WHO/CDD/SER/80.3

Programme for
CONTROL OF DIARRHOEAL DISEASES

GUIDELINES FOR THE PRODUCTION OF ORAL REHYDRATION SALTS

World Health Organization

WHO also welcomes comments on these guidelines and information on experience in their use or adaptation; these should be addressed to: The Programme Manager, Diarrhoeal Diseases Control Programme, WHO, 1211 Geneva 27, Switzerland.

* * *

ACKNOWLEDGEMENTS

The Appropriate Technology for Health, Diarrhoeal Diseases Control, and Drug Policies and Management units of WHO, and UNICEF are grateful to Mr P. Laude, KBI, Berlin (West); Mr J. Richman, Woodstock, NY, USA; and Mr M. Stork, Benken, Switzerland, for their valuable assistance in the preparation of these guidelines. Acknowledgement is also due to many other experts for their helpful criticisms and comments.

CONTENTS

1. INTRODUCTION

Acute diarrhoeal diseases are one of the leading causes of infant mortality in many developing countries. In most cases, death is caused by dehydration. Such dehydration can be treated simply, effectively, and cheaply in all age groups by giving patients by mouth a glucose-electrolyte solution. This solution can be conveniently prepared as needed by dissolving a pre-packaged mixture of Oral Rehydration Salts (ORS) in an appropriate volume of drinking water.

Oral rehydration therapy combined with guidance on appropriate feeding practices is the basic strategy by which the WHO Programme for Control of Diarrhoeal Diseases (CDD) is trying to achieve an immediate reduction in diarrhoea-related mortality and malnutrition in children.

These guidelines have been prepared to assist national authorities in establishing facilities for the production of packets of ORS of pharmaceutical quality for use as a non-prescription drug for the prevention and treatment of clinical dehydration. Their preparation was recommended by a WHO/UNICEF-sponsored consultation on National Production, Packaging and Distribution of Oral Rehydration Salts (ORS) held in Bangkok in January 1979 and attended by experts from eight developing countries.

These guidelines are a series of examples and suggested approaches that will need to be adapted to suit local needs and conditions. They should be considered as a tool for building up national self-reliance in the supply of ORS within the overall context of national diarrhoeal diseases control activities.

Alternative preparations that have not yet been clinically evaluated, have an incomplete composition of salts, are not within the stated tolerances, or do not meet the standards described for packaging, are not discussed.

1.1 Composition of Oral Rehydration Salts (ORS)

Oral Rehydration Salts (ORS) is the non-proprietary name for a mixture of glucose and salts. This mixture is dissolved in drinking water to make a solution that can be given by mouth to treat clinical dehydration due to diarrhoea. It is considered to meet the criteria of an "essential drug" for developing countries.

The active ingredients in an ORS packet for making one litre of solution are:

Glucose, anhydrous	20.0 g
Sodium chloride	3.5 g
Sodium bicarbonate	2.5 g
Potassium chloride	1.5 g

This formulation has been used successfully to treat dehydration due to acute diarrhoeas, including cholera, in all age groups.

Dissolution of ORS in water yields the following concentrations:

glucose	111 mmol/l
Na^+	90 mmol/l
Cl^-	80 mmol/l
HCO_3^-	30 mmol/l
K^+	20 mmol/l

1.2 Estimating production needs and possibilities

For simplicity only the packet size for making one litre of ORS solution is discussed throughout the Guidelines. While more expensive to produce, smaller packet sizes for making up volumes of Solution such as 200 ml or 700 ml may be more appropriate in countries with differing measuring containers.

The ingredients are usually supplied in containers of 50 kg. In these guidelines batch sizes are based on multiples of one 50 kg container of glucose, i.e., a minimum batch size of 68.8 kg or 2500 packets.

The cost of staff and equipment for decentralized production of ORS to pharmaceutical standard is not considered to be justified below this minimum batch size.

Minimum semi-automatic packaging yields 550 000 packets per year, assuming:

(1) There are 220 working days per year

(5 days per week x 52 weeks = 260

less 10 days factory maintenance

less 30 days holidays)

(2) The production rate is 6 packets per minute

(3) One 68.8 kg batch, or 2500 packets is processed per day

$$\frac{2500}{6 \times 60} = 7 \text{ hours}$$

(4) 2500 x 220 = 550 000

Minimum automatic packaging with the smallest suitable machine currently available yields 4 400 000 packets per year, assuming:

(1) A production rate of 60 packets per minute

(2) A batch size of 137.5 kg, based on 2 x 50 kg of glucose for 5000 packets

(3) The time taken to process one batch is: $\frac{5000}{60 \times 60}$ = 1 hour 23 minutes

(4) Four batches are processed per day: 4 x 5000 x 220 = 4 400 000

Annual production may be varied to accommodate virtually any requirement based on these two formats:

- decrease by operating fewer days or producing other substances as well as ORS;
- increase by adding more machines or by working two or three shifts per day.

Before undertaking the manufacture of ORS packets, it will be necessary to estimate the number of packets that will need to be produced and the level of technology required. Elements to be considered include the capabilities of the existing pharmaceutical industry, the availability of laboratory facilities, the availability of premises and electricity, the availability of a suitable workforce, and climatic conditions. A check-list is attached as Annex 1.

If ORS packets are simply to be purchased, the specifications for ordering and testing should resemble those shown in Annex 2.

2. PREMISES FOR MANUFACTURING ORS

Even if it is possible to accommodate ORS production within the existing facilities, the following basic requirements will need to be satisfied.

General considerations

Refer to Annex 3: "Good Practices in the Manufacture and Quality Control of Drugs", sections 4.1 and 4.2, for general recommendations on premises.

More specific considerations

The space requirements shown in Table 1 are based on production of about 5 million packets per year. A greater or lesser production essentially affects only the floor space needed for rooms 1 and 5.

Rooms 1 to 5 need 3-metre ceilings.

Six separate rooms are required to separate specific operations. Only five rooms are needed if drying is not required, as sifting can be done in a screened-off portion of room 1 or room 3.

Upper limits for temperature and relative humidity are specified for rooms 1 to 4. Air conditioners, or both air conditioners and dehumidifiers may be required if the dehumidifying action of compressor-type air conditioning units is insufficient.

Windows should seal tightly when shut and be closely screened when open. Doors should be self-closing and seal tightly. All areas should have adequate ventilation.

If temperature and humidity control are required, an important energy economy can be made by carefully planning the layout of the rooms so as to minimize the total volume to be controlled.

There should be no water or drains in rooms 1 to 5. Routine cleaning of machines is by vacuum cleaners and the absence of drains eliminates a common source of contamination.

Adequate electric power must be available in the rooms.

TABLE 1. SPACE REQUIREMENTS FOR ORS PRODUCTION

Room Number	Function of Room	Approx. Surface Area (m^2)	Min. Floor Loads (t/m^2)	Min. Ceiling Height (m)	Temp. not to exceed (^oC)	Relative humid. not to exceed (%)
1	Storage of raw material	120	1.0	3	22	60
2	Drying and sifting	50	0.8	3	22	60
3	Weighing and mixing	25	1.5	3	22	60
4	Filling, sealing, packing	30	0.8	3	22	60
5	Quarantine and storage of finished product	60	0.8	3		
6	Quality control laboratory	20	0.25			
	Locker for men) Locker for women) Toilet) Storage for cleaning material)	50				
		355				

3. RAW MATERIALS

The following sections on specifications have two parts for each ingredient: specifications for ordering, and testing when an order is received. Each batch delivered should be sampled. The number of drums or sacks to be sampled is usually calculated by $0.4\sqrt{n}$, where n = the number of containers of any given batch.

The chemical ingredients are delivered in 50-kg sacks or drums by most commercial suppliers. To mix well, the particle size of the ingredients should be in the range of 100 to 400 μm. Foil for packaging usually comes in reels of 1000 m for automatic packaging. For semi-automatic production, pre-printed packets sealed on three sides are available.

When ordering chemicals ensure that each shipment is accompanied by a copy of the manufacturer's test protocols with the quality specification of the product.

In locations with monsoon-type seasons, delivery of the raw materials should be timed to occur in the dry season.

3.1 Costs

Item	Indicative FOB price on international market as of June 1980 (US $)	Cost per 1 000 000 packets (US $)
Glucose, anhydrous	650 per t	13 000
Sodium chloride	400 per t	1 400
Sodium bicarbonate	450 per t	1 125
Potassium chloride	700 per t	1 050
Aerosil *	6.50 per kg	3.25
Packaging material (including printing)	750 per 1000 m^2 (50 000 packets)	15 000
Packing boxes	determine locally	...

The cost of shipping must be added. For example, sea freight from Copenhagen to Karachi is US $ 450 per t.

3.2 Specification: Glucose

Ordering:

Good quality anhydrous food-grade glucose is quite acceptable for ORS. Pharmaceutical grade suitable for parenteral use need be considered only if tax regulations happen to make the "drug" quality cheaper than the "food" grade.

A sample specification is given in Annex 4-A.

* use of this excipient is optional.

Testing:

Each batch of glucose must pass the following tests upon receipt before it can be released for the manufacture of ORS packets:

Description	
Identity	Specific optical rotation
Moisture content	Chlorides
Sulfated ash	Sulfates
Assay	Heavy metals
Acidity	Standard plate count

Test procedures are given in Annex 5-A.

3.3 Specification: Sodium chloride

Ordering:

Pharmaceutical grade sodium chloride should be ordered: IP, USP, NF, BP, EurP, PhUSSR, or equivalent. It should be packed in strong, moisture-proof containers.

A copy of the manufacturer's protocols with the quality specifications of each batch should be provided.

An example is given in Annex 4-B.

Testing:

Upon receipt of each order of sodium chloride, each batch should be verified for:

Description
Identity
Moisture content
Assay

Test procedures are given in Annex 5-B.

3.4 Specification: Sodium bicarbonate

Ordering:

Pharmaceutical grade sodium bicarbonate should be ordered: IP, USP, NF, BP, EurP, PhUSSR, or equivalent. It should be packed in strong, moisture-proof containers.

A copy of the manufacturer's protocols with the quality specifications of each batch should be provided.

An example is given in Annex 4-C.

Testing:

Upon receipt of each order of sodium bicarbonate, each batch should be verified for:

Description
Identity
Moisture content
Assay

Test procedures are given in Annex 5-C.

3.5 Specification: Potassium chloride

Ordering:

Pharmaceutical grade potassium chloride should be ordered: IP, USP, NF, BP, EurP, PhUSSR, or equivalent. It should be packed in strong, moisture-proof containers.

A copy of the manufacturer's protocols with the quality specifications of each batch should be provided.

An example is given in Annex 4-D.

Testing:

Upon receipt of each order of potassium chloride, each batch should be verified for:

Description
Identity
Moisture content
Assay

Test procedures are given in Annex 5-D.

3.6 Specification: Aerosil

The use of Aerosil is optional. Aerosil is a proprietary name for coloidal silicon dioxide. In ORS, 0.02% Aerosil (200 g per 100 kg):

- improves the free-flowing properties of the mixture for easier filling of packets
- takes up residual moisture
- speeds up the dissolving of the mixture.

Aerosil is harmless in this concentration and is widely used in dietetic powders, and pharmaceutical and cosmetic products. It is insoluble and makes the ORS solution very slightly turbid.

Order: by name.

Test for identification on receipt (Annex 5-E).

3.7 Specification: Packaging material

Aluminium foil coated on two sides is recommended for forming hermetically sealed packets to protect the ORS powder from humidity.

Foil is supplied commercially in reels for automatic packaging or as pre-formed packets sealed on three sides for semi-automatic packaging. Pre-formed packets are often available locally. The label is usually printed on foil by the supplier.

The foil must be of good quality with no pin holes and with a coating of uniform thickness for satisfactory packaging. It should be obtained only from reputable suppliers.

Foil must be stored away from direct sunlight, preferably in an ambient temperature not exceeding 25°C, and relative humidity not exceeding 60%. Under these conditions it can be stored for 12 months without deterioration. If not properly stored, the polyethylene layer will dry out and prevent correct sealing.

Ordering:

Foil for forming packets of dimensions approximately 90 mm x 100 mm

inside : polyethylene 50 g/m^2

middle : aluminium 15 μm

outside: polyester 15 g/m^2

Printing on inside of polyester coat.

Always ensure the packaging material is supplied in a format compatible with the packaging machine used.

3.8 Labelling

It is important that ORS packets be presented in an attractive format. Considerable effort should be devoted to designing the packet to encourage people to use ORS. Factors to be considered include:

- colour
- language (written, pictorial)
- layout
- national requirements for drug packaging

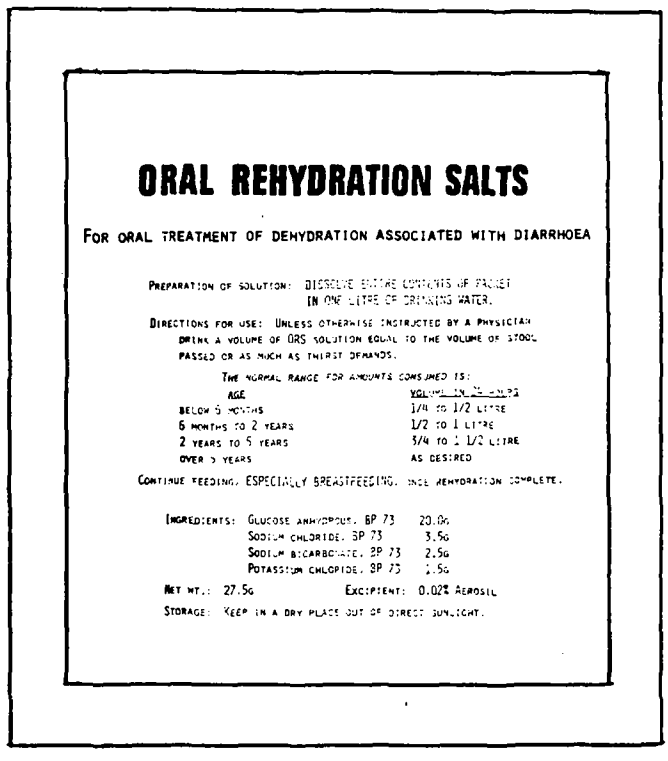
If a more detailed instruction sheet or pamphlet is to be distributed with the packets, the labelling may reflect this by referring to the instruction sheet, or having the same colour scheme or logo.

Minimum information (based on Annex 3, section 9)

1.	Non-proprietary name	Oral Rehydration Salts
2.	Ingredients	Glucose (....) 20.0 g
	(pharmacopoeial standard)	Sodium chloride (....) 3.5 g
		Sodium bicarbonate (....) 2.5 g
		Potassium chloride (....) 1.5 g
		Net weight 27.5 g
		excipient 0.02% Aerosil
3.	Batch number	00 (two digits)
4.	Date of manufacture	month, year (four digits)

5.	Directions for use	"for oral treatment of dehydration. Dissolve entire contents of packet in one litre of drinking water."
6.	Storage conditions	"Store in a dry place out of direct sunlight."
7.	Name of manufacturer	.....

Fig. 1. EXAMPLE OF A LABEL FOR AN ORS PACKET



4. EQUIPMENT

4.1 Production equipment : Itemized costing and power requirements

Item	Remarks	Cost FOB June 1980 (US $)	Power Requirement
* Air conditioner	29 000 BTU	1 500	4.0 kW
* Dehumidifier	Extracts 26 l in 24 h at 25°C and 60% rel. humidity	2 400	1.9 kW
* Dryer, Tray	2.5 m^3, blows 60°C heated air, dries 430 kg in 12 h	18 000	18 kW
* Dryer, Tray	400 l, blows 60°C heated air, dries 80 kg in 12 h	5 000	6 kW
* Dryer, Fluid Bed	All-electric, price of ducting and installation not included, dries 100 kg in 1 h	50 000	100 kW
* Dryer, Fluid Bed	Steam, price of ducting and installation not included, dries 100 kg in 1 h	42 400	7.5 kW 180 kg/h steam
Scale: 100 kg ± 1.0 g	for ingredients	3 500	...
Scale: 20 kg ± 0.1 g	for ingredients		
± Scale: 100 g ± 0.1 g	for process control of packets		
Mixer, 300-litre	plough-type with chopper	21 000	6.0 kW
Drum, 50-litre	Stainless steel (or aluminium) with hermetically sealing lids, 10 required	180 (each)	...
Sifter	Has grating action to break up lumps	3 500	1.5 kW
Vacuum cleaner	Industrial quality	500	0.50 kW
Air compressor	If no other source of compressed air is available	1 000	0.75 kW
Moveable hoist	Or equivalent system for manipulating drums	3 700	...

* Optional

Item	Remarks	Cost FOB June 1980 (US $)	Power Requirement
AUTOMATIC PACKAGING			
Packaging machine	Packet forming, filling, sealing	52 000	4.0 kW
* Voltage stabilizer	-	3 400	...
SEMI-AUTOMATIC PACKAGING			
Doser	Fills packets	8 000	0.5 kW
Sealer	Heat, pressure	1 000	0.8 kW
Imprinter	7-digits, hand-operated, impresses batch number and manufacturing date in edge of packet seal	2 000	...

4.2 Quality control equipment: Itemized costing and list of reagents

List of equipment

Item	Cost FOB June 1980 (US $)
Moisture balance	1 200
Analytical balance	1 100
Flame photometer	800
Polarimeter	2 200
Water bath, controlled temperature	400
Colony counter	300
Incubator	700
Water still, 4 l per h	400
Vacuum desiccator	40
Beakers - 10 each: 100 ml, 250 ml, 500 ml, 1000 ml	1.50 each
Erlenmeyer flasks - 10 each: 100 ml, 250 ml	2.00 each
Comparison tubes - 2 each: 40 and 50 ml marks, 45 and 50 ml marks	2.00 each
Bottles with glass stoppers - 5 each: 250 ml, 500 ml	4.00 each
Pipettes, volumetric - 10 each: 10 ml, 1 ml	1.00 each

* Optional

Item				Cost FOB June 1980 (US $)
Graduated titrating pipettes - 10 each: 50 ml, 10 ml, 5 ml, 1 ml				1.00 each
Bacteriological pipettes - 10 each: 10 ml, 1 ml				1.00 each
Dilution blanks - 10 each: 90 ml				1.00 each
Crucibles, silica - 10 each: 5 ml, 10 ml				1.50 each
Crucibles, nickel - 10 each: 10 ml, 25 ml				3.50 each
Crucible, platinium - 10 ml				500 each
Petri dishes - 30 of about 100 mm diameter				.10 each
Miscellaneous:	rubber stoppers	platinum wire	)	
	rubber tubing	bunsen burner	)	
	glass tubing	test tubes	)	
	wash bottles	filter and paper	)	150.00
	drop bottles	holders	)	
		brushes	)	
		detergent	)	

List of reagents

1. acetic acid (~300 g/1) TS
2. acetic acid (~60g/1) PbTS
3. agar
4. ammonia (~100g/1) TS
5. ammonia (~100g/1) PbTS
6. ammonium molybdate TS
7. barium chloride (0.5 mol/1) VS
8. barium hydroxide (~15 g/1) TS
9. carbon dioxide-free water R
10. carbonate-free sodium hydroxide (0.02 mol/1) VS
11. cupric sulfate R
12. distilled Water
13. hydrochloric acid (~250 g/1) TS
14. hydrochloric acid (1.0 mol/1) VS
15. hydrochloric acid (0.1 mol/1) VS
16. hydrogen sulfide R
17. iodine (0.1 mol/1) VS
18. lead nitrate R
19. methyl orange TS
20. nitric acid (~1000 g/1) TS
21. nitric acid (~130 g/1) TS
22. peptone
23. phenolphthalein/ethanol TS
24. potassium carbonate, anhydrous, R
25. potassium chromate TS
26. potassium sodium tartrate R
27. potassium sulfate (174 mg/1) TS
28. silver nitrate (~40 g/1) TS
29. silver nitrate (0.1 mol/1) VS
30. silver nitrate (0.1 mmol/1) VS
31. sodium carbonate (~50 g/1) TS
32. sodium hydroxide R
33. sodium hydroxide (~80 g/1) TS
34. sodium tetraphenylborate (~30 g/1) TS
35. sodium thiosulfate (0.1 mol/1) VS
36. starch TS

R = reagent
TS = test solution
VS = volumetric solution

37. sulfate-free ethanol (≈750 g/l) TS
38. sulfuric acid (≈1760 g/l) TS
39. sulfuric acid (≈100 g/l) TS

Ordering minimum quantities commercially available, these 39 items would cost about US $ 300.

4.3 General considerations on equipment

Care should be taken to select equipment that:

- is as simple as possible
- is reliable and robust
- can be properly repaired locally
- is compatible with existing equipment, facilities and power sources.

It should be kept in mind that a potential saving on the initial purchase price of a piece of equipment will be very quickly lost if production is slowed down or halted by premature equipment failure or excessively long repair times because the fixed costs of the operation for premises, power and personnel will continue.

Equipment and processes are continually evolving and it is advisable to review what is available on the market before ordering equipment. Both WHO and UNICEF have world-wide purchasing experience which may be called upon.

Due consideration should always be given to buying two small and simple machines to increase production capacity rather than one higher capacity but more complicated machine. With two machines production can still be continued if one breaks down.

4.4 Discussion of equipment

Air conditioners and/or dehumidifiers

These may or may not be required, depending on the climate where the manufacturing plant is located. Satisfactory ORS packets are produced in Europe under contract to UNICEF in plants that have neither.

The power and number of machines required depends on the ambient temperature and the volume of the room.

Note that air conditioners which use compressors also dehumidify to a certain degree.

Dryers: tray, electric-powered; or fluid bed, electric-or steam-powered.

The requirement for and use of dryers should be avoided if possible. Dryers are an additional capital expense; they consume a lot of power; they add one more step to the manufacturing process.

A dryer should not be purchased unless it can be demonstrated that without a dryer the final product is unsatisfactory, for example, if the glucose frequently does not meet the required specifications and there is no alternative source of supply.

IF drying is required at all, the choice of dryer will depend on the amount and frequency of drying. The characteristics of the two types of dryers are compared below:

Fluid bed dryers
- more efficient but much more complicated to run than a tray dryer
- performance: about 100 kg in 40 minutes
- power consumption: 7.5 kW & 180 kg/h steam, or 100 kW all electric
- operating temperature: 40°C to 50°C

Tray dryers
- easier to run, but consume more power, slower than fluid bed dryer
- performance of a 2.5 m^3 unit is 500 kg in 12 hours, blowing air heated to 60°C
- power consumption: 18 kW

Sifter with 1-mm to 3-mm screens

Ingredients can become caked or clumped when sacks have been stacked one on top of another for a certain time, or after drying.

Sifting machines with a grating action are available to rapidly break up clumps that may have formed and ensure homogeneous mixing of the ingredients. Plough-type mixers equipped with a chopper can also break up lumps very effectively.

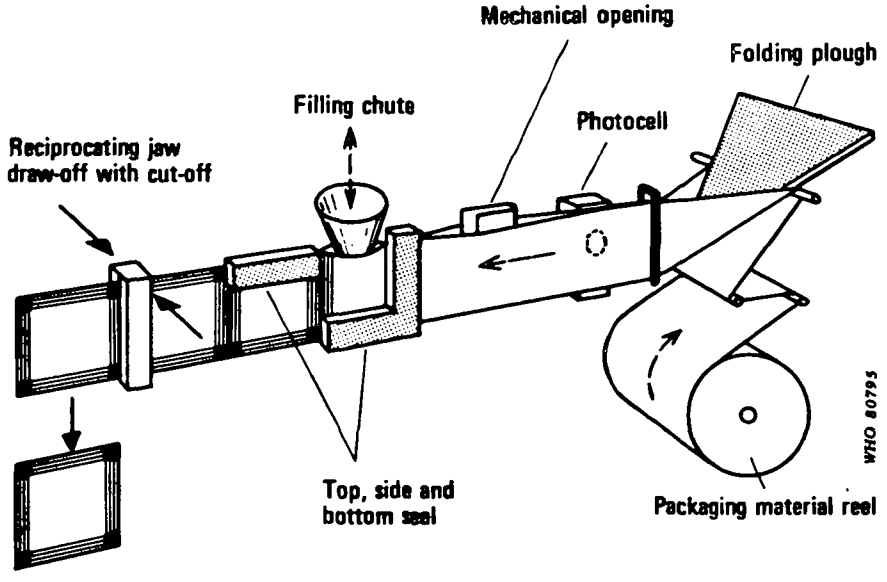
A comminuting machine (for milling or grinding) to obtain a regular particle size should not be required if ingredients are to specification. It is not required for glucose.

Packet forming, filling, sealing

In automatic packaging these three steps are performed by a single machine.

Figure 2 outlines the basic operations of forming the packet from a reel of preprinted foil, filling the packet, then sealing the fourth side and cutting.

Fig. 2 AUTOMATIC PACKAGING MACHINE OPERATION



Experience in Europe has shown that a slide dosing unit is more suitable for ORS packaging than an auger filler.

A voltage stabilizer should be provided if fluctuations exceed ± 15%.

Semi-automatic packaging uses a separate filling machine and sealing machine.

Packets are supplied pre-printed and pre-sealed on three sides. They are placed by hand under the nozzle of the filling machine which dispenses the required dose of powder. Dosing can be foot-actuated or set for a standard interval. The machine may have a slide or auger filler.

Filled packets are passed by hand to a second worker who seals the fourth side with a foot-operated sealer using heat and pressure. Ouput will be be at least 6 packets per minute.

Scales for weighing out ingredients

one of 100-kg capacity and accuracy ± 1.0 g

one of 20-kg capacity and accuracy ± 0.1 g

Mixer

The characteristics of the different types are listed below:

		Mixing time (min)	Capacity (litres)
	plough type with chopper	3-5	300
use only if already available	planetary	20-30	300
	ribbon	20-30	300
	paddle	20-30	300

For semi-automatic packaging, capacity need only be 150 l.

The mixer opening for filling should be covered by a 5-mm sieve. This may need to be specially made.

Mixers should not be loaded beyond 80% of their stated capacity. The ORS mixture has a specific gravity of about 0.6.

Drums for transporting mixture and ingredients

Ten 50-l stainless steel drums with hermetically sealing lids.

These can be fitted with special hoppers equipped with a valve for feeding directly into the dosing/packaging machine.

Hoists, fixed or portable, may be purchased or fabricated locally to facilitate shifting and loading operations, which may otherwise be done by hand.

5. PERSONNEL

The basic number of persons needed for both automatic and semi-automatic packaging is eight:

1 Production supervisor

- takes overall responsibility for quantity and quality of packets produced including:

  ordering of raw materials,

  approving materials for use in production,

  releasing packets for distribution,

  supervising personnel and weighing operations;

- should be a pharmacist (or a pharmacist should be readily available for consultation).

1 Laboratory technician

- responsible for performing all quality control analyses on ingredients

upon receipt and during processing, and on the finished product;

- responsible for proper maintenance of the control laboratory equipment and reordering of equipment, reagents, and chemicals as necessary through the supervisor.

2 Workers

- perform drying, sifting, weighing, mixing and feeding operations.

Automatic operation

1 Operator

- runs the packet forming, filling, sealing machine. Checks packets on ± scale while machine is running and mades adjustments, including dosage and sealing as necessary, and changes foil;

- responsible for routine maintenance of machine; informs supervisor if a repair engineer is required.

3 Workers

- put packets into boxes, and boxes into cartons.

Semi-automatic operation

1 Worker - dosing and filling.

1 Worker - sealing.

1 Worker - impressing the manufacturing date and batch number.

1 Worker - packing into boxes and cartons.

For maintenance of an automatic packaging machine, if an experienced electrician or mechanic is not already available locally, either the operator can be sent to the factory for three months' training or arrangements can be made with the manufacturer to ensure that a technician is always rapidly available from elsewhere in the country or region.

6. PRODUCTION STEPS

The steps in the production of ORS packets are summarized in the flow chart (Fig. 3).

The production steps for each batch are monitored with a Process Control Sheet (Annex 6). This record, the record of the results of the quality testing of each batch, and a sample of the final product are always retained for each batch.

Batch sizes are based on increments of 50 kg of glucose, as explained in the Introduction. Semi-automatic packaging is based on processing one 68.8-kg batch, or 2500 packets per day. Automatic packaging is based on processing four batches of 137.5 kg (5 000 packets) per day for a total daily production of 20 000 packets.

The time lapse between opening the moisture-proof containers in which the dry ingredients are supplied and sealing the mixed ingredients in the packets should be as short as possible to avoid picking up moisture from the air. This is most relevant for the glucose.

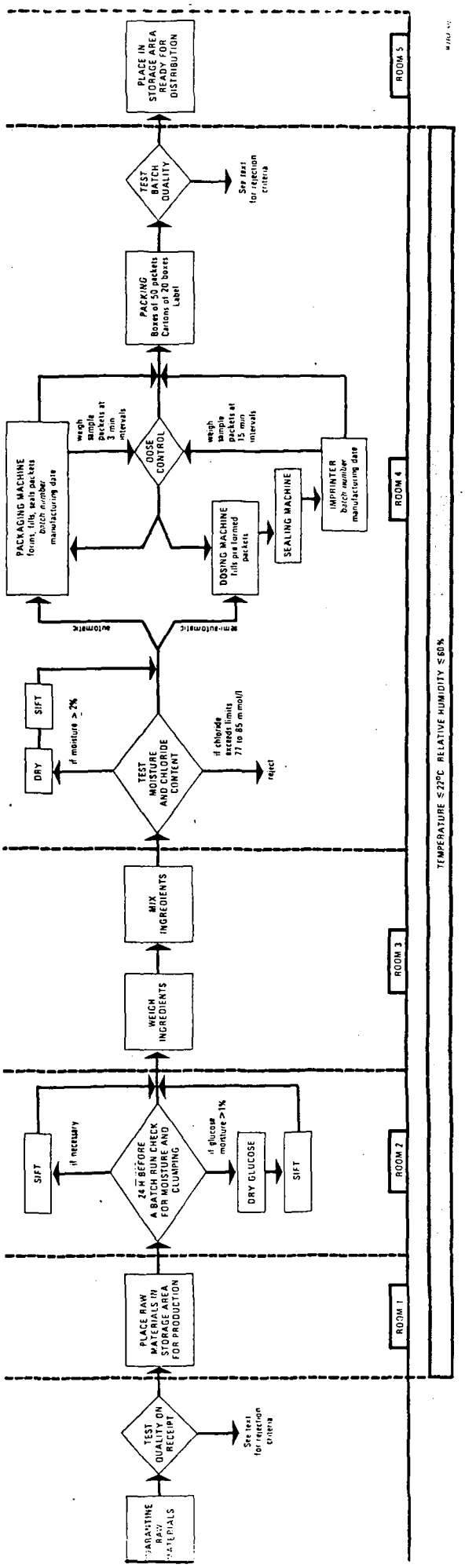


FIG. 3 STEPS IN PRODUCTION OF ORS PACKETS

6.1 Raw materials

These must be verified by the control laboratory for content and purity when first received (see section 3). Separate areas should be clearly marked in the storage room for materials which are quarantined and those which have been tested satisfactorily.

Normal stock rotating practices should be observed.

Twenty-four hours before a batch run, the ingredients should be checked:

- glucose for moisture, using a moisture balance
- salts for clumping

and drying and sifting performed as necessary.

The ingredients should be retained in the production area under controlled temperature and humidity.

The need for a dryer should be avoided, if at all possible, by utilizing good quality ingredients and minimizing the time of their exposure to the air during production. Using Aerosil as an excipient will help to reduce residual moisture. Normally, glucose is the only product requiring this precaution, as it comprises over 70% of the total mixture.

However, should the glucose need to be dried, this may be done overnight (12 h for 500 kg in a tray dryer). The glucose can be sifted, if necessary, and weighed the following morning for immediate processing. Dryers should not be left unattended when operating overnight because of the fire hazard.

6.2 Weighing

Batch sizes are based on increments of 50-kg containers of glucose, giving the proportions:

	Contents one packet	Semi-automatic batch size	Automatic batch size
Glucose, anhydrous	20 g	50.0 kg	100.0 kg
Sodium chloride	3.5 g	8.75 kg	17.50 kg
Sodium bicarbonate	2.5 g	6.25 kg	12.50 kg
Potassium chloride	1.5 g	3.75 kg	7.50 kg
Aerosil	0.0055 g	0.01375 kg	0.0275 kg
	27.5055 g	68.76375 kg	137.52750 kg

For the glucose, it should be possible to establish the normal weight of the containers so that if the gross weight of a full container is within certain limits, its contents can be dumped straight into the mixer.

WEIGHING THE INGREDIENTS CORRECTLY IS THE SINGLE MOST IMPORTANT STEP IN THE PRODUCTION OF ORS

Weighing is done by two persons: one to call out the reading, and one to verify and fill out the Process Control Sheet.

Pre-weighing of Aerosil into appropriate portions may prove useful. This may be done more easily by measuring portions by volume.

6.3 Mixing

Ingredients are weighed and placed directly into the mixer. Mixers should should not be filled to more than 80% of their stated capacity. The exact time for mixing is determined by type of machine and actual experience. A 5-mm sieve on the mouth of the mixer prevents unwanted objects from accidentally falling in.

The mixture is drawn off into the 50-l drums for loading the filling machine. These containers should be marked with the batch number throughout the rest of the process.

6.4 Control of chloride and moisture content

The test of chloride content is a quick and easy in-process check of the mixture. The test procedure is given in Annex 7.

Moisture content is determined with the moisture balance.

6.5 Filling and sealing packets

This is done automatically or semi-automatically. Operating instructions vary according to the equipment actually being used (see also "Equipment", section 4).

The mixture is transferred in drums from the mixer to the hopper of the dosing unit either manually or by a portable hoist or sling. AVOID DUST. Use a cloth skirt around the mouth of the hopper if the drums are not made to be fitted directly on the filling machine.

Too fine a powder causes too much dust and can seriously interfere with the automatic packaging process. A vacuum cleaner as well as compressed air are required. Normally, machines have a dust extraction system.

In automatic packaging, a single machine forms, fills, and seals the packets. Semi-automatic packaging uses separate machines for filling and sealing.

Control of the packet weight approximately every 3 minutes for automatic packaging, or every 15 minutes for semi-automatic packaging, is necessary to maintain the mixture dose within acceptable limits. This control can be accomplished quickly and easily during a production run with a ± scale by first establishing the gross packet weight which corresponds to the specified net weight of 27.5 g. A permanent record is kept of the weights determined for each batch, as shown in Annex 8. Reference to this graph clearly indicates what adjustments to the dosing mechanism of the machine may be necessary.

6.6 Packing

As finished packets come off the line, they can fall directly into boxes or fall on a slide leading to a table or small conveyor belt. They are usually packed by hand in boxes of 50.

Boxes are more conveniently transported when packed into cartons. A practical size of carton contains 20 boxes of 50 packets each for a total of 1000 packets per carton, and weighs about 30 kg.

The cartons should be labelled with: name of product, quantity, manufacturer, batch number, manufacturing date. A standard stencil or rubber stamp can be used and the date and batch number filled in by hand or with a second stamp.

6.7 Control and release of batches

An entire batch run is kept in a separate quarantine area until it has passed the quality control tests (see section 7). When cleared by quality control, the cartons are moved to the storage area ready for distribution. Production records and a box of packets from each batch are retained for at least three years.

7. PRODUCTION QUALITY CONTROL: Criteria for accepting or rejecting a batch

7.1 Sample size

From each batch, a random sample of 10 packets is taken during the course of the batch run by the person responsible for quality control. These can include the packets weighed to regulate the dosage during the batch run.

7.2 Tests

	Limits
Check 10 packets for net weight, labelling, and seal	26.1 g - 28.9 g
Check 1 packet for moisture content	≤ 3%
Check 1 packet for chemical content	
- Glucose, anhydrous	19.0 g - 21.0 g
- Sodium chloride	3.33 g - 3.68 g
- Sodium bicarbonate	2.38 g - 2.63 g
- Potassium chloride	1.35 g - 1.65 g

Test procedures for quality control of finished ORS packets are given in Annex 9.

8. BIBLIOGRAPHY

1. International Commission on Microbiological Specifications for Foods (ICMSF). Micro-organisms in Foods: Their Significance and Methods of Enumeration, Second Edition. University of Toronto Press, Toronto (1978).

2. The International Pharmacopoeia, Third Edition, Volume 1 - General Methods of Analysis. WHO, Geneva (1979).

3. National Formulary XIV. American Pharmaceutical Association, Washington, DC (1975).

4. Report of the WHO/UNICEF Consultation on the National Production, Packaging and Distribution of Oral Rehydration Salts (ORS), Bangkok 23-26 January 1979. Unpublished WHO document ATH/79.1.

5. Specifications for the Quality Control of Pharmaceutical Preparations, Second Edition of the International Pharmacopoeia. WHO, Geneva (1967).

6. Specifications for Reagents Mentioned in the International Pharmacopoeia. WHO, Geneva (1963).

7. WHO Expert Committee on the Selection of Essential Drugs. WHO Technical Report Series No. 645. WHO, Geneva (1979).

8. WHO Expert Committee on Specifications for Pharmaceutical Preparations, Twenty-fifth report, WHO Technical Report Series, No. 567. WHO, Geneva (1975).

These documents and publications form the basis for the Guidelines. It would be useful to manufacturers of ORS to have copies available.

ANNEX 1

CHECKLIST

I. Estimated number of packets to be produced

1. Population to be reached

   1st year
   2nd year
   3rd year
   4th year
   5th year

2. Average number of episodes of diarrhoea per annum

3. ORS production rates projected for first 5 years of production

   1st year
   2nd year
   3rd year
   4th year
   5th year

4. Exportation of packets envisaged

II. Climate

1. Range of daytime temperature at production site by season

2. Range of % relative humidity at production site by season

III. Availability of industrial and laboratory facilities

1. Local pharmaceutical industry

   (a) exists/to be developed

   (b) ORS production to be located where? In same premises?

   (c) Production plant a governmental/commercial/ joint governmental and commercial operation?

2. Laboratory facilities

   (a) available/to be developed

   (b) in same premises as production

   (c) list tests, if any, existing facilities unable to perform

ANNEX 1

IV. Staff (available/trained/need training)

1. Experienced management for supervising manufacture and quality control of ORS
2. Laboratory staff
3. Machine operator
4. Repair technician
5. Workers

V. Electricity (available/to be installed)

(a) voltage - AC or DC

(b) Hz (cycles)

(c) number of phases

(d) number of wires

(e) free capacity in kW

VI. Production equipment (available/needed)

1. Air-conditioning
   (a) temperature $\leq 22^{\circ}C$ maintained at all times
   (b) in all rooms
   (c) capacity
2. Dehumidification
   (a) relative humidity $\leq$ 60% maintained at all times
   (b) in all rooms
   (c) capacity
3. Sifter/strainer
   capacity and specifications
4. Dryer
   capacity and specifications
5. Scales
   capacity and specifications

6. Mixer

   capacity and specifications

7. Automatic or semi-automatic machine(s) for:

   - packet forming
   - dosing and filling
   - sealing

VII. Equipment servicing

Exists/does not exist

If exists, explain how (manufacturer's representative, local workshop, trained staff, etc.)

VIII. Raw materials

	Available locally	Grade	To be imported
Glucose, anhydrous			
Sodium chloride			
Sodium bicarbonate			
Potassium chloride			
Aerosil			
Packaging material (foil in reels or pre-formed packets)			

ANNEX 2

EXAMPLE SPECIFICATIONS FOR ORDERING AND TESTING FINISHED PACKETS OF ORAL REHYDRATION SALTS

Ordering

1. Mixture of glucose and electrolytes, dry, finely powdered, homogeneous, packed in hermetically sealed polyethylene-lined aluminium packets, two-colour printing.

2. Each packet to contain:

Glucose, anhydrous	20.0 g
Sodium chloride	3.5 g
Sodium bicarbonate	2.5 g
Potassium chloride	1.5 g

Aerosil up to 0.02% may be added at the manufacturer's discretion as an excipient.

3. Ingredients must be of recognized pharmaceutical grade and absolutely dry to prevent caking and discolouring during storage. The product must have a shelf life of three years stored in tropical conditions. The per cent residual moisture which the product must not exceed at the time of delivery should be stated.

4. Packet specifications: size about 90 x 100 mm, polyethylene 50 g/m^2 (inside) aluminium 15 μm (middle) polyester 15 g/m^2 (outside). The type of laminate used should be specified.

5. The contents of one packet should be readily soluble in one litre of cold water giving:

	mmol/l
Glucose	111
Na^+	90
Cl^-	80
HCO_3^-	30
K^+	20

6. Packing in boxes of 50 packets and in cartons of up to 20 boxes.

ANNEX 2

Testing

On receipt of a shipment of ORS packets, the following should be tested:

Labelling	should be legible
Seal	no leaks
Net weight	26.1 g to 28.9 g
Moisture	$\leq$ 3.0%
Glucose anhydrous	19.0 g to 21.0 g
NaCl	3.33 g to 3.68 g
$NaHCO_3$	2.38 g to 2.63 g
KCl	1.35 g to 1.65 g
Heavy metals	$\leq$ 100 μg/g
pH of reconstituted solution	7.2 to 8.8

Source: Wld. Hlth. Org. Techn. Rep. Ser., No. 567 (1975)

GOOD PRACTICES IN THE MANUFACTURE AND QUALITY CONTROL OF DRUGS *

1. General considerations

In the manufacture of drugs, overall control is essential to ensure that the consumer receives drugs of high quality. Haphazard operations cannot be permitted in the manufacture of substances that may be necessary to save life or to restore or preserve health.

Difficulties will undoubtedly arise in establishing the necessary criteria for the manufacture of drugs that will meet established specifications and that can, therefore, be used with confidence. Recommended practices for the manufacture of drugs of desired quality are set forth below. Adherence to these practices, complementing the various control tests followed from the beginning to the end of the manufacturing cycle, will contribute substantially to the manufacture of consistently uniform batches of high-quality drugs.

The manufacturer must assume responsibility for the quality of the drugs he produces. He alone can avoid mistakes and prevent mishaps by exercising adequate care in both his manufacturing and control procedures.

The good practices outlined below should be considered as general guides; whenever necessary, they may be adapted to meet individual needs, provided the established standards of drug quality are still achieved.[a] They are intended to apply to the manufacturing processes (including packaging and labelling) used in the production of drugs in their finished dosage forms.

Sometimes it occurs that several firms cooperate in the production (including packing and labelling) of the finished dosage forms of drugs. It may also occur that a finished, packed, and labelled drug is repacked and/or relabelled, giving it a new designation. It should be pointed out that since such procedures constitute part of a manufacturing operation, they should be subject to the relevant requirements of those proposed below.

The requirements set forth herein are intended to apply primarily to preparations for human administration. However, equal attention should be given to quality in the manufacture of veterinary preparations.

2. Definitions

For the purposes of this document, the following definitions are adopted.

Drug. Any substance or mixture of substances that is manufactured, sold, offered for sale, or represented for use in (1) the treatment, mitigation, prevention, or diagnosis of disease, an abnormal physical state, or the symptoms thereof in man or animal; or (2) the restoration, correction, or modification of organic functions in man or animal.

Manufacturing. All operations involved in the production of a drug, including processing, compounding, formulating, filling, packaging, and labelling.

Starting materials. All substances, whether active or inactive or whether they remain unchanged or become altered, that are employed in the manufacture of drugs.

Batch. A quantity of any drug produced during a given cycle of manufacture. The essence of a manufacturing batch is its homogeneity.

Batch number. A designation (in numbers and/or letters) that identifies the batch and that permits the production history of the batch, including all stages of manufacture and control, to be traced and reviewed.

Quarantine. The status of a material that is set apart and that is not available for use until released.

Quality control. All measures designed to ensure the output of uniform batches of drugs that conform to established specifications of identity, strength, purity, and other characteristics.

"Half-finished" product. Any material or mixture of materials that must undergo further manufacture.

3. Personnel

Experts responsible for supervising the manufacture and quality control of drugs should possess the qualifications of scientific education and practical experience required by national legislation. Their education should include

---

* These requirements are a revised version of those published in WHO Official Records, No. 176, 1969, pp. 99–104 (see this report, p. 5).

[a] Additional recommendations specifically applicable to biological products are set forth in a number of sets of Requirements for Biological Substances adopted by the WHO Expert Committee on Biological Standardization and other WHO expert groups and published in the WHO *Technical Report Series*.

For the manufacture of drugs that can be sterilized in their final containers, the requirements given above are considered essential, with the exception of mandatory sterilization of air supplies. The design of areas used for this purpose should preclude the possibility that products intended for sterilization could be mixed with, or taken to be, products already sterilized. This may conveniently be effected by the use of double-ended sterilization apparatus opening into separate and non-communicating areas.

5. Equipment

Manufacturing equipment should be designed, placed, and maintained in such a way as to

(1) be suitable for its intended use ;

(2) facilitate thorough cleaning wherever necessary ;

(3) minimize any contamination of drugs and their containers during manufacture ; and

(4) minimize the risk of confusion or the omission of a processing step such as filtration or sterilization.

Operating conditions within an apparatus used to sterilize products should be monitored by means of recording devices, which should be initially calibrated and checked at approved intervals by approved methods. Suitable standardized microbiological indicators may be used to demonstrate the adequacy of the sterilization process.

Manufacturing equipment and utensils should be thoroughly cleaned and, when necessary, sterilized, and should be maintained in accordance with specific written directions. When indicated, all equipment should be disassembled and thoroughly cleaned, to preclude the carry-over of drug residues from previous operations. Adequate records of such procedures should be maintained.

Equipment used for aseptic filling should be checked at suitable intervals by microbiological methods.[a] Weighing and measuring equipment used in production and quality control should be calibrated and checked at suitable intervals by appropriate methods. Adequate records of such tests should be maintained.

[a] This may be accomplished by conducting normal filling operations using suitable sterile liquid bacteriological media or other media suitable for dry powder filling, as the case may be, taking into consideration the risks of microbiological contamination of the equipment.

6. Sanitation

Manufacturing premises should be maintained in accordance with the sanitary standards issued by the appropriate health authority. They should be clean and free from accumulated waste, orderly, and free from vermin. A written sanitation programme should be available, indicating :

(1) areas to be cleaned, and cleaning intervals ;

(2) cleaning procedures to be followed and, if necessary, equipment and materials to be used for cleaning ; and

(3) personnel assigned to and responsible for cleaning operations.

Eating, smoking, and unhygienic practices should not be permitted in manufacturing areas.

Sufficient clean, well-ventilated toilet facilities, including facilities for hand washing and rooms for changing clothes, should be available near working areas for the use of manufacturing personnel.

7. Starting materials

An inventory should be made of all starting materials to be used at any stage in the manufacture of drugs, and records should be kept of the supplier, the origin (if possible), date of receipt, date of analysis, date of release by the quality control department, and their subsequent use in manufacture.

All such materials must be :

(1) identified, and their containers examined for damage ;

(2) properly stored in quarantine ;

(3) properly sampled by the quality control department ;

(4) tested for compliance with requirements (all materials should be marked to indicate that they are undergoing testing) ; and

(5) released from quarantine by the quality control department by means of written instructions.

Starting materials that are accepted or approved should be properly and conspicuously labelled as such, and should then be transferred, if necessary, to areas designated for the storage of such materials.

All rejected starting materials should be conspicuously identified as such, and should be destroyed or returned to the supplier as soon as possible.

the study of an appropriate combination of (*a*) chemistry (analytical chemistry, biochemistry, etc.); (*b*) chemical engineering; (*c*) microbiology; (*d*) pharmaceutical sciences and technology; (*e*) pharmacology and toxicology; (*f*) physiology and histology; and (*g*) other related sciences. They should also have adequate practical experience in the manufacture and quality control of drugs. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgement, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of drugs.

Such experts should preferably not have any interests outside the manufacturer's organization that (*a*) prevent or restrict their devoting the necessary time to their assigned responsibilities or (*b*) may be considered to entail a conflict of financial interest. Finally, they should be given full authority and the facilities necessary to carry out their duties effectively.

In addition to the experts noted above, an adequate number of technically trained personnel should be available to carry out the manufacturing and quality control operations in accordance with established procedures and specifications. All personnel should be motivated towards the establishment and maintenance of high-quality standards.

4. Premises

4.1 *General*

Drugs should be manufactured, processed, packaged, labelled, and tested in premises that are suitable for these purposes.

In determining the suitability of premises regard should be paid to:

(1) the compatibility of other manufacturing operations that may be carried out in the same or adjacent premises;

(2) the adequacy of the working space, which should allow orderly and logical placement of equipment and materials so as to (*a*) minimize the risk of confusion between different drugs or their components, (*b*) control the possibility of cross-contamination by other drugs or substances, and (*c*) minimize the risk of omission of any manufacturing or control step;

(3) those physical aspects of the premises that could affect the quality and safety of products: buildings should be so designed and constructed as to prevent the entry of animals and insects; interior surfaces (walls, floors and ceilings) should be smooth and free from cracks, should not shed particulate matter, and should permit easy cleaning and if necessary disinfection;

(4) lighting, heating and ventilation and, if necessary, air conditioning required to maintain a satisfactory temperature and relative humidity that will not adversely affect the drug during manufacture and storage, nor the accuracy and functioning of laboratory instruments.

4.2 *Storage areas*

The suitability of storage areas cannot be strictly specified in a manner that meets all possible contingencies. However, the following principles should be observed:

(1) storage areas should provide adequate space, suitable lighting, and should be arranged and equipped to allow dry, clean, and orderly placement of stored materials and products, whenever necessary under controlled conditions of temperature and humidity;

(2) such areas should provide for suitable and effective separation of quarantined and other materials and products;

(3) special and segregated areas should be available for storage of

(*a*) substances presenting special risks of fire and explosion;

(*b*) highly toxic, narcotic, and other dangerous drugs (these areas should be adequately protected against theft);

(*c*) rejected and recalled materials and products.

4.3 *Special*

For special purposes, such as the manufacture of drugs that are intended to be sterile but cannot be sterilized in their final containers, separate enclosed areas, specifically designed for the purpose, should be provided. These areas should be entered through an air-lock and should be essentially dust-free and ventilated with an air supply through bacteria-retaining filters giving a pressure higher than in adjacent areas. Such filters should be checked for performance on installation and periodically thereafter. All surfaces in manufacturing areas should be designed to facilitate cleaning and disinfection.

Routine microbe counts of the air in the areas described above should be carried out before and during manufacturing operations. The results of such counts should be checked against established standards, and adequate records of the counts should be maintained.

8. Manufacturing operations

Manufacturing operations and controls should be carried out under the supervision of experts, as specified in section 3.

8.1 *Cleanliness*

Before any manufacturing operation is begun, a check should be made to ensure that all apparatus and equipment to be used in the operation has been cleaned and/or sterilized (see section 5).

8.2 *Equipment and containers*

The contents of all vessels and containers used in manufacture and storage between manufacturing stages must be identified by conspicuously placed and clearly legible labels, bearing the name and/or identification code of the processed materials and the necessary batch identification data. Similar labels should be attached to mechanical manufacturing equipment during its operation.

8.3 *Precautions against contamination and confusion (mix-up)*

All manufacturing operations should be confined to separate areas intended for such purposes, with complete equipment used exclusively in those areas, or measures should be taken to ensure that neither cross-contamination nor confusion (mix-up) can occur.[a]

In manufacturing areas, clean working garments should be worn over, or in place of, street clothing.

The manufacture of drugs intended to be sterile should be performed in areas specially designed and constructed, as indicated in section 4.3. Whenever the different operations are not physically separated, and there is a possibility that unsterilized and sterilized products might be confused, all containers of batches of products for sterilization should bear a clear indication of whether or not their contents have been sterilized.

Products that undergo sterile operations should be protected from contamination by using methods such as laminar-flow techniques, and by ensuring that personnel wear clean, sterile gowns, head coverings, masks, rubber gloves, and shoe coverings. Before dressing and entering sterile areas, personnel must wash their hands with a suitable disinfectant.

All dust-producing operations involving highly potent substances, particularly antibiotics, should be conducted in confined areas that are provided with adequate exhaust systems or that are maintained under appropriate pressure, so as to prevent cross-contamination. Adequate precautions should be taken to prevent the recirculation of contaminated air.

[a] The simultaneous manufacture, in adjacent areas that are not physically separated, of drugs that are similar in appearance should be avoided.

8.4 *Manufacturing personnel*

No person known to be affected with a disease in a communicable form, or to be the carrier of such a disease, and no person with open lesions on the exposed surface of the body, should be engaged in the manufacture of drugs. Manufacturing personnel should undergo periodic health checks. In order to prevent any impairment of health caused by the handling of hazardous or potent materials, manufacturing personnel should, whenever necessary, wear protective clothing, shoes, headgear, dust masks, etc., and such protective clothing should remain in the area in which it is used. In some instances, it may be necessary to have restrictions on the movement of personnel to and/or from special working areas.

8.5 *Documents relating to manufacturing procedures*

Documents[a] relating to manufacturing procedures should be prepared for each drug under the direct supervision of experts (see section 3) who have the necessary authority. They should contain at least the following information for each drug:

(1) its name and dosage form;

(2) a description or identification of the final container(s), packaging material(s), and labels and, where applicable, of the closure(s) to be used;

(3) the identity, quantity, and quality of each starting material to be used, irrespective of whether or not it appears in the finished drug (the permissible excess ("overage") that may be included in a formulated batch should be indicated);

(4) the theoretical yields to be expected from the formulation at different stages of manufacture and the permissible yield limits;

(5) detailed instructions for, and precautions to be taken in, manufacture and storage of the drug and of "half-finished" products; and

[a] Such documents should not be handwritten nor contain handwritten amendments or comments. When necessary they should be rewritten and all outdated instructions withdrawn, to avoid the possibility of re-use. They should be suitable for copying in a manner that avoids any possibility of a transcription error.

(6) a description of all necessary quality control tests and analyses to be carried out during each stage of manufacture, including the designation of persons or departments responsible for or charged with the execution of such tests and analyses.

8.6 *Batch manufacturing records*

Manufacturing records must provide a complete account of the manufacturing history of each batch of a drug, showing that it has been manufactured, tested, and analysed in accordance with the manufacturing procedures and written instructions described in section 8.5. A separate batch manufacturing record should be prepared for each batch of drug produced, and should include the following information :

(1) name and dosage form ;

(2) date of manufacture ;

(3) batch identification ;

(4) complete formulation of the batch (see section 8.5, point 3) ;

(5) the batch number (or analytical control number) of each component used in the formulation ;

(6) the actual yield obtained at different stages of manufacture of the batch as compared with the theoretical yield (see section 8.5, point 4) ;

(7) a duly signed record of each step followed, precautions taken, and special observations made throughout the manufacture of the batch ;

(8) a record of all in-process controls followed and of the results obtained ;

(9) a specimen of the actual coded label used ;

(10) identification of packaging materials, containers, and, where applicable, closures used ;

(11) signature of the expert responsible for the manufacturing operations, and the date of his signature ;

(12) an analytical report showing whether the batch complies with the prescribed specifications for the drug, dated and duly signed by the responsible expert ;

(13) a record of the decision regarding the release or rejection of the batch by the quality control department (see section 10.1(5)) ; and

(14) if the batch is rejected, a record of its disposal or utilization.

8.7 *Maintenance of batch manufacturing records*

For reference purposes, all batch manufacturing records should be retained for a specified period.

9. Labelling and packaging

Labelling and packaging materials, including leaflets, should be stored and handled in such a way as to ensure that labels, packaging materials and leaflets relating to different products do not become intermixed. Access to such materials should be restricted to authorized personnel.

Prior to packaging and labelling of a given batch of a drug, the manufacturing and control records specified in section 8.6 should show that the batch has been duly tested, approved, and released by the responsible quality control expert. Prior to being issued, all labels for containers, cartons, and boxes and all circulars, inserts, leaflets, etc., should be examined and released as satisfactory for use by the designated person(s) (see section 10.1(4)).

To prevent packaging and labelling errors, a known number of labelling and packaging units should be issued and, if required, coded. Such issuance should be made against a written, signed request that indicates the quantity and types required.

Upon completion of the packaging and labelling operation, a comparison should be made between the number of labelling and packaging units issued and the number of items labelled and packaged plus the number of units not used. All coded unused units should be destroyed. Any significant or unusual discrepancy in the numbers should be carefully investigated.

All finished drugs should be identified by labelling that should bear, clearly indicated, at least the following information :

(1) the name of the drug ;

(2) a list of the active ingredients, showing the amount of each present, and a statement of the net contents, e.g., number of dosage units, weight or volume ;

(3) the batch number assigned by the manufacturer ;

(4) the expiry date, if required (see 10.1 (8)) ;

(5) any special storage conditions or handling precautions that may be necessary ;

(6) directions for use, and warnings and precautions that may be necessary ; and

(7) the name and address of the manufacturer or the person responsible for placing the drug on the market.

10. The quality control system

10.1 *Quality control department*

Every manufacturing establishment must have a quality control department supervised by a suitably qualified expert directly responsible to management but independent of other departments. The quality control department should control all starting materials, monitor the quality aspects of manufacturing operations, and control the quality and stability of drugs.

The quality control department should have the following principal duties:

(1) to prepare detailed instructions, in writing, for carrying out each test and analysis;

(2) to release or reject each batch of starting material;

(3) to release or reject " half-finished " products, if necessary;

(4) to release or reject packaging and labelling materials and the final containers in which drugs are to be placed;

(5) to release or reject each batch of finished drug that is ready for distribution;

(6) to evaluate the adequacy of the conditions under which starting materials, " half-finished " products, and finished drugs are stored;

(7) to evaluate the quality and stability of finished drugs and, when necessary, of starting materials and " half-finished " products;

(8) to establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions;

(9) to establish, and when necessary revise, control procedures and specifications; and

(10) to be responsible for the examination of returned drugs, to determine whether such drugs should be released, reprocessed, or destroyed. Adequate records of the disposition of such drugs should be maintained.

In order to fulfil its responsibilities, the quality control department should take samples (e.g., of starting materials and finished drugs), according to established procedures. The samples should be properly labelled, and portions should be kept for future reference.

The quality control department should maintain adequate analytical records concerning the examination of all samples taken. Such records should include:

(*a*) the result of every test performed, including observations and calculations, relating to compliance with the established specifications;

(*b*) the source of the specifications used;

(*c*) the signature(s) of the person(s) who performed the quality control procedures; and

(*d*) a final review, the decision taken, and a dated endorsement by a duly authorized expert.

10.2 *Quality control laboratory*

The quality control department should have a laboratory available to it. The laboratory should:

(1) be adequately staffed and fully equipped for performing all quality control tests and analyses required during and after manufacture;[a]

(2) be supervised by a qualified expert (see section 3).

11. Self-inspection

In order to maintain strict adherence to all manufacturing procedures and prescribed controls, it may be advisable for a firm to designate an expert or a team of experts to conduct regularly scheduled inspections of its overall manufacturing and control operations. However, this should not be taken to mean that any firm that exercises self-inspection should be exempt from the official inspections required by the laws and regulations of the country in which it is located.

12. Distribution records

Adequate records should be maintained of the distribution of a finished batch of a drug in order to facilitate prompt and complete recall of the batch if necessary.

---

[a] If animal tests are necessary, the animals should be given adequate quarters and care (for further information, see WHO Technical Report Series, No. 323, 1966, pp. 14, 16). The use of outside independent laboratories may be advisable for specialized and complex analytical and biological procedures that require the use of costly equipment and that can be performed only by technicians with specialized training. Such laboratories should be adequately staffed and fully equipped to perform such analyses.

ANNEX 4-A

EXAMPLE

ORDER SPECIFICATIONS:

GLUCOSE ANHYDROUS ORAL QUALITY

White crystalline powder; odourless; sweet taste

Moisture content	$\leq$ 1.0%
Sulfated ash	$\leq$ 0.1%
Assay	$\geq$ 99.9%
Acidity	$\leq$ 0.50 ml sodium hydroxide (0.1 ~ mol/l)VS for 5-g sample
Specific optical rotation	$[\alpha]_D^{20^\circ C}$ = +52.5° to +53.0°
Chlorides	$\leq$ 200 µg/g
Sulfates	$\leq$ 200 µg/g
Heavy metals	$\leq$ 1 µg/g
Microbiological conditions	
Standard plate count	$\leq$ 200/g
Moulds and yeasts	$\leq$ 10/g
Osmophilic yeasts	$\leq$ 20/g
E. coli (37°C)	negative/g
Packing	Polyethylene coated paper bags of 50 kg net

ANNEX 4-B

EXAMPLE

ORDER SPECIFICATIONS:

SODIUM CHLORIDE R

NaCl Mol.Wt. 58.44

Colourless, odourless, crystals or a white powder

Moisture content	≤ 1.0%
Assay	NaCl ≥ 99.0%
Insoluble matter	≤ 50 µg/g
Acidity and alkalinity	pH 8.2 to 10.0
Chlorate and nitrate	ClO_3 ≤ 10 µg/g
	NO_3 ≤ 30 µg/g
Phosphate	≤ 5 µg/g
Sulfate	≤ 30 µg/g
Ammonium	≤ 10 µg/g
Barium	≤ 10 µg/g
Calcium and magnesium	≤ 50 µg/g
Heavy metals	≤ 10 µg/g
Iron	≤ 5 µg/g
Potassium	≤ 100 µg/g

ANNEX 4-C

EXAMPLE

ORDER SPECIFICATIONS:

SODIUM BICARBONATE R

$NaHCO_3$ Mol. Wt. 84.01

White, crystalline powder

Moisture content	≤ 1.0%
Assay	$NaHCO_3$ ≥ 99.0%
Insoluble matter	≤ 150 µg/g
Chloride	≤ 50 µg/g
Phosphate	≤ 10 µg/g
Sulfate	≤ 50 µg/g
Ammonium	≤ 5 µg/g
Calcium and magnesium	≤ 100 µg/g
Heavy metals	≤ 10 µg/g
Iron	≤ 10 µg/g

ANNEX 4-D

EXAMPLE

ORDER SPECIFICATIONS

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 matter	≤ 50 µg/g
Acidity and alkalinity	pH 8.2 to 10.0
Nitrate	≤ 30 µg/g
Sulfate	≤ 30 µg/g
Ammonium	≤ 10 µg/g
Barium	≤ 30 µg/g
Calcium and magnesium	≤ 50 µg/g
Heavy metals	≤ 10 µg/g
Iron	≤ 5 µg/g
Sodium	≤ 200 µg/g

ANNEX 5-A

TEST PROCEDURES: GLUCOSE ANHYDROUS ORAL QUALITY

Description	Acidity	Heavy metals
Identification	Specific optical rotation	Standard plate count
Moisture content	Chlorides	
Sulfated ash	Sulfates	
Assay		

1. Description

Colourless crystals or a white, crystalline or granular powder

2. Identification

(1) Heat a small amount. Glucose melts, swells up, and burns giving off an odour of burnt sugar.

(2) (a) Dissolve 0.10 g in 2 ml water

(b) Add 2 drops to 5 ml of hot potassio-cupric tartrate TS solution

(c) A copious, red precipitate should be produced.

Potassio-cupric Tartrate TS

(1) Dissolve 7 g cupric sulfate R in water and make up to 100 ml.

(2) In a separate flask, dissolve 35 g potassium sodium tartrate R and 10 g sodium hydroxide R in water and make up to 100 ml.

(3) Mix equal volumes of 1 and 2 shortly before use.

3. Moisture ($\leq$ 1%)

(1) Tare a crucible. (W_1)

(2) Weigh accurately the crucible with 1-2 g of sample. (W_2)

(3) Dry at 80°C for 2 hours then let cool to room temperature in a desiccator.

(4) Reweigh crucible and sample. (W_3)

(5) Calculate:

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

Note: Some of the dried sample may be used for the Assay.

ANNEX 5-A

4. Sulfated ash (≤0.1%)

(1) Tare a crucible. (W_1)

(2) Weigh accurately about 1 g of the sample and the crucible. (W_2)

(3) Moisten with concentrated sulfuric acid (≈1760 g/l) TS, heat gently to remove excess acid, ignite at about 800°C until all black particles have disappeared.

(4) Again moisten with concentrated sulfuric acid (≈1760 g/l) TS and re-ignite.

(5) Add a small amount of ammonium carbonate R and ignite to constant weight. (W_3)

(6) Calculate:

$$\frac{(W_2 - W_3) \times 100}{(W_2 - W_1)} = \% \text{ sulfated ash}$$

5. Assay (≥ 99.9% $C_6H_{12}O_6$)

(1) Weigh accurately about 100 mg of dried sample (sample can be used from moisture test). (W_1)

(2) Dissolve sample in 50 ml of water in a glass-stoppered flask, add 25.0 ml of iodine (0.1 mol/l) VS and 10 ml of sodium carbonate (≈50 g/l) TS.

(3) Allow solution to stand in darkness for 20 minutes.

(4) Add 15 ml sulfuric acid (≈100 g/l) TS.

(5) Titrate with sodium thiosulfate (0.1 mol/l) VS, using starch TS as indicator. (ml_1)

(6) Calculate:

$$\frac{9.008 \times ml_1 \times 100}{W_1} = \% \ C_6H_{12}O_6$$

6. Acidity (≤0.50 ml of titrant)

(1) Dissolve 5.0 g of sample in 50 ml of carbon dioxide-free water R.

(2) Titrate with carbonate-free NaOH (0.02 mol/l) VS, using phenolphthalein/ethanol TS indicator.

(3) Not more than 0.5 ml of titrant should reach the midpoint of the indicator (pink).

7. Specific optical rotation ($[\alpha]_D^{20°C}$ = +52.5° to + 53.0°)

Polarimeters *are used to measure specific optical rotation. They are generally accurate to 0.05° of angular rotation and commercial instruments for visual measurement normally use sodium light or a mercury-vapour lamp. The manufacturer's instructions relating to a suitable light source should be followed.*

The discussion on specifications herein deals with a sodium D line light source with wavelength value 589.3 nm.

ANNEX 5-A

$[\alpha]_D^{20^\circ}$ - *is angular rotation at 20°C using sodium D line light*

$+52.5^\circ$ - *is dextro-rotation of 52.5° or rotation of polarized light clockwise when looking towards the light source.*

General considerations for accurate measurements

The optical elements of the instrument must be brilliantly clean and in exact alignment. The match point should lie close to the normal zero mark. The light source should be rigidly set and well aligned with respect to the optical bench. It should be supplemented by a filtering system capable of transmitting light of a sufficiently monochromatic nature. Precision polarimeters are generally designed to accommodate interchangeable discs to isolate the D line from sodium light or the 546.1 nm line from the mercury spectrum. With polarimeters not thus designed, cells containing suitably coloured liquids may be employed as filters.

Observations should be accurate and reproducible to the extent that differences between replicates, or between observed and true value of rotation (the latter value having been established by calibration of the polarimeter scale with suitable standards), shall not exceed one-fourth of the range specified for the rotation of the substance being tested.

Polarimeter tubes should be filled carefully to avoid creating or leaving air bubbles which interfere with the passage of the beam of light. Interference from bubbles is minimized with tubes in which the bore is expanded at one end.

In closing tubes having removable end-plates fitted with gaskets and caps, the latter should be tightened only enough to ensure a leak-proof seal between the end-plate and the body of the tube. Excessive pressure on the end-plate may set up strains that result in interference with the measurement.

Procedure

Test solution

(1) Dissolve 100 g of dried (80°C for 2 h) sample in about 50 ml of water in a volumetric flask, add 0.20 ml of ammonia (~100 g/l) TS and make up to 100 ml with water, bringing the meniscus close to but still below the mark and adjust the temperature to 20°C by suspending the flask in a constant temperature bath for 30 minutes. Add water to bring up to 100-ml mark.

Blank solution

(2) Take 0.20 ml of ammonia (~100 g/l) TS and make up almost to 100 ml with water as in (1), place in a 20°C bath for 30 minutes, then bring up to mark.

Measurements

(3) Take 6 readings of the observed rotation of the test solution, half the measurements clockwise and other half counter-clockwise. Average the readings.

(4) Repeat procedure in (3) for the blank solution.

(5) Make the zero correction by subtracting the average of the blank readings from the average test solution if the two figures are of the same sign or by adding if they are opposite in sign to get the corrected observed rotation (a).

(6) Calculate:

$$\text{specific rotation} = \frac{10\,000a}{lc} = \frac{10\,000a}{1 \times 10.0}$$

a = corrected observed rotation

l = length of solution traversed by light in mm

c = no. of grams of sample in 100 ml of solution.

8. Chlorides ($\leq 200\,\mu g/g$)

(1) Weigh 10.0 g of sample and dissolve in 30 ml of water in a 100-ml Erlenmeyer flask.

(2) Using about 0.5 ml potassium chromate TS as indicator, titrate with silver nitrate (0.01 mol/l) VS.

No more than 5.64 ml should be required to reach the end point.

(3) Calculate amount of chloride present:

ml of titer x 35.45 = $\mu g/g$.

Silver nitrate (0.1 mol/l) VS. Silver nitrate R, dissolved in water to contain 16.99 g of $AgNO_3$ in 1000 ml.

Method of standardization. Ascertain the exact concentration of 0.1 mol/l solution.

(1) Dilute 40.0 ml of the silver nitrate solution with 100 ml of water.

(2) Heat the solution and add slowly, with continuous stirring, hydrochloric acid (~ 70 g/l) TS until precipitation of the silver is complete.

(3) Boil the mixture cautiously for about 5 minutes, then allow it to stand in the dark until the precipitate has settled and the supernatant liquid has become clear.

(4) Transfer the precipitate completely to a tared filtering crucible and wash it with small portions of water that is slightly acidified with nitric acid (~1000 g/l) TS.

(5) Dry the precipitate to constant weight at 110°C.

ANNEX 5-A

(6) From the weight of silver chloride calculate the molarity of the silver nitrate solution.

Protect the silver chloride from light as much as possible during the determination.

To prepare 0.01 mol/l solution, place a 10-ml aliquot of silver nitrate (0.1 mol/l) VS in a graduated flask and make up to 100 ml with water.

9. Sulfates (≤200 µg/g).

This limit test compares the turbidity of the test solution against a standard solution containing 480 µg of SO_4^{--} more than the standard barium sulfate suspension.

The test is carried out in matched flat-bottomed comparison tubes of transparent glass of about 70-ml capacity and about 23-mm internal diameter, bearing 45-ml and 50-ml marks. Nessler cylinders complying with the above dimensions are suitable.

Test Solution

(1) Dissolve 2.5 g of sample in a comparison tube with 25 ml of water.

(2) Make up to 45 ml with water, add 5.0 ml of barium sulfate suspension TS, stir immediately with a glass rod and let stand for 10 minutes.

Standard solution

(1) Measure 1.0 ml of sulfuric acid (0.005 mol/l) VS and 3 ml hydrochloric acid (~ 70g/l) TS into a comparison tube.

(2) Dilute to 45 ml with water, add 5 ml of barium sulfate suspension TS, stir immediately and let stand for 10 minutes.

Comparison

(1) The turbidity produced in the test solution should not be greater than the turbidity of the standard solution when viewed down the vertical axis of the comparison tube in diffused light against a black background.

Barium sulfate suspension TS - Note: must be freshly prepared.

Mix 15 ml of barium chloride (0.5 mol/l) VS with 55 ml of water and 20 ml of sulfate-free ethanol (~750 g/l) TS. Add 5 ml of potassium sulfate (174 mg/l) TS, and make up to 100 ml with water.

ANNEX 5-A

10. Limit Test for Heavy Metals ($\leq 1 \mu g/g$)

The limit test determines if the content of metallic impurities coloured by hydrogen sulfide in the test solution exceeds the heavy metals limit specifications in terms of micrograms of lead per gram.

The reaction with hydrogen sulfide is carried out by mixing a test solution with freshly prepared hydrogen sulfide TS. The colour obtained is compared in suitable comparison tubes to the colour produced by a standard lead solution.

The test is carried out in matched flat-bottom comparison tubes of transparent glass of about 70-ml capacity and about 23-mm internal diameter, bearing 40-ml and 50-ml marks. Nessler cylinders complying with the above dimensions are suitable. For mixing the solutions use a stirring rod, preferably with a loop on the lower end.

Standard solution

(1) In a comparison tube, dilute 1 ml of freshly prepared solution lead, dilute PbTS with 25 ml water, adjust pH to 3-4, with acetic acid (~60 g/l) PbTS or ammonia (~100 g/l) PbTS, dilute to 40 ml with water, and mix.

Test solution

(1) In a comparison tube dissolve 10.0 g glucose in 25 ml water, adjust pH to 3-4 with acetic acid (~60 g/l) PbTS or ammonia (~100 g/l) PbTS, dilute to 40 ml with water, and mix.

Colour development and measurement

(1) To each comparison tube, add 10 ml of freshly prepared hydrogen sulfide TS, mix and allow to stand for 5 minutes.

(2) 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.

Lead, strong PbTS:

Dissolve 0.1598 g of lead nitrate R in 5 ml nitric acid (~1000 g/l) TS and sufficient water to produce 1000 ml.

Lead, dilute, PbTS:

Dilute 10 ml of lead, strong, PbTS with sufficient water to produce 100 ml. This solution must be freshly prepared from lead, strong PbTS. One ml contains 10 µg lead.

Hydrogen sulfide TS:

A saturated solution of hydrogen sulfide R in cold water. Must be freshly prepared.

ANNEX 5-A

11. Standard Plate Count (≤ 200/g)

This Standard Plate Count procedure is recommended for samples where the count of aerobic mesophilic organisms is less than 3000/g.

Apparatus and materials:

Petri dishes

1-ml and 10-ml bacteriological pipettes

90-ml dilution blanks

Water bath or air incubator for tempering agar, 44-46°C

Incubator, 29-31°C

Colony counter (Quebec dark field model or euqivalent)

Plate Count Agar (Standard Methods Agar; Medium 92)

Procedure

(1) Weigh 50.0 g of sample and dissolve in 100 ml of Peptone Dilution Fluid (0.1% peptone in distilled water). This provides a dilution of .33.

(2) Measure 10 ml of .33 dilution into a 90-ml dilution blank. Shake vigorously 25 times in a 30-cm arc. This provides a dilution of .033.

(3) Repeat (2) with .033 dilution to provide a .0033 dilution.

(4) To duplicate sets of Petri dishes, pipette 1-ml aliquots from .33, .033, and .0033 dilutions.

(5) Melt Plate Count Agar in flowing steam or boiling water, but do not expose it to such 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.

(6) Immediately mix aliquots with the agar medium by tilting and rotating the Petri dishes. A satisfactory sequence of steps is as follows: (a) tilt dish to and fro 5 times in one direction, (b) rotate it clockwise 5 times, (c) tilt it to and from again 5 times in a direction at right angles to that used the first time, and (d) rotate it counter-clockwise 5 times.

(7) As a sterility check, pour one or several plates with uninoculated agar medium and with uninoculated diluent. After incubation, the number of colonies on these plates should not be enough to distort the count by more than one unit in the second significant figure.

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

(9) Compute Standard Plate Count (SPC):

(a) Select two plates corresponding to one dilution and showing between 30 and 300 colonies per plate. Count all colonies on each plate using the colony counter and tally register. Take the arithmetic average of the two counts and multiply by the dilution factor (i.e., the reciprocal of the dilution used: 3, 30, 300) to get the SPC.

(b) Both plates should be counted even if one of them should give a count of fewer than 30 or more than 300. Again, take the average of the two counts and multiply by the dilution factor and report the resulting number as the SPC.

(c) If plates from two consecutive decimal dilutions fall into the countable range of 30-300 colonies, compute the Standard Plate Count for each of the dilutions as directed above and report the average of the two values obtained, unless the higher computed count is more than twice the lower one, in which case report the lower computed count as the Standard Plate Count.

Note: The specification is SPC ≤ 200/g. This corresponds to a count of 67 colonies on the .33 dilution plates.

ANNEX 5-B

TEST PROCEDURES: SODIUM CHLORIDE

Description

Identification

Moisture content

Assay

1. Description

Colourless, odourless crystals or a white powder; salty taste.

2. Identification

Sodium: (1) Moisten a small quantity of the sample with hydrochloric acid (~250 g/l) TS.

(2) Dip a loop of platinum wire in the solution and place in the flame of a bunsen burner.

(3) Sodium compounds produce an intense yellow colour.

Chloride: (1) Dissolve 1 g of sample in 10 ml of water. Acidify with 1 ml nitric acid (~ 130 g/l) TS.

(2) Slowly add silver nitrate (40 g/l) TS. A white curdy precipitate is produced.

(3) Collect some precipitate by filtering and divide in two. The precipitate is soluble in ammonia (~100 g/l) TS and practically insoluble in nitric acid (~1000 g/l) TS.

3. Moisture content ($\leq$ 1.0%)

(1) Tare a crucible. (W_1)

(2) Accurately weigh the crucible with about 2 g of sample. (W_2)

(3) Dry to constant weight at 130°C in the crucible. (W_3)

(4) Calculate:

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

4. Assay (NaCl $\geq$ 99.0%)

(1) Accurately weigh about 0.25 g of dried sample (W_1)

(2) Titrate with silver nitrate (0.1 mol/l) VS using potassium chromate TS as indicator (ml_1)

(3) Calculate:

$$\frac{ml_1 \times 0.5844}{W_1} = \% \text{ NaCl}$$

ANNEX 5-C

TEST PROCEDURES: SODIUM BICARBONATE

Description

Identification

Moisture content

Assay

1. Description

White crystalline powder.

2. Identification

Sodium: (1) Moisten a small quantity of the sample with hydrochloric acid (~250 g/l) TS.

(2) Dip a loop of platinum wire in the solution and place in the flame of a bunsen burner.

(3) Sodium compounds produce an intense yellow colour.

Carbonate: (1) Place about 0.1 g of sample in a test tube.

(2) Add 2 ml of water then 1 ml of acetic acid (~300 g/l) TS.

(3) Quickly close the tube with a stopper fitted with a tube bent at two right angles.

(4) Heat gently and collect the gas in 5 ml of freshly prepared barium hydroxide (~15 g/l) TS.

(5) Bicarbonates produce a white precipitate that dissolves when excess hydrochloric acid (~250 g/l) TS is added.

3. Moisture content ($\leq$ 1.0%)

(1) Tare a crucible. (W_1)

(2) Weigh accurately the crucible with about 3 g of sample. (W_2)

(3) Dry over silica gel R in a desiccator for four hours and weigh. (W_3)

(4) Calculate:

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

ANNEX 5-C

4. Assay ($NaHCO_3 \geq 99.0\%$)

(1) Weigh accurately about 3 g of dried sample (from moisture test) and dissolve in 50 ml of water. (W_1)

(2) Titrate with hydrochloric acid (1.0 mol/l) VS, using methyl orange TS as indicator. (ml_1)

(3) Calculate:

$$\frac{ml_1 \times 8.401}{W_1} = \% \ NaHCO_3$$

ANNEX 5-D

TEST PROCEDURES: POTASSIUM CHLORIDE

Description

Identification

Moisture content

Assay

1. Description: Colourless, odourless crystals or a white granular powder.

2. Identification:

Potassium: (1) Dissolve 1 g of sample in 10 ml of water and make alkaline with 1 ml sodium hydroxide ($\sim$ 80 g/l) TS.

(2) Adding sodium tetraphenylborate ($\sim$30 g/l) TS produces a white precipitate.

Chloride: (1) Dissolve 1 g of sample in 10 ml of water and acidify with 1 ml nitric acid ($\sim$130 g/l) TS.

(2) Slowly add silver nitrate (40 g/l) TS. A white curdy precipitate is produced.

(3) Collect some precipitate by filtering and divide in two. The precipitate is soluble in ammonia ($\sim$100 g/l) TS and practically insoluble in nitric acid ($\sim$1000 g/l) TS

3. Moisture content ($\leq$1.0%)

(1) Tare a crucible. (W_1)

(2) Accurately weigh the crucible with about 2 g of sample. (W_2)

(3) Dry to constant weight in the crucible at 130°C. (W_3)

(4) Calculate:

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

4. Assay (KCl $\geq$ 99.0%)

(1) Accurately weigh about 0.25 g of dried sample (from moisture test) and dissolve in 50 ml of water. (W_1)

(2) Titrate with silver nitrate (0.1 mol/l) VS, using potassium chromate TS as indicator. (ml_1)

(3) Calculate:

$$\frac{ml_1 \times 0.7456}{W_1} = \% \text{ KCl}$$

ANNEX 5-E

TEST PROCEDURES: AEROSIL

Identification

(1) Transfer about 5 mg of Aerosil (Colloidal Silicon Dioxide) to a platinum crucible and mix with about 200 mg of potassium carbonate, anhydrous R.

(2) Ignite at red heat for about 10 minutes over a burner and cool.

(3) Dissolve the melt in 2 ml of freshly distilled water, warming if necessary.

(4) The slow addition of 2 ml of ammonium molybdate TS should produce a deep yellow colour.

ANNEX 6

EXAMPLE

PRODUCTION CONTROL SHEET

Name of product: _____ Date: _____

Name of manufacturer: _____ Batch size: _____

Batch number: _____ Theoretical number of packets: _____

Preparation of mixture

	Weight	Initialled by:
Glucose	_____	_____
NaCl	_____	_____
$NaHCO_3$	_____	_____
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

ANNEX 7

PRODUCTION CONTROL: CHLORIDE TEST

Test for chloride (80 mmol/l)

(1) Dissolve 27.5 g of sample in 1000 ml of water.

(2) Place a 10-ml aliquot of the solution in a 100-ml Erlenmeyer flask.

(3) Add about 0.5 ml potassium chromate TS as indicator and titrate with silver nitrate (0.1 mmol/l) VS until a brick red colour is obtained. (ml_1)

(4) Calculate:

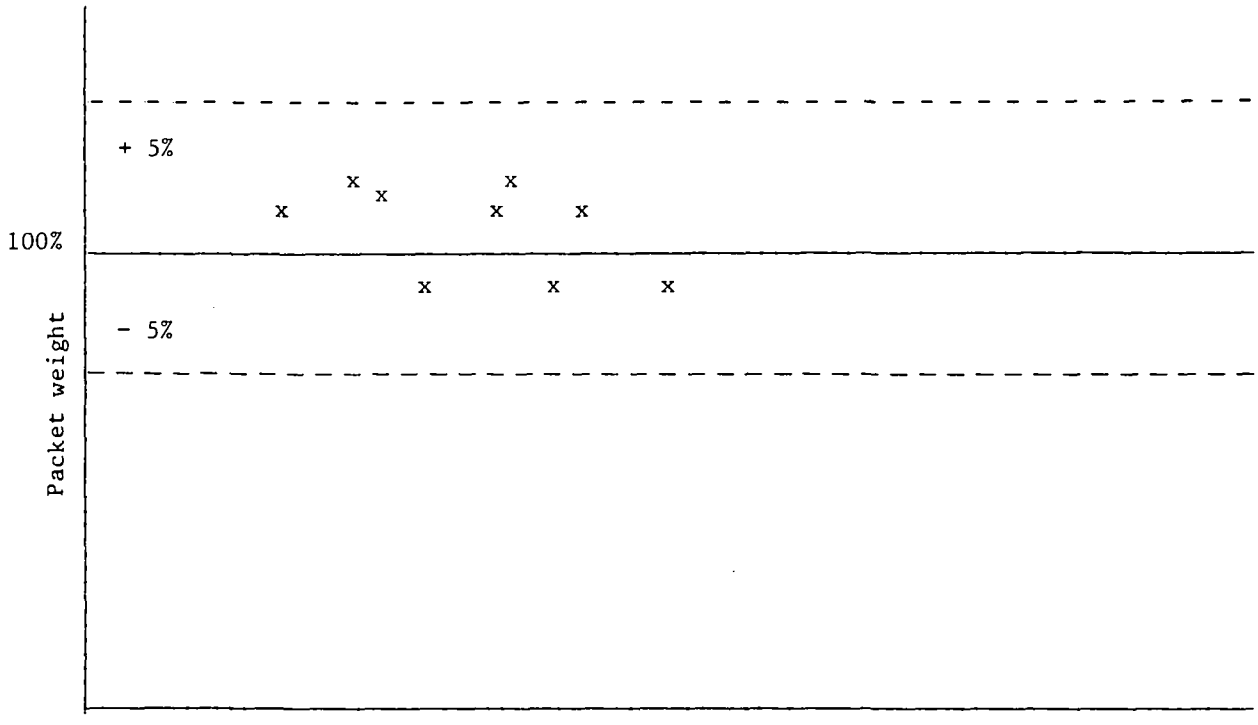
$$10 \times ml_1 = \text{mmol/l}$$

(5) Acceptable limits: 75 to 85 mmol/l.

ANNEX 8

EXAMPLE

DOSAGE CONTROL RECORD SHEET



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

ANNEX 9

TEST PROCEDURES FOR QUALITY CONTROL OF FINISHED ORS PACKETS.

1. Net weight of packet ingredients: limits 26.1 g to 28.9 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 additonal 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).

2. 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.

3. 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.

4. 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.

5. Chemical composition

	Limits
glucose, anhydrous	19.0 g - 21.0 g
sodium chloride	3.33 g - 3.68 g
sodium bicarbonate	2.38 g - 2.63 g
potassium chloride	1.35 g - 1.65 g

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 of iodine (0.1 mol/l) VS, and 10 ml of sodium carbonate (~50 g/l) TS.

(2) Allow solution to stand in darkness for 20 minutes.

(3) Add 15 ml sulfuric acid (~100 g/l) TS.

(4) Titrate with sodium thiosulfate (0.1 mol/l) VS, using starch TS as indicator. (ml_1)

(5) Calculate:

$$9.008 \times ml_1 = g/l$$

Sodium bicarbonate

(1) Titrate 25.0 ml of the test solution and 100 ml of water with hydrochloric acid (0.1 mol/l) VS, using methyl orange TS as indicator. (ml_1)

(2) Calculate:

$$ml_1 \times 8.401 \times 1000 \times 40 = g/l$$

Potassium chloride

Determine g/l using a flame spectrophotometer.

Sodium chloride

Determine g/l using a flame spectrophotometer.

ANNEX 9

Flame spectrophotometry

The flame photometric method depends upon the measurement of radiation emitted by the element being determined, when the sample to be analyzed is excited by introducing it into a flame, usually as a solution spray. This radiation is isolated by passage through either an optical filter or a monochromator, and is compared directly or indirectly with that given by a prepared solution of known composition. Owing to phenomena such as flame saturation, the intensity of radiation is proportional to concentration only over a limited range and low concentration favours proportionality.

Detailed instructions for operating spectrophotometers are supplied by the manufacturers. To achieve significant and valid results, the operator of a spectrophotometer should be aware of its limitations and of potential sources of error and variation. The instruction manual should be followed closely on such matters as care, cleaning, and calibration of the instrument, and instructions for operation. Where double-beam recording instruments are used, the cell containing solvent only is placed in the reference beam.

The cleanliness of absorption cells should receive particular attention. Usually, after treatment with an appropriate cleansing medium, the cells should be rinsed with distilled water and then with a volatile organic solvent to promote drying. Test solutions should not be left in the cells longer than necessary for carrying out the measurement. When handling the cells, special care should be taken never to touch the external surfaces through which the light beam passes. When the solvent and the test solution are transferred to the cells, care is to be taken that the liquids do not contaminate the outer surfaces.

A generalized example of a procedure to determine potassium chloride content would be:

(1) Dilute 10 ml of test solution to 100 with water. Further dilute 10 ml of this solution to 100 ml with water.

(2) Measure the potassium content using a flame spectrophotometer following the manufacturer's instructions.

(3) Calculate:

$$\left[\frac{\text{Reading}}{1000} \times \frac{1000}{10} \times \frac{100}{10} \times \frac{100}{1000}\right] \times 74.55 = \text{g/l}$$

= = =