steel pipes
- chilled water	steel pipes
- distilled water	stainless steel pipes
- steam	steel pipes
- condensate	steel pipes
- clean steam	stainless steel pipes
- compressed air	galvanized pipes
- vacuum	steel pipes, polypropylene
- gas	steel pipes

3. AIR CONDITIONING

The offices, the laboratories, the working areas, with particular regard to the filling area, are air conditioned at a temperature of about 25°C.

The conditioning is effected with fan coils fed with cold water from the chiller.

3.1 TEN FAN COILS, installed in the floor or walls, connected to cold water network to the chiller, suitable to keep, inside the rooms, a temperature of about 25°C, one air exchange every hour.

Capacity 2/3000 refrigerating units/hour (each). The fan coils are mounted in a zinc coated, painted cabinet.

Regulation thermostat is provided for each unit.

3.2 WATER CHILLER for cold water production, inlet 12°C - outlet 7°C.

The chiller is equipped with:

- one refrigerating group with condenser cooled with tower water,
- compressor, semi-hermetic type,
- copper condenser and tube nest
- copper evaporator and tube nest
- two pressure regulators for high and low pressures
- regulation thermostat for working at 100% - 75% - 50% - 0
- safety thermostat anti-freeze type
- thermometer for temperature control
- panel with 3 manometers for high-low gas pressure and for oil
- electric panel
- operating and control panel safety devices
- fairing and frame in galvanized steel, painted
- filter, solenoid valve, indicator of gas passage.

The chiller is working also for cooling the distilled water.

3.3 CENTRIFUGAL PUMP for circulation of the chilled water to the fan coils, delivery cu.m/h.25, head 20 m, coupled to electric motor.

4. COOLING WATER TOWERS

With the aim of reducing remarkably the consumption of the cooling water for the water still, the chiller and the autoclave, we suggest installing two towers for water cooling, one for the chiller and the water still, the second for the cooling water of the autoclave.

The two towers are independent, provided with by-pass for emergency and safety.

It is advisable to install two towers, and not one bigger, because the tower working with the cooling water of the autoclave has great temperature variations, and this variation of temperature affects negatively the working capacity of the chiller, which requires constant temperatures at inlet and outlet.

5. AIR FILTERING, AIR DEDUSTING, AIR STERILIZATION

In the pharmaceutical industry very high standards are demanded concerning the cleanliness of air within the plant or facility.

The air supply, circulated by air conditioning or ventilation units, not only has to be dedusted, but also sanitized and, in some cases, sterilized.

To attain such clean air conditions, several filtering stages are required.

(i) The first stage of air filtering is the rough filtering. These filters are manufactured from glass fibre mats. They are reusable and washable. The rough filter absorbs the dust and dirt particles from the normal road dust. Their efficiency lies between 50 and 70 per cent.

(ii) The second stage of air filtering is the fine filtering. These filters are called pocket filters. The filter medium is manufactured from glass fibre mats.

To protect the filter medium against mechanical loads, the filter surface is covered by a fibrous web. The pocket filters are used because - with their very fine glass fibre medium mostly not self-supporting - they are stretched in a corresponding supporting structure which gives the filters the necessary support even in very high operating conditions. The fine filter mats are thrown away after 1 or 2 times of regeneration. The pocket filter absorbs the very fine dust and dirt particles from normal road dust with an efficiency of 85 to 95 per cent.

Fine filters of synthetic materials are very resistant to humidity and chemical influences.

(iii) The third stage of air filtering involves high efficiency submicron particulate air filters. These absolute filters consist of a superfine glass fibre paper with a thickness from 0.8 to 1.5 mm which is crimped to a papyraceous bonded fibre fabric and thickened with a casting compound in a frame. The absolute filter is not reuseable. It will need replacement depending on the operating conditions after a few months or a few years.

The submicron air filters absorb from the air fine dust, fungi and bacteria.

These submicron air filters are installed where germ-free air has to be provided to meet the highest requirements. Their efficiency lies between 99.5 and 99.99 per cent. For air conditioning and ventilating plants of this kind, the air resistance will be unavoidably very high. For this reason, centrifugal fans are required to guarantee operating conditions.

6. HEATING SYSTEMS COMBINED WITH AIR CONDITIONING AND VENTILATING PLANTS

Each single room air conditioner can be equipped with an electric heating element. The heating output can be adjusted or individually changed by a multi-step switch on the unit to provide partial or full-load heating for any room, depending on the existing requirements.

7. CONTROL LABORATORIES

The factory is equipped with the following laboratories: - analytical chemical laboratory; - physico-chemical laboratory; - microbiological laboratory; - biological laboratory and animal house.

These laboratories are required for testing the quality of active ingredients, excipients, materials in-process as well as finished products and packaging materials.

7.1 Analytical chemical laboratory

The furnishings should consist of a work-bench with an acid-resistant surface located in the middle of the room, cupboard and drawer space should also be made available.

The work bench contains a sink complete with drain. Shelves are provided on top of the bench.

The following may be available: water, gas, vacuum, compressed air and possibly inert gas.

Further laboratory furnishings consist of one or more wall benches, tables, chairs, a weighing table, a fume hood with aspirator, as well as one or more built-in cupboards.

7.2 Physico-chemical laboratory

The furnishings of this unit are similar to the chemical laboratory. A large area for instruments and appliances is required in this laboratory.

7.3 Microbiological laboratory

The independent air conditioning system of this laboratory is of the high efficiency submicron particulate type for the sterility test room only. The laboratory is furnished with tables covered with synthetic resin.

As an alternative to the separate air conditioning system and the Hepafilters, it is possible to install laminar flow hoods, meeting or exceeding the specification requirements as outlined in Fed. Std. 209B.

7.4 Biological laboratory*

The current U.S.P. provides, by the L.A.L. Test (85 Bacterial Endotoxins Test U.S.P. XX1) for assay of pyrogens in injectable products. We suggest setting up a rabbits' warren and an animal house as soon as possible and to equip the biological laboratory with the instruments necessary to carry out the pyrogen test with the rabbits as described in all pharmacopoeias.

* N.B. It is of utmost importance to have the Biological Laboratory under separate H.V.A.C. Systems. The rabbits should be maintained under controlled environmental conditions at all times and especially under test conditions.

TECHNICAL DATA AND SPECIFICATIONS
=====

TECHNICAL DATA

Effective story heights (See drawing No.5.)

Production building	3.0 m
Warehouse	6.0 m
Services	3.0 m

Imposed load on ground floor

Production	1000 kg/m ²
Main warehouse	1500 kg/m ²
Laboratories and kitchen	800 kg/m ²
All other rooms	500 kg/m ²

Compressed air supply

Pressure 6 bar for production and regulating appliances. Consumption approximately 150 m³/hour.

Power supply

The power requirement for the described industrial plant (Model B) is approximately 150 kw/h.

The capacity of the connection must be 200 kw/h.

Light intensity

Production and control laboratories	300 lux
Offices, canteen and kitchen	200 lux
All other rooms	150 lux

Air conditioning for the production units - control laboratories

Temperature	about 25°C
Air humidity	55% + 10%

Air ventilation of main warehouse

Temperature	max 28°C
-------------	----------

Water requirements

The water requirements for the described industrial plant amount to the following quantities:

- cold water	150 m ³ /day
- de-ionized water	13 m ³ /day
- distilled water	7-8 m ³ /day

The air-flow from the production process

The flow of the air from the production process is effected by overpressure and special air-outlet directly outside the process rooms.

Floor covering

- Production: clinker slabs, artificial stone slabs, terrazzo or epoxy covering.
- Packaging: artificial stone slabs, PVC tiles or epoxy covering.
- Control laboratories: clinker slabs, artificial stone slabs, terrazzo, or epoxy covering
- Main warehouse: cement finish.
- All other rooms: clinker slabs or artificial stone slabs (in the canteen, PVC tiles can be used).

Steam

For the need of the plant a steam generator for the production of dry, filtered steam is recommended.

Pressure: 12 bar
Capacity: 2000 kg/h

ROOM PROGRAMME LIST

(See drawing No.3.)

The list contains the room programme for the industrial plant (Model B).

<u>1. Warehousing</u>	<u>m²/net</u>
No 101 Main warehouse - receiving and delivering	947.0
No 102 Raw materials warehouse	192.0
No 103 Office	10.0
No 104 Quarantine	295.0
No 105 Dispensing room	30.0
<u>2. Processing and packaging</u>	
No 201 Air-lock	3.0
No 202 Changing-room	6.0
No 203 Sterile entry	4.0
No 204 Distilled water production	37.0
No 205 Solutions preparation	37.0
No 206 Bags filling & sealing	32.0
No 207 Sterilization - Packaging & quarantine	219.0

3. General Services

No 301 Secretary office	16.0
No 302 Plant & production manager office	28.0
No 303 Quality control head office	13.5
No 304 Toilet	5.0
No 304 Toilet	6.0
No 304 Toilet	5.0
No 305 Telephone exchange room)
No 306 Waiting room)10.0
No 307 Locker male	47.0
No 308 Locker female	47.0
No 309 Janitor's room	12.0
No 310 Chemical laboratory	26.0
No 311 Physical laboratory	13.0
No 312 Microbiological laboratory	24.0
No 313 Sterility test room	15.0
No 314 Air-lock	4.0
No 315 Animal house	31.5
No 316 Biological lab (pyrogen test room)	10.0
No 317 Engineer office	16.0
No 318 Medical room	10.0
No 319 Administrative manager office	18.0
No 320 Clerks	18.0
No 321 Canteen	75.0

4. Infrastructurem²/net

No 401 Workshop	42.0
No 402 Air compressor & waterchiller	21.0
No 403 Raw water demineralizer	21.0
No 404 Raw water pumps	21.0
No 405 Steam generator	42.0
No 406 Power central panel	21.0
No 407 E.m.f. generator	under shed
No 408 Oil tank	buried
No 409 Raw water reservoir	buried

5. Total floor areas/gross

Warehouse	1,474.0 m ²
Production	338.0 m ²
Services (including corridors, aisles)	618.0 m ²
Infrastructure	168.0 m ²

Total gross area approx.

2,598.0 m²
=====

RECOMMENDED AIR CONDITIONING SYSTEM

Designation	Hospital size plant Model A	Room No.	Ind. plant Model B
Main warehouse	-	101	X
Raw material warehouse	-	102	X
Office	-	103	X
Quarantine	-	104	X
Dispensing room	-	105	X
Air-lock	overpressure flow	201	overpressure flow
Changing room	overpressure flow	202	overpressure flow
Sterile entry	overpressure flow	203	overpressure flow
Distilled water production	ventilation only	204	ventilation only
Solutions preparation	X	205	X
Bags filling & sealing	X	206	X
Sterilization	ventilation only	207	ventilation only
Packaging	X	207	X
Secretary office	-	301	X
Plant & production manager office	-	302	X
Quality control head office	-	303	X
Toilet	exhaust only	304	exhaust only
Telephone exchange room	-	305	X
Waiting room	-	306	X
Locker male	exhaust only	307	exhaust only
Locker female	exhaust only	308	exhaust only
Janitor's room	-	309	X
Chemical laboratory	X	310	X
Physical laboratory	-	311	X
Microbiological laboratory	X	312	X
Sterility test room	X	313	X
Air lock	-	314	-
Animal house	X	315	X
Biological lab. (pyrogen test room)	X	316	X

ANNEX III

PRODUCTION EQUIPMENT AND QUALITY CONTROL INSTRUMENTS

A list of production equipment and quality control instruments (see below) was prepared, based on an estimated production which would service a model population of about 10-15 million consumers. The list of production equipment was based solely on the capacity to produce the most cost-effective batch size. In the final selection of equipment for the purpose of procurement, each piece should be evaluated to ensure compliance with Good Manufacturing Practices standards, taking the following factors into consideration:

- (a) Contact surfaces should be non-reacting and non-additive, e.g., stainless steel, borosilicate glass, teflon-coated surfaces; they should not emit metal particles, etc.;
- (b) Manufacturing materials such as lubricants should not contaminate the product;
- (c) Cleaning, maintenance and operation should be simple;
- (d) The least infrastructure should be required;
- (e) Adequate safety devices should be provided.

PRODUCTION/ENGINEERING EQUIPMENT AND QUALITY CONTROL INSTRUMENTS

1. PRODUCTION

1.1 DISPENSING ROOM

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Floor scale	0-150 kg + TARE
1	Table scale	0-20 kg
1	Top-loading balance	0-1200 g
1	Fork lift	1 ton
1	Vacuum cleaner	550 W
Various	Accessories for weighing: spoons, containers, dust mask, etc.	

1.2 WATER DEMINERALIZED ROOM

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Demineralizer	5.000 ltr/h
1	Storage tank for dem. water	6 cu.m
1	Pump	1,5 cu.m/h
1	Pump	2,0 cu.m/h

1.3 DISTILLED WATER ROOM

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Water still	1000 lt./h
1	Storage tank for dist. water	5000 lt./cap.
1	Pump	3000 lt./h
1	Filter for steam	
1	Distilled water cooler	
1	Chiller for cooling water (if necessary)	

1.4 SOLUTION PREPARATION AND STERILIZING FILTRATION ROOM

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
2	Stainless steel vessels with stirrer	2000 lt. (useful cap.)
2	Pumps	1500 lt./h
1	Multiplate filter	
2	Stainless steel membrane filter holders for sterilizing filtration	
1	Floor scale	0-200 kg
1	Table scale	0-20 kg
1	Top loading balance	0-2 kg

Various accessories, prefilter pads, membrane filter, stainless steel connection, silicone rubber tubes, etc.

1.5 BAGS FILLING AND SEALING

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
3	Bags filling and sealing machines	400-500 pcs/h (500 ml cap.)
1	Laminar flow hood	
1	Feeding tank for sterile solution	
3	Tables for the machines	
1	Conveyor belt	
	Various accessories	

1.6 STERILIZATION

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Autoclave (2-door type)	8 cu.m
12	Trays (stainless steel)	
12	Trucks	
12	Sets of st. st. shelves	

1.7 PACKAGING

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Coding machine	
2	Liquid viewers	
1	Conveyor belt	
1	Roller belt	
2	Electric welding machines	
1	Sealing machine for boxes	
2	Traspallets	1000 kg

1.8 STORES

<u>Quantity</u>	<u>Description of equipment</u>	<u>Capacity</u>
1	Floor scale	0-200 kg
1	Table scale	0-30 kg
1	Top loading balance	0-1200 g
1	Electric fork lift	1 ton.
1	Washing - drying machine	650 w
Various	Storage (racks and shelves)	
Various	Accessories for packing and sealing, pallets, etc.	

2. ENGINEERING

2.1 INFRASTRUCTURE EQUIPMENT

<u>Quantity</u>	<u>Description of equipment</u>
1	Deep well pump 5-7 H ₃ P. (if necessary)
1	Storage tank 100-150 m ³ (depending on requirements)
2	Pressure pumps
1	Fire pump (preferably diesel)
1	Hot water generator, steam-heated (if necessary)

2.2 STEAM

<u>Quantity</u>	<u>Description of equipment</u>
1	Boiler, until 2 t/h capacity + water-softening equipment
1	Oil storage tank (size depends on delivery terms)
1	Condensate return tank
2	Fuel pumps
2	Feed-water pumps

2.3 AIR CONDITIONING (depends on system)

<u>Quantity</u>	<u>Description of equipment</u>
1	Chiller unit with compressor and air-cooled condensing coils Chilled water pumps Electric control panel for AC plant

2.4 COMPRESSED AIR

<u>Quantity</u>	<u>Description of equipment</u>
1	Oil-free compressor 150 N m ³ /h
1	Air dehydrator
1	Compressed air storage tank 3 cu.m cap.

2.5 Electricity

<u>Quantity</u>	<u>Description of equipment</u>
1	Transformer 200-250 KVA
1	Emergency generator 150/200 KVA
1	Switchboard for low tension
1	Transformer 60-90 KVA (light)

2.6 Water treatment plant

Depends on local requirements.

2.7 Workshop equipment

<u>Quantity</u>	<u>Description of equipment</u>
1	Pipe-bending machine
1	Circular saw for wood
1	Wood planing machine
1	Pedestal grinder
1	Bench grinder
1	Pipe threading machine
1	Pedestal drilling machine
1	Bench drilling machine

1	Power bench saw
	Bench vices (diverse)
1	Gas welding and cutting set
1	Rectifier welding set with attachment for argon welding
1	Welding set, transformer type (general purpose)
1	Welding set, transformer type (light-duty, portable)
1	Centre lathe
	Diverse tool sets

3. QUALITY CONTROL LABORATORIES

3.1 CHEMICAL LABORATORY

- Central bench
- Fume cupboard
- Wall benches
- Cupboards
- Analytical balance, with 300 gr. capacity, weighing 200 gr. - reading precision 0,01 gr.
- Tables for balances
- Technical Balance: cap. 1 kg + 1 kg tare, precision 0,1 gr.
- Spectrophotometer, for UV and visible
- Two digital laboratory pH-mV meters with: no. 2 glass electrodes, no. 2 PT-probes 100 Ohm. at 0°C for the automatic temperature adjusting, no. 1 buffer solution pH 10,00 (500 ml), 2 electrode holding clamps.
- Polarimeter suitable for tubes with length up to 220 mm with single inclined focusable eyepiece, tube holder seat, the sodium vapour lamp, polarizer, analyzer
- Manual particle-counter for counting particles included between 1:75 microns, coulter calculation system, reproductibility \pm 1%.
- Conductivity meter
- Muffle oven, chamber mm 170 x 120 x 250, with electronic pyrometer for temperature regulation up to 1,000°C
- Flame-photometer for determination of Na and K
- Water-bath with three independent baths
- Thermostatic oven, forced air ventilation model
Range: + 35 + 300°C
Inside dimensions 51 x 45 x 60 cm
- Two electromagnetic stirrers, with heating plate, controlled by thermostat
- Various equipment and different material such as: conical flasks, beakers, funnels, filters, volumetric flasks, thermometers, evaporating dishes, porcelain crucibles, weighing bottles, chemical reagents, stands, tripods, bunsen burners, vacuum dessicators, etc.

3.2 MICROBIOLOGICAL LABORATORY

- ORV heat oven for depyrogenation, 250°C - 300°C capability
- Two water circulation incubators, one with refrigerating group
- Refrigerator, capacity 275 lt.
- Laminar flow hood "class 100" - board in stainless steel
- Vertical autoclave, in stainless steel, capacity about 140 lt., hinged cover with fast central tightening, complete with two st. baskets holding the material to be sterilized
- Two stainless steel sinks, with wash basins and support shelves
- Two tables with stainless steel shelf, on trucks with rubber wheels
- Technical balance, capacity 5 kg, precision 0,1 gr.
- Microscope, binocular clear field, power 4 X - 10 X - 40 X - 100 X
- Centrifuge with 30 positions for 15 cc., 5 adjustable speeds

- Sterility control system for 6 tests/day complete with various accessories
- Various glass equipment and different materials: filters, thermometers, bottles for reagents, pyrex funnels, microbiological pyrex test tubes, 38 x 200, autoclavable CAP-0-TEST, etc.
- Temperature-Block Module Heater, 37°C + 1°C (L.A.L. Tests), Vortex-Genie

3.3 BIOLOGICAL LABORATORY AND PYROGEN TEST

- Shelving with 12 restraining cages for pyrogen control
- Shelving with 12 warrens in stainless steel for rabbits
- Shelving with 30 places for mice
- Balance for rabbits with stainless steel tank
- Balance for mice with PVC tank
- Electric thermometer at high precision, digital reading for pyrogen test, complete with 9 probes
- Tank for cage washing
- Two tables with stainless steel shelf
- Two insecticide lamps - high voltage type

3.4 RABBITS WARREN

- Boxes, arranged on batteries, complete with feed-box and watering place with stainless steel valve, protection shelves, support structures hot dip galvanized
- Nests for delivery
- Gutters for evacuation
- Brackets with 2 buckets at 10 lt. constant level for water distribution with flexible pipe
- Two insecticide lamps - high voltage type

ANNEX IV

PERSONNEL QUALIFICATIONS AND TRAINING OF PERSONNEL

1. ORGANIZATION

As recommended by the WHO Guidelines on Good Manufacturing Practices (GMP), as well as to ensure efficient operation of the plant, the organizational chart shown in Table 10 is recommended.

In order to achieve better quality drugs, the quality control department should report directly to the Plant Manager rather than to the Production Manager.

2. PERSONNEL REQUIREMENTS

Depending on the degree of automation, the total personnel requirement for the industrial plant is between 35-40 persons.

Management

Plant Manager
Secretary

Warehouse and Dispensing

Manager (Pharmacist)
Supervisors
Clerks
Secretary
Workers

Production

Manager (Pharmacist)
Pharmacists
Supervisors
Secretary
Operators and workers

Control laboratory

Manager (Pharmacist)
University graduates in sciences
Supervisors and Technicians
Secretary
Operators

Engineering department

Manager (Engineer)
Technicians
Secretary
Workers

Personnel and administration department

Manager
Accountant
Clerks
Secretaries

3. QUALIFICATIONS

Good Manufacturing Practices standards require that each person engaged in the manufacture, processing, packaging or holding of a drug product should have the education, training and experience to enable that person to perform the assigned tasks, with the specific additional provision that those who are supervising such activities are able to function in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality and purity it purports or is said to possess.

Heads of departments such as production, quality control, engineering, etc., should be persons with university degrees in pharmacy, chemistry, engineering or in any other related scientific field. If possible, some operational units or sections for preparation of solutions, bag filling, dispensing and packaging units or sections should also be filled by staff with university degrees, such as pharmacists.

Operators and first-level supervisors are usually persons with a high school or equivalent education. Proficient and dependable operators are usually promoted to first-level supervision. Occasionally, second-level supervision may be filled by such individuals.

Whenever possible, other workers such as packers, storemen, those involved in production, cleaners, etc., should be able to read and write properly.

4. TRAINING

(a) Production personnel

It is important that the jobs in production activities are not labelled as purely manual labour. The need for alertness and awareness in individuals employed, and especially understanding of the job to be performed, should be emphasized.

Therefore, there is little argument that, for an industry whose products demand personnel with a high sense of responsibility, motivation and training are crucial.

The importance of job rotation, chances of further training for capable candidates in order to improve his/her capabilities or to open possibilities for promotion or some sort of incentive scheme should not be overlooked.

On-the-spot training in Good Manufacturing Practices (GMP), especially on problem oriented teaching, e.g., personal hygiene, health habits, quality, etc., is important.

Key personnel in injectable drugs production could be given the following training programme:

- (i) Introduction to relevant legislation with particular emphasis on GMP quality assurance, safety and health;
- (ii) Personal hygiene;
- (iii) Introduction to injectable dosage forms;
- (iv) Introduction to weighing and measuring;
- (v) Information on available mixers and introduction to preparation of solutions, sterile filtration and different systems of sterilization;
- (vi) Procedures used to ensure required standards of cleanliness in equipment and retention of product integrity and purity;
- (vii) Introduction to and information on filling-sealing and in-process control during operation;
- (viii) Introduction to containers, batches, tooling, maintenance and packaging;
- (ix) Introduction to recording and reporting techniques.

(b) Quality control personnel

The contents of a programme for quality control key personnel could be as follows:

- (i) Theoretical aspects of quality control methods and equipment, discussion of the products to be manufactured, methods of manufacturing and equipment required as well as the necessary in-process quality control to be performed;
- (ii) Practical training on the several methods of control, preparation of the reagents, completing protocol, etc;
- (iii) Sampling procedures and techniques;
- (iv) Supervision of the implementation of GMP, stability tests, etc;
- (v) Stability testing;
- (vi) Bioavailability testing;

(vii) Investigation of manufacturing variances

(viii) Management of field complaints;

(ix) Periodic auditing of the plant.

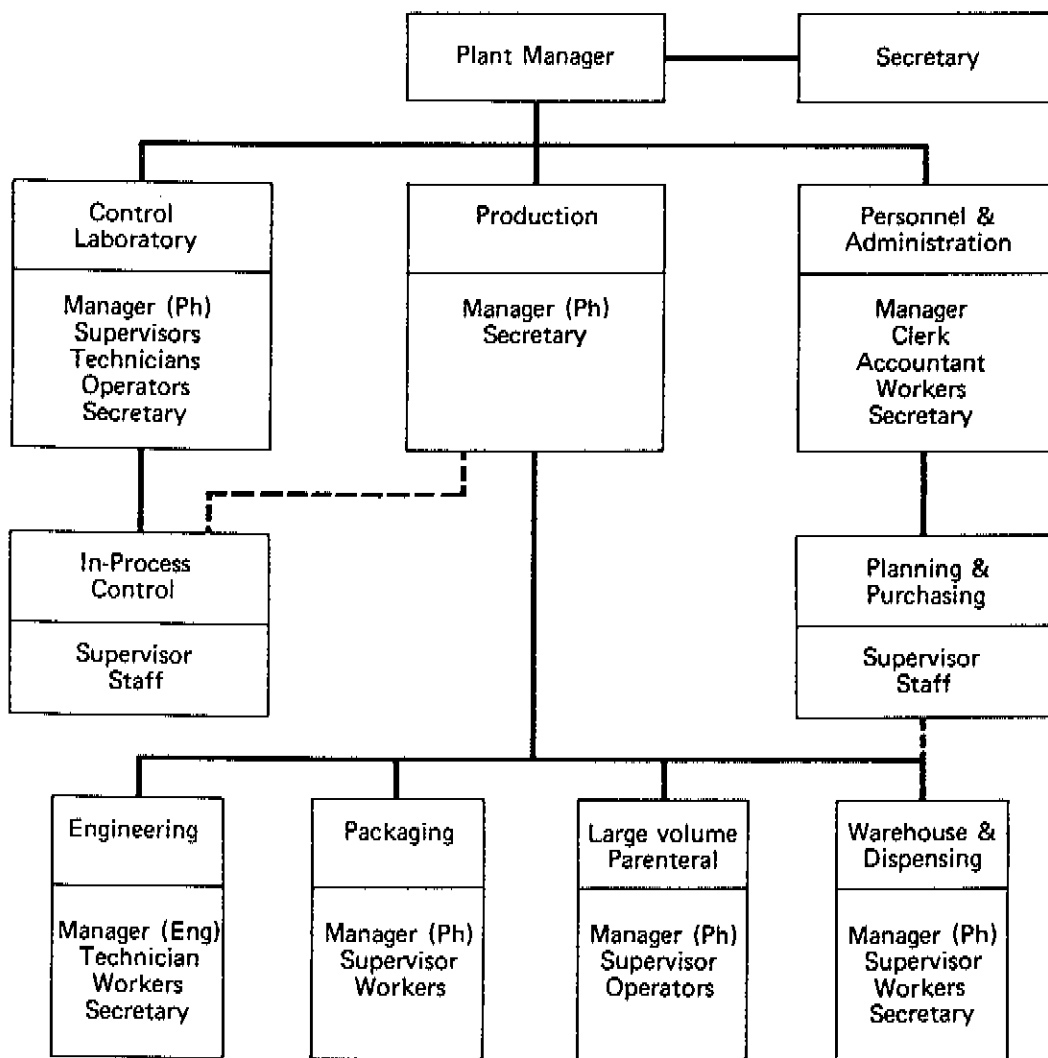
(c) Consultants

Since the manufacturing of large volume parenteral solutions is a rather simple process but requires highly skilled personnel and a high degree of quality standards, technical personnel with much experience is recommended. It is suggested that at the initial stage, two years at least, to have the support of three experts in charge of:

- plant & production manager
- quality control manager
- engineering & maintenance manager.

During the stay on the spot the three experts will cooperate with the national staff in their work and they will continue the training programme in order to complete, as soon as possible, the transfer of the management and technical responsibilities of the plant.

TABLE 10
PROPOSED ORGANIZATIONAL CHART



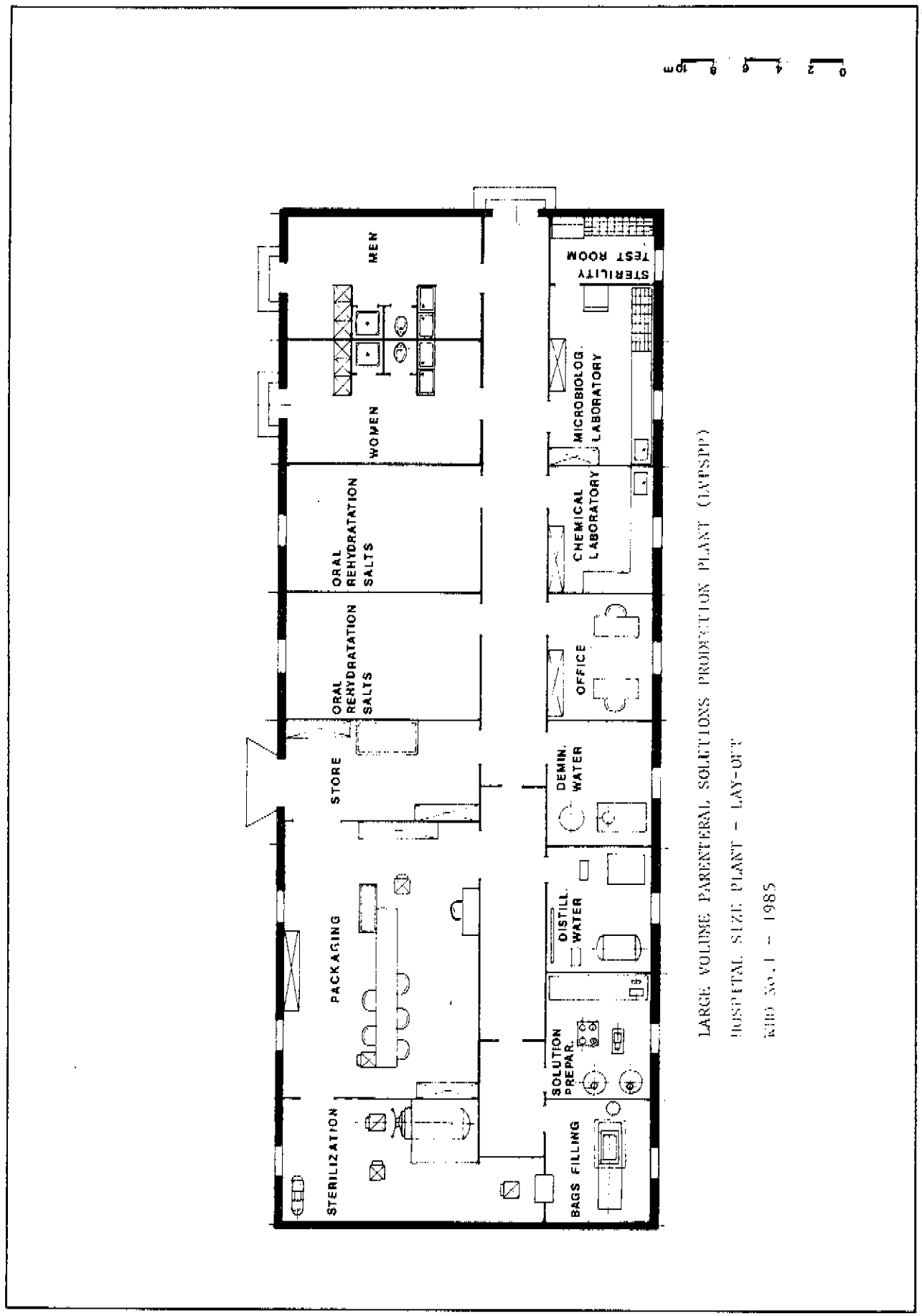
Ph = Pharmacist
Eng = Engineer

WHO 86541

ANNEX V

WHO DRAWINGS SCHEDULE

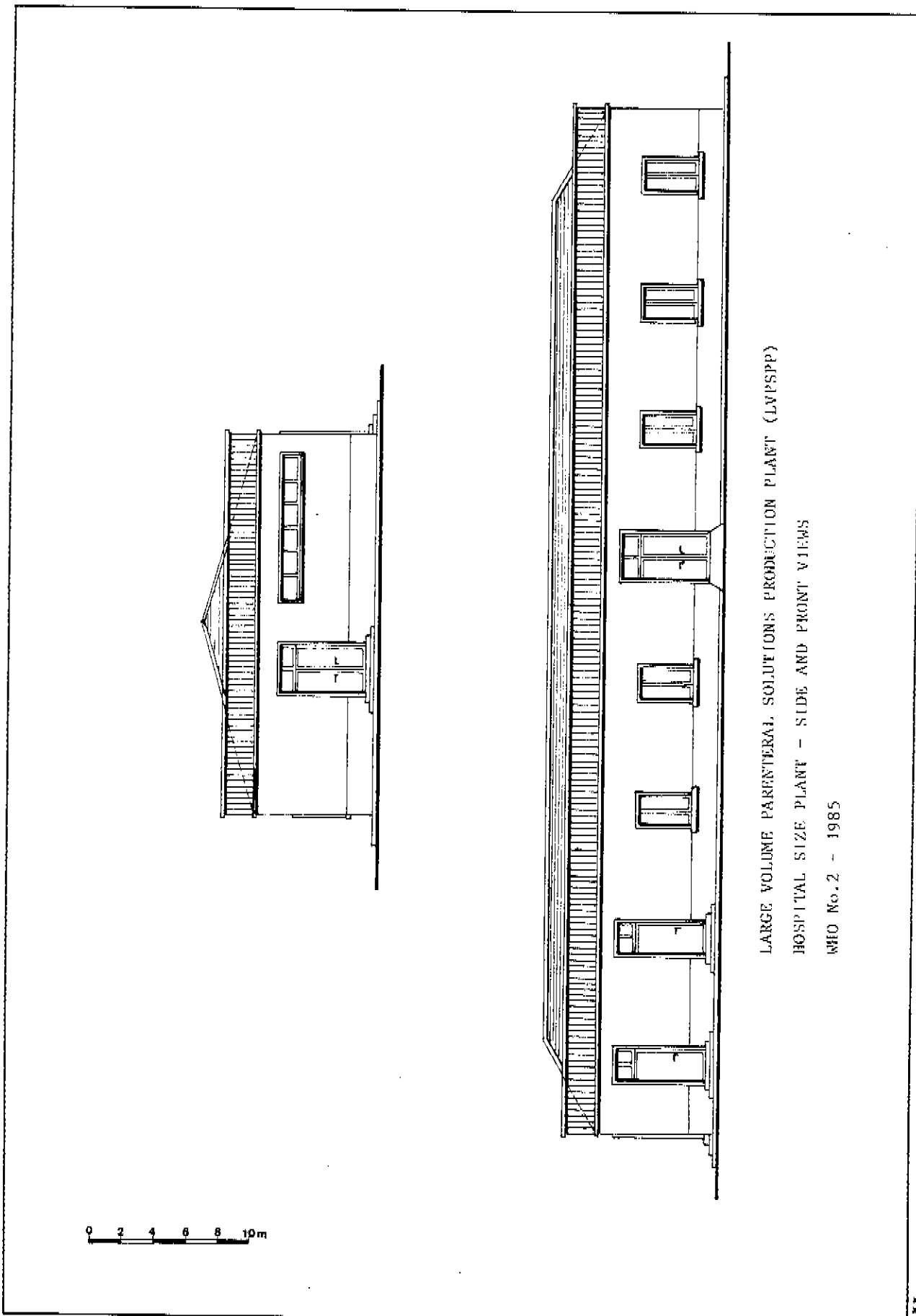
- No.1 - Hospital size plant (Model A): Lay-out
- No.2 - Hospital size plant (Model A): Side and front views
- No.3 - Industrial size plant (Model B): Lay-out
- No.4 - Industrial size plant (Model B): Side and front views
- No.5 - Industrial size plant (Model B): Section
- No.6 - Industrial size plant (Model B): Master plan
- No.7 - Industrial size plant (Model B): Panoramic view



LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSP)

HOSPITAL SIZE PLANT - LAY-OUT

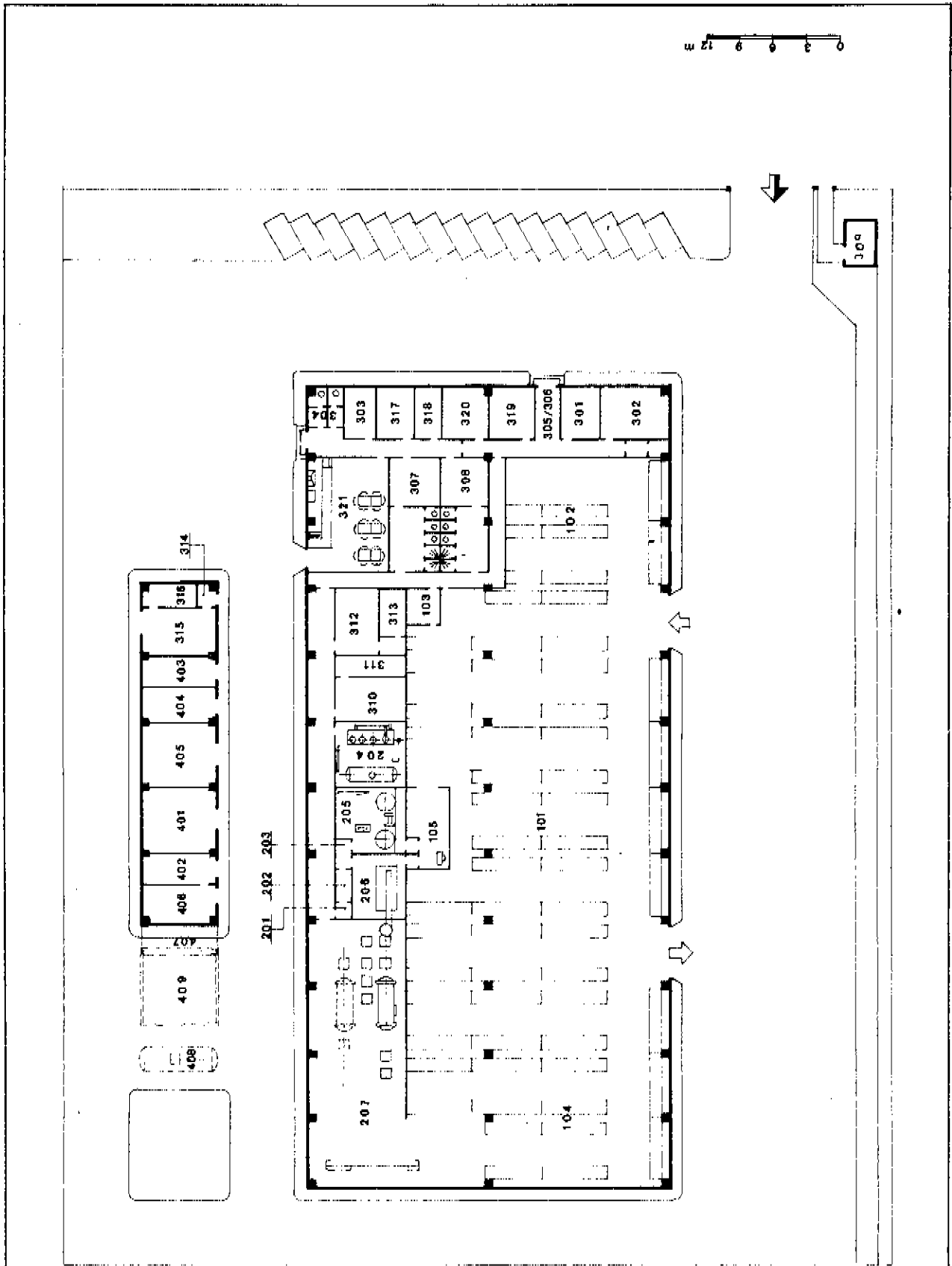
WHD No. 1 - 1985



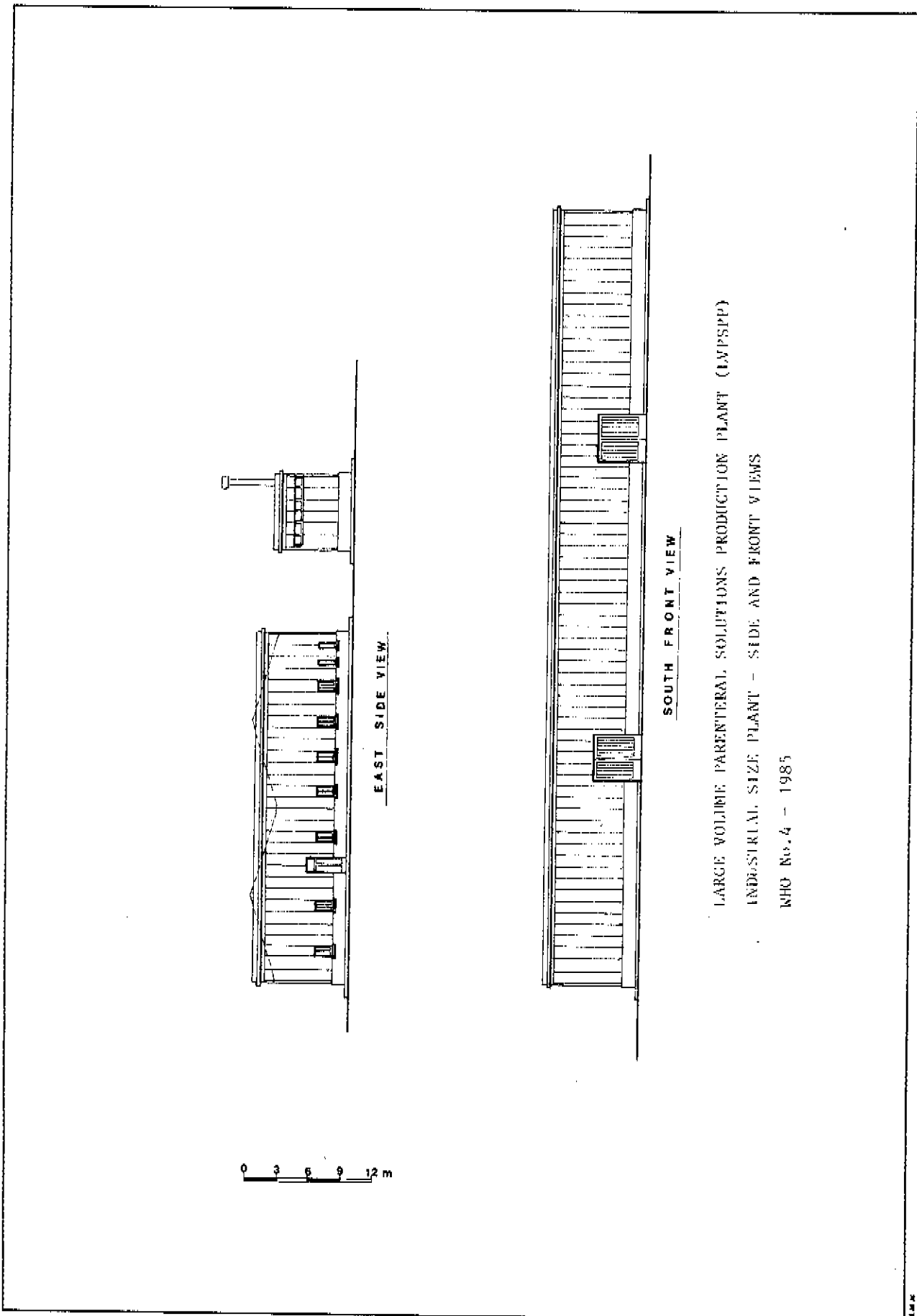
LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSPP)

HOSPITAL SIZE PLANT - SIDE AND FRONT VIEWS

WFO No.2 - 1985



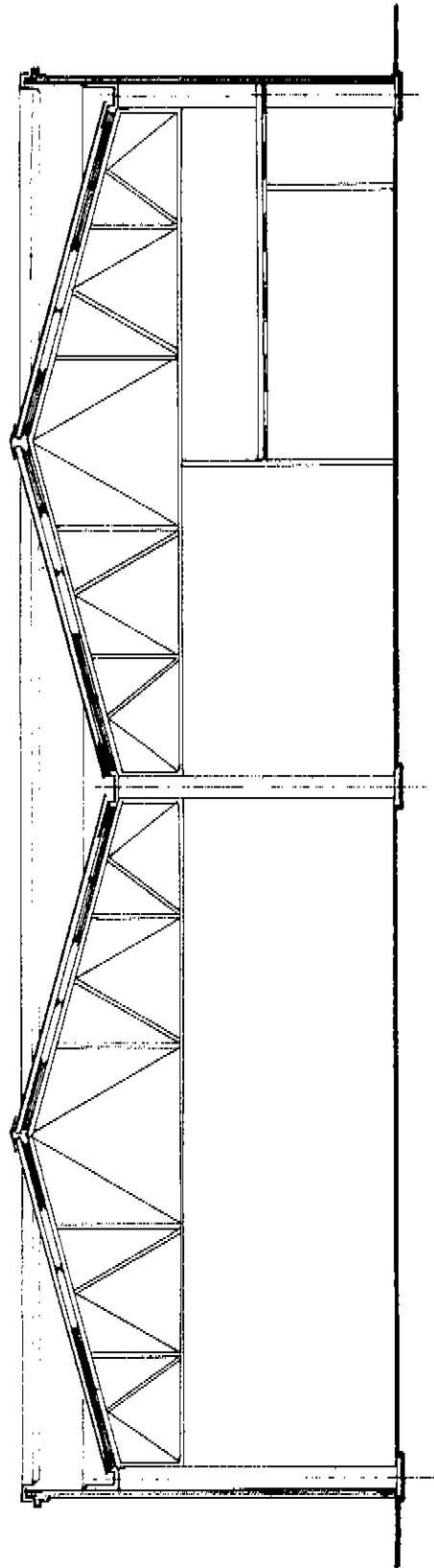
LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSPP)
INDUSTRIAL SIZE PLANT - LAY-OUT
WHO No. 3 - 1985



LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSP)

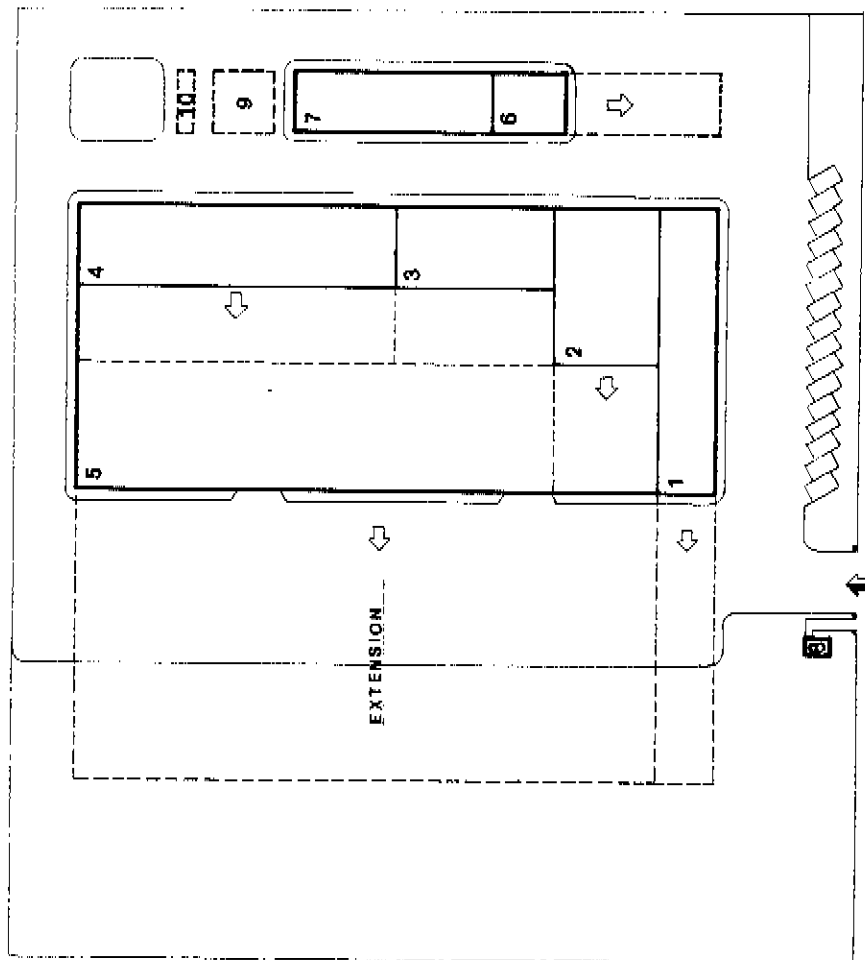
INDUSTRIAL SIZE PLANT - SIDE AND FRONT VIEWS

WHO No. 4 - 1985



LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSP)
INDUSTRIAL SIZE PLANT - SECTION
WHO No.5 - 1985



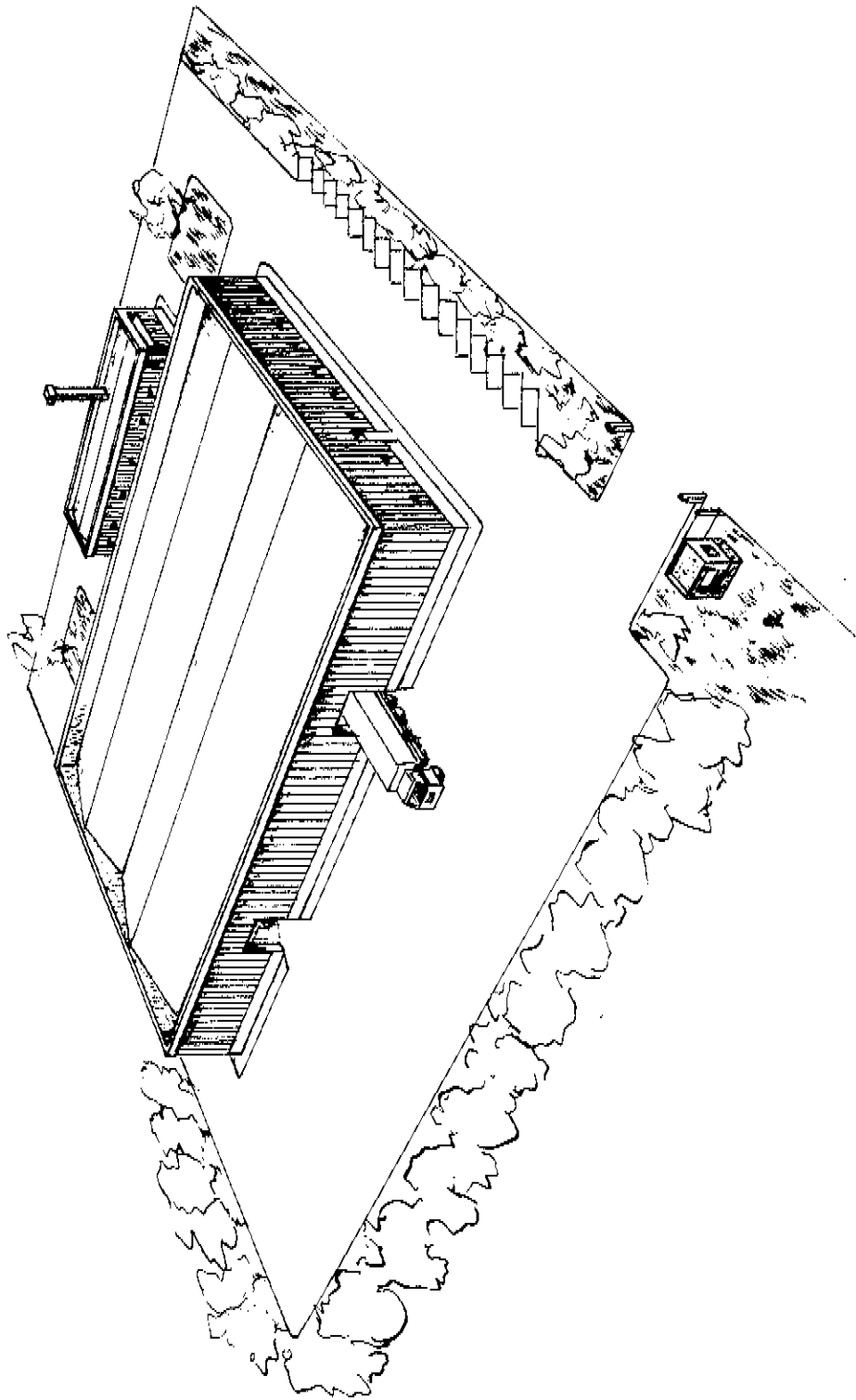


- 1 OFFICES
- 2 SERVICES
- 3 CONTROL LABORATORIES
- 4 MANUFACTURING/PACKAGING
- 5 WAREHOUSE
- 6 ANIMAL HOUSE
- 7 TECHNICAL SERVICES
- 8 GATE
- 9 RAW WATER RESERVOIR
- 10 OIL TANK

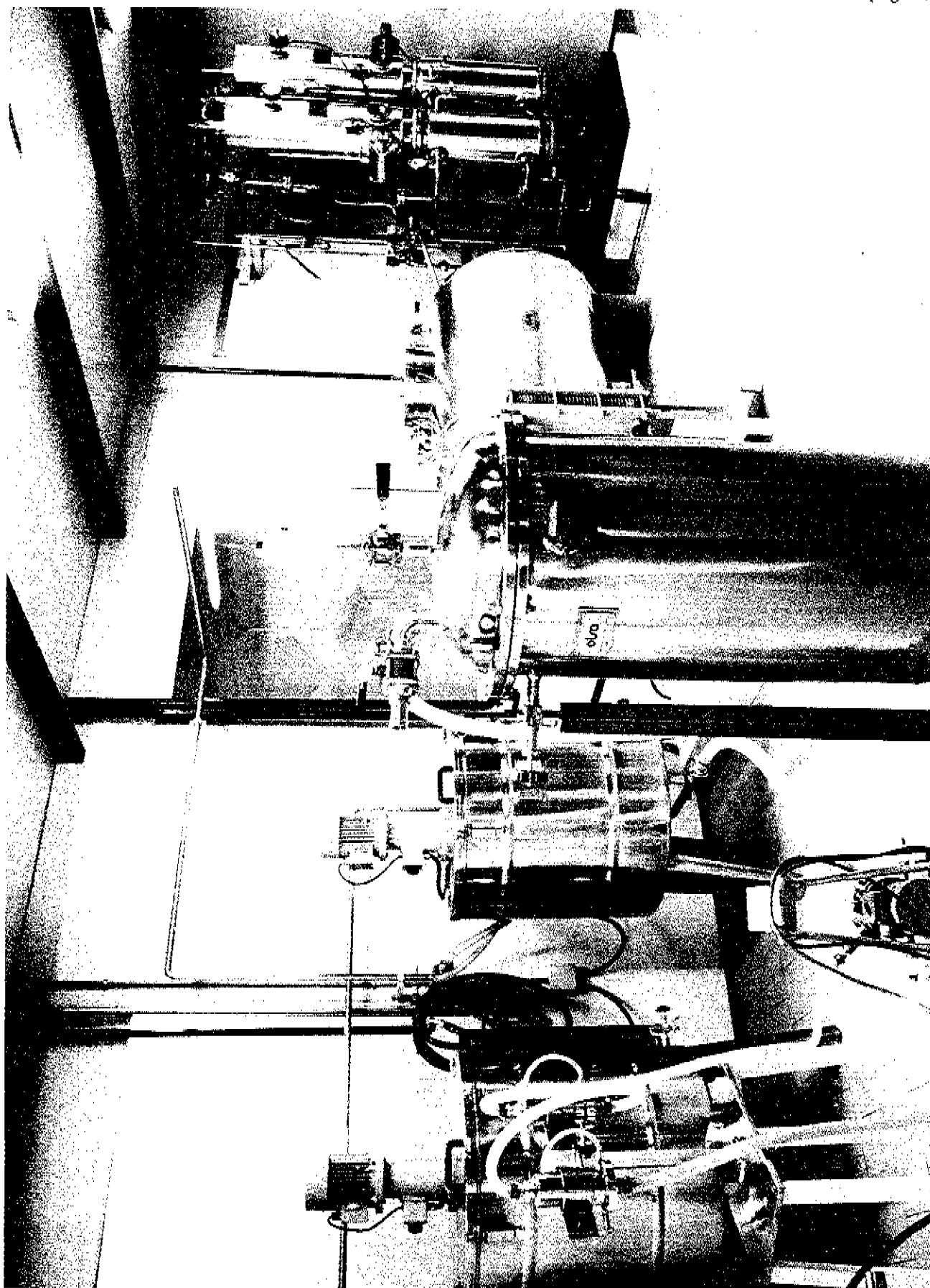
LARGE VOLUME PARENTERAL SOLUTIONS PLANT (LVPSP)
INDUSTRIAL SIZE PLANT - MASTER PLAN

WBO No.6 - 1985





LARGE VOLUME PARENTERAL SOLUTIONS PRODUCTION PLANT (LVPSPP)
INDUSTRIAL SIZE PLANT - PANORAMIC VIEW
WHO No. 7 - '985



Partial view of a prototype LVPSPP, especially designed for developing countries
(reproduction of photograph courtesy of Gruppo Marcucci-Castelvecchio, Toscana, Italy)