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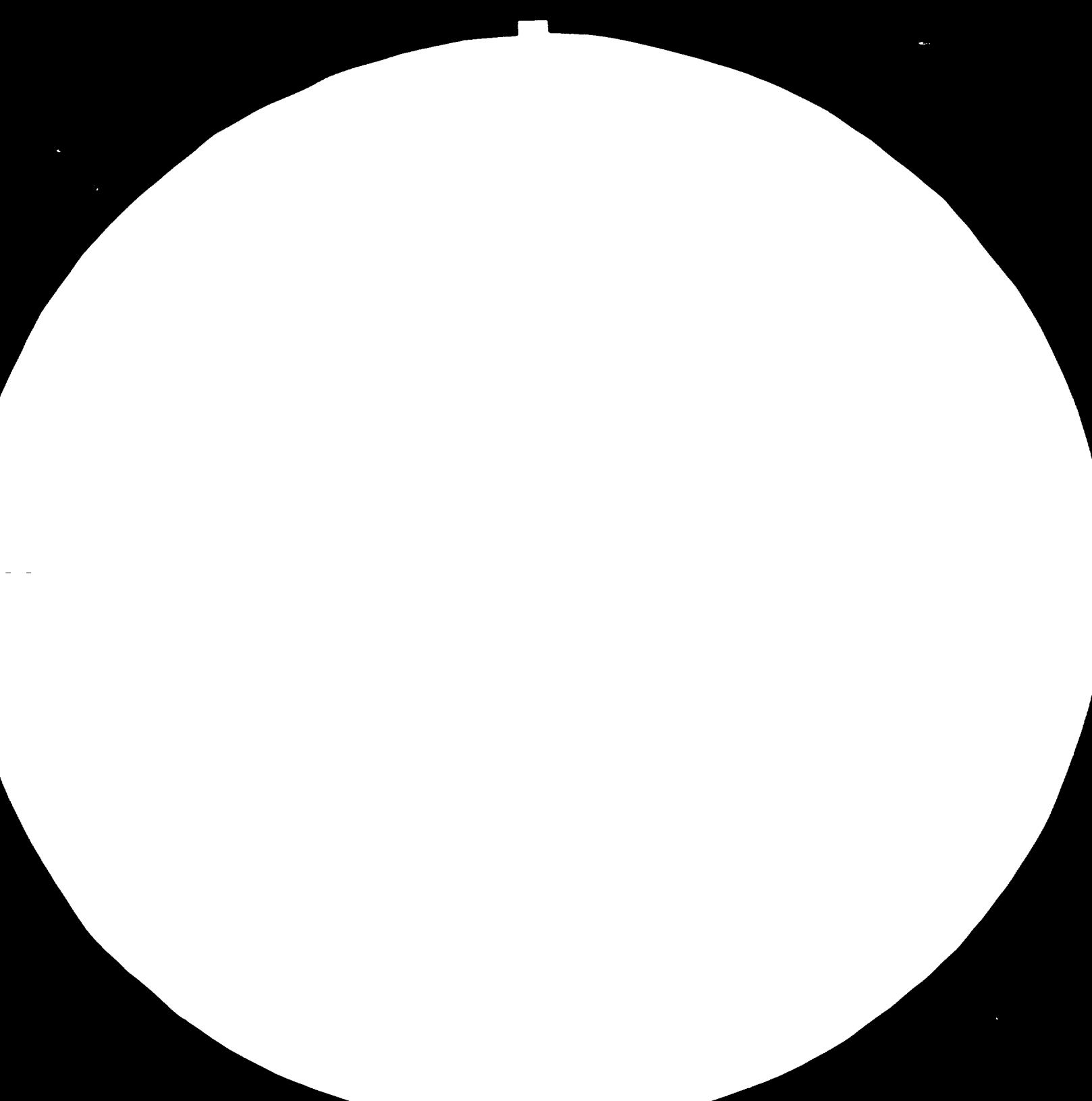
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MICROCOPY RESOLUTION TEST CHART

NATIONAL BUREAU OF STANDARDS-1963-A

12899

U. N. I. D. O.  
Vienna

PROJECT No. DP/MOZ/017  
ACTIVITY CODE 10.20.31.1.

MOZAMBIQUE.

ESTABLISHMENT OF AN ORAL REHYDRATION SALTS PRODUCTION UNIT,

IN  
MOZAMBIQUE

DP/MOZ/80/017

## FINAL REPORT.

M. Kovacs

-6. Juli 1983

787

Budapest, May. 1983.

U. N. I. D. O.

Vienna

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IN  
MOZAMBIQUE

FINAL REPORT

by

M. KOVÁCS

Budapest, May. 1983.

FINAL REPORT  
ON  
ORAL REHYDRATION SALTS PLANT  
IN  
MOZAMBIQUE

**Introduction**

In accordance with the UNIDO - TESCO contract No T81/14 for establishing an Oral Rehydration Salts Plant in Mozambique, the Hungarian team arrived at the site in May, 1981, in order to carry on talks on the establishment of the plant.

The results of the talks and the tasks to be performed are included in the Interim Performance Report which serves as a basis for the Mozambique contracting party with regard to the completion of the plant and to the quality of materials to be purchased, and contains a brief technological and organizational description as well.

At the request of the UNDP/UNIDO, I arrived in Mozambique in January, 1982, in order to take part in equipping the plant and giving a start to production. However, due to the protracted construction period and a shortage in basic materials, this work could not be completed. An account of our activity there is included in the Draft Final Report made in April, 1982.

After the contract was prolonged and the Mozambique UNDP reported that the plant was ready for starting the trial operation, I arrived in Mozambique again on 12th January, 1983, with the purpose of completing the work there.

Activity on the site

Having arrived in Maputo, I was informed on the circumstances of the plant by the local representatives of the UNDP/UNIDO and had detailed talks with the competent officials of Ministry of Health. On the course of the talks, Dr. R. Pereira said that though the construction of the plant was completed, the basic and packaging materials had arrived, the storing conditions didn't meet the requirements given by us /according to GMP standards/. We were informed that the main problem was that of the electric energy supply, due to the sabotage actions frequently occurring in Beira. We got such information that it was planned to buy a current generating station for the plant. In consideration of the storing conditions /a temperature of 40-45°C, relative humidity above 90%/, the deputy of Resident Representative, Mr. Francais asked me to test the basic materials with regard to their applicability.

Arriving in Beira, first I examined the storing circumstances and the condition of the basic materials. The situation corresponded to the previous information.

The quality tests on the basic materials were performed in a laboratory of the local hospital. The quality of the basic materials proved to be satisfactory, though the quality parameters of those remarkably changed for the worse in comparison with the quality certificates of the manufacturer.

Surveying the plant, I established that the storehouse for local storing of the end product /15-day stock/, as well as the transformer station and the transformer were not completed. The rainwater disposal round the house is not satisfactory. The newly built basic ma-

terial storehouse has direct contact with the open air and its roof leaks. It was necessary to effect some changes in certain rooms of the plant, in some parts of the electric power lines and in the furniture of the laboratories.

The machinery, equipment and different materials supplied by us were found in good condition, so having completed the above changes, I could give a start to the process of equipping the plant.

As the building and fitting of the plant protracted, it took about two months to install the producing equipment and the furniture of the laboratories. Besides the frequent and long power- and water supply failures, the work was also delayed by the fact that for the lack of a transformer station - in order to avoid overloading - it was possible to try the machines only one by one, that is, the continual production could not be started.

Mrs. Sándorné Tóth, analyst, who arrived in Beira late in February, 1983, was of great help to me in putting the plant into operation and equipping the laboratory. Two other members of the team, Dr. Lajos Aradi and Dr. Áron Jakabos arrived in Maputo early in March, where we were received by Mr. Goulart on the part of the UNIDO, then by the Resident Representative, Mr. J. Dames. Then we carried on talks in the Ministry of Health in order to solve the difficulties emerged.

The competent officials of the Ministry of Health and those of the UNIDO arrived in Beira early in March in order to study the problems of putting the plant into operation on the site. While they were there, we were promised that the transformer station would be installed and the power supply assured as soon as possible.



In their presence, we tried the producing equipment one by one, which worked perfectly.

The continual trial operation could be started on 24th of March, 1983, and from this time the power supply of the plant was undisturbed. In the course of the trial operation the different working processes and laboratory tests were presented and the working system was organized. The English and Portuguese language documents of manufacturing technology had previously been put at their disposal. The operating manuals and the instructions for maintenance of the machinery also were handed over.

It must be mentioned that in the course of the trial operation skilled labour power were not available in the production or in the control processes, so we are not sure of the undisturbed operation of the plant in the future. With regard to this, the officials on the part of UNDP of Maputo and those of the Ministry of Health held the same opinion, and at the end of our commission, they asked for help of the Hungarian team from the UNIDO in Vienna for the purposes of further manpower training and production control.

In the course of the trial operation under our control more than 50,000 bags of ORS were manufactured. Depending on the circumstances, 2 to 4 charges were produced daily, which proved that in case of a one-shift labour system the plant is able to produce 2 million units yearly.

At the end of the work, a written documentation including the successful completion of the trial run, the experiences and the further tasks were made, which are enclosed here. The Hungarian team made a promise to undertake further training of manpower, at a date or period determined by the UNIDO. At the same time, the team suggested that it would be possible to show the plant to experts

of developing countries purposed to establish similar ones in their country.

Mrs. Sándorné Tóth and I reported on our work to Mr. Polietkov in the UNIDO Centre in Vienna, and then arrived home on 15 th of April, 1983.

Budapest, 9th May, 1983.

*Levan Mihály*  
Mihály Kovács  
team leader

**Supplements:**

- Oral Rehydration Salts /ORS/ Specification of the Manufacturing Process
- Certificate

THE UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION  
Vienna

Project No. DP/MOZ/017  
Activity Code 10.20.31.1

ORAL REHYDRATION SALTS / O R S /  
SPECIFICATION OF THE MANUFACTURING PROCESS

By  
M. Kovács  
A. Tóth  
L. Aradi  
A. Jakabos

Date of the specification: 25/05/1983

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1. Names of the Preparation

1.1. Name used in the literature

Oral Rehydration Salts

Sais de Rehidratacao Oral - S.R.O.

1.2. Name used in the National Formulation /Mozambique/

Polielectrolitiev glicosado-pó

1.3. Name according to the Geneva Nomenclature System

UNICEF and WHO name: O.R.S.

1.4. Popular name used at the plant

ORS



2. Physical and Chemical Characteristics of the Preparation

Oral Rehydration Salts /ORS/ is the non-registered name of a mixture consisting of glucose and inorganic salts.

ORS is a mixture of glucose and inorganic salts.

2.1. Physical properties

White, odourless, slightly hygroscopic powder.

2.2. Chemical properties

It is decomposed both by heating and by acids and alkalis. It is readily soluble in water. /In the case of using Aerosil, the solution is slightly turbid because of the insolubility of Aerosil/. When the content of a package is dissolved in 1 litre of water, then the pH of the solution is 7.2-8.8.

2.3. Package

The preparation is packaged as 27,5 g formulation in an aluminium foil covered by polyethylene and polyester. Fifty pieces of the hermetically closed bags are placed in a collecting box and 20 boxes are placed in a board.

3. Quality Requirements of the Preparation

The preparation should satisfy the following quality requirements:

Labelling	should be legible
Seal	no leaks
Net weight	24,8 g to 30,3 g
Moisture	$\leq 3.0 \%$
Glucose, anhydrous	18,0 g to 22.0 g
NaCl	3.15 g to 3,85 g
NaHCO <sub>3</sub>	2,25 g to 2.75 g
KCl	1.35 g to 1.65 g

4. Quality Requirements of the Preparation of the basic and auxiliary and formulating materials

Order Specifications

4.1. Quality requirements of the oral anhydrous glucose

White crystalline, odourless powder with a sweet taste

Moisture content	$\leq 1.0\%$
Sulfated ash	$\leq 0.2\%$
Assay	$\geq 99.9\%$
Acidity	$\leq 0.50$ ml NaOH

Specific optical rotation  $[\alpha]_D^{20^\circ} = + 52.5^\circ$  to  $+ 53.0^\circ$   
/0.1 mol/l/Vs for 5g sample

Chlorides	$\leq 200$ $\mu\text{g/g}$
Sulfates	$\leq 200$ $\mu\text{g/g}$
Heavy metals	$\leq 10$ $\mu\text{g/g}$

Microbiological conditions

Standard plate count	$\leq 2$
Moulds and yeasts	$\leq 10/\text{g}$
Osmophilic yeasts	$\leq 20/\text{g}$
<u>B. coli</u> /37°C/	negative/g

Packing

Polyethylene coated paper bags of 50 kg net in strong, moisture-proof containers.

/Food-grade glucose is acceptable/

Some Suppliers

Oxyde-Joba B.V., Biesbosch 225, Amstelveen, Holland, B.V.  
Meelunic, Herengracht 209, 1016 BE Amsterdam, Holland,  
Deutsche Maizenwerke GmbH, Maizenhaus, D-2000 Hamburg 1  
Laevosan-Gesellschaft GmbH & Co. WG, Estermannstrasse 17  
A-1021 Linz, Austria/

4.2. Sodium chloride R

NaCl Mol. Wt. 58.44  
Colourless, odourless white powder  
or crystals

Moisture content	$\leq 1.0\%$
Assay	NaCl $\geq 99.0\%$
Insoluble material	$\leq 50, \mu\text{g/g}$
Acidity or alkalinity	pH 8.2 to 10.0
Chlorate and nitrate	$\text{ClO}_3 \leq 10, \mu\text{g/g}$ $\text{NO}_3 \leq 30, \mu\text{g/g}$
Phosphate	$\leq 5, \mu\text{g/g}$
Sulfate	$\leq 30, \mu\text{g/g}$
Ammonium	$\leq 10, \mu\text{g/g}$
Barium	$\leq 10, \mu\text{g/g}$
Calcium and magnesium	$\leq 50, \mu\text{g/g}$
Heavy metals	$\leq 10, \mu\text{g/g}$
Iron	$\leq 5, \mu\text{g/g}$
Potassium	$\leq 100, \mu\text{g/g}$

/Pharmaceutical grade sodium chloride should be ordered in strong, moisture-proof containers according to IP, USP, NF, BP, EurP, PhUSSR, PhHg, or equivalent./

Some suppliers

E. Merck AG, P.O. Box 4119 D-6100 Darmstadt, WG. Riedel-de Haen AG, Wunsterfer Str. 40, D-3016 Seelze 1, WG. Chemische Fabrik Lehrte, Dr. Andreas Mossel GmbH Postfach 1220, D-3160 Lehrte, WG.

4.3. Sodium hydrogen carbonate R



Mol. Wt. 84.01

White, crystalline powder

Moisture content	$\leq 1.0\%$
Assay	$\text{NaHCO}_3 \geq 99.0\%$
Insoluble material	$\leq 150 \mu\text{g/g}$
Chloride	$\leq 50 \mu\text{g/g}$
Phosphate	$\leq 10 \mu\text{g/g}$
Sulfate	$\leq 50 \mu\text{g/g}$
Ammonium	$\leq 5 \mu\text{g/g}$
Calcium and magnesium	$\leq 100 \mu\text{g/g}$
Heavy metals	$\leq 10 \mu\text{g/g}$
Iron	$\leq 10 \mu\text{g/g}$

/Pharmaceutical grade sodium hydrogen carbonate should be ordered in strong, moisture-proof containers according to IP, USP, NF, BP, EurP, PhUSSR, PhHg, or equivalents./

Some suppliers

E. Merck Ag, P.O. Box 4119 D-6100 Darmstadt, WG. Riedel-de Haen AG, Wunsterfer Str. 40, D-3016 Seelze 1, WG. Chemische Fabrik Lehrte, Dr. Andreas Kossel GmbH Postfach 1220, D-3160 Lehrte, WG.

4.4. Potassium chloride R

KCl

Mol. Wt. 74.55

Colourless, odourless crystals or a white, granular powder

Moisture content		≤ 1.0%
Assay	KCl	≥ 99.0%
Insoluble material		≤ 50,ug/g
Acidity or alkalinity	pH	8.2 to 10.0
Nitrate		≤ 30,ug/g
Sulfate		≤ 30,ug/g
Ammonium		≤ 10,ug/g
Barium		≤ 30,ug/g
Calcium and magnesium		≤ 50,ug/g
Heavy metals		≤ 10,ug/g
Iron		≤ 5,ug/g
Sodium		≤ 200,ug/g

/Pharmaceutical grade potassium chloride should be ordered in strong, moisture-proof containers according to IP, USP, NF, BP, EurP, PhUSSR, PhHg, or equivalent./

Some suppliers

E. Merck AG, P.O. Box 4119 D-6100 Darmstadt, WG. Riedel-de Haen AG, Wunsterfer Str. 40, D-3016 Seelze, 1, WG. Chemische Fabrik Lehrte, Dr. Andreas Kossel GmbH Postfach 1220, D-3160 Lehrte, WG.

4.5. Aerosil

Aerosil is the proprietary name for colloidal silicon dioxide

Aerosil should be ordered in 2-5 kg net weight in strong, moisture-proof containers.

Supplier e.g.

Degussa, p.o. box 2644, D-6000 Frankfurt 1, Germany.

#### 4.6. Packing material

It is aluminum foil coated on both sides. The foil should be continuous with a coating of uniform thickness. The foil has to be suitable for forming packets of dimensions approximately 90 mm x 100 mm.

Inside: polyethylene	50 g/m <sup>2</sup>
Middle: aluminum	15 μm
Outside: polyester	15 g/m <sup>2</sup>

Printing on inside of the polyester coating, with the following labelling in one colour, light blue/

#### Label of the ORS packet

Sais de Rehidratação Oral - S.R.O  
/Polielectrolitico glicosado-pó/

Indicacao: Tratamento por via oral da desidratação por diarreia

Preparação: Dissolver o contendo total do saco em 1 litro de água potavel.

Modo de emprego: Salvo indicação contraria do médico, beber un volume de S.R.O. igual ao volume de fezes evacuadas ou de acordo com a sede.

As quantidades normalmente consumidas são as seguintes:

<u>Idade</u>	<u>Volume em 24 horas</u>
Menos de 6 meses	1/4 a 1/2 litro
6 meses a 2 anos	1/2 a 1 litro
2 anos a 5 anos	3/4 a 1 1/2 litro
Mais de 5 anos	de acordo com a sede

Retomar a alimentação, especialmente o aleitamento materno, logo que a rehidratação esteja realizada.



Composição:	Glucose anidra, BP 73:	20,0 gramas
	Cloreto de sódio, BP 73:	3,5 gramas
	Bicarbonato de sódio, BP 73:	2,5 gramas
	Cloreto de potássio, BP 73:	1,5 gramas

Peso total: 27,5 g                      Excipiente 0,02 % de Aercsil

Conservar ao abrigo da humidade a dos raios solares

Produzido por EMOFAR - Empresa Moçambicana de Produtos Farmaceuticos - RP. de Moçambique

-----  
Carried out by the help of UNIDO-HUMAN-TESCO Hungary

Some suppliers

Ivers - Lee .AG, Chemopack Service, CH - 3400 Burgdorf,  
Schwitzerland

Tielebier GmbH. Thomas Tamossino Str. 6. A - 2340 Mödling

4.7. Collecting box and collecting board

The collecting box has suitable dimension to take in 50 ORS containing bags.

The collecting board is capable of taking in 20 boxes. It is constructed of such a material as to be suitable to transport a load of about 30 kg, with a good safety under the conditions of Mozambique.

4.8. Board label

The collecting boards should be provided with labels.

The following data are indicated on the label:

The name of the preparation: Sais de Rehidrataçãõ -  
S. R. O.

Amount:	1000 bags
Manufacturing company:	Produzido por EMOFAR, Beira, Mozambique
Charge number:	
Time of manufacturing:	

5. The Short Story of Introduction of the Preparation

Acute diarrhoeal diseases are among the most important causes of childhood mortality and morbidity in Mozambique. The acute diarrhoea is also a significant cause of morbidity and lost of working time among adults. A significant development in recent years has been the discovery that dehydration by acute diarrhoea of all etiologies and in all age groups can be safely and effectively treated by the simple method of oral rehydration using a single fluid.

Death by acute diarrhoea is most often due to dehydration resulting from the excessive loss of body water and salts in stools, vomitus, urine, sweats and insible losses. Patients with dehydration associated with acute diarrhoea usually have a lack of sodium, potassium and water and an acidosis due to base lack. Thus, it is reasonable to use rehydration solutions to treat dehydration associated with diarrhoea of all causes in all age groups.

The formula for Oral Rehydration Salts /ORS; non-proprietary name recommended by WHO, first used in 1971/ is as follows:

Glucose. anhydrous	20,0 g
Sodium chloride	3,5 g
Sodium hydrogen carbonate	2,5 g
Potassium chloride	1,5 g

The quantities shown are necessary to prepare 1 litre of ORS solution. When properly prepared and administered, ORS solution provides adequate quantities of electrolytes to correct the lacks associated with the acute diarrhoea. The presence of potassium in the solution is important in view of the large body potassium losses associated with the acute diarrhoea, as specially in infants. The sodium hydrogen carbonate present in ORS solution is resorbed in amounts adequate to correct the acidosis. The resorption

of sodium and water in the small intestine is more rapid in the presence of glucose. This fact remains true irrespective of the cause of diarrhoea and forms the physiological basis of oral rehydration therapy using ORS solution.

Thus, the solution can be prepared as needed by dissolving a prepackaged mixture of ORS in an appropriate volume of drinking water.

In view of the manufacturing of ORS, a consultation was held in Bangkok under the sponsorship of WHO and UNICEF in 1979.

## 6. Schematic Description of the Manufacturing

### 6.1. Qualification of basic materials

Concerning the basic materials, the analytical laboratory carries out quality control examinations, according to the specifications. The unsuitable materials are rejected.

### 6.2. Storage of the basic materials till the use

The controlled and suitable basic material is stored as separated from the materials not examined up to the time of use.

### 6.3. Last quality control before use

At 24 hours before use, the materials are controlled concerning moisture content and knottiness.

### 6.4. Drying

The glucose has to be dried when its moisture content exceeds 1 %.

### 6.5. Sieving

The salts and glucose are sieved. This operation is carried out by turbosieve or by a hand-sieve.

### 6.6. Weighing- in and homogenization of the basic materials

The basic materials are weighed in the drum mixer, and homogenization is started after closing hermetically.

### 6.7. Control during the production

The homogenized material is sampled and the moisture and chloride content of this sample are determined. When the chloride content is not satisfactory, the material is rejected.

When the moisture content exceeds 2%, then drying and sieving should be repeated.

### 6.8. Dosing, sealing, designation

When the powder mixture satisfies the quality speci-

cations, then 27,5 g amounts of it are filled in mounted aluminium foil bags. After dosing, the bags are immediately sealed and provided with batch number and date.

6.9. Weight control

Samples are taken from the designated bags for weight control in every 15 minutes.

6.10. Packing

Fifty pieces of the sealed and designated bags are placed in a box, while 20 boxes are set in a board. The boards are provided with a label.

6.11. Sampling

The analytical and counter-sample are taken from the boards after packing.

6.12. Storage of the formulated product

During the control examinations, the formulated product is stored in quarantine. After releasing, they are stored in the expedition store.

## 7. Description of the Manufacturing Equipments

### 7.1. Drying oven

Type: LP-320/2

Manufacturing Company: LABOR MIM, HUNGARY

LP-320/2 is a drying oven with a working volume of 400 litres, provided with a ventilator, where the material can be dried in trays placed on shelves.

Limits of the heating temperature:  $+30^{\circ}\text{C}$  and  $+300^{\circ}\text{C}$

Dimensions of the working volume: 1100 x 670 x 533 mm.

The shelves can be placed in a distance of 6 cm from each other.

The regulating and controlling equipments are placed in the inner wall of the switchboard except the control thermometer built in the door.

The material of inner mantle of the drying oven is stainless steel.

Operation: at 3<sup>rd</sup>0V, 50 Hz

Output: 4620 W

### 7.2. Sieving equipment

Type: Jesma Turbo Sieve 110/250

Manufacturing Company: Hans Jesen Machineworks LTD  
Denmark, 7100, Vejle

This equipment is prepared from stainless steel, with changeable sieves. The material feeded in is pressed by a transporting scroll through the sieve. The sieved particles get into a collecting funnel, while strange materials and particles not penetrating through the sieve are removed through an outlet.

### 7.3. Sieve /hand-operated/

This is an equipment which can be operated by hands. The sieve cloth is permeable for particles of 1-2 mm. The sieve is surrounded by a dust-catching cloth for



preventing the exit of dust. The sieved material gets into a collecting vessel through a collecting funnel.

#### 7.4. Homogenizer

Type: Drum Mixer

Manufacturing Company: Ganson LTD, Bombay, India

Drive: TEFC electromotor

Output: 1 horse power /HP/

Voltage: 380V

Speed: 1440/min

The drum is placed in an angle of 25° on the hoop. Its mounting permits the motion together with the hoop.

Dimensions of the barrel: 600 mm in diameter

685 mm in height

Total volume: 200 l

Useful volume: 120 l /70 kg of material as a maximum/

#### 7.5. Filling machine

Type: 51045/C scroll feeder

Manufacturing Company: Élelmiszeripari Gépgyár, Budapest  
HUNGARY

It is a machine with electric control and mechanical driving. The equipment is driven by a triphase motor.

The revolution number of the motor can be changed depending upon the position of the V-belt.

In the feeding funnel, a stirrer continuously keeps the material feeded in moving and assures the homogeneous distribution. The filling is carried out by a feeding scroll.

Volume of the feeding funnel: 29 l.

Maximum output of the machine: 100 l/hr.

Minimum space requirement of the machine: 1000 x 1600 mm

Output of the motor: 1,1 kW.

Mains voltage needed: 3 x 380 V.

7.6. Closing machine

Type: Thimotherm K 20 C

Manufacturing Company: Thimounier, Lyon, France

The equipment has 2 closing jaws, the temperature of which can be regulated between 100 and 200°C.

The closing jaws can be set in two positions depending whether the equipment is used to closing or to the preparation of bags.

The closing machine can be operated manually or by foot.  
Mains voltage: 220 V.

7.7. Designating equipment

It is an individually manufactured equipment, where the dye gets to the designating stamp by the means of a designating cylindre. The designating dye has to be applied to the cylindre by a brush.

The equipment is operated by pressing down a foot treadle. The bags to be designated are manually changed.

On adjustment of a new batch number and production time, the numbers in the designating stamp can be changed by a pincers.

7.8. Balances for weighing-in

7.8.1. The 100 kg balance

Type: 105789

Manufacturing Company: METRIPOND, Hódmezővásárhely  
HUNGARY

Minimum measurable weight: 5 dkg

Maximum measurable weight: 100 kg

7.8.2. The 15 kg counterbalance

Type: SJ 15 PRL 315

Manufacturing Company: Lubelski Fabryki WAG,  
POLAND

Factory number: NR 2041



### 8.3. Water still

The LD-103/2 type equipment, a "Labor" MIM product is suitable for the preparation of distilled water for laboratory use.

Distillation performance: 10 l/hr

Supply voltage: 380/220 V, 50 Hz, triphase alternating voltage

Consumed power: 3 x 2,4 kW = 7,2 kW

Dimensions: 1145 x 400 x 460 mm

Weight: about 25 kg

The equipment is operated with supply water. The water is boiled by tube-heating bodies heated electrically. The distillation of water begins 10-12 minutes after switching in the heating. A device controlling the lack of water is built in the equipment that switches off the current and thus, prevents the burn-out of the heating tubes, when the water stops coming during operation.

### 8.5. Anaerobic thermostat

The LP-115 ABS-30 type equipment, a "Labor" MIM product, can be operated between +30°C +70°C at an adjustable temperature. The working space of the equipment is prepared from stainless material. Its door and temperature regulation can be locked by key and thus, any strange intervention is prevented. The equipment is protected by a separate regulator from overheating.

Supply voltage: 220 V, 50/60 Hz

Consumed power: 0,67 kW

Dimensions: width: 550 mm

height: 520 mm

depth: 660 mm

Useful volume of the working space: about 30 l.

8.5. Flame photometer

The Flapho 4 type instrument, manufactured by Zeiss, is suitable to determine sodium, potassium etc. content.

Mains voltage: 220 V, 50/60 Hz

Consumed power: 18 VA; at starting: about 50 VA

Dimensions: 50 kg

Interference filters, operating at suitable wavelengths, are used to assay the various cations.

Sensing element: selenium photoelement Type SeF.

Measuring range

	Concentration /mg/l/ /ppm/ necessary for maximum amplitude		Detection limit /mg/l/ /ppm/	
	Propane- butane/air with flame	Acetylene/ air with flame	Propane- butane/air with flame	Acetylene/ air with flame
Na 589 nm	0,1	0,1	0,001	0,0001
K 768 nm	0,2	2	0,001	0,01
Ca 625 nm	6	1	0,1	0,01
Li 671	0,5	0,1	0,01	0,002

Gas supply system

Two-stage pressure reducer	for compressed air	for PB gas	for acetylene
<p>First stage is connected to the gas bottle</p> <p>Measuring range of the high-pressure manometer:</p> <p>Measuring range of the manometer connected to the gas bottle</p> <p>Steady pressure necessary for operation of the instrument</p>	<p>0-250 kp/cm<sup>2</sup></p> <p>0-15 kp/cm<sup>2</sup></p> <p>about 5 kp/cm<sup>2</sup></p>	<p>0-40 kp/cm<sup>2</sup></p> <p>0- 4 kp/cm<sup>2</sup></p> <p>about 0,8 kp/m<sup>2</sup></p>	<p>0-40 kp/cm<sup>2</sup></p> <p>0- 4 kp/cm<sup>2</sup></p> <p>about 1 kp/cm<sup>2</sup></p>
<p>The second stage is connected to the instrument:</p>	<p>0-1,5 kp/cm<sup>2</sup></p>	<p>0-400 water column mm</p>	<p>0-400 water column mm</p>
<p>Measurement limits of the flow meters measuring the gas flow:</p>	<p>0-800 l/hr</p>	<p>0-25 l/hr</p>	<p>0-200 l/hr</p>

Approximately 800 l/hr of air are necessary for the burning head. The atomiser is constructed of stainless steel. About 0.3 ml of liquid is needed for one measurement /when two elements are determined/. The liquid consumption is 1 ml/min.

8.6. pH meter

The measuring range of the PHM 25 type instrument, a Radiometer product, is 0-14 pH and 0 ± 1400 mV  
 Minimum measurable value: 0,1 pH and 10 mV.

Reproducibility:  $\pm 0,01$  pH and  $\pm 1$  mV

Minimum measurable value with stretched scale: 0,01 pH

Reproducibility:  $\pm 0,002$  pH and  $\pm 0,1$  mV

Temperature range: it can be changed by 2 C<sup>o</sup> from 0<sup>o</sup>C to 100<sup>o</sup>C

Mains voltage: 220 V 50/60 Hz

Dimensions: width: 280 mm

height: 320 mm

depth: 300 mm

Electrodes used to pH determination: G 202 B type glass electrode  
K 401 type calomel electrode

#### 8.7. Water bath

The LW 4 type equipment, an WSL product with an automatic thermoregulator, is useful to heat to 100<sup>o</sup>C.

Mains voltage: 220 V  $\pm 10\%$ , 50 Hz

Consumed power: 800 W

Capacity of the water bath: 6,5 l

Temperature stability:  $\pm 2$  C<sup>o</sup>

Dimension of the water bath without the frame rods:

480 x 330 x 120 mm

Weight /empty/: about 9,5 kg.

9. The Plant: General Description, Energy System, Organisation, Spheres of Authority

9.1. General description

The plant is able to manufacture 2,000,000 of the most commonly used 28 gr ORS yearly. The plant meets WHO's Good Manufacturing Practice and UNICEF recommendations.

It is designed to combine efficiently semi-automatic and manual processes. The general dimension of the building, including ceiling heights, room sizes, construction materials, have all been considered to provide efficiency in the activities programmed for ORS plant. The building materials /for reconstruction only/ are selected for minimum maintenance.

The space requirements shown in Drawing enclosed are based on production of 2 million packets per year. Nine separate rooms are required to isolate the specific operations. At the space requirements, the GMP requirements were taken into account which prevent mix-ups and contamination, including contamination by different batches, by operating personnel. There are areas provided for segregating untested materials, in-process materials, finished product from tested materials through quarantine area and released materials area.

The flow of materials is designed to prevent back-tracking, thus avoiding possibilities of mix-up. The plant is designed to meet all safety standards including fire hazards, accidents due to machinery, etc.

The construction and finishing materials recommended were selected for their ease of cleaning. This is true of floor, wall and ceiling finishes.

The windows should seal tightly when shut and be



closely screened when open. Door should be self-closing and seal tightly.

**Effective storey heights:**

Production rooms, storage and service rooms are 3,2 m in height.

**Imposed load on ground floor**

Production rooms	1000 kg/m <sup>2</sup>
Storage	1500 kg/m <sup>2</sup>
All other rooms	700 kg/m <sup>2</sup>

**9.2. Installations**

**Electrical Plant**

A low voltage connection of 380/220 V, 50 Hz is installed up to the main distribution point.

The power meters are centrally placed. No emergency power is required. All cables, switches and sockets are to be located in recesses.

**Light fixtures:**

Production room - fluorescent lights, with a light intensity of 600 luxes, all other rooms with bulb, light intensity 400 luxes.

The power requirement for ORS plant is 50 KW/hr.

Ground connection and neutral phase /0/ are necessary.

The available water should be suitable for drinking. The water has to be sufficient for fire extinguishing, production and the sanitary system. The water for the sanitary system is heated in electrically heated boilers /one with a volume of 250 litres, one with a volume of 60 litres/.

For the pipelines, we propose zinc-rolled steel materials or synthetics.

The water requirement for the plant is  $10^3$ /day, top consumption is 100 litres/min at 3,5 bar pressure.

### 9.3. Organisation

As recommended by the WHO Guidelines on Good Manufacturing Practices /GMP/, as well as to ensure efficient operation of the plant, the following organisation chart can be suggested :

<u>Plant General Manager</u>		<u>Secretary</u>
<u>Control Laboratory</u>	<u>Production</u>	<u>Administration</u>
Manager	Manager	Manager /1/
Technician /1/	Secretary	Clerk /2/
Workers /3/	Machine operators /2/	Accountant /1/
	Repair tech. /3/	Secretary /1/
	Workers /10/	Storeman /3/
	Cleaners /2/	Helper /3/
	Foreman	Doorkeeper /3/
		Gardener /1/

### 9.4. Qualifications

GMP standards require that each person engaged in the processing and packaging should have the education, training and experience enabling that person to perform the assigned tasks, with the specific

additional provision that those supervising such activities /control lab. manager, prod. manager/ are able to function in such a manner as to provide assistance that the ORS product, as a drug should have the safety, identity, strength, quality and purity for its therapeutic purpose.

Heads of departments such as production, quality control should be persons with university degrees in pharmacy, chemistry or in any other relevant field.

Operators are usually persons with a high school or equivalent education. If possible, other workers such as packers, storemen, those involved in production, cleaners, etc. should be able to read and write properly.

The production manager:

- takes overall responsibility for quantity and quality of packets produced including
    - ordering raw materials,
    - approving materials for distribution,
    - releasing packets for distribution,
    - supervising personnel and weighing operations;
- The production manager should be a pharmacist or chemist.

The laboratory manager:

- takes overall responsibility for quality control of raw materials, finished product and other analyses.
- The laboratory manager should be a pharmacist or doctor /or a pharmacist or doctor should be readily available for consultation and approval/.

The laboratory technician:

- is responsible for performing all quality control analyses on ingredients upon receipt and during processing and on the finished product;
- is responsible for proper maintenance of the control laboratory equipment and reordering of equipment, reagents and chemicals, as necessary through the laboratory manager or production manager /at minimum 9-class level/.

The foreman:

directly guides the production on the basis of the instructions of the production manager;

- takes out the raw, auxiliary and formulating materials which are necessary for production;
- informs the Control Laboratory about the raw materials to be used and semi-finished products, concerning sample taking;
- personally controls each phase of the production;
- registers the steps of production on the Production Control Sheet;
- directs the material handling within the plant;
- holds a direct connection with the production manager, with stores, Control Laboratory and maintenance men.

**Workers:**

- perform drying, sifting, weighing, mixing, dosing-filling, sealing, impressing the manufacturing date and batch number, packing into boxes and cartons/at minimum 4-class level/.

**Operators:**

- run the mixing and packet filling machine; check packets on  $\pm$  scale, while machines are running and make adjustments /at minimum 6-class level/.

**Maintenance:**

For maintenance of machines, an experienced electrician, mechanic or car repairer is necessary.

People have to be taught to give the first aid, too.

**Training:**

**Production personnel**

During the training period, the following main ideas are to be followed.

The jobs in production activities are not purely ma-

nual works. The need for alertness and awareness in individuals employed, and especially, understanding of the job to be performed should be emphasized. Therefore, it stands to reason that, for an industry the products of which demand personnel with a high sense of responsibility, motivation and training are crucial.

The importance of job rotation, chances of further training for fitting candidates in order to improve their capabilities or the opening of possibilities for promotion or any sort of incentives should not be overlooked. /Note: this is also a basic training for the pharmaceutical manufacturing unit, which has to be established sooner or later./

On-the-spot training in GMP, especially on problem-oriented teaching, e.g. personal hygiene, health habits, quality, etc. are important.

The following programme will be given for the training:

- introduction to relevant legislation with particular emphasis on GMP, quality assurance, safety and health;
- personal hygiene;
- introduction to powder dosage form;
- introduction to weighing and measuring;
- information on mixing, drying, screening, dosing, filling, etc.;
- procedures used to ensure required standards of cleanliness in equipment and retention of product integrity and purity;
- introduction to recording and reporting techniques.

Quality control personnel:

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

- theoretical aspects of quality control methods and equipment, discussion of ORS, method of manufacturing and equipment as well as the necessary in-process quality control to be performed;

Practical training on the following methods:

- description
- identification
- moisture content
- sulphated ash
- assay
- acidity
- specific optical rotation
- chlorides
- sulphates
- heavy metals
- standard plate count
- dosage control
- seal control
- labelling control
- pH determination;

- sampling procedures and techniques and volumetric solutions;
- supervision of the implementation of GMP, stability tests.

10. Layout Design of the Plant

/See Drawing No.1/

11. Name of the Rooms

- Room No. 1a. Storage for tested basic materials
- Room No. 1b. Storage for finished product /quarantine/
- Room No. 2 Drying room
- Room No. 3 Sifter
- Room No. 4 Weighing room
- Room No. 5 Mixing room
- Room No. 6 Filling room I
- Room No. 7 Filling room II
- Room No. 8a. Sealing, packing room
- Room No. 8b. Store /storage of formulated products/
- Room No. 9 Quality control laboratory
- Room No.10 Dressing and locker for women
- Room No.11 Dressing and locker for men
- Room No.12 Office
- Room No.13 Office
- Room No.14 Toilet for women
- Room No.15 Toilet for men
- Room No.16 Store /storage of basic materials/
- Room No.17 Canteen, kitchen
- Room No.18 Storage for spare parts
- Room No.19 Maintenance room
- Room No.20,21Offices
- Room No.22 First-aid room

## 12. Detailed Description of the Manufacturing

### 12.1 Order of the basic, auxiliary and formulating materials

The above materials should be ordered with consideration of the quality requirements described in paragraph 4. Concerning their quality, the suppliers enclose a certificate. The materials should be purchased during the dry season.

### 12.2 Storage of the basic, auxiliary and formulating materials

These materials are stored in the storeroom No.16. The package of these materials, coming in strong, waterproof containers, e.g. barrels, should be open only for sample taking, for the possibly minimum time needed.

The aluminum foil bags should be stored in an area protected from intensive sunlight. Barrows with rubber tyres are used to carry the materials. This is performed by hand-operation.

### 12.3 Sampling for quality control

In order to control the quality of basic and auxiliary materials, the appointed coworker of the control laboratory takes a sample from each batch. The number of containers to be sampled should be determined according to the formula  $0,4 \sqrt{n}$  where n means the number of containers within one factory number. The sample should rapidly be taken for avoiding moisture absorption. Then the containers should hermetically be sealed if possible.

### 12.4 Storage of the controlled materials

The batches of basic and auxiliary materials which have proved to be of satisfactory quality, are stored in the storeroom No. 1a. till the use. It has to be



attended that the analytical examination numbers be safely indicated on each container.

#### 12.5 Control before use

At 24 hours before use, the moisture content of glucose is examined and the knottiness of all basic and auxiliary materials is controlled.

One barrel /50 kg/ of the glucose which is used in daily 4 x 50 kg amounts, is examined for moisture content.

If a barrel had previously been opened, a sample has to be taken from it.

When the moisture content exceeds 1%, then the glucose has to be dried.

The salts becoming knotty during storage should be sieved.

#### 12.6 Drying

The glucose to be dried is placed in pure aluminum trays with even layers in lots of 2,5 kg. The drying is performed in the room No. 2. in the LP 320/2 type hot-air-sterilizer. The temperature of drying is 60°C, the duration is about 12 hours dependently upon the moisture content of the material.

This operation has to be started in the afternoon and thus, the drying of the material is finished up to the weighing-in in the morning. During the drying operation, the ventilator has to be used. The equipment should only be operated under supervision. /The night control can be provided by the watchman, too./ After drying, the moisture content has repeatedly to be determined.

#### 12.7 Grinding, sieving

The glucose which likely becomes knotty in the course of drying, is subjected to sieving. This operation is carried

out in the room No.4. The sieving should be performed rapidly in order to minimize the taking up of moisture. For the prevention of dusting, the open part of the sieve is covered with a cloth during operation. The salts should be sieved before weighing-in. The particle size of the basic materials should be between 100 and 400 $\mu$ m in order to assure the good mixing. The sieved salts are collected in plastic bags and stored in barrels in the room where they are weighed. The sieving is carried out in an air-conditioned room.

12.8. Weighing-in of the basic materials

The basic materials are weighed in the room No.3. For one charge the following amounts are weighed in:

Glucose anhydrous	50.0 kg
Sodium chloride	8.75 kg
Sodium hydrogen carbonate	6.25 kg
Potassium chloride	3.75 kg
Aerosil	0.01375 kg

Two persons perform the weighing-in: the one carries out the weighings needed on the balance and the other one, i.e. the production manager controls the amounts weighed-in.

The quantities weighed-in are registered on the charge protocol.

The control of the filling in of the protocol is the task of the production manager.

Glucose is weighed on the 100 kg balance by means of weighing back the barrel and plastic bag used for storage. The material directly gets to the pure and dry homogenizing drum of 200 l volume. It should be attended that any loss of glucose must be avoided. The other materials are weighed on the 15 kg balance. The materials are weighed in plastic boxes and immediately poured to

the homogenizing drum. The charge number has to be indicated on the drum. The drum is hermetically sealed and transported into the homogenizing room. The weighings should be performed within the shortest time.

The weighing room is provided with an equipment for air condition.

#### 12.9. Homogenization

The homogenization is carried out by means of the homogenizer in the room No. 5. The hermetically sealed drum is fixed on the wheel of the Drum Mixer and they are together placed onto the driving wheels. Thereafter homogenization is started. The duration of the homogenization is 10 minutes. The homogenizing room is air-conditioned.

#### 12.10. Control during the production

Before filling, a control examination from the homogenized mixture is performed by the analytical laboratory.

This control concerns the chloride and moisture content of the mixture. When the moisture content assayed exceeds 2%, then repeated drying and sieving are carried out in the manner described above. When the chloride content of the homogenate does not fall between 72-88 mmoles/l, the material should be rejected.

Until the in-production control is ended, the homogenized material is kept in the hermetically sealed barrels. In the course of repeated drying, the charge number should be indicated on the equipments used for both drying and sieving.

The results of the in-production control and the further way of the material are laid down on the manufacturing table.

#### 12.11. Dosing

The dosing occurs in the rooms Nos. 6. and 7., respectively having a common air-space, separated by a partition-wall. These rooms are air-conditioned.

The dosing of the charges is carried out in separate room in order to avoid confusion. Each a filling equipment operates in both rooms.

The dosing is performed in prefabricated open bags. The material should be transported from the barrel to the tank or the screw filling machine with minimizing any dusting.

Before filling, the weight of filling /27,5 g/ should be adjusted and then the filling is started. In course of the filling a great care should be taken that the material be at nearly identical level in the tank of the equipment at any time.

#### 12.12. Sealing

The filled bags should be sealed on the sealing machines, sited next to the filling machines, withing the shortest period. The temperature and duration are experimentally and previously determined on the sealing machines. The service of the 2 filling machines is performed by 4 K-20/C type sealing machines. The sealed bags are collected in boards and then transported to packing.

#### 12.13. Designation

In room No. 8 a. two designating machine is operated. This machine can be operated by hands or by an air cylindre, The different charges should separately be designated. In the course of designation, the factory number and the time of production are indicated on the bags. The first three figures of the

factory number mean the order of production, the following two figures mean the month of production and the next two figures mean the last two numerals of the year of production.

A factory number e.g. 0070383 means that this is the 7th charge produced March 1982. The date of production is indicated in the following way. The first two figures mean the month of the production, the following two figures mean the last two numerals of the year of production. Designation should be done on empty peaches.

A black, rapidly drying designating dye is used for designation. Up to drying of the dye, the designated bags should be placed beneath together in such a manner that the designation remains intact.

#### 12.14. Control of the filling weight

A sample is taken from the sealed bags in every 15th minute and the weight of the filled material is determined with an accuracy of 0,1 g. The control is performed on the balances placed near to the sealing machines, in the rooms No. 6. and No. 7., respectively.

The content of the bag is discharged as completely as possible in the casserole of the balance. It should be attended that both balances would be operated at a site free of shocks and draught, in horizontal position. The results of the weighings are registered on the weight control table as a function of the time-point of control.

The weight difference can be  $\pm 10\%$  as calculated from the declared value. This means that the weight of the filled material can amount from 24,8 to 30,3 g. When the divergence from the average value is more significant, then the filling should be stopped, and the adequate filling weight has to be adjusted repeatedly.

12.15. Packing

The bags are packed in paper boxes containing 50 pieces. Twenty boxes are placed in a collecting board. The boards are provided with labels.

12.16. Sampling

The head of the control laboratory takes a counter-sample from the packed charges. For this purpose, 25 pieces of bags should be kept at least for 3 years. /This is stored in the room No.8b./The head of the analytical laboratory takes samples from the sealed and designated bags too for the final analysis. The number of samples is 10 pieces for each charge. The results of the analytical examinations should be kept together with the manufacturing control tables at least 3 years.

12.17. Storage of the formulated product in quarantine

After sampling and packing, the material is transported to the storeroom No. 1b. This room is capable of receiving the production of about 2 weeks. The transportation of the material is carried out by rubber-tyred vehicles. The charges should be stored in a well separated position. The clerk of the plant keeps a diary containing the deliveries to the store. The supervisor of the store certifies the receipt with signation and simultaneously, he notes the receipt in his receipt diary.

12.19. Storage in the expedition store

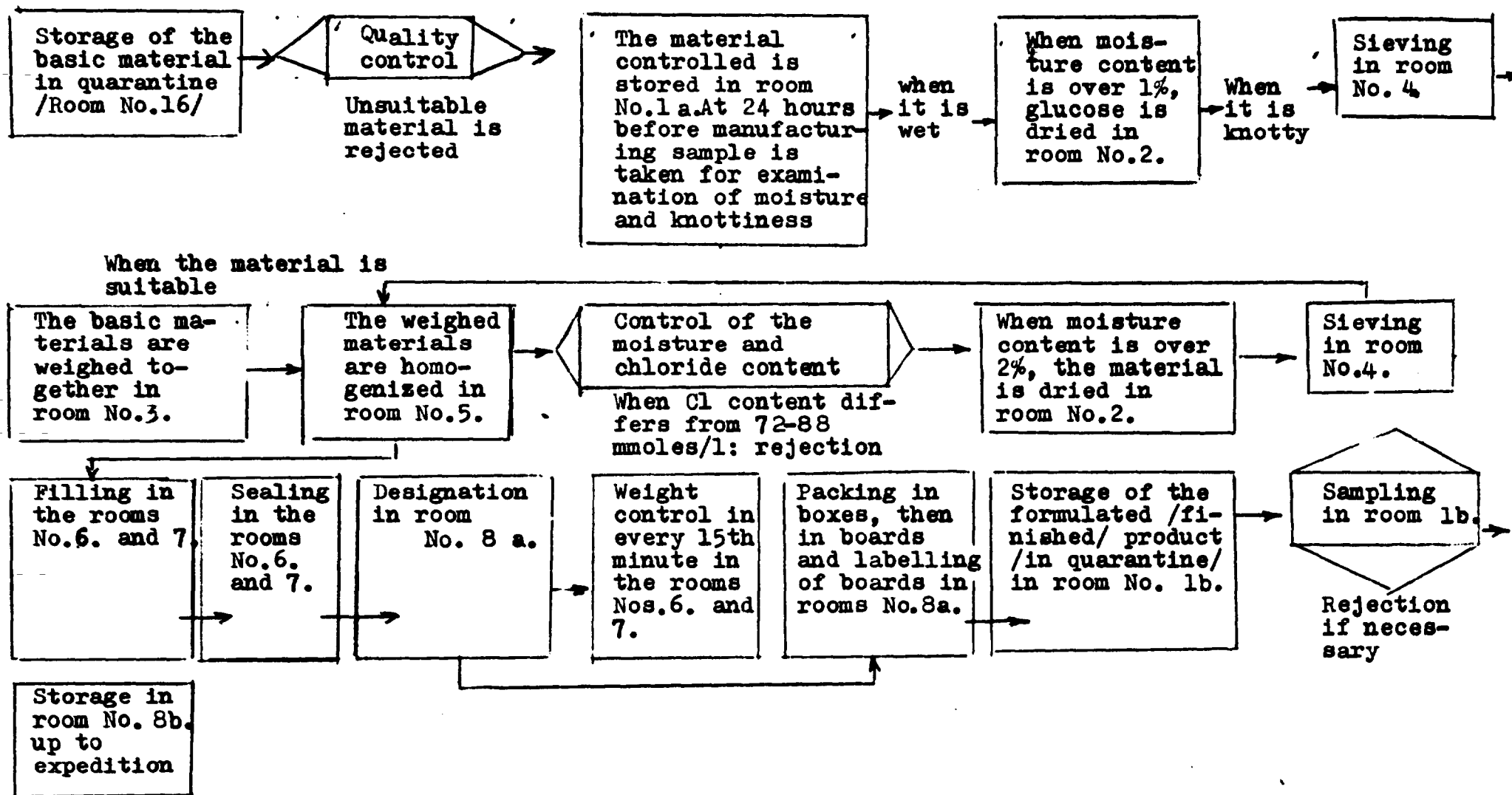
Those charges qualified as suitable by the analytical laboratory, are transported from the quarantine to the expedition store /store of finished products, store of formulated products, room No.8b./.

The delivery is carried out from this store.

The group-leaders of both stores firm the delivery and receipt in a diary and certify with signing. In order to avoid confusion, care should be taken of the separated store of charges. In the course of expedition, the head of the expedition-store controls the charges going out.

12.19.

Flow diagram of the manufacturing





### 13. Quality Control in the Analytical Laboratory

#### 13.1. Quality control of basic and auxiliary materials

The quality control examinations of the basic and auxiliary materials are carried out by the quality control laboratory from the representative sample taken as described above.

The head of the quality control laboratory gives a written approval of the usability of the material, when the results of the examinations are satisfactory. Materials not satisfying the requirements are rejected. The materials to be rejected should be transported from the plant within 48 hours.

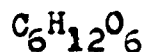
##### 13.1.1. Quality control of the anhydrous glucose

The examinations are performed in the following directions:

- description of the material
- identity tests
- moisture content
- sulfate ash
- quantitative assay
- acidity
- specific optical rotatory power
- chloride content
- sulfate content
- heavy metal content
- standard plate count

Name: Glucose anhydrous

Synonyms: Saccharum uvae, Saccharum amylaceum, Dextrosum, Grape sugar, Dextrose



Mol. Wt. 180,15

Description: White, odourless, crystalline powder,  
with sweet taste.

Solubility: Soluble in a part of water or in 55 parts  
of alcohol /90 v/v percent/. Practically insoluble in  
ether and in chloroform.

Packing and storage: Preserve in well-closed containers

Identification:

- a./ Heat a small amount of glucose. It melts and burns  
giving the odour of burnt sugar.
- b./ Dissolve 0,1 g glucose in 2 ml water. Add the  
solution to 5 ml of hot potassium-cupric tartrate  
solution.

A copious, red precipitate should be produced.

Potassium-cupric tartrate solution is prepared as  
follows: In a volumetric flask dissolve 7 g  $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$   
in water and make up to 100 ml. In a separate  
flask, dissolve 35 g potassium sodium tartrate and  
10 g sodium hydroxide in water and make up to 100 ml.  
Mix equal volumes of the two solutions shortly  
before use.

Loss on drying / $\leq 1,0\%$ /:

Tare a glass-stoppered, shallow weighing bottle / $W_1$ / that  
has been dried for 30 minutes under the same conditions  
to be employed in the determination. If the sample is in  
the form of large crystals, reduce the particle size to  
about 2 mm by quickly crushing. Weigh accurately the  
crucible with about 6-7 g glucose / $W_2$ /. By gentle, side-  
wise shaking, distribute the sample as evenly as  
practicable to a depth of about 5 mm generally, and not  
over 10 mm. Dry the loaded bottle at  $80^\circ\text{C}$  for 2 hours  
without stopper. Close the bottle before removing it  
from the drying oven, place the hot vessel into a  
desiccator over silicagel and let it cool to room  
temperature.

Reweight the crucible with sample  $/W_3/$ .

Calculation:

$$\frac{/W_2 - W_3/}{/W_2 - W_1/} \times 100 = \% \text{ moisture lost on drying}$$

Note: The dried sample may be used for the assay.

Sulfate ash  $/\leq 0,2\%/$

Ignite a platinum, porcelain or silica crucible, cool in a desiccator, and weight accurately  $/W_1/$ .

Weight accurately about 1 g glucose in the crucible  $/W_2/$ .

Moisten with concentrated sulfuric acid, heat gently to remove excess acid and ignite at about  $500^{\circ}\text{C}$  until all black particles have disappeared. Moisten again with concentrated sulfuric acid and re-ignite until the carbon completely disappears to constant weight.

$$\text{Calculation: } \frac{W_2 - W_3}{W_2 - W_1} \times 100 = \% \text{ sulfate ash}$$

Quantitative assay  $/\geq 99,9\% \text{ C}_6\text{H}_{12}\text{O}_6/$

Weight accurately about 5 g dried glucose  $/W_1/$ , dissolve in 40 ml water, add 0,1 ml ammonia solution /make up 74,4 ml concentrated ammonia solution /25%/ with water to 500 ml/ and complete the volume to 50 ml with water, bringing the meniscus close to but still below the mark and adjust the temperature to  $20^{\circ}\text{C}$  by keeping the flask in a constant temperature bath for 30 minutes.

Add water to bring up to the 50 ml mark.

Transfer the solution into a 20,0 cm tube. The polarimeter tube should be filled carefully to avoid creating or leaving air bubbles which interfere with the passage of the beam of light. Then stopper carefully the polarimeter tube. The glass plates should not be pressed strongly to the tube

since, due to pressure, the glass becomes double-refractive which may cause some error in the reading. Adjust the analyzer to darker half-shade and read the angle. Take 6 readings: half the measurements clockwise and other half counter-clockwise. Average the readings. Then fill the tube with the solvent applied, this is the blank solution: take 0,1 ml ammonia solution /make up 74,4 ml concentrated ammonia solution with water to 500 ml/ and make up to nearly 50 ml with water, place in a 20°C bath for 30 minutes, then bring up to mark. Repeat the measurement with the blank solution. Make the zero correction by subtracting the average of the blank readings from the average of the test solution.

$$\text{Calculation: } \frac{a \times 10^6}{2 \times 52,6 \times l \times W_1} = \% \text{ glucose}$$

a : corrected observed rotation

l : length of the solution traversed by light in mm

$W_1$  : weight of glucose in grammes

52,6 : specific rotatory power of glucose for the D-line of sodium

$$/Na_D = 589,3 \text{ nm/}$$

Acidity /≤ 0,5 ml of 0,1 mol/l sodium hydroxide/

Dissolve 5,0 g of glucose in 50 ml of freshly boiled and cooled water, add 2 drops of phenolphthalein indicator /1 g/100 ml ethanol/. Titrate with 0,1 mol/l sodium hydroxide /4 g/1000 ml/. Not more than 0,5 ml of titrant should reach the midpoint of the indicator /pink/.

Chlorides /≤ 200 μg/g/

Weigh 10,0 g glucose and dissolve in 30 ml water in a 100 ml Erlenmeyer flask. Using about 0,5 ml potassium chromate indicator /4,86 g/100 ml/, titrate with 0,01 mol/l silver nitrate. Not more than 5,64 ml should be required to reach the end point.

Calculation: ml of silver nitrate x 35,46 =  $\mu$ g chloride  
0,1 mol/l silver nitrate solution is prepared as follows:  
Each ml of the solution contains 16,989 mg silver nitrate.  
Powder about 20 g of silver nitrate, analytical grade in a  
clean porcelain mortar, and dry for one hour at 80°C. Allow  
to cool in a desiccator. Dissolve 16,989 g, accurately  
weighed, in a 50 ml beaker in 20 ml of water and transfer  
the solution with 20 ml portions of water into a 1000 ml  
volumetric flask.

Adjust the temperature of the solution to 20°C and add water  
of 20°C to produce 1000 ml of solution. The titre of the  
solution prepared in this way is practically 1,000.

Standardization of the solution

Titrate 10 ml 0,1 mol/l of sodium chlorite solution  
/5,845 g/1000 ml/ with the 0,1 mol/l of silver nitrate to be  
checked, using 0,5 ml of potassium chromate indicator  
/4,86 g/100 ml/.

Calculation:

$$F_s = \frac{10}{\text{ml silver nitrate}}$$

To prepare 0,01 mol/l silver nitrate solution, place a 10 ml  
aliquot of 0,1 mol/l silver nitrate in a graduated flask and  
make up to 100 ml with water.

Sulfates / $\leq$  200  $\mu$ g/g/

Transfer 2 drops of sulfate limit solution /50  $\mu$ g of  $\text{SO}_4$ /ml/  
into each one of two test tubes /production of sulfate limit  
solution /50  $\mu$ g  $\text{SO}_4$ /ml/: place 5,21 ml of 0,01 mol/l sulfuric  
acid /0,3 ml of concentrated sulfuric acid /500 ml/ in a  
graduated flask and make up to 100 ml with water /.

Add 1,0 ml of barium chloride solution /6,11 g/100 ml/ and  
1,0 ml of 2 mol/l hydrochloric acid /100 ml of concentrated

hydrochloric acid with 400 ml water/. Shake the mixtures for 30 seconds.

Dissolve 2,5 g of glucose in 100 ml of water. Dilute 10 ml of glucose solution to 13 ml, and add this solution into one of the test tubes containing the prepared reagent. Transfer a mixture of 1,0 ml of sulfate limit solution /50,ug SO<sub>4</sub>/ and 12 ml of water into the other test tube. Shake both test tubes.

Perform the tests simultaneously and compare the contents of the test tubes after 10 minutes.

Any change observed in the test solution must not exceed the change in the sulfate limit solution.

Heavy metals /- 10,ug/g/

In a test tube dissolve 1 g glucose in 15 ml water. Transfer in another test tube 1,0 ml of lead limit solution /10,ug Pb/, and in a third test tube 1,0 ml of iron limit solution. Dilute the volumes of the liquids in each of the test tubes to 15 ml, add 0,5 g of ammonium chloride, 2 drops of ammonia solution /make up 74,4 ml of concentrated ammonia solution with water to 500 ml/ and 5 drops of sodium sulfide solution to each test tube, and shake the mixtures.

Perform the tests simultaneously, and compare the solutions after 5 minutes. Compare the colours by viewing down the vertical axis of the tube in diffused light against a white back-ground. Any change in the test solution must not exceed the brown colour developed in the lead limit solution, and the greyish green colour developed in the iron limit solution respectively.

Lead, strong, Pb solution

Dissolve 0,160 g of lead nitrate in 0,5 ml of mol/l nitric acid /67,5 ml of concentrated nitric acid /500 ml/ and sufficient water to produce 100 ml.

Lead limit solution /10,ug Pb/ml

Dilute 1 ml of lead, strong, Pb solution with sufficient water to produce 100 ml. This solution must be freshly prepared from lead, strong, Pb solution.

Iron, strong, Fe solution

Dissolve 0,351 g of ferrous ammonium sulfate  $[\text{Fe}/\text{NH}_4/2/\text{SO}_4/2^x \times 6\text{H}_2\text{O}/$ , 2 ml of 2 mol/l sulfuric acid /29,5 ml of concentrated sulfuric acid /500 ml/ and sufficient water to produce 100 ml.

Iron limit solution /10,ug Fe/ml/

Dilute 2 ml of iron, strong Fe solution with sufficient water to produce 100 ml.

Sodium sulfide solution

In a well-closed flask dissolve 5 g of sodium sulfide  $[\text{Na}_2\text{S} \times 9\text{H}_2\text{O}/$  in 10 ml of water and add 30 ml of glycerol. After a few days, filter the solution through a small, with ethanol previously washed cotton-wool bunch; if necessary, re-filter until a clear solution is obtained. The solution is suitable for about 6 months, if it keeps its colour.

Standard Plate Count  $/\leq 200/\text{g}/$

Weight 50,0 g of sample and dissolve in 100 ml water. This provides a dilution of 0,33.

Dilute 10 ml of 0,33 dilution with sufficient water to produce 100 ml. This provides a dilution of 0,033.

Dilute 10 ml of 0,033 dilution with sufficient water to produce 100 ml. This provides a 0,0033 dilution.

To duplicate sets of Petri dishes, pipette 1 ml aliquots from 0,33, 0,033 and 0,0033 dilutions, respectively.

Melt Plate Count Agar in boiling water, while do not expose it to such a heat for a prolonged period. Temper the

agar to 44-46°C and control its temperature carefully to avoid killing bacteria in the diluted sample.

Promptly pour into the Petri dishes 10-15 ml of melted and tempered agar. Fewer than 20 minutes, and preferably less than 10 minutes should elapse between making the dilution and pouring the agar.

Immediately mix aliquots with the agar medium by carefully tilting and rotating the Petri dishes.

As a sterility check, pour one or several plates with uninoculated agar medium and with uninoculated diluent.

After the agar has solidified, invert the Petri dishes and incubate them at 29-31°C for 48 ± 3 hours.

Compute the Standard Plate Count from the dilutions showing between 30 and 300 colonies per plate, multiply by the dilution factor /i.e., the reciprocal of the dilution used: 3, 30, 300/ and take the arithmetic average.

The specification is SPC = 200/g corresponding to a count of 67 colonies on the 0,33 dilution plates.

The determination can be considered if the control plates after incubation are sterile, or the number of colonies on these plates do not distort the statistical appraisal.

#### Agar Culture Medium

Bacto-Peptone	5 g
Sodium Chloride	3 g
Disodium Hydrogen Phosphate /Na <sub>2</sub> HPO <sub>4</sub> x2H <sub>2</sub> O/	0,4 g
Agar	9 g
Water	1000 ml

Dissolve Bacto-Peptone and Sodium Chloride in cold distilled water. Adjust to pH 7,5 ± 0,2 by addition of sodium hydroxide /40 per cent/. Add the disodium hydrogen phosphate while warming the solution to 75-80°C. Add the agar and mix the solution well to dissolve the medium completely.



Boil the solution for 1-2 minutes. Final pH of the medium will be 7,4-7,5.

Distribute it in flasks and sterilize in the autoclave for 30 minutes at 121°C.

### 13.1.2. Sodium chloride

Synonyms: Natrium chloratum, Chlornatrium rock salt  
NaCl Mol. Wt. 58,45

#### Description:

Colourless, cubic crystals or a white crystalline powder, odourless, with a saline taste.

#### Solubility:

Soluble in 2,8 parts of water, in 2,7 parts of hot water, in 5 parts of glycerol and in 160 parts of alcohol /90 v/v per cent/.

#### Packing and storage:

Preserve in well-closed containers.

#### Identification:

##### a./ Sodium:

On a previously ignited platinum wire heat, a small powdered and moistened sample with hydrochloric acid of 2 mol/l /100 ml concentrated hydrochloric acid with 400 ml water/, in a nonluminous flame of a Bunsen burner. An intense yellow colour should appear in the flame.

##### b./ Chloride:

Dissolve 0,05 g sodium chloride in 2 ml water. Add one drop of 2 mol/l nitric acid /67,5 ml concentrated nitric acid to 500 ml/ and 1 ml of 0,1 mol/l silver nitrate solution. A curdy, white precipitate is produced which dissolves in an excess of 2 mol/l

ammonia solution /74,4 ml of concentrated ammonia solution 25% /to 500 ml/ but is practically insoluble in nitric acid /54 ml of concentrated nitric acid with 24 ml water/.

Loss on drying / $\leq 1,0\%$ /

Tare a glass-stoppered, shallow weighing bottle  $/W_1/$  that has been dried for 30 minutes under the same conditions to be employed in the determination. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Weigh accurately the crucible with about 2 g sodium chloride  $/W_2/$ . By gentle, side-wise shaking distribute the sample as evenly as practicable to a depth of about 5 mm generally, and not over 10 mm.

Dry the charged bottle at  $130^{\circ}\text{C}$  to constant weight by removing the stopper. Close the bottle before removing it from the drying oven, place the hot vessel into a desiccator over silica gel and let it cool to room temperature. Reweigh crucible and sample  $/W_3/$ .

Calculation:

$$\frac{W_2 - W_3}{W_2 - W_1} \times 100, = \% \text{ moisture lost on drying}$$

Note: The dried sample may be used for the assay.

Assay  $/\text{NaCl} \geq 99,0\%$

Accurately weigh about 0,05 g of dried sample  $/W_1/$  and dissolve in 20 ml of water. Titrate with 0,1 mol/l silver nitrate  $/ml_1/$  using potassium chromate indicator /4,86 g/100 ml/.

Calculation:

$$\frac{ml_1 \times 0,5844}{W_1} = \% \text{ sodium chloride}$$

Note: the preparation of 0,1 mol/l silver nitrate is

given in the article of Glucose anhydrous at Chloride Determination.

### 13.1.3. Potassium chloride

Synonym: Kalium chloratum

KCl

#### Description:

Colourless crystals or a white, crystalline, odourless powder with a slightly bitter taste.

#### Solubility:

Soluble in 3 parts of water, in 1,8 parts of hot water and in 400 parts of alcohol /90 v/v per cent/.

#### Packing and storage:

Preserve in well-closed containers.

#### Identification:

##### a./ Potassium:

Dissolve 1 g of potassium chloride in 10 ml of water and make alkaline with 1 ml of 2 mol/l sodium hydroxide /8 g/100 ml/. Adding 0,1 mol/l sodium tetraphenylborate /3,4 g/100 ml/ produces a white precipitate.

##### b./ Chloride:

Dissolve 0,05 g of potassium chloride in 2 ml of water. Add one drop of 2 mol/l nitric acid /67,5 ml of concentrated nitric acid to 500 ml/ and 1 ml of 0,1 mol/l silver nitrate solution. A curdy, white precipitate is produced which dissolves in an excess of 2 mol/l ammonia solution /25%/ to 500 ml/ but is practically insoluble in nitric acid /54 ml of concentrated nitric acid with 24 ml of water/.

Loss on drying / $\leq$  1,0%/

Tare a glass-stoppered, shallow weighing bottle  $/W_1/$  that has been dried for 30 minutes under the same conditions to be employed in the determination. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Weigh accurately the crucible with about 2 g sodium chloride  $/W_2/$ . By gentle, sidewise shaking distribute the sample as evenly as practicable to a depth of about 5 mm generally, and not over 10 mm. Dry the charged bottle at  $130^{\circ}\text{C}$  to constant weight by removing the stopper. Close the bottle before removing it from the drying oven, place the hot vessel into a desiccator over silica gel and let it cool to room temperature. Reweigh crucible and sample  $/W_3/$ .

Calculation:

$$\frac{/W_2 - W_3/}{/W_2 - W_1/} \times 100 = \% \text{ moisture lost on drying}$$

Note: the dried sample may be used for the assay.

Assay  $/\text{KCl} \geq 99,0\%/$

Weigh accurately about 0,05 g of dried sample  $/W_1/$  and dissolve in 20 ml water. Titrate with 0,1 mol/silver nitrate  $/ml_1/$  using potassium chromate indicator  $/4,86 \text{ g}/100 \text{ ml}/$ .

Calculation:

$$\frac{ml_1 \times 0,5844}{W_1} = \text{potassium chloride}$$

Note: the preparation of 0,1 mol/l silver nitrate is given in the article of Glucose anhydrous at Chloride Determination.

13.1.4. Sodium hydrogen carbonate

Synonyms: Natrium bicarbonicum, Natrium hydrocarbonicum, Natrium hydrogencarbonicum, Sodium bicarbonate, Carbonic acid monosodium salt, Monosodium carbonate

$\text{NaHCO}_3$

Mol. Wt. 84,01

Description:

A white, crystalline odourless powder, with a slightly alkaline, saline taste. It is stable in dry air, but slowly decomposes in moist air. Its solutions, when freshly prepared with cold water without shaking, are alkaline. The alkalinity increases, if the solutions stand, are agitated or heated.

Solubility:

Soluble at 20°C in 11 parts of water; insoluble in alcohol.

Packing and storage:

Preserve in well-closed containers in a cool place.

Identification:

a./ Sodium:

On a previously ignited platinum wire heat a small powdered and moistened sample with hydrochloric acid of 2 ml/l /100 ml concentrated hydrochloric acid with 400 ml water/, in a nonluminous flame of a Bunsen burner. An intense yellow colour should appear in the flame.

b./ Hydrogen carbonate:

A 0,05 g sample should dissolve in 2 ml of hydrochloric acid of 2 mol/l /100 ml concentrated hydrochloric

acid with 400 ml water/ under vigorous gas evolution.  
The developed gas is odourless.

Dissolve a 0,1 g sample in 4 ml water and add 1 ml of magnesium sulfate solution /12,3 g magnesium sulfate. 7H<sub>2</sub>O /100 ml/. The mixture must not change. When boiled, a white precipitate should separate.

Loss on drying / ≤ 1,0% /:

Tare a glass-stoppered, shallow weighing bottle /W<sub>1</sub>/ that has been dried for 30 minutes under the same conditions to be employed in the determination.

If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Weigh accurately the crucible with about 3 g of sample /W<sub>2</sub>/. By gentle, sidewise shaking, distribute the sample as evenly as practicable to a depth of about 5 mm generally, and not over 10 mm. Place the charged bottle in the desiccator over silica gel, by removing the stopper and leaving it also in the desiccator. Dry the sample for four hours and weigh /W<sub>3</sub>/.

$$\text{Calculation: } \frac{W_2 - W_3}{W_2 - W_1} \times 100 = \% \text{ moisture}$$

Assay /NaHCO<sub>3</sub> ≥ 99,0% /

Dissolve about 1,0 g of sodium hydrogen carbonate, accurately weighed in a volumetric flask in water to produce 100 ml of solution. Titrate a 10,00 ml portion of the solution with 0,1 mol/l hydrochloric acid, using 2 drops of methyl red indicator /0,05 g/ 100 ml ethanol/. Before ending the titration, remove carbon dioxide by boiling the liquid, and complete the titration in the cooled solution.

Each ml 0,1 mol/l hydrochlorid acid is equivalent to

8,402 mg sodium hydrogen carbonate.

0,1 mol/l hydrochloric acid solution

Each ml of the solution contains 3,6465 mg of hydrochloric acid. Dilute 8,1 ml of concentrated hydrochloric acid in a volumetric flask with water to produce 1000 ml of solution.

Standardization of the solution

Titrate 10 ml of 0,1 mol/l potassium hydrogen carbonate solution /1,0012 g/100 ml/ with the 0,1 mol/l hydrochloric acid to be checked, using 2 drops of methyl red indicator. Before ending the titration, remove carbon dioxide by boiling the liquid, and complete the titration in the cooled solution.

Calculate the factor  $F_n$  of the 0,1 mol/l hydrochloric acid solution by the formula:

$$F_h = \frac{10}{\text{ml hydrochloric acid}}$$

13.1.5. Aerosil

Synonyms: Acidum silicium colloidal, Colloidal silicium dioxide

1./ Description:

White or faintly bluish-white, light, odourless, tasteless fine powder. It is readily dispersed as a colloid in water, in organic solvents or in fixed oils.

2./ Solubility:

Insoluble in water and organic solvents. Soluble in solutions of alkali hydroxides.

3./ Packing and storage:

Preserve in well-closed containers.

4./ Identification:

- a./ Dissolve 400 mg of aerosil in a mixture of 4 ml of water and 6 ml of 2 mol/l sodium hydroxide solution /8 g/100 ml/ under boiling. Use this solution for tests under b./, c./.
- b./ Add 1 ml of 0,08 mol/l ammonium molybdate solution /10 g/100 ml/ to 1 drop of solution under a./. The solution becomes yellow, when 1 drop of 2 mol/l hydrochloric acid /100 ml concentrated hydrochloric acid with 400 ml of water/ is added.
- c./ Shake 5 ml of solution under a./ with 6 ml of 10 per cent hydrochloric acid and with 8 ml of 10 per cent ammonia solution. A white, gelatinous precipitate is formed.



13.2. Control during the production

13.2.1. Determination of the moisture content of glucose

Tare a glass-stoppered, shallow weighing bottle /W<sub>1</sub>/ that has been dried for 30 minutes under the same conditions to be employed in the determination. If the sample is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Weigh accurately the crucible with about 6-7 g glucose /W<sub>2</sub>/. Distribute the sample by gentle, sidewise shaking as evenly as practicable to a depth of about 5 mm generally, and not over 10 mm. Dry the charged bottle at 80°C for 2 hours by removing the stopper. Close the bottle before removing it from the drying oven, place the hot vessel into a desiccator over silica gel and let it cool to room temperature. Reweigh crucible and sample /W<sub>3</sub>/

Calculation: 
$$\frac{W_2 - W_3}{W_2 - W_1} \times 100 = \% \text{ moisture lost on drying}$$

13.2.2. Determination of the chloride in the homogenized powder mixture

Dissolve 2,75 g of sample in 100 ml water. Place a 10 ml aliquot of the solution in a 100 ml Erlenmeyer flask. Add about 0,5 ml of potassium chromate TS as indicator and titrate with silver nitrate /0,1 mol/l/ VS until a brick red colour is obtained.

Calculation:

$$10 \times ml_1 = mmol/l$$

Acceptable limits: 72 to 98 moles/l

Note: the preparation of potassium chromate TS and silver nitrate /0,1 mol/l/ VS is given in the article of Glucose anhydrous at the chloride determination.

### 13.3. Quality control of the end-product

Net weight of packet ingredients: limits 24.8 g to 30.3 g. Check 10 packets:

Cut open each packet, empty contents as completely as possible, weigh contents.

If one or more packets exceeds the limits, check an additional 100 packets.

If four or more packets of the 100 exceed the limits then:

- reject the batch, or
- weigh every packet in the batch /for gross weight/

### Labelling

Check 10 packets for completeness and legibility of the label. If two or more packets are unacceptable:

- reject the batch, or
- check every packet in the batch.

### Seal

Check 10 packets:

Submerge the packets under water in a vacuum desiccator or equivalent device. Draw a vacuum of 15 cm of mercury and hold for 10 seconds.

Examine for air leakage indicated by a fine stream of bubbles.

Any packet that does inflate should be opened and examined for water penetration.

If two or more packets are unacceptable:

- reject the batch, or
- check every packet in the batch.

Moisture content /  $\leq$  3%/

Check one packet with the moisture balance

If the limit is exceeded, check the other 9 packets plus 10 more.

If one more packet is found to exceed the limit:

- reject the batch, and
- check entire production operation.

Chemical composition

Limits

glucose, anhydrous	18.0 g - 22.0 g
sodium chloride	3.15 g - 3.85g
sodium hydrogen carbonate	2.25 g - 2.75g
potassium chloride	1.35 g - 1,65g

Take one packet and measure accurately 27.5 g of the contents, dissolve in 500 ml of water and make up to 1000 ml. A double analysis using two dilutions should be performed. The measurements should be close together. If not, do a new dilution.

If the measurements are not within the limits, analyze two more packets. If any measurement exceeds the limits, reject the batch.

In the following procedure the test solution corresponds to 27.5 g of product in 1 litre of water.

Glucose

- /1/ Place 5.0 ml of the test solution in a 250 ml glass-stoppered flask. Add 50 ml of water, 25.0 ml iodine /0.1 mol/l/ VS, and 10 ml of sodium carbonate /  $\sim$  50 g/l/ TS.
- /2/ Allow solution to stand in darkness for 20 minutes.
- /3/ Add 15 ml of sulfuric acid /  $\sim$  100 g/l/ TS.

/4/ Titrate with sodium thiosulfate /0.1 mol/l/ VS,  
using starch TS as indicator /ml<sub>1</sub>/

/5/ Calculation:

$$9.008 \times \text{ml}_1 = \text{g/l}$$

Sodium hydrogen carbonate

/1/ Titrate 25.0 ml of test solution and 100 ml of  
water with hydrochloric acid /0.1 mol/l/ VS,  
using methyl orange TS as indicator. /ml<sub>1</sub>/

/2/ Calculation:

$$\frac{\text{ml}_1 \times 8.401 \times 40}{1000} = \text{g/l}$$

Potassium chloride

Determine g/l using a flame spectrophotometer.

Sodium chloride

Determine g/l using a flame spectrophotometer.

Determination of potassium and sodium by flame photometry

On beginning to operate the instrument, the feeding of  
air has at first to be started, then the taps of the pipes  
for the combustible gas should be opened. The flame has to be  
lighted by the short-time use of the electric firing. The  
amplifier of the instrument should be turned on and the  
instrument has to be null-read. for distilled water.

As standard solution, solutions containing the allowed  
minimum and maximum quantity of salt components are used .  
/Sodium: 81 millivalents/l and 99 millivalents/l; potassium:  
18 millivalents/l and 22 millivalents/l/

The sodium and potassium content of the sample examined should fall between the values determined for these two standard solutions.

One ml of the solutions to be tested should be diluted to 100 ml. The measurements should be repeated at least three times and the mean values are accepted.

Calculation of the potassium chloride content:

$$\frac{\text{Read off value}}{1000} \times 10 \times 74,55 \text{ g/l}$$

Calculation of the sodium chloride content:

$$\begin{aligned} \text{/Read-off value} - \frac{\text{sodium hydrogen carbonate /g/l} \times 1000}{84,02} / \times \\ \times \frac{58,45}{1000} = \text{g/l} \end{aligned}$$

After completion of the measurement, distilled water is sprayed to the burner for about 3 minutes, then the amplifier of the instrument is turned off, and the bottle containing the combustible gas is closed. For 2 minutes air is only flown through the equipment, then the feeding of the compressed air is stopped.

The burner is weekly cleaned. Concentrated "Hypo" solution is sprayed into the instrument by air, then the feeding of the compressed air is stopped for 2-3 minutes, then distilled water is sprayed in by air.

Measuring solutions and reagents for the quantitative assay of the chemical composition of ORS

Hydrochloric acid /0,1 mol/l VS

8,1 ml concentrated hydrochloric acid is diluted to 1000 ml.

Control of the titre of solution /f<sub>s</sub>/

10 ml of 0,1 mol/l potassium hydrogen carbonate solution /1,0012 g/100 ml/ is tetrated with the 0,1 mol/l hydrochloric acid measuring solution to be checked using 2 drops of methyl red indicator. Before ending the titration, the carbon dioxide is removed from the solution by boiling and the tetrating is completed in the cooled solution.

Calculation:  $f_s = \frac{10}{\text{ml hydrochloric acid}}$

Iodine /0,05 mol/l/ VS

One ml solution contains 12,692 mg of iodine in 2,5 % potassium iodide solution.

25 g of potassium iodide are dissolved in 25 ml of water in a 100 ml beaker and 12,6 g of iodine /weighed on the hand-scales/ are added to the solution. After dissolution of the iodine, the solution is washed to a 1000 ml volumetric flask with water and the flask is filled up to the mark with water.

Determination of the titre of solution

40 ml of water and then 10,00 ml of 0,05 mol/l iodine solution are poured in a glass-stoppered Erlenmeyer flask and the solution is acidified with 5 ml of 2 mol/l sulfuric acid /29,5 ml of concentrated sulfuric acid is diluted to 500 ml/.

The solution is titrated with 0,1 mol/l sodium thiosulfate solution using starch solution as indicator.

The titre of the solution is as follows:

$$F = \frac{a}{b} \times F_a$$

where "a" means the number of milliliters of the 0,1 mol/l sodium thiosulfate solution, and  $F_a$  means the titre of this solution;

"b" means the number of milliliters of the 0,05 mol/l iodine solution.

The solution is stored in well-closed, glass-stoppered glass-bottle as protected from light. The titre of the solution should frequently be checked.

#### Sodium thiosulfate /0,1 mol/l/ VS

One ml solution contains 24,8206 mg of sodium thiosulfate / $\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}$ /.

25.5 g of sodium thiosulfate are weighed on the counterbalance in a volumetric flask and dissolved in 500 ml of freshly boiled and cooled water and then filled up to 1000 ml.

#### Determination of the titre of solution

0,8-1,0 g of potassium ionide and 10 ml of 4 mol/l sulfuric acid /29,5 ml of concentrated sulfuric acid to 250 ml/ are added to 20,0 ml of accurately 0,1 mol/l potassium bromate solution /0,27835 g potassium bromate /100 ml/, the solution is shaken thoroughly and then titrated with the thiosulfate solution. Before reaching the end-point, a few ml starch solution are added to the solution.

The titre of the solution is as follows:

$$F = \frac{20,0}{a}$$

where "a" means the number of milliliters of the 0,1 mol/l sodium thiosulfate solution.

#### Methyl orange TS

0,10 g of methyl orange is dissolved with water up to 100 ml in a volumetric flask. The pH limits of the colour

change are: 3,1 - 4,4 /from red into yellow/.

Sulfuric acid / 100 g/l/ TS

29,5 ml of concentrated sulfuric acid is dissolved with water up to 1000 ml.

Starch TS

2 g of potato starch /or soluble starch/ are triturated with a little cold water to a smooth paste in a porcelain mortar, the paste is added to 400 ml of boiling water and heated to the boiling point again. The solution is let stand in a high beaker until it cools down and the insoluble particles settle down. The clear solution is cautiously decanted to a clean glass-stoppered bottle, about 5 mg of mercuric iodide are added as preservative and stored at a cold place. From this solution, 2-3 ml are used for one titration. Care should be taken during use to avoid the getting in of mercuric iodide to the solution to be titrated.



14. Minimum Quantities of Chemicals to be Ordered  
/pro anal quality/

Acetic acid	1000 g
Agar	1000 g
Alcohol cc.	1000 ml
Ammonia 25%	1000 ml
Ammonium molybdate	250 g
Ammonium chloride	1000 g
Barium chloride	1000 g
Barium hydroxide	250 g
Carbonate-free sodium hydroxide	1000 g
Cupric sulfate	1000 g
Hydrochloric acid 37%	3 x 1000 ml
Iodine	2 x 250 g
Lead nitrate	250 g
Methyl red	250 g
Methyl orange	250 g
Nitric acid 65%	1000 g
Peptone witte	250 g
Phenolphthalein	100 g
Potassium carbonate, anhydrous	250 g
Potassium chromate	2 x 250 g
Potassium sodium tartrate	1000 g
Potassium sulfate	250 g
Silver nitrate	4 x 250 g
Sodium carbonate	1000 g
Sodium sulfide	250 g
Sodium tetraphenylborate	25 g
Sodium thiosulfate	2 x 1000 g
Starch	1000 g
Sulfuric acid	2 x 1000 ml
Sulfate-free ethanol	1000 ml

Ferrous ammonium sulfate	250 g
Silica gel	5 x 1000 g
Chromic-sulfuric acid	5 x 1000 g
Glycerol	1000 g
Disodium hydrogen phosphate	1000 g
Magnesium sulfate	250 g
Potassium hydrogen carbonate	250 g

15. List of Reagents to be Prepared

1. Agar culture medium
2. Alcohol /90 v/v %/ TS
3. Ammonia /10%/ TS
4. Ammonia / $\sim 2$  mol/l/ TS
5. Ammonia / $\sim 2$  mol/l/ Pb TS
6. Ammonium molybdate / $\sim 0,0\text{E}$  mol/l/ TS
7. Barium chloride /6,11 g/100 ml / TS
8. Distilled water
9. Hydrochloric acid 10% TS
10. Hydrochloric acid / 2 mol/l / TS
11. Hydrochloric acid / 0,1 mol/l/ VS
12. Iodine /0,1 mol/l/ VS
13. Iron, strong Fe TS
14. Iron, dilute Fe TS / 10 $\mu$ g of Fe/ml/
15. Lead, strong Pb TS
16. Lead, dilute Pb TS /10 $\mu$ g of Pb/ml/
17. Magnesium sulfate /12,3 g/100 ml/ TS
18. Methyl orange TS
19. Methyl red TS
20. Nitric acid / $\sim 1000$  g/l/ TS
21. Nitric acid /2 mol/l/ TS
22. Phenolphthalein TS.
23. Potassium cupric tartarate TS
24. Potassium hydrogen carbonate /0,1 mol/l/ VS
25. Potassium chromate TS
26. Silver nitrate /0,1 mol/l/ VS
27. Silver nitrate /0,01 mol/l VS
28. Sodium chloride /0,1 mol/l/ VS
29. Sodium hydroxide 40% TS
30. Sodium hydroxide /2 mol/l/ TS
31. Sodium hydroxide /2 mol/l/ TS
31. Sodium hydroxide /0,1 mol/l/ VS

- 32. Sodium sulfide TS
- 33. Sodium tetraphenylborate /0,1 mol/l/ TS
- 34. Sodium thiosulfate /0,1 mol/l/ VS
- 35. Starch TS
- 36. Sulfate limit TS /50 $\mu$ g of SO<sub>4</sub>/ ml/
- 37. Sulfuric acid /0,02 mol/l/ TS

TS = test solution

VS = volumetric solution

16. Prescriptions for Hygienics

16.1. Personal hygienics

Healthy men should only work in the plant. Both men and women are obliged to take a shower before beginning to work. The use of a soap and a nail-brush is compulsory during the shower and hand-wash.

The suitable working-dress is obligatory during work. /The use of walking-dress and shoes is prohibited./

16.2. Supply of working-dress and protective clothing

The supply of working-dress and protective clothes as well as the cleaning of these are performed according to the local hospital prescriptions. The description is contained in Table I in detail.

16.3. Organisation of the cleaning

The manner and frequency of cleaning of the various rooms as well as of the fittings and equipments in these rooms and the disinfectants to be used are summarized in Table II.

The production manager is responsible for keeping the hygienic prescriptions.

Table 1

Supply of working-dress and protective clothing

	Work sites: in Rooms Nos. 1., 8.-25.	Work sites: in Rooms Nos. 2.-7.
Protective clothing	White overcoat or two-piece man suit	White overcoat + cotton underclothes /tricot, trousers, anklets/, or two-piece man suit + cot- ton underclothes /tri- cot, trousers, anklets/
Change cleaning	Two times in a week Disinfecting wash ac- cording to the prescrip- tions of the local hos- pital	Daily once Disinfecting wash accor- ding to the prescriptions of the local hospital
Shoes	Tie shoes or medici- nal clogs	Tie shoes or medicinal clogs
Cleaning	Regularly cleaned	Regularly cleaned
Hair-pre- tectant change	—————	Surgeon's cap or linen kerchief Daily once
Head-mask or mouth-ker- chief		It can be discribed or a clean one has to be used daily

Table II  
Organisation of the Cleaning

Name of the room	Frequency and time-point of cleaning	Cleaning and disinfecting agents according to the equipments				
		Floor	Tile	Fittings and equipments	Ceiling, walls	Lavatory, Sink
Storage of tested raw materials /Room No. 1./	Daily once after work	Washing with a detergent, 5% Hypo	Washing with a detergent	Dusting	Painting one in a year	----
Dryer room No.2./	"	Vacuum cleaning /brooming is forbidden!/ preceeds the wet cleaning Washing with water and 5% Hypo	Washing with water then with 5% Hypo	Washing with water and with alcohol	"	-----
Sifter /Room No.3./	"	"	"	"	"	-----
Weighing room /Room No.4/	"	"	"	"	"	-----
Mixing, sealing, packing I. Room No.6./	"	"	"	"	"	-----

/Table II - continued/

Name of the room	Frequency and time-point of cleaning	Cleaning and disinfecting agents according to the equipments				
		Floor	Tile	Fittings and equipments	Ceiling walls	Lavatory, Sink
Filling, sealing, packing II	Daily once after work	Vacuum cleaning /brooming is forbidden! /preceeds the wet cleaning Washing with water and then 5% Hypo	Washing with water then with 5% Hypo	Washing with water and then with alcohol	Painting once in a year	-----
Storage for finished product /Room No.8./	"	Washing with water	Washing with water	Dusting	"	-----
Quality Control Lab.	Daily twice before and after work	Washing with detergent, 5% Hypo	Washing with detergent	Washing with detergent, then with 5% Hypo	"	Washing with detergent and acidizing once in a week
Dressing and locker for women /Room No.10./	Daily once, after work	Washing with a detergent	"	"	"	"



Table II - continued

Name of the room	Frequency and time-point of cleaning	Cleaning and disinfecting agents according to the equipments				
		Floor	Tile	Fittings and equipments	Ceiling, walls	Lavatory, Sink
Dressing and locker for men /Room No.11./	Daily once, after work	Washing with a detergent	Washing with detergent	Washing with detergent, then with 5% Hypo	Painting once in a year	-----
Office /Room No.12./	"	"	"	Dusting	"	-
Resting /Room No.13./	"	Washing with detergent then 5% Hypo	-	"	"	Washing with detergent and acidizing one in a week
Toilet for Nomen /Room No.14./	"	"	Washing with detergent, then with 5% Hypo	Washing with detergent	"	"
Toilet for men /Room No.15./	"	"	"	"	"	"

/Table II - continued/

Name of the room	Frequency and time-point of cleaning	Cleaning and disinfecting agents according to the equipments				
		Floor	Tile	Fittings and equipments	Ceiling, walls	Lavatory, Sink
Storage for spare parts and cleaning materials /Room No.18./	Daily once, after work	Washing with detergent	-	Dusting	Painting once in a year	-
Maintenance /Room No.19./	"	"	-	"	"	Washing with detergent and acidizing once in a week
Offices /Rooms Nos. 20., 21., 22./	"	"	Washing with detergent	"	"	-
First-aid /Room No.25./	"	"	Washing with detergent	"	"	Washing with detergent, acidizing once in a week

## 17. Regulations for labour safety and Operational Safety

### 17.1. General regulations

The worker directing and carrying out of the work is obliged to acquire and keep the regulations of safe and healthy work and to participate actively of the prevention of accidents and professional diseases.

In the plant area, at the work site all behaviours are forbidden /lack of disciplins, plays, etc./ that hinder the healthy and safe working.

The head of a given work site is obliged to check and provide regularly the following:

- The work sites and working tools should satisfy the labour safety requirements;
- The workers should acquire the knowledges of labour safety connected with their work and use the required protective equipments;
- Tidiness and discipline should be at the work site directed by him.

The subordinate workers are obliged to use the machines, equipments, tools and materials as well as protective equipments according to the labour safety requirements. The worker is also obliged to report immediately to his leader on the least hurt, indisposition or disease and to ask for the first-aid. When this is impossible because of his health state, his coworker is obliged to report.

### 17.2. Possibilities of accidents during manufacturing and their prevention

On the transport of materials, the loads should be arranged in the loading surface of the vehicle in such a manner that those could not tip over, slide or fall out of the vehicle.

The manual transport and loading are carried out by two persons in the case of barrels containing basic materials or boards containing the finished /formulated/ product. During transport and loading works, the workers are forbidden to wear rings, bracelets or necklaces. Transport of persons is forbidden on vehicles for the transport of materials. A great care should be taken of the manual transport of materials in the storerooms. During operation of the homogenizing drums loaded with raw materials, the physical safety of all workers, being present in the room, has to be taken in consideration.

The weighing-in, filling in the homogenizing drums and filling machines of the raw materials should be performed with the least dusting. Similarly, the dusting has to be avoided when the drying trays are charged.

It is forbidden to dip the hand into an operating machine. Electrically heated drying equipments can be operated only in the case when their technical condition satisfies the concerning safety requirements and the protection from shock is assured.

The above prescription also concerns other machines operated electrically /homogenizer, grinding equipment, filling and sealing machine, electric instruments and equipments/.

The electric equipments can mounted, handled and repaired only by workers who are adequately trained, entrusted with the work and possess the labour safety knowledges.

In order to avoid burning and knock injuries, the sealing and designation of the bags should be performed with an increased attention.

17.3. Possibilities of accidents during laboratory work and their preventions

Chemicals.

Concentrated, caustic acids

/Concentrated sulfuric, hydrochloric, nitric, acetic, etc. acid/

When these chemicals get to the skin surface or eyes, severe injuries can be caused. The skin surface has to be wiped with a dry cloth and washed with 1,5%  $\text{NaHCO}_3$  /sodium hydrogen carbonate/ solution.

When those get to the eye, then the eye should be washed with a plenty of water and subsequently with 0,5% sodium hydrogen carbonate solution.

The use of rubber gloves and protective mask is obligatory while working with these chemicals.

Concentrated, caustic alkalis

/Potassium hydroxide, sodium hydroxide, ammonium hydroxide, etc./

When these materials get to the skin, then 1,5% acetic acid or 2% boric acid should be used for neutralization. When those get to the eye, then a washing should be made with a plenty of water and then with 0,5% boric acid solution. Protective clothes: rubber gloves, protective apron.

When an inflammable liquid is stored in the laboratory in an amount exceeding 10 litres /the maximum is 20 litres!/, then it can be kept in glass-bottles with strong walls only in the case when those are placed in a metal cabinet or in a covered metal box or in a cabinet with metal frame, provided with glass of 5 mm

in thickness. All bottles containing inflammable liquid should be provided with the label "Inflammable". The name of the liquid has also to be indicated. Any work with inflammable liquids must be carried out with a satisfactory aeration or exhaustion. The exhaustor should be operated before, during and for 15 minutes following the incendiary process.

Inflammable liquids must be heated only in an indirect manner. When an inflammable liquid streams out, it has to be immediately cleared away and removed from the room. Fire should immediately be reported to the fire-guard. The powder extinguishers placed at the walls serve for firefighting. Care should be taken that the powder extinguishers permanently be charged. It is forbidden to fight an electrical fire with water!

Poisoning chemicals are stored in a poison-cabinet that can be closed by key. Any incompetent person can get the poisoning materials.

#### Glassware

It is forbidden to work in the laboratory with crazy or broken glass devices. The washing of glassware should very cautiously be performed. Gas bottles can only be operated by workers trained for this purpose. The quality of the connections of gas bottles and the leakages should regularly be controlled.

The basic instruments, bandages and drug supply for first-aid should be assured.

#### Instruments and equipments

The electric laboratory instruments and equipments are handled only by skilled persons. For avoiding failures and accidents, the person performing the work is

obliged to keep precisely the directions for use. After use, the instruments and equipments should be put out of action. The person working with the flame photometer has to be skilled in operating gas bottles. The directions for use of the gas bottle should be sticked up on the wall, near to the bottle. The cooling water supply of distillation equipments has to be attended. The compressor should only be operated with adequate indicating device and protective equipment.

18. Arrangement of the Administration

The production manager prepares the production plan in a monthly schedule. According to the plan, he orders basic /raw/ materials, bags, boxes and boards. The raw materials are ordered in such a schedule that they arrive in the plant during the dry season.

The manufacturer gives a quality certificate of the quality of raw materials coming to the plant. The received basic /raw/ materials are taken in to the Registration Sheet for Materials by the Registry of Materials and by the Store. The delivery note is kept in the Registry, the quality certificate of the raw materials is given to the leader of the Laboratory for Quality Control.

The Laboratory for Quality Control takes samples from the raw materials received. The sample-taking is registered in a record /diary/.

The results of the control examinations are indicated in an examination certificate /2 copies/.

A copy of the laboratory examination certificate and the quality certificate of the manufacturing company are sent by the leader of the laboratory to the production manager who decides the suitability of raw materials and informs the leader of the store in a written form.

After having received this information, the leader of store transports the suitable raw materials to the Store I. The raw and auxiliary materials as well as the bags are taken out by the foreman. The taking out of the store is carried out on the demand and delivery sheet for materials by the signature of the production manager /3 copies/.

The storeman registers the amounts of materials taken out for the production on the registering sheet for materials and then informs the workshop and the Registry for Materials



about the materials delivered on the demand and delivery sheet; he keeps the third copy of the demand and delivery sheet.

The daily production is directed by the foreman, on the basis of the instructions of the production manager. One day before production, he verbally informs the leader of the Laboratory for Quality Control of the examination number of raw materials next to be used, in order to take samples.

Next morning, the production manager receives a written information of the examination results and on the basis of these, he gives further instructions concerning production or drying and sieving. Each one step of the production should be registered on the production control sheet. The foreman takes care of keeping the production control sheet and the production manager certifies the registration by his signature.

The weighing-in of basic /raw/ materials is controlled by the production manager personally. The in-production control /chloride and moisture content/ is performed in the Laboratory for Quality Control and the results are registered in the diary and on the production control sheet. The filling weight /dosage/ is performed by a worker of the filling unit who indicates the results on the dosage control record sheet. The batches produced is delivered by the plant to the quarantine store after Registration in the plant delivery diary. The receipt is certified by the signature of the storeman and takes in the material received in his own diary.

The release of the material occurs the production control sheet. The Laboratory Quality Control gives a quality certificate of examination results of the ORS batches produced and declares the marketing /or rejection/ of the material.

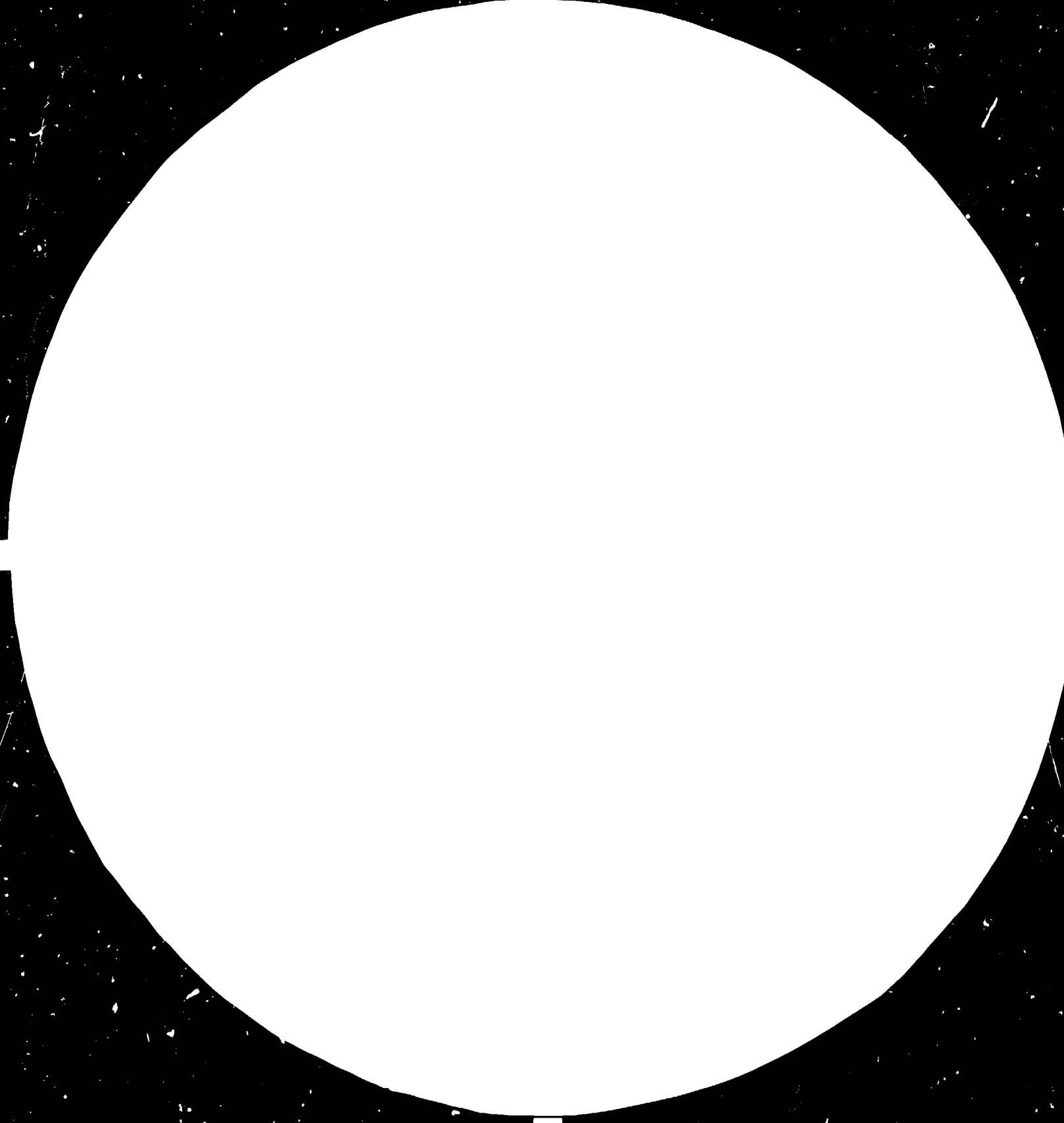
The leader of the laboratory indicates on the production control sheet that the batch satisfies the quality control specifications or it is to be rejected.

The production control sheets and the quality certificate should be kept for one year following its expiration.

The production manager indicates on the production control sheet that the product can be conveyed /delivered, carried out/ and gives a written instruction for the store /quarantine/ that the product can be transported to the Expedition Store. This delivery is registered in the diary and certified by the signature of leader of the Expedition Store.

The product, coming in for expedition, is taken in by the leader of the Expedition Store on the product registering sheet; it is written off when it is delivered.

On delivery a delivery note is filled out in four copies. One copy is sent to the Registry for Materials, where it is booked on the product-registering sheet.



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1.4

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1.8

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2.25

2.5

2.8

3.15

3.6

4.0

4.5

19. Working Time and Working Order

The workers of the plant work in a 8-hour working time, in an extra-time turn. In the night, drying is only performed under control. The number of working days are 5 in a week. The maintenance work should be carried out after the working time; the yearly maintenance has to be performed in the designed days when the plant stops. The collection and screening of the dried raw materials are started by the workers of the earlier turn. The weighing of the raw materials is performed in the presence of the production manager or, when he is hampered, in that of the Control Laboratory manager. The weighing and following operation are begun in the later turn.

The air conditioning should be switched up one hour before the beginning of the turn. Before starting the work, it is to be controlled whether the temperature and moisture content of the rooms are adequate with the prescriptions.

The cleaning in the production rooms can be started after ending the work.

The workers directly participating of the production are obliged to take a shower-bath before work. Working is only permitted in clean working clothes. Ill or injured workers must not work. The foreman directly takes care of maintaining the personal hygienic conditions under the guiding of the production manager.

The production manager gives permission of leaving the workplace.

The door-keepers control the closing of the rooms, switching-off of the electrical and other power sources and the general order of the plant.

Enclosures:

- Enclosure No. 1.: Production Control Sheet
- Enclosure No. 2.: Dosage Control Record Sheet
- Enclosure No. 3.: Registering Sheet for Materials
- Enclosure No. 4.: Demand and Delivery Sheet for Materials

Enclosure No.1.

Production Control Sheet

Name of product: Oral Reh. Salts Date: \_\_\_\_\_

Name of manufacturer: \_\_\_\_\_ Batch size: \_\_\_\_\_

Theoretical number  
of packets: \_\_\_\_\_

Preparation of mixture

	Weight	Initialled by:
Glucose	_____	_____
NaCl	_____	_____
NaHCO <sub>3</sub>	_____	_____
KCl	_____	_____
Aerosil	_____	_____

In-process control

Mixing: time started \_\_\_\_\_ time finished \_\_\_\_\_

Initialled by: \_\_\_\_\_

Control: chloride \_\_\_\_\_ mmol/l Initialled by: \_\_\_\_\_

moisture \_\_\_\_\_ Initialled by: \_\_\_\_\_

Filling:

Time started \_\_\_\_\_

Interruption from \_\_\_\_\_ to \_\_\_\_\_ remarks \_\_\_\_\_

Time finished \_\_\_\_\_

Number of packets filled \_\_\_\_\_

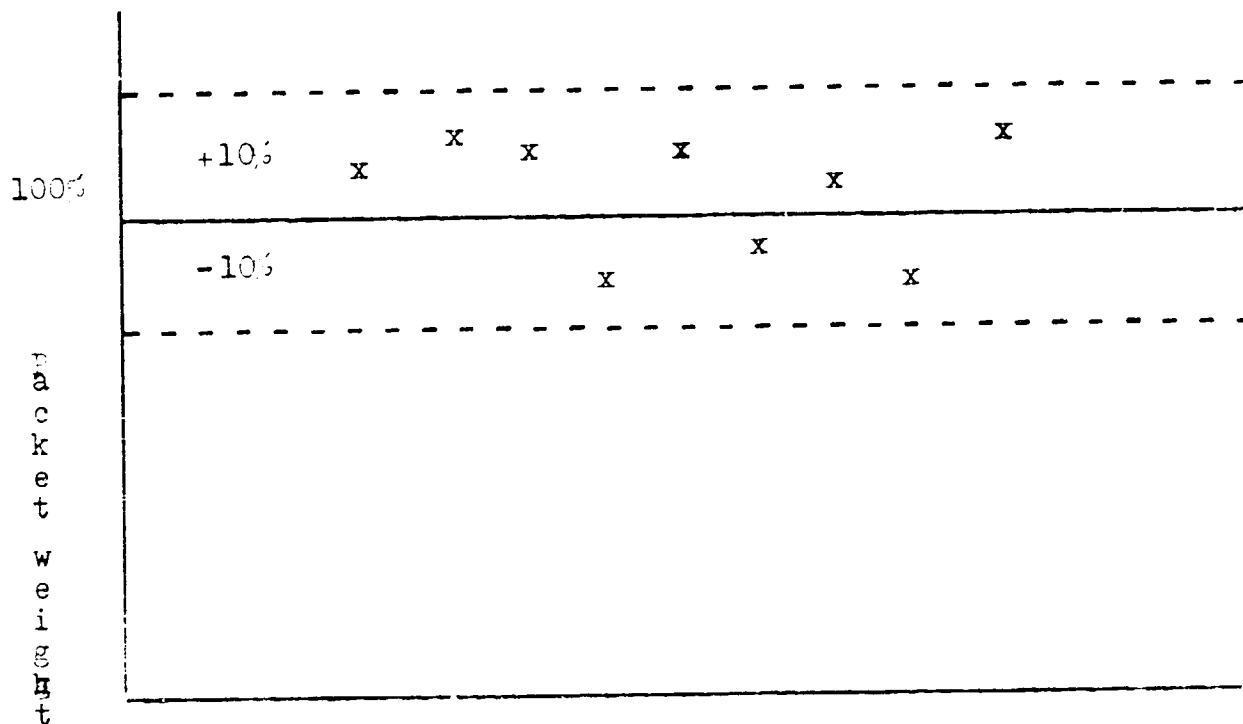
Number of packets packed \_\_\_\_\_

Signed: \_\_\_\_\_

Production supervisor

Enclosure No. 2.

Dosage Control Record Sheet



Time of run

x = weight of packets sampled during batch run plotted against in time when the sample was taken during the batch run.

Enclosure No. 3.

Registering Sheet for Materials

Registering number					Chief account-book invoice number	
Denomination				Store siting		
Largest		Least		Quantity	Unit	Accounting
		Stock		unit	price	price
Date 19..	Certificate number	Text	Receipt	Delivery	Stock	
		Carry-				
		-forward				

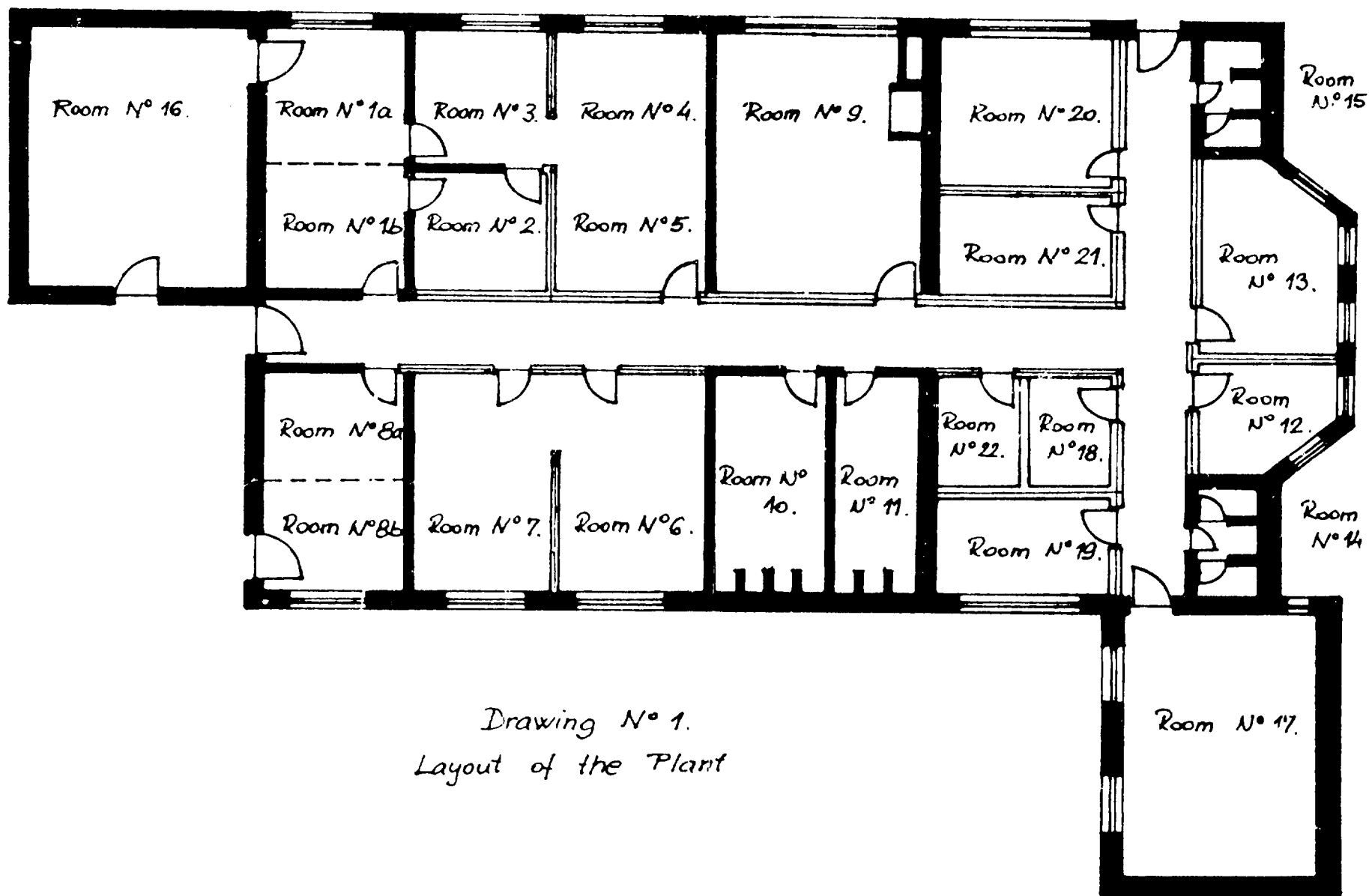


Enclosure No. 4.

Demand and Delivery Sheet for Materials

I ask to hand over the following materials for the production of ORS:

Date of demand	Material demanded			Date of delivery	Material delivered		
	Amount	Unit	Denomination		Amount	Unit	Denomination



Drawing N° 1.  
Layout of the Plant

After finishing the training the machine and equipment

and that of the various other

As the machine is used for the purpose of

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were handed over in good condition, and the factory is ready to further production.

Beira, 6. April, 1983.

Director of S.M.I.M.

T. de  
A. S. R. de  
6483

*Woods Milway*

Team leader



