PLAN FOR INDEPENDENT PRODUCTION OF ORAL REHYDRATION SALTS (ORS)

Consultancy Report
For MOH/NCDD Project

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Introduction

Pharmaceutical Industry in Egypt

This industry started in Egypt since 1938, or before, by Egyptian companies, Egyptian private laboratories, Egyptian Pharmacists in their Pharmacies. Later on, other companies, also Egyptian, were established and by the year 1961 and 1963 all Egyptian Companies and Egyptian Laboratories were nationalized by law. Private Laboratories were amalgamated in the NEW GOVERNMENTAL COMPANIES, which now form the Egyptian Pharmaceutical Manufacturing Companies. Then, few years later, foreign branches of pharmaceutical companies were granted permit to prepare their products and different dosage forms in Egypt.

Egyptian Pharmaceutical Manufacturing Companies:

1-Alexandria Company;
2-Arabian Company;
3-Chemical Industries and Development Company (C.I.D.);
4-Kahira Company;
5-Memphis Chemical Company;
6-Misr Company;
7-Nasr Company for Pharmaceutical Chemicals;
8-Nile Company.

Foreign Pharmaceutical Companies, Branches of:

1- Hoechst;
2-Pfizer;
3-Squibb;
4-Swiss Pharma (Ciba Geigy-Sandoz Wander);
5-Utsuma.

All the companies, Egyptian and foreign branches adopt Good Manufacturing Practice and Good Laboratory Practice. They prepare many dosage forms and different pharmaceutical products according to specifications of the pharmacopoeas recognized by the Ministry of Health or to their own specifications or their specialities.

One of the pharmaceutical products, prepared by C.I.D. Company, is Oral Rehydration Salts (ORS) according to WHO specifications. The product is prepackage in the company in 27.5g and 5.5g packets, for preparation of 1 liter, and 200ml, respectively.

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Oral Rehydration Salts ORS

Mixture of glucose and salts(electrolytes) dissolved in water,in specified amounts,is the new therapy for acute diarrhoeal diseases in children,to treat dehydration simply and effectively.

Composition: 27.5 g (to prepare 1 liter of solution) contain:

Glucose	20 g.
Sodium Chloride	3.5g.
Sodium Bicarbonate	2.5g.
Potassium Chloride	1.5g.

The reconstituted solution contains :

Glucose	111	mmol/liter;
Sodium Na^+	90	mmol/liter;
Chloride Cl^-	80	mmol/liter;
Bicarbonate HCO_3^-	30	mmol/liter;
Potassium K^+	20	mmol/liter.

Osmolality of the reconstituted solution is 331 mosmol/liter, which is slightly more than the osmolality of blood plasma: 270 to 310 mosmol/liter.

Different Formulations:

Fisher in 1981, in a formula to reduce osmolality,where glucose was changed to glucose polymers,reported that glucose polymers are sometimes untolerated by some children.

Sucrose was used instead of glucose in similar rehydration solutions, containing essential electrolytes,of equal osmolality.Black et al.(1981) stated that glucose is the preferred carbohydrate for oral electrolyte solutions,although sucrose can be given instead,with only minimum loss of efficacy.

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Trials to use simple sugar/salt solutions for rehydration were successful,in rapidity and improvement in metabolic acidosis as complete glucose electrolyte solutions.Drawbacks of treatment by mouth with simple sugar/salt solution were the frequent development of hypokalaemia and greater volume of vomiting during treatment.Carefully prepared sugar/salt solution if accompanied by adequate potassium supplement may be used as an alternative(Clements et al.(1981).

Nalin,et al.(1980) compared low and high sodium and potassium content in oral rehydration solutions. ORS solutions with sodium 90 and potassium 20 mmol/liter aroused fear of hypernatraemia and hypokalaemia because faecal sodium and potassium in infantile diarrhoea differ from adult diarrhoea,on which those solutions are based.

Hirschhorn et al. (1981) discussed different alternative preparations using sucrose instead of glucose, low sodium or high potassium content, for the management of the diarrhoeal diseases at the community level. The U.S. Department of Public Health, according to Conn Howard F., in Current Therapy(1981), has recommended the following regimen:

(1) Fill one glass with 8 oz.(240ml) of any fruit juice(potassium content), and add one half teaspoon of honey or corn syrup(glucose facilitates absorption of sodium and chloride) and one pinch of table salt.

(2) Fill a second glass with 8 oz of water(boiled if contamination is likely) and add one half teaspoon of baking soda(sodium bicarbonate).

(3) Drink alternately from each glass.

Role of ingredients of ORS :

Glucose facilitates and assists absorption of sodium and chloride;

Sodium chloride is most important for maintaining the osmotic tension of the blood and tissues; normal tissue fluid contains about 140 mmol/ of sodium ions Na^+ per liter and about 100 mmol of chloride ions Cl^- per liter;

Potassium chloride is important to maintain the body potassium in patients with persistent diarrhoea;

Sodium bicarbonate is of value as an antacid in treatment of vomiting in children.

Other Preparations for Oral Rehydration Treatment:

1- Compound Sodium Chloride and Dextrose Powder(Electrolyte Powder), (The Pharmaceutical Codex, 1979). 1 liter contains:

Dextrose monohydrate	40	g
Sodium chloride	1	g
Sodium bicarbonate	1.5	g
Potassium chloride	1.5	g

After reconstitution with recently boiled and cooled water, 1 liter of the solution contains:

Dextrose	200	mmol/liter
Sodium Na^+	35	mmol/liter
Chloride Cl^-	37	mmol/liter
Bicarbonate HCO_3^-	18	mmol/liter
Potassium K^+	20	mmol/liter.
Total Osmolality	310	mosmol/liter.

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2-Servidrat Effervescent Tablets(Servipharm,Switzerland)

Dissolution of one effervescent tablet in 120ml of water yields the following concentrations:

Glucose	100 mmol/liter
Sodium Na^+	90 mmol/liter
Chloride Cl^-	80 mmol/liter
Citrate	30 mmol/liter
Potassium K^+	20 mmol/liter

3-Infalyte Powder(Pennwalt Corp.,U.S.A.)

Composition: 1 liter of solution contains:

Glucose	111 mmol/liter
Sodium Na^+	50 mmol/liter
Potassium K^+	20 mmol/liter
Chloride Cl^-	40 mmol/liter
Bicarbonate HCO_3^-	30 mmol/liter

4-Pedialyte(Ross Laboratories,U.S.A.)Oral Electrolytic Solution

Composition: 1 liter contains:

Sodium Na^+	30 mEq /liter
Potassium K^+	20 mEq /liter
Calcium Ca^{++}	4 mEq /liter
Magnesium Mg^{++}	4 mEq /liter
Chloride Cl^-	30 mEq /liter
Citrate	28 mEq /liter
Dextrose	50 g /liter

5-Elkinton's Solution:

Composition: 1 liter contains:

Sodium Chloride	4.2 g
Potassium Chloride	3 g
Dipotassium Hydrogen Phosphate	3.2 g
Potassium Dihydrogen Phosphate	0.7 g
Glucose	25 g

6-Lytren Powder(Mead Johnson,U.S.A.) For Oral Electrolyte and Fluid Balance.Contains Glucose,Sodium Citrate,Sodium Biphosphate,Sodium Chloride,Potassium Chloride,Calcium Lactate,Magnesium Sulphate, Citric Acid.

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7- Sucrose Electrolyte Solution:

Composition: 1 liter contains:

Sucrose	50.9	g
Sodium Chloride	1.7	g
Potassium Bicarbonate	2	g

8- Cholera Replacement Solution(Martindale 27,The Extra Pharmacopoea 1977)

Composition: 1 liter contains:

Glucose	20	g
Sodium Chloride	4	g
Sodium Bicarbonate	4	g
Potassium Chloride	1.5	g

9- Antidehydration Mixture (National Formulary,U.A.R.,1968)(Egypt)

Composition:

Potassium Citrate	10	g
Sodium Chloride	9	g
Sodium Bicarbonate	2	g
Glucose	200	g
Chloroform Water to	1000	ml

Comments : The preparation is too much concentrated; only 5 ml dose can be given with plenty of water.
The presence of chloroform as a preservative is not now acceptable.

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Prepackaging of Oral Rehydration Salts (ORS)

The actual capacity of local prepackaging of ORS now in Egypt is far from the estimated demand of 40 million litres of reconstituted solution,per year,on the fourth year of the MOH/NCDD Project.
The necessity arises for;the establishment of an independent packager of Oral Rehydration Salts; the encouragement of preparation of 1 liter solution of ORS in the pharmacy (there are about 5378 pharmacies alover Egypt now) according to "Plan for Pharmacy-based Preparation of Oral Rehydration Salts (ORS) Solution" Consultancy Report(August 1983) submitted and prepared by Dr.M.Abdel-Moneim Hussein,to MOH/NCDD Project; the use of present facilities for packaging or/and manufacturing some simple pharmaceutical products and different simple dosage forms in some governorates;the possibility of preparation of 1 liter solution and sterile filling in plastic bottles extruded at the moment (such sterile solution can keep without any bacterial growth);other efforts of hospital pharmacies and other pharmacies of different health centers;

and other alternatives; household formulations.

Requirements for Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) in Prepackaging of Oral Rehydration Salts(ORS);

1-Personnel: a-supervisors of production;
b-supervisors of control;
these must be suitably qualified after scientific education and must have practical experience in their fields.
c-pharmaceutical technologists;
d-skillful labour.

2-Premises: a-space; b-cleanliness of walls, floors, ceiling; and continuous maintenance of cleanliness; c-lighting; d-air-conditioning, cooling and heating, with temerature control; e-dehumidifying the air, with humidity control; f-filtering the air.
The engineering design and construction materials and inner coating should fulfill the requirements for high quality pharmaceutical manufacturing, with necessary separation of areas specialized for each operation or for certain purpose.

3-Sanitation: a-continuous maintenance of cleanliness;
b-cafeteria, with special smokers' corner;
c-room for changing clothes, and toilet facilities and hand washing, clean and well-ventilated, for MEN.
d-separate similar facilities mentioned above, for WOMEN.

4-Equipment: a-designed for intended use, capacity of production, accuracy;
b-layout according to steps of production and procedures of control; and to facilitate cleaning and maintenance; and to save space for safe movement of personnel and material;
c-Cleanliness and maintenance: frequency, method, and material used according to written instructions; adequate records are kept for such procedures and before and after each working day; and before and after each batch of production.
d-machine record: date and batch number and name of product and name of operator and quantity produced during (number) of hours actually working per day; records of cleaning and maintenance. While running, the machine must be appropriately labelled. All records of the machine are kept.

5-Raw Materials: a-inventory;
b-records of supplier, original manufacturer, date of receipt, date of analysis, date of release by the qual

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acture.

c-identification and examination of containers for damage;

d-proper storage in quarantine;

e-proper sampling by the quality control department; labelling under analysis;

f-analyzed for conformity to specifications;

g-released from quarantine by the quality control department by written instructions;labelling released ;

h-transferred to proper storage areas;

i-materials refused by the quality control department are labelled refused or rejected or not conforming and are to be returned to supplier or destroyed.

6-Manufacturing Operations:

a-Cleanliness of all equipment prior to manufacturing operation;

b-labelling of all equipment and containers used in manufacture and storage between manufacturing steps:name,date, batch number

c-precautions to avoid contamination and confusion;

d-personnel in production must wear clean clothes other than those used in the street;should be free of communicable diseases;should not be carriers of such diseases;should not have open lesions on the exposed surface of the body;should undergo periodic health checks and daily medical observation for any infection of the upper respiratory tract;

e-documents of the product: name,dosage form,final container, packaging material,labelling;identity,quantity and quality of each raw material to be used;yields expected from the formulation at different steps of production;detailed instructions and precautions in manufacture and storage of the product or half-finished product;details of in-process control;batch records:name and dosage form,date,number,complete formulation,batch number and analytical control number of each component used in the formulation,actual yield at different stages of manufacture of the batch as compared with the theoretical yield,signed record of each step with any precautions or observations,record of all in-process controls followed and results,specimen of actual coded label used,

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g-identification of packaging materials,containers used,date and signature of pharmacist supervising the manufacturing operations,quality control report of the batch dated and signed by the pharmacist in charge of the quality control department showing whether the batch is conforming to the specifications of the product,record of decision to release or reject the batch by the quality control department, record of the disposal of the rejected batch,keeping all batch records.

7-Labelling and Packaging:

a-labels,packaging materials including leaflets are to be stored and handled in such a way as to prevent intermixing of materials related to different products;access to such materials should be restricted to authorized personnel;

b-beforepackaging and labelling of a batch of a product,the manufacturing and control records should show that the batch was tested,approved and released by the quality control department;before issuing labels for containers,cartons, boxes,circulars,inserts,leaflets should be all examined and released as satisfactory for use by the designated person; issuance of labelling and packaging units should be madeagainst a written signed request indicating number and types required;after the packaging and labelling operation is complete,the number of units issued is compared with the number ofitems labelled and packaged plus the number of units not used,and any discrepancy in the numbers should be investigated;any coded labels or packaging units not used should be destroyed;

c-labelling requirements:name of product;net contents(weight, volume,or number of dosage units);composition in detail (name and quantity of each ingredient);batch number;date of preparation;expiry date;storage conditions&precautions; directions for use,any necessary warnings and precautions; name and address of manufacturer;the registration number or the official Pharmacopoea adopted.

8-Quality Control:

a-Quality control department having available laboratory , adequately staffed and fully equipped,supervised by a qualified expert,for performing all quality control tests and

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of all production steps, quality control of the finished product, and its stability); other principal duties are;

b-preparation of detailed written instructions for performing each test and analysis;

c-release or rejection of each batch of raw material;

d-release or rejection of half-finished products;

e-release or rejection of packaging and labelling materials and the final containers;

f-release or rejection of each batch of finished product ready for distribution;

g-evaluation of the conditions of storage of raw materials, half-finished products and finished products;

h-evaluation of the quality and stability of finished products;

i-establishment of expiry dates and shelf-life of products on the basis of stability tests related to storage conditions;

j-establishment, and revision if necessary, of control procedures and tests and specifications;

k-examination of returned drugs and decision to release, reprocess or destroy such drugs; keeping records of the disposition of such drugs;

l-sampling of raw materials and finished products; keeping portions of properly labelled samples for future reference;

m-keeping analytical records concerning all samples taken; records include: results of all tests performed including observations and calculations relating to conformity to specifications; source of the specifications used; signature of person who performed the quality control procedures; a final review, the decision taken and signature and date of the pharmacist in charge of control department.

9-<u>Self-inspection</u>: Regularly scheduled inspections of all manufacturing and control operations by one or more experts.

10-<u>Distribution Records</u>: adequate records should be kept of the distribution of each batch of each product for easy, quick and complete recall of a batch if necessary.

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Plan for prepackaging of 10 million packets of ORS per year(27.5g)

1-Premises: a- Quarantine and storage of raw materials: area 240 m^2 x 3 m.
b- Drying and sifting:area 60 m^2 x 3 m.
c- Weighing and mixing: area 25 m^2 x 3 m.
d- Filling,sealing and packing: area 30 m^2 x 3 m.
e- Quarantine and storage of finished products: area 120 m^2x3m.
f- Quality control laboratory: 25 m^2 x 3 m.
g- Maintenance; cleaning materials ; area 10 m^2x3m.
h- Room for changing clothes and toilet facilities and hand washing for men and,separate,similar, for women; 30m^2x3m
i- cafeteria,with special smokers corner:area 50 m^2x3m.
g- Offices. area 50 m^2x3m.

2-Raw Materials: (See specifications)
a- Glucose 200 Tons
b- Sodium Chloride 35 tons
c- Sodium Bicarbonate 25 tons
d- Potassium Chloride 15 tons
e- Colloidal Silicon Dioxide (Aerosil) 55 kilograms

3-Packaging Materials: 200 reels of two-colour printed aluminium foil (see specifications) 1000 m^2 each.
(see labelling requirements).

4-Automatic Packaging Machines: Two Machines. Total production per day (7 hours) 10 batches, 5000 packets each batch,yield in 200 days 10 million packets.
Alternatively,the two machines might be working for 5 hours and 32 minutes to fill 8 batches per day producing 40000 packets,yielding in 250 working days 10 million packets. (see specifications).

5-Equipment: air conditioner;air filter;dehumidifying apparatus;fluid bed drier electric;balances 100kg,20kg,and 100g;stainless steel mixer;stainless steel drums with tight covers (10);sifter air compressor;cleaning equipment;internal transport equipment.

6-Quality Control Equipment:Moisture balance;analytical balance;flame photometer;polarimeter;constant temperature water bath; incubator;colony counter;water distilling apparatus;vacuum desiccator;glassware;porcelain-ware;comparison tubes;

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beakers; erlenmeyer flasks; glass-stoppered bottles; pipettes; graduated titrating pipettes; burettes; bacteriological pipettes; dilution blanks; silica crucibles; nickel crucibles; platinum crucible; petri dishes; ph meter electric; device for clarity test; microscope; micropore filter; platinum wire; bunsen burners; bottled gas with regulator; rubber stoppers and tubing; glass tubing; wash bottles; dropper bottles; test tubes; filter paper; glass funnels; sintered glass funnels; burette stands; holders; brushes different sizes; detergents.

7-Reagents: acetic acid 30%w/v test solution
acetic acid 6%w/v (lead test solution)
Agar
ammonia 10%w/v test solution
ammonia 10%w/v (lead test solution)
ammonium molybdate test solution
barium chloride $\frac{N}{2}$ solution
barium hydroxide 1.5% w/v test solution
carbon dioxide-free water
sodium hydroxide $\frac{N}{50}$ (carbonate-free) solution
Cupric sulphate reagent
hydrochloric acid 25%w/v test solution
hydrochloric acid $\frac{N}{1}$ solution
hydrochloric acid $\frac{N}{10}$ solution
hydrogen sulphide reagent
iodine $\frac{N}{10}$ solution
lead nitrate reagent
methyl orange test solution
nitric acid100%w/v test solution
nitric acid 13%w/v test solution
peptone
phenolphthalein alcoholic solution
potassium carbonate anhydrous reagent
potassium chromate test solution
potassium sodium tartrate reagent
potassium sulphate 174 mg/liter test solution
silver nitrate 4%w/v test solution

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silver nitrate $\frac{N}{100}$ solution

sodium carbonate 5% w/v test solution

sodium hydroxide reagent

sodium hydroxide 8% test solution

sodium tetraphenylborate 3%w/v test solution

sodium thiosulphate $\frac{N}{10}$ solution

solution of starch

ethyl alcohol 75%w/v test solution (sulphate-free)

sulphuric acid 176% w/v test solution

sulphuric acid 10%w/v test solution

8-Personnel: pharmacist in charge of production;
pharmacist in charge of quality control;
pharmaceutical microbiologist;
6 pharmaceutical technologists;
6 skillful labor;
2 clerks
2 typists
12 workers
1 electrician
1 technician mechanic

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9-Production steps:

a-Raw materials: (1)stored separately in quarantine in storage area;sampling by control department and labelled under analysis;analysis for conformity to specifications ;release from quarantine by control department; labelled released;transferred to proper storage area;

(2)packaging materials are stored separately in special storage area;

(3)raw materials necessary for the 8 or 10 batches to be processed on the next day, are checked for moisture and clumping; they are sifted,if necessary,and if glucose moisture exceeds 1% it is dried and sifted.

(4)ingredients are weighed and mixed; each batch weighs 137.5Kg ;in-process control for moisture and chlorides.If moisture is

of 77-85 mmol/liter,ihe batch is rejected.

b-Packaging Machine forms,fills,seals packets,imprints batch number and packaging date;operation is started and dose is controlled by weighing sample packets(gross weight)every 3 minutes.

c-packing in boxes of 50 packets; and in cartons of 20 boxes.

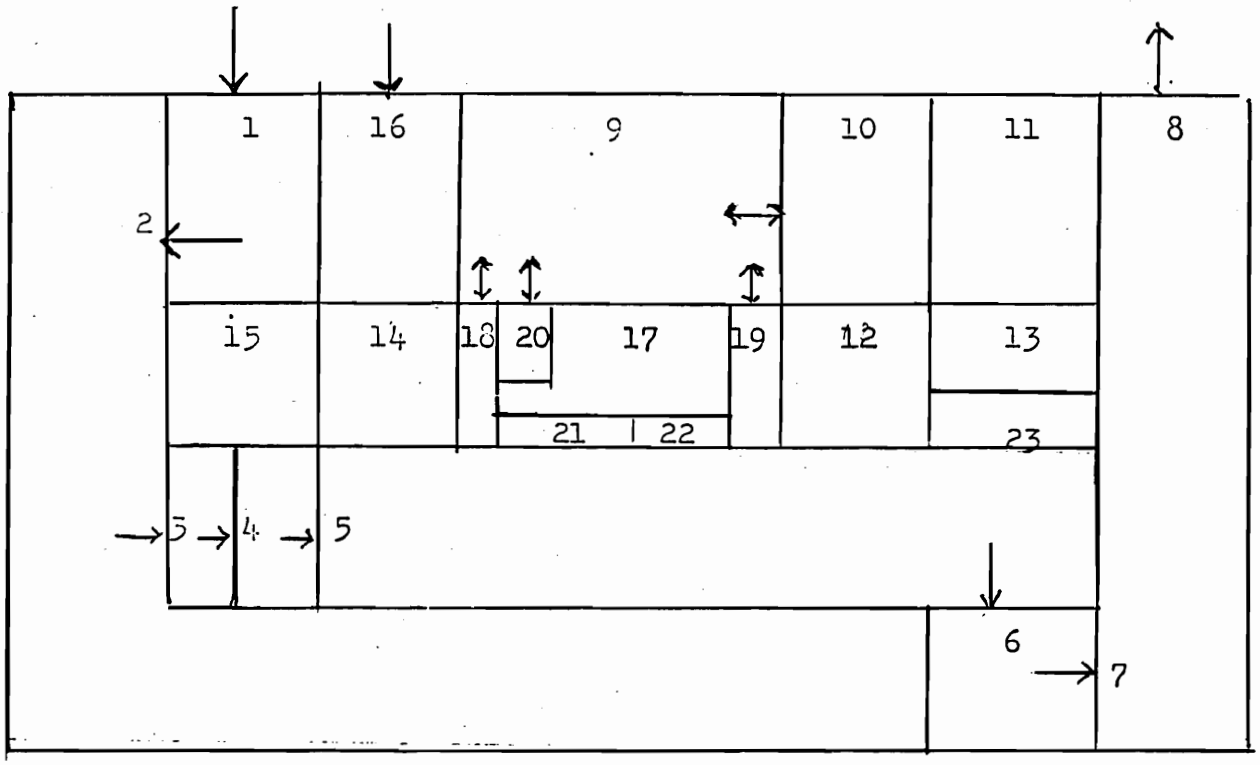
d-storage in quarantine in storage area of finished product,and labelling under analysis and samples taken by quality control department for analysis of the batch for conformity to specifications,and for stability control report;release from quarant by control department and labelled released;

e-storage in storage area of finished products,ready for distribution.

f-all storage areas and production area are kept under controlled temperature and humidity;

g-batch records,distribution records and samples of each batch are kept for future reference.

h-See flowsheet of recommended plan of production.



Flowsheet of recommended plan of production

1-Inlet of raw materials in Quarantine.
2-Storage area of raw materials.
3-Drying and Sifting.
4-Weighing and mixing.
5-Packaging Machines 1 and 2.
6-Quarantine for finished products.
7-Storage area for finished products.
8-Exit goods for distribution.
9-Open air garden area.
10-Offices production dept. clerks
11-Offices Quality Control dept. clerks.
12-Qual. Control finished product.
13-Accelerated stability tests.
14-Qual. cont. pack. mat. in-process co
15-Quality control raw materials.
16-Storage area packaging material
17-Cafeteria for eating and drinking.
18-Clothes changing, toilet, hand wash for men.
19-Clothes changing, toilet, hand washing for women.
20-Smokers corner with single door&f
21-Cleaning materials, tools, instructions; records.
22-Maintenance materials and tools, instructions, records, machines' records; operation and maintenance instructions.

23-Microbiological Laboratory.

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Specifications and Methods of Analysis of Oral Rehydration Salts

Composition : 1 packet 27.5 g to make 1 liter of solution contains:

Glucose	20 g
Sodium Chloride	3.5 g
Sodium Bicarbonate	2.5 g
Potassium Chloride	
Colloidal Silicon Dioxide (Aerosil)	0.0025 g

Physical : Colour is white.

Powder is fine and dry.

Net Weight is 27.5 g ranging from 26.1 to 28.9 g.

Moisture Content is not more than 3%

pH of Reconstituted Solution is 7.2 to 8.8

Solubility : should be readily soluble in 1 liter of cold water.

Seal: packets should be hermetically sealed with no leaks.

Test: Submerge 10 packets under water in a vacuum desiccator; apply vacuum and examine for air leakage indicated by evolution of a stream of bubbles. Some packets may inflate and when opened water may penetrate.

Clarity of Reconstituted Solution in distilled water previously filtered through sintered glass filter funnel to be free of particulate matter: The reconstituted solution should be only very slightly turbid (due to presence of Aerosil); but solution should be free of particulate matter, dust particles, fungal growth.

Labelling: complete labelling requirements:

Net Weight of contents, name of product, composition, batch number, date of preparation, expiry date, moisture content, storage method and conditions, method of use and directions not to use the reconstituted solution, or any remains of it, after 24 hours, name and address of the packaging manufacturing pharmaceutical company, price for consumer.

It is recommended to draw the attention of the

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Packets: Size 90x100 mm; foil of good quality, with no pin holes:
inside layer polyethylene 50 g/m^2;
middle layer aluminium foil 15 mm coated on 2 sides;
outside layer polyester 15 g/m^2; all uniform thicknesses

Chemical: Test Solution : 1 liter corresponds to 27.5 g of product.
Weigh accurately 27.5 g of the contents of one packet and dissolve in about 500 ml of water (pure distilled) and make up to 1000ml. Perform a double analysis using two dilutions. If the measurements are not close together, do a new dilution.
If any measurement, in the following procedures, after repeating the analysis, exceeds the limits specified in front of each of the components of the product, reject.

Glucose: 20 g ranging from 19 to 21 g.

Assay: Place 5 ml of the test solution in a 250ml glass-stoppered flask, add 50 ml of distilled water, 25 ml of iodine N/10 standard solution, and 10 ml of sodium carbonate 5% solution. Allow the solution to stand in darkness for 20 minutes. Add 15 ml sulphuric acid 10% w/v solution. Titrate with sodium thiosulphate N/10 standard solution, using solution of soluble starch as indicator. Calculate glucose content from the formula:

glucose content/liter= ml sodium thiosulphate N/10 x 9.008

Sodium Chloride: 3,5 g ranging from 3.33 to 3.68 g.

Assay: Dilute 10ml of test solution to 100 ml with distilled water. Further dilute 10ml of this solution to 100ml with distilled water. Measure the sodium content using a flame photometer following the manufacturer's instructions.
Calculate sodium chloride content per liter from formula:

$$\text{sodium chloride content per liter} = \frac{\text{Reading}}{1000} \times \frac{1000}{10} \times \frac{100}{10} \times \frac{100}{1000} \times 58.44$$

Sodium Bicarbonate: 2.5 g ranging from 2.38 to 2.63

Assay: Dilute 25ml of the test solution, accurately measured, with 100ml of distilled water, then titrate with hydrochloric acid N/10 standard solution, using methyl orange solution as indicator. Calculate sodium bicarbonate content per liter from the formula:

sodium bicarbonate content per liter = ml Hydrochloric acid N/10 x8.401x1000x40

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Potassium Chloride: 1.5 g ranging from 1.35 to 1.65 g.

Assay: Dilute 10ml of the test solution to 100ml with distilled water. Further dilute 10ml of this solution to 100ml with distilled water. Measure the potassium content using a flame photometer following the manufacturer's instructions. Calculate potassium chloride content per liter from the formula:

$$\text{potassium chloride content per liter} = \frac{\text{Reading}}{1000} \times \frac{1000}{10} \times \frac{100}{10} \times \frac{100}{1000} \times 74.55$$

Heavy Metals: limit is not more than 3.45µg per gram. (95µg/27.5 g)

N.B. The limit of Heavy Metals as specified by W.H.O. on page 29, WHO/CDD/SER/80.3 (ANNEX 2) "GUIDELINES FOR THE PRODUCTION OF ORAL REHYDRATION SALTS" is too high and it is recommended to request WHO authorities concerned, to revise this limit, and to correct it according to WHO specifications concerning heavy metal permiscible limit in each of the components. Thus, the corrected heavy metal limit should read

NOT MORE THAN 95µg per 27.5 g ORAL REHYDRATION SALTS.

Determination: based on comparison of colour, obtained by mixing 25 ml of test solution with freshly prepared hydrogen sulphide solution, with the colour obtained by mixing 0.2375 ml of dilute lead (Lead test solution) ($PbrS$) (standard lead solution 1 ml contains 10µg lead) in suitable comparison tubes.

test solution : Measure accurately 25ml of test solution, adjust ph to 3-4 with acetic acid 6%w/($PbrS$) or ammonia 10%w/v($PbrS$), dilute to 40 ml with distilled water, and mix.

Standard Solution: Measure accurately 0.2375 ml of freshly prepared standard lead solution, dilute with 25 ml of distilled water, adjust ph to 3-4 (as above), dilute to 40 ml with distilled water, and mix.

Colour Development and Measurement: To each comparison tube, add 10ml of freshly prepared hydrogen sulphide solution, mix and allow to stand for 5 minutes. Compare the colours by viewing down the vertical axis of the tube in diffused light against a white background. The colour of the test solution should not be darker than the standard solution.

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Microbiological: Standard Plate Count: should be not more than 145/g. (corresponding to 45 colonies on the .33 dilution plates), according to W.H.O. specifications and procedure, pages 46-47, ANNEX 5-A, WHO/UDD/SER/80.3, for Glucose.
Moulds and yeasts: should be not more than 7/g.
Osmophilic yeasts: should be not more than 14/g.
E.coli(37°C.) : should be absent.

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Quality Control Department

Recommended Form for Quality Control Report:

Product : Oral Rehydration Salts

Packing : 27.5 g packets

Composition: 27.5 g contain:

Glucose	20	g
Sodium Chloride	3.5	g
Sodium Bicarbonate	2.5	g
Potassium Chloride	1.5	g
Aerosil	0.0055	g

Batch Number:..... Date of Preparation ..... Expiry Date.....

(Expiry Date is determined after accelerated stability tests performed).

Storage conditions and method " " " " ").

Number of samples:..... Taken by..... Date.....

Analysis Report		Product Specifications	
Physical : Net weight/found.....		27.5g ranging from 26.1 to 28.9g	
colour	/found.....	white	Reject if discoloured
powder	/found.....	dry fine	Reject if caking presen
moisture	/found.....	not more than 3%	
pH of reconstituted solution	/found.....	7.2-8.8	
solubility	/found.....	readily soluble in 1 liter of cold water	
Seal	/found.....	hermetically sealed packets with no leak	
Labelling	/found.....	complete labelling requirements	
Packets	/found.....	conforming to specifications page 18	
Clarity of reconstituted solution in distilled water previously filtered through sintered glass filter funnel to be free of particulate matter	/found.....	only very slightly turbid(Aerosil); but solution should be free of particulate matter, dust particles, fungal growth	
Chemical: Glucose	/found.....	19-21 g by iodimetric method.	
NaCl	/found.....	3.35-3.68 g by flame photometry	
$NaHCO_3$	/found.....	2.38-2.63 g	
KCl	/found.....	1.35-1.65 g by flame photometry	
Heavy metals	/found.....	not more than 3.45 µg/g (=95 µg/27.5g)	

Reject if any measurement, after repeating the analysis, exceeds the limits, specified above.

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Recommended Form for Quality Control Report (continued)

Analysis Report	Product Specifications
Microbiological :	
Standard Plate Count/found.....	not more than 145/g, corresponding to a count of 48 colonies on the .33 dilution plates.
Moulds and yeasts /found.....	not more than 7 / g.
Osmophilic yeasts /found.....	not more than 14/g.
E.coli (37°C.) /found.....	should be absent.

Reject if counts exceed limits specified above, or if E.coli(37°C.)is found.

Stability Report:

Accelerated tests performed to determine empiry date and conditions and method of storage:

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Production Department

Recommended Batch Record Sheet (Machine No 1 or No 2)

Product : Oral Rehydration Salts

Packing : 27.5G

Batch Number..... Date.....

Batch size..... Expected number of packets.....

Weighing of Ingredients	Weight	by; (signature)	in presence of: (Si
Glucose	.....	.....	.....
Sodium Chloride	.....	.....	.....
Sodium Bicarbonate	.....	.....	.....
Potassium Chloride	.....	.....	.....
Aerosil	.....	.....	.....

Inprocess control

Mixing time	from ..... to.....	signature.....	
chlorides	..... mmol/liter	signature.....	
Moisture	.....%	signature.....	

Packaging:

	start	finished
Filling time	from.....to.....	

interruption period from..... to.....

(reasons .....)

Number of packets filled.....

Number of packets packed in boxes of 50 and 20 boxes in cartons.....

Signature
Production Department

Signature
Quality Control Department

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Alternatives for Establishing and Operating the Independent Packaging of ORS

1-One independent Packaging operation to produce 10 million packets per year.As recommended in previous pages,such an operation is to be fully financed by the NCDD Project.

2-Another alternative,is to increase capacity of production of CID company,by supplying the company with the machines they need,according to the company's report.The company has sufficient stocks of the ingredients,especially Glucose,according to the report,and the company should be given preference to produce the product before any other company.They handled the product and they are continuously producing it either in 27.5g packets ORS or 5.5g packets of their Rehydran and now the new Oral Rehydration Salts,with attractive display boxes. Further, Cairo is better than Alexandria,being much less humid. Although air conditioners and dehumidifying apparatus are used,yet the humid atmosphere would put some more burden on the capacity of the dehumidifying apparatus.

3-A third alternative,is the possibility of preparing sterile solution in 1 liter plastic bottles to be extruded at the moment of sterile filling,as recommended in Plan for Pharmacy-Based Preparation of ORS Solution,consultancy report prepared and submitted by the same consultant of this report. The extrusion machine is available in the U.S.A. and in other countries,Germany(WEST),or Italy.

4-The existing companies of the Government and those of the foreign branches in Egypt,may be all supplied with semi-automatic machines, one for each,and the ingredients necessary for the yearly production of ORS. These together with the expected new capacity of CID can produce 10 million packets.(5million for the ten companies with 10 semi-automatic machines + 5 million expected capacity of CID after the automatic machine to be supplied to CID)

5-Encouragement of Pharmacists to prepare ORS Solution in their pharmacies as recommended in the above-mentioned plan.

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Production and Packaging Costs

cost per 1 packet 27.5g

Raw Materials	L.E.0.017	
Packaging material	0.013	
	0.030	= $ 0.037 UNICEF **
+40% wages or salaries and manufacturing costs	0.012	
Total Direct costs	0.042	
+19.5% Marketing and administrative costs	0.008	
Total manufacturing costs	0.050	
+10% profit for manufacturer	0.005	
Net Manufacturer selling price	0.055	*

(these percentages are according to calculations interpreted from CID report)

Assuming public price to be	0.075	
Less 19% pharmacist discount	0.01425	
Selling price to pharmacist	0.06075	
less 7% distributor discount	0.00425	
Net manufacturer selling price	0.0565	*

the 2 figures are very close, difference is insignificant.

the cost of raw materials for CID = L.E. 0.0315 (cf. UNICEF cost = L.E. 0.017
(according to calculations interpreted from CID report)
It is recommended to enable the new company to obtain the ingredients at best prices possible, at most equal to UNICEF prices, according to which the above cost calculations are based.

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NCDD Project Participation in Establishing & Operating the Independent Packaging of ORS

It is evident that the new independent packaging operation for ORS needs comparatively big investment : land; buildings; outer and inner coatings and decorations; electricity ; water ; disposal and sanitary ; fixtures and laboratory furniture ; equipment especially air-conditioners, dehumidifying apparatus, air-filter, and other equipment as detailed in WHO/CDD/SER/80.3 and the most important the two automatic machines, the electric fluid bed drier ...etc.; the prices for the enormous quantities of ingredients to continuously load the 2 automatic machines; precautions and responsibilities and necessity to adopt good manufacturing practice and good laboratory practice and their costs.

It is also evident that the packaging materials are very important and have certain specifications, apart from their enormous amounts to continuously feed the 2 automatic machines.

It may be also necessary to recommend an important equipment to be added to the WHO list : efficient generators to work the 2 automatic machines , the air conditioners, the dehumidifying apparatus, the air filter, and all other electric equipment and apparatus, in case of current from mains is off. From experience, this happens quite often, and it is a problem and reason for many complaints from everybody.

Moreover, from the cost calculations in previous pages, the net profit for the manufacturer, the packaging company, would be only L.E.0.005 which seems to be negligible to the manufacturing company comparative to what the company can realize from other products, and without such tremendous expenditures.

It's therefore recommended that the new operation to be fully financed by the NCDD Project.

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Recommendations

1- A plan is recommended for the packaging of Oral Rehydration Salts, 27.5g for 1 liter solution, to produce 10 million packets per year. Full financing by the NCDD Project is recommended, for the big investment needed for the automatic machines, equipment like air-conditioners, denumidifying apparatus, fluid bed drier electric, generator (additional equipment recommended in this report to guard against frequent failure of electric current from mains), enormous quantities of ingredients and packaging materials; extra costs for necessity of adopting good manufacturing practice and good laboratory practice.

2- Cost calculations showed that the packaging company would have net profit of only L.E.0.005 which is very little compared to what the company could gain from other products which do not need such big investment.

3- Other alternatives are recommended:

a- to increase capacity of production of CID by supplying automatic machine according to their report; to produce 5 million packets/year;

b- to supply all the companies, egyptian and foreign branches, with semi-automatic machines (one for each), to produce collectively 5 million packets;

c- encouragement of preparation of solution of ORS in the pharmacies of Egypt(about 5378);

d- possibility of preparing sterile solution of ORS in 1 liter plastic bottles to be extruded at the moment of filling and sealing; such solution can keep without fungal growth;

4- Quality control report form is recommended;

5- Quality control report recommended includes microbiological tests for limit of colony count, limit of moulds and yeasts, limit of osmophilic yeasts; absence of E.coli (37°C.), according to WHO specifications of Glucose content in ORS. This recommendation is also of importance, as bacterial count may change on storage, extent of change depends on many factors concerned with optimum conditions of temperature, moisture (especially if there are leaks from inefficient sealing), microorganisms originally present (types and numbers..etc.);

6- Quality control report recommended includes determination of heavy metals.

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7-Specifications for Heavy metals in WHO/CDD/SER/80.3 are too high ;
it is recommended in this report to change the specifications from maximum 100 µg/g. to maximum 3.45 µg/g.(not more than 95 µg/ 27.5 g.)
It is recommended to request WHO authorities concerned to change the specifications of Heavy metal Content in ORS to read
NOT MORE THAN 3.45 µg/g. (95 µg/27.5 g.).

8-Good Manufacturing Practice and Good Laboratory Practice:
Premises,Sanitary and Personnel:
WHO/CDD/SER/80.3,Annex 3,page31: 6.Sanitation:
"Smoking is not permitted in manufacturing areas."
It is recommended in this report to specialize area for personnel to eat and drink in the cafeteria,to have toilet facilities and hand washing for MEN and similar separate for WOMEN and a closed separate smokers' corner,for protection of rights of non-smokers.
It is recommended to circulate this addition to authorities concerned with GMP and GLP in WHO;FDA U.S.A.;W.Germany;U.K.and all countries,and Egypt; and generally to all M.O.H.of all countries to protect nonsmokers rights.

9-There are pharmaceutical manufacturing facilities in the Medical Services of the Armed Forces of Egypt; and in some Governorates alover Egypt,which can be made use of for the purposes of the Project.

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