WHO/FCH/CAH/06.1

ORAL REHYDRATION SALTS

Production of the new ORS

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For further information please contact:

Department of Child and Adolescent Health and Development (CAH)
World Health Organization

20 Avenue Appia
1211 Geneva 27
Switzerland

fax + 41 22 791 48 53
email cah@who.int
web site http://www.who.int/child-adolescent-health/

UNICEF Supply Division

UNICEF Plads, Freeport
2100 Copenhagen OE
Denmark

fax + 45 35 269 421
email supply@unicef.org
web site http://www.unicef.org/supply

World Health Organization

unicef

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This document is updating a document that was originally prepared in 1985 and was reprinted in 1998 by the Division of Child and Adolescent Health and Development (CAH), which includes the former Diarrhoeal Diseases Control Programme.

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Definitions

Dehydration	Loss of water and dissolved salts from the body, occurring, for instance, as a result of diarrhoea.
Rehydration	The correction of dehydration.
Oral Rehydration Therapy (ORT)	The administration of fluid by mouth to prevent or correct the dehydration that is a consequence of diarrhoea.
Oral Rehydration Salt (ORS) solution	Specifically, the complete, new WHO/UNICEF formula.

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1 Introduction

Acute diarrhoeal diseases are one of the leading causes of mortality in infants and young children in many developing countries. In most cases, death is caused by dehydration. Dehydration from diarrhoea can be prevented by giving extra fluids at home, or it can be treated simply, effectively, and cheaply in all age-groups and in all but the most severe cases by giving patients by mouth an adequate glucose-electrolyte solution.

This way of giving fluids to prevent or treat dehydration is called oral rehydration therapy (ORT). ORT, combined with guidance on appropriate feeding practices, is the main strategy recommended by the WHO Department of Child and Adolescent Health and Development (CAH) to achieve a reduction in diarrhoea-related mortality and malnutrition in children.

To achieve this short-term objective, as well as the longer-term one of reduced diarrhoea morbidity, the CAH Department is collaborating with WHO Member States in the planning, implementation, and evaluation of national diarrhoeal diseases control activities. The United Nations Children's Fund (UNICEF) is actively supporting these activities by promoting ORT and providing large quantities of oral rehydration salts (ORS), the balanced mixture of glucose and electrolytes recommended by both organizations for the treatment of dehydration.

This document is updating an earlier document (WHO/CDD/SER/85.8), and provides information on the manufacture of the new ORS that, since 2003, is recommended by WHO and UNICEF. It has been prepared to assist national authorities in establishing the local manufacture of a product of pharmaceutical quality, in order that they may become self-reliant in meeting the needs of their national diarrhoeal diseases control activities. It is emphasized that the methods recommended in the document are meant to serve as guidelines, and that they need to be adapted to meet local requirements and conditions, provided they follow the principles of Good Manufacturing Practices for pharmaceutical products (WHO Technical Report Series, No 908, 2003) that can be found in the annexes of this document. Specific information on "Quality Management", "Personnel", "Validation" and "Qualification" can be found in this annex.

2 Oral rehydration therapy and oral rehydration salts (ORS)

2.1 Practical application

Oral rehydration therapy (ORT) can be delivered by village health workers and practiced in the home by mothers with some guidance, and thus is a technology highly suited to the primary health care approach. Moreover, when given along with advice on proper feeding practices, ORT has been found to contribute to better weight gain and thus to reduce the ill effects of diarrhoea on nutritional status.

ORT should begin at home with the use of available "home fluids" or a home-prepared "sugar and salt" solution given early during the diarrhoea episode to prevent dehydration (1). Once a child becomes dehydrated, however, ORT should be provided in the form of a balanced and complete standard mixture of glucose and salts (ORS). Detailed guidelines for the treatment of acute diarrhoea are available, as is information on the scientific basis for ORS, studies of its clinical efficacy and safety (2-4).

2.2 Composition of oral rehydration salts

Oral Rehydration Salts (ORS) is the non-proprietary name for a balanced glucose-electrolyte mixture, first used in 1969 and approved, recommended, and distributed by UNICEF and WHO as a drug for the treatment of clinical dehydration throughout the world. In 1984, another mixture containing trisodium citrate instead of sodium hydrogen carbonate (sodium bicarbonate) was developed with the aim of improving the stability of ORS in hot and humid climates. For more than 20 years, WHO and UNICEF have recommended this single formulation of ORS to prevent or treat dehydration from diarrhoea irrespective of the cause or age group affected. This product, which provides a solution containing 90 mEq/l of sodium with a total osmolarity of 311 mOsm/l, has proven effective and without apparent adverse effects in worldwide use. It has contributed substantially to the dramatic global reduction in mortality from diarrhoeal disease during the period. During this period, numerous studies have been undertaken to develop an "improved" ORS. The goal was a product that would be at least as safe and effective as standard ORS for preventing or treating dehydration from all types of diarrhoea but which, in addition, would reduce stool output or have other important clinical benefits. One approach has consisted in reducing the osmolarity of ORS solution to avoid possible adverse effects of hypertonicity on net fluid absorption. This was done by reducing the solution's glucose and salt (NaCl) concentrations.

Studies to evaluate this approach were reviewed at a consultative technical meeting held in New York (USA) in July 2001 (4), and technical recommendations were made to WHO and UNICEF on the efficacy and safety of reduced osmolarity ORS in children with acute non-cholera diarrhoea, and in adults and children with cholera.

These studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhoea is improved by reducing its sodium concentration to 75 mEq/l, its glucose

concentration to 75 mmol/l, and its total osmolarity to 245 mOsm/l. The need for unscheduled supplemental IV therapy in children given this solution was reduced by 33%. In a combined analysis of this study and studies with other reduced osmolarity ORS solutions (osmolarity 210-268 mOsm/l, sodium 50-75 mEq/l) stool output was also reduced by about 20% and the incidence of vomiting by about 30%. The 245 mOsm/l solution also appeared to be as safe and at least as effective as standard ORS for use in children with cholera.

The reduced osmolarity ORS containing 75 mEq/l sodium, 75 mmol/l glucose (total osmolarity of 245 mOsm/l) is as effective as standard ORS in adults with cholera. However, it is sometime associated with an increased incidence of transient, asymptomatic hyponatraemia.

Because of the improved effectiveness of reduced osmolarity ORS solution WHO and UNICEF now recommend that countries use and manufacture, for diarrhoea of all etiologies and in all age groups, the following formulation with a total osmolarity of 245 mOsmol/l, in place of the previously recommended ORS solution with a total osmolarity of 311 mOsm/l. It should be emphasized that the new ORS is considered as a medicine, like the old formulation, and has been included in the WHO model list of Essential Medicines. Therefore, it should be manufactured as a pharmaceutical product, following all the requirements of the Good Manufacturing Practices.

TABLE 1. Composition of the new ORS formulation

New ORS	grams/litre	%	New ORS	mmol/litre
Sodium chloride	2.6	12.683	Sodium	75
Glucose, anhydrous	13.5	65.854	Chloride	65
Potassium chloride	1.5	7.317	Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	14.146	Potassium	20
			Citrate	10
Total	**20.5**	**100.00**	**Total Osmolarity**	**245**

This ORS composition has passed extensive clinical evaluations and stability tests. The pharmacokinetics and therapeutic values of the substances are as follows:

- glucose facilitates the absorption of sodium (and hence water) on a 1:1 molar basis in the small intestine;
- sodium and potassium are needed to replace the body losses of these essential ions during diarrhoea (and vomiting);
- citrate corrects the acidosis that occurs as a result of diarrhoea and dehydration.

Dissolution in drinking water yields the following concentrations, as shown in Table 2.

TABLE 2. Substance concentrations of components of ORS solution

Molecular Formula	g/l	Relative molecular mass	mmol/l	Concentrations in mmol/l				
				Glucose	Na^+	K^+	Cl^-	$C_6H_5O_7^{3-}$
NaCl	2.6	58.44	44.5		44.5		44.5	
KCl	1.5	74.55	20.1			20.1	20.1	
$C_6H_5Na_3O_7.2H_2O$	2.9	294.10	9.9		29.6			9.9
Glucose, anhydrous	13.5	180.20	74.9	74.9				
TOTAL	**20.5**			**74.9**	**74.1**	**20.1**	**64.6**	**9.9**

In accordance with the International System of Units (SI), the concentrations are given in mmol/l. They correspond exactly to "milliequivalents"/l for all salts listed with the exception of trisodium citrate, where 9.86 mmol/l (rounded up to 9.9 mmol/l) citrate ($C_6H_5O_7$) corresponds to about 29.6 "milliequivalents" per litre.

2.3 Properties of ORS-citrate

The particular advantage of citrate containing ORS (over bicarbonate containing ORS) is its stability in tropical countries, where - up to temperatures of 60°C - no discoloration occurs. A shelf-life of 2-3 years can be assumed without any particular storage precautions.

Packing in hermetically sealed aluminum laminate is not imperative. For example, the use of polyethylene or any other locally available (permeable) packaging material is possible. This kind of material has particular advantages in dry and hot countries, where the pores allow the gradual escape of the product's evaporated water of crystallization, thus reducing the moisture content and keeping the product in free-flowing condition. On the other hand, in hot and humid climates the packing of citrate containing ORS in permeable material can have the reverse effect of causing the product to lump or harden owing to the absorption of moisture through the packaging material. This does not, however, prevent its satisfactory dissolution in water. In cases where only a perfectly free-flowing product is acceptable, it will be necessary to observe strict specifications and requirements with regard to the raw material, packaging material, and manufacturing process that are described in section 4.5.

2.4 Pharmaceutical aids

With the aim of making an essential drug available at an affordable price in the public health system, the recommended composition should contain only the four above-mentioned basic ingredients for preparing an effective (clinically tested) oral rehydration solution.

Excipient such as colloidal silicon dioxide (Aerosil) improve the flow characteristics but do not dissolve in the solution and render it turbid. Their use is normally only indicated when automatic packaging equipment is used, and only recommended if the flow properties of the available raw materials hamper accurate dosing and proper functioning of the equipment.

The four ingredients of ORS (glucose, sodium chloride, potassium chloride and trisodium citrate) in the concentrations described in this document yield an effective solution for rehydration

and for the prevention of dehydration. The addition of other ingredients, such as other minerals (especially zinc) or vitamins, has not been shown to improve the solution's efficacy. For this reason neither UNICEF nor WHO approve or provide ORS with additives. If additional ingredients are included, they should be clearly described on the packet. The responsibility for demonstrating their clinical value, safety, and chemical stability rests with the manufacturer.

Additional ingredients may increase the total and individual substance concentration of a solution. They must be considered when the total substance concentration of a new product is calculated for comparison with the criteria mentioned in this document.

A clear distinction should be made between products recommended for treating/preventing dehydration caused by diarrhoea and preparations with compositions that are designed for replacing water and salt losses during exercise (sport drinks). In order to avoid confusion among health professionals and the population at large, it is important that manufacturers of the latter limit their commercial promotion strictly to the indication of the product and that no reference is made to their use for treating diarrhoea or cholera.

The theoretical advantage of flavoured and coloured ORS is greater acceptability, and consequently increased use. Because this, in turn, might lead to over-consumption, the WHO/CDD Programme conducted a safety/efficacy study in Egypt and an acceptability study in the Philippines of flavoured and coloured ORS solutions (5,6) The results of these studies showed neither an advantage nor disadvantage for the flavoured and coloured ORS when compared to the standard ORS with regard to safety, acceptability and correct use. For this reason, and with the aim of making an essential drug available at low price in the public health system, UNICEF and WHO recommend that governments should use the ORS composition that contains only the four basic ingredients needed to effectively treat dehydration due to diarrhoea.

ORS produced for use in the private sector (commercial sales) and indicated for the prevention and treatment of dehydration due to diarrhoea, may contain flavouring or colouring agents, if this is seen as vital by a manufacturer for promoting the product or to compete with other brands. In practice, two or more types of flavouring are often needed, and saccharine is added to increase their effect. The ingredients used for flavouring ORS must be among those listed as "Generally Recognized as Safe" for their intended use by the US Food and Drug Administration (FDA) or by the US Flavour Extract Manufacturer's Association (FEMA). The responsibility for demonstrating the clinical efficacy, safety and chemical stability of such products remains with the manufacturer.

Special attention must be given to the type of sweetener used. In 1968, cyclamic acid was reported to cause cancer and is therefore banned in the USA; high dose of saccharine are suspected to be carcinogenic; dulcine is recognized as toxic and carcinogenic; and aspartame is known to be unstable at temperatures above 40 degrees Celsius. For all these products, the above mentioned guidelines specify the maximum dose to be consumed per kg of body weight and per day (i.e., aspartame 40 mg/kg body weight/day). The amount of ORS solution consumed per day is extremely variable from child to child. Some children with high purging diarrhoea may consume very large amounts of ORS solution.

Because of difficulties in controlling the amount of ORS solution consumed per kg of body weight and per day, it is almost impossible to determine whether the consumed doses of colouring and/or flavouring agents are within the safe limits. Although not documented, it also seems that certain flavouring agents can cause allergies and other side effects, particularly in infants and small children. Finally, it must be noted that the flavouring of ORS may increase cost of the product by up to 20-30%, especially when the additional ingredients must be imported.

3 Planning the provision and production of oral rehydration salts

3.1 National policies and priority health problems

The setting of national policies for primary health care normally involves the identification of priority health problems in a country. If a country has identified diarrhoeal disease control as a priority activity within its primary health care programme, it is justified in undertaking a detailed evaluation and estimation of its ORS needs.

3.2 Estimating the demand

Before a new commercial product is marketed, it is vital to evaluate carefully the demand, publicity needs, clients' purchasing power, necessary investment, and expected sales. Likewise, the health authorities should evaluate and justify the provision or production of ORS in relation to the plan of operation of the national diarrhoeal diseases control activities. Such activities normally include specific objectives, targets, and a good promotion and training component, as well as estimations of the amounts of ORS required in the years for which activities are planned, and realistic plans for its reliable distribution. (Simplified procedures for calculating the needs of ORS are presented in Annex 1.)

Once the amount of ORS required per year has been determined, the Ministry of Health will need to ensure that funds are available for local production (or for local purchase or importation) of ORS. Ideally, funds for ORS should be allocated in the national health budget. If this is not immediately possible, support may be sought from bilateral or international agencies.

3.3 National standard dose

It is important that all packets used in the country conform to a national standard dose. This will avoid confusion in the field and reduce the risk of over- or under-concentration resulting from varying packet and container sizes. The adoption of a national standard dose also simplifies the development of appropriate promotional and educational material, an important factor for the success of the national diarrhoeal diseases control activities. Depending on the plan of operation of the national diarrhoeal diseases control activities, the health authorities may find it appropriate to have one national standard dose for individual use in health centres and for distribution to mothers and another (bulk dose) for use in hospitals and possibly larger health centres. These doses are best identified at the time when the plan of operation is being prepared.

3.3.1 Standard individual dose

The dose for a one-litre solution of ORS, as provided through UNICEF, has been endorsed by and is used in most countries for the local production of ORS. The dose can, however, be adapted to

meet local requirements provided that there is an economic justification for doing so and a prior field study or investigation has shown that the most widely available and best-known containers or receptacles in the households of the country hold a different volume.

3.3.2 Hospital (bulk) dose

The size of the bulk dose should be based on the daily consumption and available containers in larger health facilities. Such doses are generally for solutions of 5-10 litres (1-2 gallons) or more. Ideal containers for daily quantities are plastic thermo-pots with a cover and spigot for dispensing the solution into glasses. Use of bulk doses not only eliminates the need for time-consuming weighing of ORS in hospitals, but also significantly reduces the cost as less packaging material is used. The saving may be considerable when compared with the use of small doses individually packed in expensive aluminium laminate to make up 5-10 litres.

Bulk preparation in larger health facilities also allows the small packets to be reserved for use at the community level where they are most needed.

3.3.3 Technical implications of the chosen dose

The choice of dose also has direct implications for the planning of production, equipment needs, and the final unit price. For example, if a machine has a capacity for packing 60 doses of 20.5 g per minute, the capacity for packing doses of 4.1 g will be almost identical (60 doses per minute) but the quantity of ORS packed will be only a fifth of the amount. Alternatives to obtain the same amount of ORS per minute would be (a) to increase the speed of the machine to 300 doses of 5.5 g per minute (which is not feasible because of dust development), or (b) to purchase 5 machines, which would add considerably to the space requirements.

The choice of dose of ORS will also have an impact on the packaging material required. For example, for 5 doses of 4.1 g respectively about 2.5 times more packaging material is required than for a dose of 20.5 g.

3.4 Presentation

3.4.1 Dosage form (final pharmaceutical product)

The recommended formulations of ORS can be produced in three dosage forms: powder, tablet, and liquid.

In view of the overriding need to make available an essential drug through the simplest and most appropriate technology at an affordable price, this document deals only with the production of ORS in powder form, which also is the the dosage form on the WHO model list of Essential Medicines.

3.4.2 Physical appearance of the packet

The physical appearance and appeal of an ORS packet are very important for its acceptance in the field. Thus, at the planning stage of local ORS production, it is advisable to consider carefully not only the ideal dose (as indicated in section 3.3) but also the choice of presentation. The presentation will normally conform to standard requirements set by the health authorities, and will usually correspond to one of the two following options:

- A packet resembling the ORS packet supplied by UNICEF and WHO in which the product is packed in laminated aluminium foil. This choice usually requires substantial foreign currency resources in countries where aluminium foil is not produced locally. Experience has shown that about 40% of the final product price is attributable to the packing material when aluminium foil is used. The available surface on the front and back of this type of packet may not allow the inclusion of diagrams or illustrations, or the printing of a text in more than one language.
- A country-specific packet, made from locally-available or locally produced packaging material, selected on the basis of the local climate, available financial resources, and standard of available local materials and production facilities.

3.4.3 Text and design of label

The following text is used at present by UNICEF and WHO on the label of their globally distributed packets:

RECTO:	VERSO:
New Formulation - Low Osmolarity Oral Rehydration Salts Ph. Int. 4th For the treatment of dehydration due to diarrhoea For children and adults Store in cool, dry place Each sachet contains: Glucose, anhydrous Food Grade 13.5 g Sodium chloride Ph. Int. 4th 2.6 g Trisodium citrate, dihydrate Ph. Int. 4th 2.9 g Potassium chloride Ph. Int. 4th 1.5 g Net weight: 20.5 g	Preparation of solution for oral use: Dissolve entire content of packet in one litre of drinking water Infants: one litre over a 24 hour period Children: one litre over an 8 to 24 hour period, according to age Adults: drink freely as required Continue treatment until diarrhoea stops WARNING: DISCARD REMAINING SOLUTION AFTER 24 HOURS

This text and label design, if adopted, need appropriate adaptation to ensure local understanding, taking into account the cultural characteristics of the population and the need to provide clear "instructions for use" in all the national languages or dialects. It is recommended that the "instructions for use" be illustrated with simple drawings or pictures (previously field-tested) that focus on the following items:

- How to measure the required amount of water, showing the amount and a picture of a common container for measuring (e.g., a cup or a bottle);
- How to mix ORS in the water, preferably showing that both elements are poured into a wide-mouthed container;
- The need to stir the solution;
- The fact that ORS is best given by spoon to infants;
- Any other health-oriented messages (e.g., breast-feeding).

It may be convenient to print the above as a separate sheet or pamphlet to be inserted in or affixed to the packet itself.

3.4.4 Specific brand name

The adoption of a specific brand name which is locally recognized as a symbol or synonym of rehydration can further help to popularize the product. Examples of ORS product names from various countries include: Chorosol (India); Dextrolyte (Iraq); Gesolyte (Malaysia); Jeevan Jal (Nepal); Jeevanee (Sri Lanka); Litrosol (Honduras); Nimkol (Pakistan); Oralit (Indonesia); Orasaline (Bangladesh); Oresol (Philippines); Prodia (Burkina Faso); Salvadora (Peru); Serum Oral (Haiti); Sueroral (Costa Rica, Colombia).

3.5 Options for provision

Once the required amount of ORS per year has been estimated, the national standard dose identified, the desired presentation determined, and the required funds made available, the health authorities will have to evaluate ways of procuring ORS. The following options exist:

3.5.1 Importation

- Importation of ORS packets (registered brand with WHO-recommended formula) from a commercial ORS manufacturer abroad, preferably based on tender.
- Importation of ORS packets produced and packed on a contractual basis by a private packaging company abroad which does not produce its own brand of ORS (identical procedure to UNICEF's purchases of ORS based on tender).
- Importation of ORS packets through UNICEF (warehouse in Copenhagen) on a reimbursable basis.

3.5.2 Local purchase

- Purchase of ORS packets from a local manufacturer in the country, if possible based on tender.
- Purchase of ORS packets produced and packed under contract by a private local pharmaceutical or food company which does not produce its own brand of ORS (identical to UNICEF's international purchases of ORS based on tender).

3.5.3 National production (government-owned)

- ORS production integrated into an existing government-owned pharmaceutical factory or laboratory.
- Production of ORS in facilities erected exclusively for this purpose and owned by the Government
- Decentralized mixing and packing of ORS (e.g., "cottage industry") in regions/districts; responsibility for logistics, supervision, and quality control rests with the health authorities.
- Hospital-based preparation of ORS (in liquid or powder form) for in- and outpatients only.

One of the main criteria in choosing among the above-listed options is the number of ORS packets required per year. The following summary may be used as a guide for such evaluations:

Number of packets needed per year:	Recommended type of provision
1-50 000	importation purchase from local sources hospital-based preparation
50 000 - 500 000	importation purchase from local sources hospital-based preparation integration into government-owned pharmaceutical laboratory
500 000 - 3 000 000	importation purchase from local sources decentralized hospital-based preparation integration into government-owned pharmaceutical laboratory
3 000 000 - 10 000 000	purchase from local sources integration into government-owned pharmaceutical laboratory independent, central production unit (if justified by economic evaluation study)

3.6 Approaches to national production

Although the manufacture of ORS does not require complicated production procedures and sophisticated equipment, it nevertheless needs proper planning which includes (besides the points mentioned in sections 3.1-3.5) an evaluation of the available infrastructure, production facilities, competent manpower, and existing distribution system. In addition, a country has to choose between the following broad approaches to ORS production: central or decentralized, integrated or independent, and seasonal or regular production.

3.6.1 Central production

This type of production is, in general, the most economic. Logistic problems are at a minimum, since the procurement and storage of raw materials, supervision of production activities, quality control, and distribution of the finished product are handled in a single location.

However, faced with certain constraints (e.g., seasonal transport problems, high transport costs, poor road conditions, fluctuating demand etc.), a country may find that the above considerations are outweighed by the need to ensure a steady and guaranteed supply of ORS at the regional or district level.

3.6.2 Decentralized production

Decentralization of production facilities - e.g., on a regional or district basis - can be particularly advantageous in situations (e.g., large countries) where the required raw and packaging materials are already available. However, when these conditions are not present, and transportation and distribution of ORS, vaccines, or other essential drugs from central production units are unsatisfactory or unreliable, it can be assumed that the same logistic constraints will also occur in the delivery of raw materials to decentralized ones. Smooth production and steady supply of ORS in the region will not be guaranteed unless these constraints are carefully considered in the production planning stage.

The ingredients of ORS can usually be purchased at a lower price if ordered in large quantities. Decentralized production does not normally require such large orders, and therefore a higher price is paid for ingredients than would be the case with central production. Depending on the quantities of raw materials required, central procurement for all production units may offer the same advantages, but involves an additional logistic load at the central level - e.g., ordering, receipt of material, quality control, transit handling, and distribution to regions.

Another important factor to be considered in planning decentralized production (whether this is industrial or a "cottage industry") is control of the product's safety and quality. Since the same specifications are to be applied regardless of quantity and type of production, even a modest production unit producing a limited number of packets will have to be equipped with quality control facilities. Therefore, depending on the quantities produced, the control costs will have a direct influence on the price of the product, and will need careful consideration in the planning and evaluation stage.

3.6.3 Integrated or independent ORS production

Generally, the most appropriate approach to ORS production is to integrate it into an existing pharmaceutical production facility, preferably one that is producing other essential drugs and where ORS can be manufactured according to demand with existing equipment that is used for other drugs in powder form.

Separate, independent sections or decentralized units established exclusively for ORS production are economically (investment) and managerially (employment of staff) justified only if regular production of large quantities of ORS throughout the year is guaranteed. Small quantities are economically unattractive in such cases as the overhead costs of infrastructure, maintenance, and labour have all to be charged to a single product, i.e., ORS, which increases the price of the final product.

3.7 Price of ORS and evaluation of costs

ORS is produced commercially by several companies and is available in different presentations and doses as an OTC (Over The Counter) product. The prices vary considerably; some are relatively high, mostly because their compositions are not the same as the WHO/UNICEF-recommended formula or because additional ingredients, such as food colouring, sweetener, vitamins, etc., have been added.

Standard packets, containing the complete WHO/UNICEF-recommended formula for one litre of solution, are produced for UNICEF by various manufacturers on a contract basis (tender). The product is listed in the UNIPAC** Catalogue as "Salts oral rehydration powder for 1 Ltr", and has the code number S1561121 for export packet of 1000 sachets and code number S1561120 for boxes of 100 sachets. The present price ex UNIPAC is approximately US$ 0.05 per sachet (depending on the current exchange rate), not including sea freight, land transport costs, and handling charges. Thus, depending on the country's location and access to international transport routes, the price of an imported packet may finally vary from US$ 0.06 - 0.10. This price may be taken as a guide when evaluating local procurement or the feasibility of local ORS production.

As noted above, the main cost factor in an ORS packet is the packaging material, which in the case of laminated aluminium foil can account for 40% of the total cost of a dose for one litre. Other important factors are the required investment (depending on whether ORS production is

integrated into existing facilities or established in a new independent unit), the local labour costs, and the number of packets to be produced. All of these will eventually have a direct influence on the final price of the product.

The cost evaluation forms in Annex 2 and Annex 3 indicate a procedure that can be followed for a comprehensive study and estimation of production costs and the final price of locally produced ORS in comparison with an imported product. Although the national product is usually no less expensive than imported packets, local production in most cases offers other advantages which cannot be expressed in monetary terms. Not only does it conform to the important principle of national self-reliance, it provides the flexibility to produce ORS according to local needs (including the ability to respond immediately in the case of an emergency), the liberty to choose a dose that is adapted to a commonly available container, and the important opportunity to produce an illustrated label with instructions for use in local languages; the latter is a particular advantage which often cannot be obtained with an imported packet.

4 Raw materials

This section provides specifications for each of the raw materials used in the ORS mixture and describes the procedures for quality control tests. It also includes specifications and other information on various types of packaging material. Before suppliers are approved and included in the approved supplier's list or specifications, they should have been evaluated (see Good Manufacturing Practices for Pharmaceutical Products. in annex 4).

4.1 Glucose[1]

- **Glucose, anhydrous**

Molecular formula	$C_6H_{12}O_6$
Relative molecular mass:	180.2
Chemical name:	α-D-Glucopyranose;
	CAS Reg. No. 492-62-6 (anhydrous)

- **Glucose, monohydrate**

Molecular formula:	$C_6H_{12}O_6,H_2O$
Relative molecular mass:	198.2
Chemical name:	α-D-Glucopyranose monohydrate
	CAS Reg. No. 14431-43-7 (monohydrate)

- **Other name: Dextrose**

4.1.1 Description

Glucose is a sugar, usually obtained by the hydrolysis of corn, potatoes, or tapioca originating starch. It either contains one molecule of water of hydration (monohydrate) or is anhydrous. It is commercially available in the form of colourless crystals or a white, crystalline or granular powder; it is odourless.

4.1.2 Quality for use in ORS

The use of glucose for the preparation of an oral rehydration solution does not require a pyrogen-free, pharmaceutical grade such as that used for parenteral preparations, except where tax regulations indicate that the latter would be economically advantageous compared with other qualities. An "oral grade" quality is therefore fully acceptable, provided that the quality is within the limits set in the International Pharmacopoeia (Ph. Int., 4th ed).

[1] Glucosum - International Pharmacopoeia (Ph. Int., 4th ed).

If such a quality is not available, or the limits set in the specifications prove to be a serious constraint for the establishment of local production and the provision of ORS in general, the health authorities may adopt the food standard "Codex Stan 212-1999 (Amd-1-2001)" set by the Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme (*http://www.codexalimentarius.net/download/standards/338/CXS_212e.pdf*)

Although preference is given to glucose because it is more efficacious in mediating the absorption of electrolytes, health authorities may wish (in exceptional cases or if glucose is not available) to replace it by sucrose (40 g for a one-litre solution), and apply "Codex Stan 212-1999 (Amd-1-2001)" set by the Codex Alimentarius Commission of the Joint FAO/WHO Food Standards Programme (*http://www.codexalimentarius.net/download/standards/338/CXS_212e.pdf*)

Only anhydrous glucose is recommended. Contact of glucose monohydrate with trisodium citrate and prolonged exposure to tropical (hot and humid) conditions can lead to liquefaction of the whole mixture.

4.1.3 Bulk density

Depending on the manufacturing process of the glucose and the given particle size, the bulk density can vary between 500 - 900 g per litre.

Experience has shown that often no guarantee is given by manufacturers of uniformity in the bulk density, even throughout a single shipment. It is therefore strongly recommended that this fact be taken into consideration when deciding on the size of the packet for the final ORS mixture.

4.1.4 Price

Depending on the type of packaging material (e.g., multi-ply paper/ polyethylene bags, corrugated cardboard boxes, fibre drums, steel drums) and the size of the order (e.g., container load), the price for glucose (anhydrous and monohydrate) ex factory is normally within the range of US $0.43 - 0.85 per kilo.

4.1.5 Order specifications

Reference is normally made to the relevant monograph in a recognized national or international pharmacopoeia. However, in certain circumstances the health authorities may wish to establish country-specific requirements. The following order specifications are given as an example and may need to be revised, completed, or adapted in each particular case. The same specifications may also be used as a "tender document" for obtaining comparable quotations from various bidders.

- **Glucose, anhydrous, oral grade**

  Colourless crystals or a white, crystalline or granular powder; odourless

- **Specify:** according to Ph. Int., 4th ed. or
  according to "Codex Stan 212-1999 (Amd-1-2001)", Codex Alimentarius Commission, or
  with at least the following essential requirements:

Assay	min. 99% (calculated with reference to the dried substance)
Heavy metals	max. 5 µg/g
Sulfated ash	max. 2.5 mg/g max
Loss on drying	max. 10 mg/g

The three quality standards mentioned above are not comparable and may vary considerably in price. Only the endorsed quality should therefore be mentioned.

Additional requirement - Whenever appropriate facilities for microbiological control are available, it is recommended that the microbiological purity of the glucose be checked. Relevant methods and limits are described in the report of the Committee of Official Laboratories and Drug Control Services and the Sections of Industrial Pharmacists FIP, July 1975, in the article "Microbiological purity of non-compulsorily sterile pharmaceutical preparations, methods of examination", published in Pharmaceutica Acta Helvetiae, 51(3): 33 - 40 (1976).

- **Quantity**: …kg net.
- **Packing**: in multi-ply polyethylene/paper or polyester bags of 25 or 50 kg (max.),
  shrink-wrapped on standard pallets
  shipped in standard overseas containers (if consignment is over 17 000 kg)
- **Labeling**: The following information has to be given on each bag with weatherproof ink:
  - name of the product
  - quality or grade of the product
  - name and address of the manufacturer
  - country of origin
  - lot identification (batch number)
  - net weight
- **Quality certificate** For each batch a detailed analytical quality certificate with reference to the ordered standard must be supplied with the goods.

4.1.6 Quality assurance/test procedures

After receipt of the glucose, the whole shipment is placed in a quarantine area. It may be transferred to the final storage place in the warehouse only after the quality control laboratory has analyzed each batch of the supply and released it for production. Normally, the product should be analyzed fully according to the monograph in the pharmacopoeia indicated by the manufacturer. However, for the preparation of ORS, the various tests may be reduced to the four essential requirements given above. In cases where the required instruments, facilities, and resources are not available, at least the WHO-recommended "Basic Tests" should be applied. The two options mentioned are as follows:

4.1.6.1 Identification (basic tests)

- **Description**: Colourless crystals or a white, crystalline or granular powder; odourless.
- **Melting behaviour**: Heat gently a small quantity of the test substance; it melts. The melt becomes yellow, then brown and an odour of burning sugar is perceptible. On ignition the melt swells, then ignites and chars.
- **Colour and other reactions:** Dissolve 250 mg of glucose in 5 ml of water. Add a few drops of this solution to 5 ml of hot potassio-cupric tartrate TS; a copious red precipitate is produced.
- **Alternative test allowing the distinction between different sugars**: Dissolve 0.05 g in 5 ml of water, add 1.0 ml of copper (II) acetate (45 g/l) TS and heat for 10 minutes in a water-bath; a fine red precipitate is formed, which adheres to the walls and the bottom of the test-tube (distinction from lactose and sucrose, which produce green or brown precipitates).

4.1.6.2 Purity and Assay

- **Heavy metals (max 5 µg/g):** The limit test for heavy metals is performed to demonstrate that the content of metallic impurities that are coloured by sulfide ions does not exceed the heavy metals limit given in terms of micrograms of lead per gram of the test substance.

  The test consists of two operations: preparation of the test solution, and comparison of the colour obtained with that produced with standard lead solution.

  The test solution is prepared as specified below. A blank is prepared in a similar manner.

  The reaction with sulfide ions is carried out by mixing the test solution with freshly prepared thioacetamide (6.5 g/l) TS. The colour thus obtained is directly compared with the coloration of the liquid in suitable comparison tubes.

  Carry out the test in comparison tubes of transparent glass of about 20 ml capacity. Nessler cylinders are suitable.

  Buffer solution: dissolve 5 g of ammonium acetate R in 5 ml of water and add 8 ml of hydrochloric acid (~250 g/l) TS. Check the pH, correct it if necessary to 3.5, and add 20 ml of water.

  Stock solution: dissolve 5.0 g glucose in 25 ml of water.

  Test solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 12 ml of stock solution and 2 ml of buffer solution and mix.

  Reference solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 9 ml of water, 1.0 ml of solution lead, dilute PbTS, 2 ml of stock solution, and 2 ml of buffer solution and mix.

  After 2 minutes the colour of the test solution should not be darker than that of the reference solution.

- **Sulfated ash (max. 2.5 mg/g)**

  Tare a crucible . . . . . g_1

  Weigh accurately with about 1 g of sample and the crucible . . . . . g_2

  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.

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

  Add a small amount of ammonium carbonate R and ignite to constant weight . . . . . g_3

$$\text{Calculate: } \frac{(g_3 - g_1) \times 1000}{(g_2 - g_1)} = \text{sulfated ash (mg/g)}$$

- **Loss on drying:** Glucose, anhydrous: max. 10 mg/g, and
  Glucose, monohydrate: max. 100 mg/g

  Tare a crucible or weighing bottle . . . . . g_1
  Weigh accurately the crucible or the weighing bottle with 1-2 g of sample . . . . . g_2
  Dry at 80°C for 2 hours, then let cool to room temperature in a desiccator.
  Reweigh crucible or weighing bottle and sample . . . . . g_3

$$\text{Calculate: } \frac{(g_3 - g_1) \times 1000}{(g_2 - g_1)} = \text{loss on drying (mg/g)}$$

- **Assay (min. 99%)**

  Weigh accurately about 100 mg of sample . . . . . mg
  Place the sample in a 250-ml glass-stoppered flask. Add 50 ml of water, 25 ml of iodine (0.05 mol/l) VS, and 10 ml of sodium carbonate (50 g/l) TS.
  Keep the solution in the dark for 20 minutes, shaking it from time to time.
  Add 15 ml of sulfuric acid (~100 g/l) TS.
  Titrate the excess of iodine with sodium thiosulfate (0.1 mol/l) VS, using starch TS as indicator . . . . . ml_1
  Repeat operations (2) - (5) without the sample. . . . . ml_2

$$\text{Calculate: } \frac{(ml_2 - ml_1) \times 900.8}{mg \times f} = \text{\% glucose, anhydrous}$$

$$\text{or: } \frac{(ml_2 - ml_1) \times 990.8}{mg \times f} = \text{\% glucose, monohydrate}$$

$$\text{where } f = \frac{1000 - \text{loss of drying (mg/g)}}{1000}$$

4.2 Sodium Chloride[1]

Molecular formula:	NaCl
Relative molecular mass:	58.44 (Na = 22.99, Cl = 35.45)
Chemical name:	Sodium chloride;
	CAS Reg. No. 7647-14-5.

4.2.1 Description

It is commercially available as colourless crystals or a white, crystalline powder; it is odourless. It is listed in the category of ionic equilibration agents.

4.2.2 Quality for use in ORS

The oral rehydration mixture (ORS) is considered as a pharmaceutical preparation, and reference is therefore made to the monograph in the International Pharmacopoeia. However, if sodium chloride is produced locally, but is not of the mentioned pharmaceutical grade, the health authority may apply a standard for a food grade quality.

4.2.3 Price

The pharmaceutical grade of sodium chloride is normally supplied in steel drums containing 25-50 kg. With this type of packing, and depending on the size of the order, the price may vary between US $0.19 and 0.72 per kg.

4.2.4 Order specifications

Reference is normally made to the relevant monograph in a recognized national or international pharmacopoeia. However, in certain circumstances as when sodium chloride is produced locally, the health authorities may wish to establish country-specific requirements. The following order specifications are given as an example, and may need to be revised, completed, or adapted in each particular case. The specifications may also be used as a "tender document" for obtaining comparable quotations from various bidders.

- **Sodium chloride**

  Colourless crystals or a white, crystalline powder; odourless.

- **Specify**: according to Ph. Int., 4th ed. or

  with at least the following essential requirements:

Assay	min. 97% (calculated with reference to the dried substance)
Heavy metals	max. 10 µg/g
Loss on drying	max. 10 mg/g

Food grade salt may contain anti-caking agents (max. 20 mg/g), free-flowing agents (max. 10 µ/g), and processing aids (max. 10 µ/g).

[1] Natrii chloridum - Ph. Int., 4th ed.

The two quality standards listed above are not comparable and may vary considerably in price. Only the endorsed quality should therefore be mentioned.

- **Quantity**: ….kg net
- **Packing**: quantities of 25 to 50 kg (max.), sealed in heavy duty polyethylene bags, packed in airtight steel or fibre drums,
  shrink-wrapped on standard pallets,
  shipped in standard overseas containers.

Minimum order for shipment in a container is about 17,000 kg. If this product is shipped together with potassium chloride and trisodium citrate, dihydrate, the total order may reach the minimum quantity for shipping in a container.

- **Labeling**: The following information has to be indicated on each drum with weatherproof ink:
  - name of the product
  - quality or grade of the product
  - name and address of the manufacturer
  - country of origin
  - lot identification (batch number)
  - net weight
- **Quality certificate** For each batch a detailed analytical quality certificate with reference to the ordered standard must be supplied with the goods.

If salt contains fluoride or iodine, it must be declared as "fluoridated salt" or "iodized salt":

4.2.5 Quality assurance/test procedures

After receipt of the sodium chloride, the whole shipment is placed in a quarantine area. It may be transferred to the final storage place in the warehouse only after the quality control laboratory has analyzed each batch of the supplied material and released it for production. Normally the product should be analyzed fully according to the monograph in the pharmacopoeia indicated by the manufacturer. However, for the preparation of ORS, the various tests may be reduced to the three essential requirements given above. In cases where the required instruments, facilities, and resources are not available, at least the WHO-recommended "Basic Tests" should be applied. The two options mentioned are as follows:

4.2.5.1 Identification (Basic tests)

- **Description**

  Colourless crystals or a white, crystalline powder; odourless.

- **Colour and other reactions**

  Apply one of the following alternatives:

  a. Moisten a small quantity of the substance with hydrochloric acid (~250 g/l) TS and introduce it into a non-luminous flame using a magnesia stick, or a nichrome or platinum wire sealed to a glass rod; a strong yellow colour can be observed (sodium).

b. Dissolve 0.10 g in 1.0 ml of water, acidify with acetic acid (~300 g/l) TS and add 2.0 ml of magnesium uranyl acetate TS: a light yellow, crystalline precipitate is formed (sodium).

c. Dissolve 250 mg of the test substance in 5 ml of water and add 5 ml of potassium pyroantimonate (13 g/l) TS. A white, crystalline precipitate is formed. If necessary, heat the solution to obtain a precipitate (sodium).

d. Dissolve 25 mg of the test substance in 5 ml of water, add 0.5 ml of nitric acid (~130 g/l) TS and 0.5 ml of silver nitrate (40 g/l) TS; a white, curdy precipitate is formed. Separate the precipitate, wash with water, and add an excess of ammonia (~100 g/l) TS; the precipitate dissolves (chlorides).

4.2.5.2 Purity and Assay

- **Heavy metals (max. 10 µg/g)**

The limit test for heavy metals is performed to demonstrate that the content of metallic impurities that are coloured by sulfide ions does not exceed the heavy metals limit given in terms of micrograms of lead per gram of the test substance.

The test consists of two operations: preparation of the test solution, and comparison of the colour obtained with that produced with standard lead solution.

The test solution is prepared as specified below. A blank is prepared in a similar manner.

The reaction with sulfide ions is carried out by mixing the test solution with freshly prepared thioacetamide (6.5 g/l) TS. The colour thus obtained is compared directly with the coloration of the liquid in suitable comparison tubes.

Carry out the test in comparison tubes of transparent glass of about 20 ml capacity. Nessler cylinders are suitable.

Buffer solution: dissolve 5 g of ammonium acetate R in 5 ml of water and add 8 ml of hydrochloric acid (~250 g/l) TS. Check the pH, correct it if necessary to 3.5, and add 20 ml of water.

Stock solution: dissolve 2.5 g of sodium chloride in 25 ml of water.

Test solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 12 ml of stock solution and 2 ml of buffer solution and mix.

Reference solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 9 ml of water, 1 ml of solution lead, dilute PbTS, 2 ml of stock solution, and 2 ml of buffer solution and mix.

After 2 minutes the colour of the test solution should not be darker than that of the reference solution.

- **Loss on drying (max. 10 mg/g)**

Tare a crucible or weighing bottle . . . . . g_1

Weigh accurately the crucible or the weighing bottle with 1-2 g of sample . . . . . g_2

Dry at 130°C for 2 hours, then let cool to room temperature in a desiccator.

Reweigh crucible or weighing bottle and sample . . . . . g_3

$$\text{Calculate: } \frac{(g_2 - g_3) \times 1000}{(g_2 - g_1)} = \text{loss on drying (mg/g)}$$

- **Assay (min. 97%)**

  Accurately weigh about 100 mg of dried sample (from the last-mentioned test) . . . . mg
  Titrate with silver nitrate (0.1 mol/l) VS using potassium chromate (50 g/l) TS as indicator . . . . . ml

$$\text{Calculate: } \frac{\text{ml} \times 584.4}{\text{mg}} = \% \text{ of NaCl}$$

4.3 Potassium Chloride[1]

Potassium chloride (non-injectable)	Potassium chloride for parenteral use
Molecular formula:	KCl
Relative molecular mass:	74.55 (K = 39.10, Cl = 35.45)
Chemical name:	Potassium chloride;
	CAS Reg. No. 7447-40-7.
Other names:	Sylvine, Sylvite.

4.3.1 Description

It is commercially available as colourless crystals or a white, crystalline powder; it is odourless. It is listed in the category of ionic equilibration agents.

4.3.2 Quality for use in ORS

The oral rehydration mixture (ORS) is considered as a pharmaceutical preparation, and reference is therefore made to the monograph in the International Pharmacopoeia. However, if potassium chloride is produced locally, but is not of the mentioned pharmaceutical grade, the health authority may apply the standard for a food grade quality such as that set in the FAO Food and Nutrition Paper IECFA 23, Vol. 12, page 90, "Food colours, flavouring agents and other food additives".

4.3.3 Price

The pharmaceutical grade of potassium chloride is normally supplied in airtight steel drums containing 25-50 kg. With this type of packing, and depending on the size of the order, the price may vary between US $0.90 and 1.75 per kg.

4.3.4 Order specifications

Reference is normally made to the relevant monograph in a recognized national or international pharmacopoeia. However, in certain circumstances or when potassium chloride is produced locally,

[1] Kalii chloridum - Ph. Int., 4th ed.

the health authorities may wish to establish country-specific requirements. The following order specifications are given as an example, and may need to be revised, completed, or adapted in each particular case. The same specifications may also be used as a "tender document" for obtaining comparable quotations from the various bidders.

- **Potassium chloride (non-injectable)**

  Colourless crystals or a white, crystalline powder; odourless.

- **Specify**: according to Ph. Int., 4th ed. or

  according to FAO Food and Nutrition Paper JECFA 23, Vol.12, page 90, "Food colours, flavouring agents and other food additives", or

  with at least the following essential requirements:

Assay	min. 99% (calculated with reference to the dried substance)
Heavy metals	max. 10 µg/g
Loss on drying	max. 10 mg/g

The three quality standards mentioned above are not comparable and may vary considerably in price. Only the endorsed quality should therefore be mentioned.

- **Quantity:** ….. kg net
- **Packing** quantities of 25 to 50 kg (max.), sealed in heavy duty polyethylene bags, packed in airtight steel or fibre drums,

  shrink-wrapped on standard pallets,

  shipped in standard overseas containers

Minimum order for shipment in a container is about 17,000 kg. If this product is shipped together with sodium chloride and trisodium citrate, dihydrate, the total order may reach the minimum quantity for shipping in a container.

- **Labeling**: The following information has to be indicated on each drum, with weatherproof ink:
  - the name of the product
  - quality or grade of the product
  - name and address of the manufacturer
  - country of origin
  - lot identification (batch number)
  - net weight
- **Quality certificate** For each batch a detailed analytical quality certificate with reference to the ordered standard must be supplied with the goods.

4.3.5 Quality assurance/test procedures

After receipt of the potassium chloride, the whole shipment is placed in a quarantine area. It may be transferred to the final storage place in the warehouse only after the quality control laboratory has analyzed each batch of the supplied material, and released it for production. Normally, the

product should be analyzed fully according to the monograph in the pharmacopoeia indicated by the manufacturer. However, for the preparation of ORS, the various tests may be reduced to the three essential requirements given above. In cases where the required instruments, facilities, and resources are not available, at least the WHO-recommended "Basic Tests" should be applied. The two options mentioned are as follows:

4.3.6.1 Identification (Basic tests)

- **Description**

  Colourless crystals or a white, crystalline powder; odourless.

- **Colour and other reactions**

  Dissolve 5 mg of the test substance in 2 ml of water, add 4 drops of sodium cobaltinitrite (100 g/l) TS; a yellow-orange precipitate is produced (potassium).

  Dissolve 10 mg of the test substance in 4 ml of water, add 5 drops of silver nitrate (40 g/l) TS; a white, curdy precipitate is formed. Separate the precipitate, wash it with water, and add an excess of ammonia (~100 g/l) TS; the precipitate dissolves (chlorides).

  Heat a small amount of the test substance with a few drops of sodium hydroxide (~ 80 g/l) TS; no odour of ammonia is perceptible.

  Moisten a small amount with hydrochloric acid (~ 420 g/l) TS and introduce the mixture into a non-luminous flame using a magnesia stick or a nichrome or platinum wire sealed to a glass rod; a violet colour is observed and, when viewed through a suitable blue glass, the flame is reddish purple (potassium).

4.3.6.2 Purity and Assay

- **Heavy metals (max. 10 µg/g)**

  The limit test for heavy metals is performed to demonstrate that the content of metallic impurities that are coloured by sulfide ions does not exceed the heavy metals limit given in terms of micrograms of lead per gram of the test substance.

  The test consists of two operations: preparation of the test solution, and comparison of the colour obtained with that produced with standard lead solution.

  The test solution is prepared as specified below. A blank is prepared in a similar manner.

  The reaction with sulfide ions is carried out by mixing the test solution with freshly prepared thioacetamide (6.5 g/l) TS. The colour thus obtained is compared directly with the coloration of the liquid in suitable comparison tubes.

  Carry out the test in comparison tubes of transparent glass of about 20 ml capacity. Nessler cylinders are suitable.

  Buffer solution: dissolve 5 g of ammonium acetate R in 5 ml of water and add 8 ml of hydrochloric acid (~ 250 g/l) TS. Check the pH, correct it if necessary to 3.5 and add 20 ml of water.

  Stock solution: dissolve 2.5 g of potassium chloride in 25 ml of water.

  Test solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 12 ml of stock solution and 2 ml of buffer solution and mix.

  Reference solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 9 ml of water, 1 ml of solution lead, dilute PbTS, 2 ml of stock solution and 2 ml of buffer solution and mix.

  After 2 minutes the colour of the test solution should not be darker than that of the reference solution.

- **Loss on drying (max. 10 mg/g)**

  Tare a crucible or weighing bottle . . . . . g_1

  Weigh accurately the crucible or the weighing bottle with 1-2 g of sample . . . . . g_2

  Dry at 130°C for 2 hours, then let cool to room temperature in a desiccator.

  Reweigh crucible or weighing bottle and sample . . . . . g_3

$$\text{Calculate: } \frac{(g_2 - g_3) \times 1000}{(g_2 - g_1)} = \text{loss on drying (mg/g)}$$

- **Assay (min. 99%)**

  Accurately weigh about 100 mg of dried sample (from the last-mentioned test) and dissolve it in 50 ml of water . . . . . mg

  Titrate with silver nitrate (0.1 mol/l) VS, using potassium chromate (50 g/l) TS as indicator . . . . . ml

$$\text{Calculate: } \frac{\text{ml} \times 745.5}{\text{mg}} = \% \text{ KCl}$$

4.4 Sodium Citrate[1]

- **Sodium citrate, anhydrous:**

Molecular formula:	$C_6H_5Na_3O_7$	
Relative molecular mass:	258.1 (anhydrous)	(C_6 = 72.07)
		(H_5 = 5.04)
		(Na_3 = 68.97)
		(O_7 = 112.00)
Chemical name:	Trisodium citrate, anhydrous;	
	CAS Reg. No. 68-04-2 (anhydrous)	

- **Sodium citrate, dihydrate**

Molecular formula:	$C_6H_5Na_30_7,2H_20$
Relative molecular mass:	294.1 (dihydrate)
Chemical name:	Trisodium citrate, dihydrate
	CAS Reg. No. 6132-04-3

4.4.1 Description

Sodium citrate is commercially available in the form of colourless crystals or a white, crystalline powder; it is odourless. It is slightly deliquescent in moist air. It is listed in the category of systemic alkalizing agents and is used as a buffer, sequestrant, and emulsion stabilizer. It is freely soluble in water; practically insoluble in ethanol.

[1] Natrii citras - Ph. Int., 4th ed.

4.4.2 Quality for use in ORS

To achieve the required pH limits in the ORS solution, only trisodium citrate is indicated.

The recommended ORS-citrate composition contains trisodium citrate, dihydrate in view of the fact that this quality is more widely available on the market and produced in large quantities. Anhydrous trisodium citrate can, however, be used without hesitation where such a quality is available and preferred, but a higher price (by about 40%) must be expected.

It might seem logical to replace anhydrous glucose with the monohydrate quality where trisodium citrate, dihydrate is used; however, stability tests have shown that such a combination is far less stable, and the high total content of water of crystallization in both ingredients eventually leads to a liquefaction if packed in polyethylene and exposed to tropical conditions (23°-40°C and 82%-92% Rh).

The oral rehydration mixture is considered as a pharmaceutical preparation and reference is therefore made to the monograph in the International Pharmacopoeia. However, if sodium citrate is produced locally, but is not of the mentioned pharmaceutical grade, the health authority may apply the standard set in the specifications for identity and purity of some food additives prepared at the 19th JECFA (1975), published in NMRS 55B (1976) and in FNP 52 (1992).

4.4.3 Price

The pharmaceutical grade of sodium citrate is normally supplied in airtight steel drums containing 25 kg to 50 kg (max.). With this type of packing, and depending on the size of the order, the price may vary between US $1.25 and 2.00 per kg.

4.4.4 Order specifications

Reference is normally made to the relevant monograph in a recognized national or international pharmacopoeia. However, in certain circumstances, as when sodium citrate is produced locally, the health authorities may wish to establish country-specific requirements. The following order specifications are given as an example, and may need to be revised, completed, or adapted in each particular case. The same specifications may also be used as a "tender document" for obtaining comparable quotations from various bidders.

- **Trisodium citrate, dihydrate**

  Colourless crystals or a white, crystalline powder; odourless.

- **Specify**: according to Ph. Int., 4th ed. or

  according to the specifications for identity and purity of some food additives, 19th JECFA (1975), published in NMRS 55B (1976) and in FNP 52 (1992), or

  with at least the following essential requirements:

Assay	min. 99% (calculated with reference to the dried substance)
Heavy metals	max. 20 µg/g
Water	min. 100 - max. 130 mg/g

The three quality standards mentioned above are not comparable, and may vary considerably in price. Only the endorsed quality should therefore be mentioned.

- **Quantity**: …kg net.
- **Packing**: quantities of 25 to 50 kg (max.). sealed in heavy duty polyethylene bags, protected from humidity, packed in airtight steel or fibre drums,
  shrink-wrapped on standard pallets,
  shipped in overseas containers.

Minimum order for shipment in a container is about 17,000 kg. If this product is shipped together with potassium chloride and sodium chloride, the total order may reach the minimum quantity for shipping in a container.

- **Labelling**: The following information has to be indicated on each drum with weatherproof ink:
  - name of the product
  - quality or grade of the product
  - name and address of the manufacturer
  - country of origin
  - lot identification (batch number)
  - net weight

- **Quality certificate** For each batch a detailed analytical quality certificate with reference to the ordered standard must be supplied with the goods.

4.4.5 Quality assurance/test procedures

After receipt of the sodium citrate, the whole shipment is placed in a quarantine area. It may be transferred to the final storage place in the warehouse only after the quality control laboratory has analyzed each batch of the supplied material and released it for production. Normally the product should be analyzed fully according to the monograph in the pharmacopoeia indicated by the manufacturer. However, for the preparation of ORS, the various tests may be reduced to the three essential requirements given above. In cases where the required instruments, facilities, and resources are not available, at least the WHO-recommended "Basic Tests" should be applied. The two options mentioned are as follows

4.4.5.1 Identification (Basic tests)

- **Description**

  Colourless crystals or a white, crystalline powder; odourless.

- **Colour and other reactions**

  Test solution: dissolve 1.0 g of sodium citrate in 20 ml of water.

  Apply one of the following alternatives:

  a. Moisten a small quantity of the substance with hydrochloric acid (~250 g/l) TS and introduce it into a non-luminous flame using a magnesia stick or a nichrome or platinum wire sealed to a glass rod; a strong yellow colour can be observed (sodium).

  b. Acidify 2.0 ml of the solution from test 1 with acetic acid (~300 g/l) TS and add 2.0 ml of magnesium uranyl acetate TS: a light yellow, crystalline precipitate is produced (sodium).

c. To 5 ml of the test solution add 5 ml of potassium pyroantimonate (13 g/l) TS. A white crystalline precipitate is formed. If necessary, heat the solution to obtain a precipitate (sodium).

d. To 1.0 ml of the test solution add 4 ml of water and 3 ml of mercuric chloride (65 g/l) TS, and heat to boiling. To the boiling solution add a few drops of potassium permanganate (10 g/l) TS the violet colour is immediately discharged and a white precipitate is produced (citrate).

e. The test solution is slightly alkaline when tested with pH-indicator paper R (citrate).

4.4.5.2 Purity and Assay

- **Heavy metals (max. 20 µg/g)**

  The limit test for heavy metals is performed to demonstrate that the content of metallic impurities that are coloured by sulfide ions does not exceed the heavy metals limit given in terms of micrograms of lead per gram of the test substance.

  The test consists of two operations: preparation of the test solution, and comparison of the colour obtained with that produced with standard lead solution.

  The test solution is prepared as specified below. A blank is prepared in a similar manner.

  The reaction with sulfide ions is carried out by mixing the test solution with freshly prepared thioacetamide (6.5 g/l) TS. The colour thus obtained is compared directly with the coloration of the liquid in suitable comparison tubes.

  Carry out the test in comparison tubes of transparent glass of about 20 ml capacity. Nessler cylinders are suitable.

  Buffer solution: dissolve 5 g of ammonium acetate R in 5 ml of water and add 8 ml of hydrochloric acid (~250 g/l) TS. Check the pH, correct it if necessary to 3.5 and add 20 ml of water.

  Stock solution: dissolve 1.25 g of sodium citrate in 25 ml of water.

  Test solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 12 ml of stock solution and 2 ml of buffer solution and mix.

  Reference solution: to 1.2 ml thioacetamide (6.5 g/l) TS add a mixture of 9 ml of water, 1 ml of solution lead, dilute PbTS, 2 ml of stock solution, and 2 ml of buffer solution and mix.

  After 2 minutes the colour of the test solution should not be darker than that of the reference solution.

- **Loss on drying (100 - 130 mg/g)**

  Tare a crucible . . . . . g_1

  Weigh accurately the crucible with 1-2 g of sample . . . . . g_2

  Dry at 180° C to constant weight, then let cool to room temperature in a desiccator.

  Reweigh crucible and sample . . . . . g_3

  $$\text{Calculate: } \frac{(g_2 - g_3) \times 1000}{(g_2 - g_1)} = \text{loss on drying (mg/g)}$$

- **Assay (min. 99%)**

  Dissolve about 150 mg of sodium citrate, accurately weighed, in 20 ml of glacial acetic acid R, heat to about 50 C, and allow to cool to room temperature . . . mg

  Titrate with perchloric acid (0.1 mol/l) VS, using 0.25 ml 1-naphtholbenzeine/acetic acid TS as indicator, or determine the end point potentiometrically . . . . . ml_1

  Repeat the titration without the sample in the same manner . . . . . ml_2

$$\text{Calculate: } \frac{(ml_1 - ml_2) \times 860.3}{mg \times f} = \% \text{ sodium citrate}$$

$$\text{where } f = \frac{1000 - \text{loss on drying (mg/g)}}{1000}$$

4.5 Packaging material

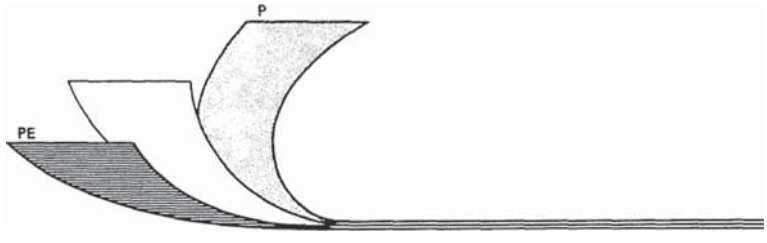
The kind of packaging material to be used for ORS depends mainly on the required standard of stability, the climatic conditions, and the available resources.

4.5.1 Multi-ply laminations with aluminium foil

Specifications

This type of packaging material is available in numerous different combinations of compounds. A compound of polyethylene, aluminium, and polyester (or any other suitable coating compound) has proved to be a very satisfactory combination for packing ORS. The polyethylene on the inner side is essential for heat-sealing the compound together, the aluminium in the middle reduces the permeability to gas and steam (so that it is no longer effectively measurable[1]), and the polyester on the outside protects the aluminium, and the ink on the aluminium, and improves the mechanical qualities in general.

FIGURE 1. Laminated aluminium foil



[1] International standards allow aluminium foil of less than 20 microns to have 100 pin holes per 100 cm^2. Only foil of more than 20 microns has to be free of pin holes.

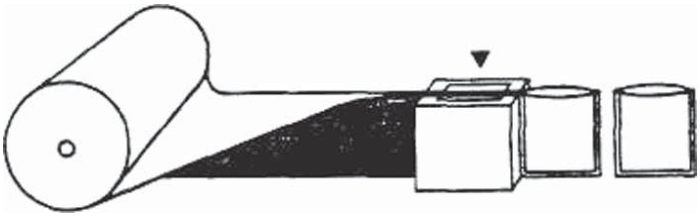
For recommended ORS compositions the thickness should, whenever possible, be selected within the following limits:

INSIDE:	Polyethylene (PE)	0.040 - 0.050 mm or 36.9 - 46.1 g/m^2
MIDDLE:	Aluminium (ALU)	0.009 - 0.015 mm or 24.3 - 40.5 g/m^2
OUTSIDE:	Polyester (P)	0.012 - 0.015 mm or 12.9 - 20.9 g/m^2

Choice of the recommended compound does not guarantee a stable and satisfactory product if the raw material is not dry, the sealing is imperfect, and the final product is not stored appropriately.

The laminations with aluminium foil are available in printed form on rolls, cut according to the required width for handling on automatic dosing/sealing equipment, or as ready-made pouches sealed on 3 sides and printed, for use with semi-automatic dosing equipment.

FIGURE 2. Manufacture of pouches from aluminium foil on rolls



It is normally more economical to purchase printed aluminium foil in quantities for at least one million packets, since the initial costs for the printing cliches or cylinders are much less for large quantities than for small orders.

The price of laminations with aluminium foil depends mainly on the thickness of the aluminium foil, as well as the particular combination, the type of printing, the ink coverage, and the reel width. A detailed and exact specification is therefore important if valid and comparable prices are to be obtained. The following example may be used as a guide, and adapted as required:

Product to be packed:	13.6 g glucose, anhydrous 2.6 g sodium chloride 2.9 g trisodium citrate, dihydrate 1.5 g potassium chloride
Format of packet:	75 mm x 105 mm
Quantity:	for 1 million packets (16 000 m^2 or about 70 000 metres incl. waste)

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Quality:	Polyethylene 50 microns Aluminium 9 microns Polyester 12 microns shiny side of alu foil outside roll width 220 mm cut off 90 mm roll ext. dia. 390 mm max. flexoprint, 2 colours ink coverage 80%
Packing:	in heavy wooden cases of 500 kg max., safely protected and secured against friction

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The price of this particular quality, and for the minimum quantity specified above, is approx. US $50.00 per 100 m, inclusive of overseas packing ex factory but excluding transport/shipping costs. This total cost represents an approximate price per packet of US $0.010. Ready-made pouches (sealed on three sides), meeting basically the same quality specifications as above, would cost approximately US $0.016. The prices are directly dependent on the price of aluminium on the world market, and may change at any time.

Precautions for handling and storage

For satisfactory use of this type of packaging material, particularly on automatic machines, the following precautions are recommended:

- Do not drop the wooden cases containing aluminium foil. Only mechanical handling, either with hand pallet trucks or mechanical lifters, should be permitted.
- Store and keep aluminium foil in its original packing material, such as wooden overseas freight cases, until the foil is used on an automatic packaging machine. If this is not possible, do not stack more than 4-5 rolls on top of each other.
- Handle rolls of aluminium laminate very carefully. Never roll them on the floor, but use a small trolley for transport from one room to another. Avoid damaging the edge of the rolls, since this can seriously affect the proper sealing of packets on automatic equipment.
- Never store the material directly exposed to sunlight and heat.
- Optimal storage conditions: 20°C and 60% relative humidity.

It is not recommended that the material be kept in a cold store, but rather in a constant, ambient atmosphere, to exclude the possibility of condensation at the time of use.

- Manufacturers normally guarantee a shelf-life of one year, if foil is stored under normal conditions. Material stored for a longer period may still be usable, but it would be best to have the material analyzed by the manufacturer, and to obtain his release or extension of guarantee.

4.5.2 Polyethylene foil

ORS can in certain cases be perfectly well packed in transparent or printed polyethylene (low density), which in fact offers a particular advantage in dry and hot climates; in such conditions the evaporating water of crystallization in the raw material can escape through the pores of the

foil and thus the moisture content of the product is reduced. In hot and humid climates, however, the reaction may be the reverse, and the moisture may penetrate through the pores into the packet, where it is absorbed by the mixture, causing lumping or even deterioration.

ORS-citrate does not absolutely require an impermeable packaging material. If packed in polyethylene it may, however, absorb moisture and some lumping, which is usually acceptable. The possibilities for the use of polyethylene packets are basically as follows:

- use of a single polyethylene bag for the whole ORS mixture, with the composition, instructions, brand, and other information printed on the polyethylene,
- use of two unprinted polyethylene bags, one for the whole ORS mixture and a second to hold together the first bag containing ORS and a printed insert (with composition, instructions for use, illustrations, etc.).

Suitable sizes for these packets and the minimal gauges of polyethylene recommended for each are as follows:

	Size of bag	Gauge of PE
Inner bag containing glucose, KCl, NaCl, and trisodium citrate (27.9 g)	65 mm x 100 mm	min. 0.04 mm
Outer bag holding ORS and label	70 mm x 120 mm	min. 05 mm

The price for a set of two bags may vary between US $0,005 - 0.01, costs for sea or airfreight not included.

4.5.3 Collecting boxes

Whether ORS is packed in aluminium laminate or polyethylene, the finished product will need to be packed in boxes for easy handling, transport and distribution. Collecting boxes normally contain between 25 and 50 ORS packets of 20.5 g, representing a total weight of 0.520 - 1.05 kg. The total number of packets in a collecting box may, however, be much higher, particularly if packets containing smaller doses (4.1 g) are packed. Therefore, the type and quality of carton to be used (common carton, 2-ply, or 3-ply corrugated cardboard) will depend on the size of the box, the total weight, the expected strain, and finally, on the local availability of packing material.

These collecting boxes, containing 25-50 packets, are themselves normally packed in a transport carton, which again should not be too heavy for manual handling. The standard quantity held by one carton is normally between 500 packets (approx. 15 kg) and 1000 packets (31 kg, such as supplied by UNIPAC).

5 Production premises

5.1 General

In view of the fact that ORS is considered as a drug, and is included in the WHO model list of Essential Medicines, it is strongly recommended that countries apply and use as a guide, wherever possible, the standards laid down in the document "Good Manufacturing Practices for pharmaceutical products: main principles" when planning manufacturing premises and production procedures (see Annex 4).

The main requirements that have a direct influence on the kind of construction and finishing material used inside the rooms are: prevention of cross-contamination with other pharmaceutical products produced in the same facility, prevention of mix-up with other chemicals, cleanliness in general, and minimal maintenance.

The flow of material should be designed in such a way that back-tracking and possible confusion with other materials/chemicals are avoided. The same precaution should be observed with regard to the possible contamination of products or personnel.

Depending on the country's climatic conditions, the type of packing equipment required, and the ORS composition chosen, special attention must be given to the treatment of air, which can vary from simple air filtration to dehumidification, with all the necessary instruments, controls, and constructional features. In the context of planning ORS production, whether it is to be included in an existing factory or an independent unit, it is essential to take into account the need for adequate space for storing material and appropriate staff facilities.

For an average annual production of 3-4 million packets of ORS containing a dose for one litre of solution, regardless of whether packaging is automatic or semi-automatic, the premises should include the following rooms and facilities:

- **Section I**
  - (i) Warehouse for raw and packaging materials (including quarantine, reception, and handling area)
  - (ii) Warehouse for finished product
- **Section II**
  - (i) Airlock (with cleaning facilities for incoming goods)
  - (ii) Bulkstore for raw and packaging materials (covering one week's production) approx. 25 m^2
  - (iii) Room for grating, sifting, sieving (possibly drying), weighing, and mixing approx. 30 m^2
  - (iv) Cubicle for washing equipment approx. 6 m^2
  - (v) In-process quality control laboratory approx. 15 m^2
  - (vi) Room for dosing, sealing, and packing approx. 45 m^2
  - (vii) Bulkstore for finished product (quarantine) approx. 20 m^2

- **Section III**

(i)	Office for production manager/supervisor	10 m^2
(ii)	Recreation room for personnel	15 m^2
(iii)	Lockers for men	10 m^2
(iv)	Lockers for women	10 m^2
(v)	Toilet for women	10 m^2
(vi)	Toilet for men	8 m^2
(vii)	Cupboard for cleaning materials	1 m^2
(viii)	Storeroom for uniforms, spare parts, tools (preferably a separate room)	10 m^2
(ix)	Storeroom for reference samples (preferably a separate room)	10 m^2

The proportion of space required for each of the three main sections can vary considerably, and depends mainly on how the raw material is ordered and stored. The following example may illustrate the allocation of space in a case where raw materials for 2 million packets are ordered once a year and all stored on the floor:

- storage area: 70%
- production area: 16%
- staff facilities: 14%

These figures clearly show that the most economical solution is to incorporate ORS production into a larger plant where storage and staff facilities are already available. Where there is no other alternative to independent ORS production, the total infrastructure and all possible additional services (e.g.; quality control; laundering, catering, waste water treatment) will have to be included in the cost estimate and considered when planning ORS production.

The cost of civil works depends mainly on the availability of construction materials. Experience has shown that costs can vary from US$130 - 750 per square metre. It is therefore advisable to evaluate these costs locally.

5.2 Storage facilities

Whether ORS is imported or locally produced, and whether it is produced on a large or small scale, in all cases sufficient and adequate storage space must be available or prepared. If ORS is produced locally, space for both raw material and finished product may need to be considered in the planning stage. Information on storage can be obtained in the document entitled "Guide to Good Storage Practices for Pharmaceuticals", WHO Technical Report Series, No 908, 2003, Annex 9, pages 125-136 (*http://www.who.int/medicines/library/TRS/trs908/trs908-9.pdf*).

The storage area or warehouse should be well-ventilated, dry, and ideally have a ceiling height of at least 350 cm. The door width should be at least 100 cm, and the door height around 230 cm, for easy passage of pallets, equipment, and other items. ORS is relatively heavy, a carton of 1000 packets weighing 25 kg. Therefore, it is more conveniently handled mechanically, particularly if produced in large quantities. For this reason the storage area should preferably have a smooth floor, and be constructed to support the expected load (tons/m2); this is particularly important in a multi-storey building. The required load capacity will mainly depend on whether goods are

stored on racks or exclusively on the floor. The normal capacity requirement in a warehouse with racks is about 1500 - 2000 kg/m^2. It is, however, strongly recommended that the required floor load capacity (in tons per square metre) be evaluated and calculated in each individual case.

Exclusively horizontal storage of pallets (at floor level only) normally requires an extensive storage area, particularly if large quantities of goods have to be stored. The use of racks, however, can drastically reduce the need for floor surface, depending on how many stock levels are created. In cases where a hand stacker with a lifting height capacity of 1625-2900 mm is used, but also for safety reasons, it is preferable to limit the stock levels to three (floor level, 135 cm above floor level, and 250 cm max. above floor level).

The racks should preferably be of a strong and solid quality, designed for storing pallets; all the required frames, adjustable beams, crossbars, and diagonal strips should be made of rolled sheet steel and specified (safe) for the expected total load of goods to be stored. The suppliers of racks normally offer consulting services to help identify the parts and accessories needed in order to assure safety and provision of the capacity required for storage of a given total quantity.

5.3 Handling and transportation of goods

The storage of goods directly on the floor should be avoided wherever possible, particularly in countries where humidity can penetrate the packaging material and eventually harm the products. For this reason, but also for more convenient handling and transportation, it is strongly recommended that movable pallets be used, which in most countries can be purchased or manufactured locally. The standard pallet size that is most suitable for pharmaceutical production is 80 x 120 cm. This standard pallet size (EURONORM, DIN 15146) is commercially available in wood or plastic and normally has a load capacity of 1000 kg. If used for storing ORS or raw materials, the following are the quantities of each product that can reasonably be placed on one pallet and used as a standard for calculating the number of pallets and the total storage space required:

- 12 000 packets of ORS (dose for one litre) in 12 cartons measuring 80 x 38 x 24 cm, with a total weight of 300 kg per pallet;

  OR
- approx. 10 bags of glucose each containing 50 kg, with a total weight of 500 kg per pallet;

  OR
- 3-5 drums (depending on the diameter), each containing 50 kg of salts, with a total weight of 150-250 kg per pallet;

A loaded pallet can easily be removed from the storage area and transported to another location. This is preferably done mechanically with a hand-operated pallet truck and, if racks are used, with a hand- or battery-operated stacker.

5.4 Storage space requirements

The required storage space depends basically on two main factors: storage system (with or without racks), and quantity of goods.

The quantity of goods in turn depends on the sequence of ordering: whether the ingredients for ORS are ordered and delivered only once a year or deliveries are staggered over the year, and

whether the finished goods are kept in the same store or handed over to a central medical store immediately after production.

The variety of country-specific factors does not allow the preparation of a table indicating the required storage space in relation to the number of packets to be produced. It is therefore essential that the required storage space be calculated individually in each particular case, considering all the above-mentioned aspects. A simple method of calculation is given below:

For each specific item:

(1) Determine the quantity of goods to be stored on one pallet, preferably no higher than 100 cm above the pallet . . . . (A)

(2) Determine the total quantity of goods to be stored at the same time . . . . (B)

(3) Calculate the total amount of pallets required:

$$\frac{B}{A} = \text{total pallets required} \quad \ldots\ldots (C)$$

(4) Calculate the total storage space needed: C x 1.2 m^2 = total storage space in m^2 . . . .(D)

Space for access to pallets (corridors) in warehouse is not included in this calculation.

(5) The figure (D) represents the required storage space, but not the required floor space if racks (vertical storage) are available. In such case, the following calculation can be made:

$$\frac{D}{\text{No. of stock levels}} = \text{total required floor space (net) in } m^2 \quad \ldots\ldots (E)$$

EXAMPLE

The following may serve as a rough guide and illustration of the importance of careful planning and calculation of storage space for raw materials in each individual case:

(a) Available information:	yearly ORS production	1 million packets
	ordering of raw material	once a year only
	storage system	horizontal (no racks)
(b) Calculation:	14 175 kg glucose (500 kg per pallet)	29 pallets
	2 730 kg sodium chloride (150 kg per pallet)	19 pallets
	1 575 kg potassium chloride (150 kg per pallet)	11 pallets
	60 000 m aluminium foil (24 000 m per pallet)	3 pallets
	20 000 collecting boxes for 50 packets	10 pallets
	2 000 collecting boxes for 10 boxes	10 pallets
	Labels, rubber gum tape	2 pallets
	Total pallets for raw material for 1 million packets of ORS	84 pallets
	Required net storage space 84 x 1.2 m^2	101 m^2
	Required store-room size, with corridor: 36 x 5.5 metres or 18 x 11 metres	200 m^2

5.5 Production rooms

The production rooms should allow a logical and easy flow of material once all the equipment is installed. The manufacturing process and required space must therefore be studied carefully, and all relevant technical information about the planned equipment (size, power supply, load) should be available in advance. The floor must be smooth, and allow easy cleaning, including the corners. The walls and ceiling should also have a smooth finish and, if possible, should be washable.

The ideal room height is 300 cm, but another measurement may be required depending on the kind and height of the equipment to be installed. The door width should be at least 100 cm and the door height around 230 cm, for easy passage of pallets, equipment, and other items. In tropical climates, the number of windows should be kept to the strict necessary, and where possible avoided altogether, so that heat transfer can be kept to a minimum or totally prevented. The window sill should be at a minimum of 200 cm above floor level, or better still, not lower than door height; a row of small windows just below the ceiling may provide sufficient daylight. Where air conditioning is used, the walls and ceiling may need to be isolated against condensation. For this reason also, windows should preferably be made of double glass panels and all joints hermetically sealed.

Production rooms should never be directly exposed to outside or ambient conditions. Wherever possible, access to production rooms should be through an airlock, which in fact can be a corridor with self-closing doors at both ends. Internal partitions/walls can be made of wood or aluminium, with single glass panels for easy supervision of production activities. Depending on the nature of the production equipment, the necessary infrastructure (single phase/three-phase electricity, gas, compressed air, water, drain, exhaust) will have to be installed in the respective rooms. In the actual production rooms, no water and drainage should be installed.

5.6 Staff facilities

In the case of an established pharmaceutical plant, such facilities are normally shared by all employees in the factory. In an independent unit, however, at least the most important facilities such as changing rooms (with lockers), showers, toilets, and a recreation room must be installed. All these rooms should be well-ventilated and not depend on artificial light. The rooms should be functional and can be built according to local housing standards (e.g., with septic tank).

5.7 Air treatment

The required ambient conditions for producing pharmaceutical preparations are product-specific.

In the case of ORS-citrate, if a perfectly free-flowing product (packed in aluminium laminate), is desired, and particularly if packing is done on automatic equipment, the conditions in the production room will need to be within reasonable limits and not exceed 24°C and 60% Rh (about 11 g water/m^3).

Where ORS is packed manually or semi-automatically in polyethylene, the required conditions are no longer product-specific; rather they are set to provide convenient working conditions.

Before the air is treated to a specific temperature and humidity, three important requirements have to be observed if ORS production is to conform to the "Good Manufacturing Practices for pharmaceutical products: main principles" WHO Technical Report Series. No 908, 2003, (see Annex 4):

- Filtration of outdoor air at the entry points to the production room (with washable pre-filter, G3 or EU4/DIN 24185)

- Change of air at least 8 times per room per hour
- Extraction of dust on equipment with mobile vacuum cleaner.

Depending on the composition and packaging material chosen, these three minimal requirements may be sufficient where local ambient conditions are stable throughout the year and within a range of 20°-25°C and 40%-60% Rh. However, where temperature and humidity are expected to be higher or lower, either heating or cooling, or both, and possibly dehumidification, may be necessary to achieve the required conditions.

Cooling with air conditioners (window type), such as UNIPAC 01 001 10, can be quite satisfactory. The capacity (BTU) or the number of units will depend on the size of the room (volume of air to be cooled) and the expected heat load. The joints between the air conditioner and the wall are normally very difficult to seal, and do not prevent humidity (event insects) from entering the room. As the units are normally not designed for use in pharmaceutical production rooms, they usually are not equipped with the required filter quality, and as a result the ORS powder may enter the air conditioner and ultimately cause damage.

The split-type air conditioner has none of the negative aspects mentioned above, reduces noise, and is easier to maintain. The fan coil can be positioned in the most convenient place in the room to achieve a proper airflow.

Cooling of the air alone does not necessarily mean that the air is dried; in fact, the relative humidity may be increased. For example, ambient air of 30°C and 60% Rh contains 17 g water/m^3. If cooled down to 24°C the air would still contain 17 g water/m^3, but the relative humidity would increase to 88%, since the dew point (saturation temperature) is only at 22.5°C.

The ideal conditions of 22°C and 40% Rh for the manufacture of ORS are therefore equivalent to other conditions such as 18°C and 50% Rh or 27°C and 30% Rh, all of which have the same absolute humidity of 7 g/m^3 but different relative humidity.

Therefore, window and split-type air conditioning units normally do not dehumidify sufficiently. If, in cases where such units are installed, the humidity has to be reduced further, a mobile dehumidifier can normally provide this additional function. The type and size to be chosen depend again on the volume of air to be treated and the degree of dehumidification required. Dehumidifiers may cause slight air turbulence in the room.

If central air conditioning is available, the type of diffuser should be carefully chosen and placed in such a way that turbulence in the room is avoided. This is best done by placing the return air duct openings (with dust filter) near to floor level, which allows a laminar flow of air through the room and prevents cross contamination.

Experience has shown that the costs of the required air conditioning (electricity) can be extremely high, and may indirectly influence the final price of ORS. One way to reduce these costs is to keep the heat load in the room to a minimum. This can be done by reducing window surfaces as much as possible, installing double glass panels, insulating walls and ceilings, and hermetically sealing all joints and cracks that might allow the penetration of heat, moisture, and insects. Such insulation has an important additional value in places where the difference between the inside and outside temperature is such that the outside (saturated) air condenses on all parts of the building that have been cooled down to the temperature in the room (windows, walls). Such condensation normally has undesirable results such as wet walls, mould, deterioration of wooden window frames, etc.

The most suitable insulation material, and its quality and thickness, will depend on the type of construction, the orientation of the room, and the climatic conditions.

6 Manufacturing procedure

Whether ORS is produced in a hospital on a very small scale, or industrially in large quantities, the basic procedure remains the same. The only difference is the requirement for space, particularly for storing raw materials, and the methods of packing ORS, which for large quantities is normally most efficiently done by mechanical means on suitable equipment. This section focuses only on procedures that are directly related to ORS production.

Additional information on manufacturing procedures can be obtained in the document entitled "Good Manufacturing Practices for Pharmaceutical Products: main principles", WHO Technical Report Series. No 908, 2003, Annex 4, pages 37-89 (see Annex 4). Information on storage can be obtained in the document entitled "Guide to Good Storage Practices for Pharmaceuticals", WHO Technical Report Series, No 908, 2003, Annex 9, pages 125-136, *http://www.who.int/medicines/library/TRS/trs908/trs908-9.pdf*).

6.1 Identity test

If a raw material arriving in the ORS production unit has already been analyzed for its identity and quality by a government owned or central quality control laboratory, and has been released for production, the identity test to be performed before production may be considered as optional. The same applies in places where goods have been analyzed in house and released for production. However, if the goods have not previously been analyzed or quality control facilities are not available, an identity test is strongly recommended.

6.2 Drying

After prolonged storage in hot and humid climates, the raw materials may have absorbed a substantial amount of moisture, and have a water content higher than the indicated limit of 1%. The use of such ingredients for the manufacture of ORS may result in accelerated decomposition. Therefore, if a raw material containing water in excess of the indicated limit is to be used, it is preferable to dry it at the recommended temperature, as follows:

Glucose, anhydrous	at max. 105°C
Sodium chloride	at max. 130°C
Potassium chloride	at max. 130°C
Citrate tri-sodium	at max. 130°C

The time required for drying to the specified limit depends on the amount of water absorbed, but should not exceed 16 hours (overnight). In tropical countries, special attention must be given to the temperature and relative humidity of the air to be used for drying. For example, outside air of 33°C and 95% Rh (about 33 g water/m^3), heated up to 50°C, has its relative humidity reduced by 40%, but the water content per m^3 is still 33 g. These conditions may not be sufficient to dry

the raw material properly, and higher drying temperatures, or pre-drying of the intake of air, will be necessary.

It is therefore important to compare the moisture content in the raw material both before and after the drying process, in order to ascertain the extent of water loss during drying (efficacy of drying). The condition of the intake of air is less critical in countries with a cold and dry climate.

Fluid bed dryers have been found suitable for drying the raw materials for ORS since the drying system, with its turbulence, can have an abrasive effect on the crystals so that a considerable portion of the raw material becomes a dust-like powder, which later cannot be packed on automatic equipment.

Whenever possible, for economic and practical reasons, drying should be avoided. This can be done by ordering raw materials with a specified low water content, or by placing orders at intervals so that the goods are fresh when used, and storing them in such a way that they are protected from humidity, rain, and other possible negative influences.

Dried material should not be exposed to high humidity and heat after it has been taken out of the dryer. It is therefore advisable to install the drying equipment in a controlled, air-conditioned room where the dried material can be filled into airtight drums and safely stored until required for use.

6.3 Grating/Sifting/Sieving

In most cases the raw materials are imported, which means that they may have been stacked for long periods, and thus may not have the same characteristics on arrival as when they left the factory (free-flowing). They may therefore need chopping and grating. The most suitable sizes of perforations on the grating drum are 3.0 mm and 6.0 mm. Sifting (possibly milling) may be required to obtain a uniform particle size, which is important for uniform mixing of the product. Sieving is recommended to screen off any foreign particles such as fibre, wood, paper, plastic, hairs, etc., and assure an uncontaminated product. The recommended meshes for obtaining particle sizes between 1000 and 1500 microns are 1.0 mm and 1.5 mm (equivalent to mesh numbers B.S. 16 and 12 or A.S.T.M. 18 and 14).

6.4 Weighing

The ingredients are normally weighted in batches, the size of which is determined by the capacity of the mixer. Whenever possible, and depending on the bulk density of the raw materials, the batch sizes can also be based on the standard bags containing 50 kg of glucose, giving for example the following proportions:

50.000 kg	glucose anhydrous	65.854%
9.630 kg	sodium chloride	12.683%
5.555 kg	potassium chloride	7.317%
10.740 kg	trisodium citrate, dihydrate	14.146%
75.925 kg	total batch size	100.00%

The weighting of the ingredients should be done only when they are ready for mixing - that is, after drying, grating, and sieving. The containers from which the raw materials are taken and the containers or plastic bags into which the desired quantities are filled must be clearly marked with the names of the respective ingredient to avoid any error of weighting and incorrect mixing of ingredients.

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

All the ingredients are white, and a mistake can easily happen if precautions are not taken. The ingredients must therefore be filled after weighing into individual, labeled containers (plastic bags) and kept separate from each other until mixing is initiated. All the weighed materials for each batch should be double checked and verified by a second person, who fills out the "Process Control Sheet".

6.5 Mixing

Mixing is not only the fundamental operation in ORS production, but one of the basic processes in pharmaceutical production in general. Thus, a country setting up ORS production will have a corner-stone on which gradually to build up the production of other essential drugs.

Mixing may appear to be a very simple operation, but in fact good and uniform blending can be rather demanding. The reasons may be the type of mixer, the mixing time, and the different densities of the components, but are primarily the differences in particle size of the four ingredients, which may produce a dispersing effect and unfavorable cohesive forces. All four ingredients should therefore be of the same medium or fine crystalline grade, and all below 1000 microns, a requirement which can be specified when the ingredients are ordered, but is in fact usually difficult to obtain. Occasionally, therefore, milling, grinding, or sifting to the required uniform particle size may be required.

6.5.1 Type of mixer

The ploughshare mixer, with chopper, provides an excellent and uniform mixture. However, if used for blending ORS, particularly in tropical countries, the following points should be noted:

- Glucose, with its abrasive characteristics and especially when it is in fine powder form, may enter into the mechanical parts and damage shaft-seals and gaskets; it may even cause the product to become contaminated with fine particles from the seals. In such case, the ordinary shaft-seals should be replaced by air-purged seals, using compressed air (oil-free and dry).
- ORS, with its tendency to caramelize rapidly in humidity and heat, requires almost daily cleaning of the mixing machine. Ideally, the machine should be taken out of the production room, if this is dehumidified and air conditioned, and cleaned in a cubicle or elsewhere, since cleaning with water in a dehumidified room is counter-productive. The ploughshare mixer normally is a fixed installation, which means that it cannot be removed from the room for cleaning.

Therefore, whenever possible, it is advisable to select and use a mixer that can be easily cleaned, has no shaft passing through the mixing container, and in which none of the product can come

into contact with lubricated mechanical parts such as ball bearings, motors, gears, etc: Two mixers that have proved to be ideal are the tumbler with kinematics principles (inversion) and the drum hoop mixer, with its two traditional and fundamental motions (rotation and translation). The advantages of these mixers are that they use the product's holding drum, so that the handling of dusty material, and the filling and emptying of mixing containers are avoided; and the hoop is designed for the dual purpose of tumbling and conveying the mixing drum to the washing room for cleaning or to the storage site. Drums are available in sizes from 20 to 900 litres, and therefore the mixers can be used for small, medium, and large-scale ORS production.

The mixing time is product-specific, and is normally between 10 and 20 minutes for a drum-mixer.

In order to obtain exactly the same mixing time for all batches, and avoid over- or under-mixing, it is recommended that a timer be installed between the main switch and the mixer.

6.5.2 Size of mixer

There is a tendency to calculate the capacity of a mixer according to the quantity of ORS to be produced per day. In such case, only a single batch is mixed per day, an approach which keeps the cost of analytical control to a minimum, but does not make efficient use of the equipment unless the mixer is used for mixing other products. Batches of 75-150 kg are ideal and can still be handled manually. It is therefore preferable to divide large quantities into such batch sizes, unless the necessary mixing and handling equipment is available. However, if ORS is produced regularly (every day) the blender should, for practical reasons and if possible, not be used to produce other drugs, which would require repeated extensive cleaning before use for ORS production, and always be a possible source of contamination.

Satisfactory blending can be achieved only if the recommended minimal and maximal quantities (capacity) are observed. Normally these limits are 30-70% of the blender's volume, but reconfirmation for each particular type is recommended. This detail is of particular importance where production is planned for half working days, and only half the quantity of ORS is to be mixed in a large blender.

6.5.3 Validation of mixer

It is essential to determine the correct mixing time for the available ingredients on the available mixer. This can be done by mixing the ingredients for 20 minutes, during which time samples are taken every 2 minutes from at least 4 different places in the mixer (e.g., bottom, top, left side, right side). Based on these results, the optimum mixing time can be determined. New deliveries of raw materials and supplies from other manufacturers may have different characteristics. It is therefore most important to verify the characteristics of new deliveries, or of supplies from a new source, and repeat each time the procedure to identify the correct mixing time.

6.5.4 Uniformity test of mixture

Before a batch is transferred to the packaging room for filling into packets, the mixture must be analyzed for uniformity. For this purpose, samples are taken from various places in the mixer (e.g., top, bottom, left and right sides). Recommended methods for analysing the mixture are given in section 7. The batch is released for packing only if the results are satisfactory. In ORS production, this analytical procedure is considered as in-process control.

6.6 Dosing/filling/sealing

The various options and systems for dosing, filling, and sealing are described below.

6.6.1 Hand dosing

This is normally done by weighing each individual dose, or by using a container (plastic cup) representing the volume of the required weight in grams of ORS. These methods are normally not very accurate and the uniformity of the weight basically depends on the worker's individual performance. Where the volumetric method (with cups) is used, special attention must be given to the bulk density of the product, particularly the glucose. It is very important to compare the volume with the required weight each time a new delivery of goods is received, and to replace the dosing utensils (cups) or adapt them to the new volume.

Approximately 10-15 packets per minute can normally be dosed and filled by hand; the capacity may be much higher depending on the worker's experience, routine, and individual ability.

6.6.2 Hand sealing

For the hand sealing of filled packets a large variety of welding machines are available on the market. However, there is a distinct difference between the sealing of polyethylene and aluminium laminate:

- **Heat impulse sealing:** Heat impulse sealing is a method for bonding thin, thermoplastic film. The advantage is that the sealing period can be accurately set, and the sealed surface can be cooled under pressure, which will result in a perfectly tight and clean-looking seal.

  To seal, the sealing bar is firmly pressed against the plastic film to be sealed, and the heater band is heated by means of a short, powerful current impulse from the impulse sender. The voltage required for heating depends on the specific resistance and length of the heater band, as well as on the required strength of current. The sealing bars are best equipped with a heater band 4 mm wide, which provides a seal of pertinent width without separating the film. A coding device is unfortunately not possible with this method of sealing. For places where ready-made bags are not available, such a film welding unit (as described in section 8) can be complemented with a cutting device which cuts the bags to the specific length required, and a rolling-off device, which can hold the polyethylene film rolls (polyethylene tube).
- **Heat welding:** Heat welding is the traditional method for welding all kinds of laminates, particularly compounds with aluminium. With this system the two sealing jaws are constantly heated and uniformly pressed together during an adjustable sealing time. The most common types of jaws are:
  - smooth jaws (mainly for products in liquid form)
  - vertically corrugated jaws
  - horizontally corrugated jaws
  - diamond-point jaws

  In some models, a device can be incorporated that allow coding of the packet at the time of sealing.

6.6.3 Semi-automatic dosing

The three most common methods for dosing and filling powder (ORS), whether for semi-automatic or automatic equipment, are as follows:

(a) slide filler

(b) volumetric cup filler

(c) auger filler

Experience in the field has shown that, for semi-automatic dosing of ORS, the auger system has particular advantages in tropical countries. Besides its high degree of accuracy in dosing (even for doses of 2.5 grams), the equipment allows easy daily cleaning and requires a minimum of maintenance. The capacity of such a machine depends on the dose selected, the type of packaging material, and the ability of the operator. With some practice, an operator can fill up to 25 or more doses per minute. This equipment does not demand any particular type of packaging material, and ORS can be dosed and filled directly in polyethylene bags, packets of aluminium laminate, plastic containers, bottles, etc. The dosing can easily be adjusted and both small and large doses filled on the same machine by simply changing the auger worm and funnel. It is therefore ideal equipment for universal use, being easily adaptable to all situations.

6.6.4 Automatic dosing and filling

Automatic dosing and filling is usually combined with sealing, coding and cutting of the packet. For this kind of equipment also, and especially if used in tropical conditions, preference is given to the auger feeding method. Other dosing methods may be perfectly suitable, but a practical trial with the product prior to ordering the equipment is advisable.

Depending on the quality of the raw materials, particularly glucose, the handling of ORS on automatic equipment is normally accompanied by the development of dust, which can negatively influence the sealing operation. The intensity of dust formation is directly linked to the speed of the machine, and experience has shown that an output of 50-60 packets per minute is a reasonable rate from this point of view. A higher output can be achieved only if all the ingredients in the ORS mixer are of a dust-free, uniform medium crystalline or granular size, which guarantees an easy flow.

The machines are normally equipped with a general dedusting system (vacuum cleaner). It should be possible to adjust each of the suction nozzles so that the sealing jaws can be kept clean; but the suction should not be so strong that all small particles are sucked up and the chemical composition is altered.

Automatic equipment is normally designed exclusively for use with laminated packing material, which is available in rolls of 24-25,000 metres length and a width according to the size of the packet. There is usually some flexibility for adjustment to other sizes of packet, though rather limited. Dosing and filling in anything other than the specific packets (e.g.; bottles, plastic containers) is not possible.

Hand feeding of the hopper with ORS mixture should be avoided where possible. This is particularly important when packets of 20.5 g are to be filled, when the frequent supply of the product to the hopper, if done by hand, may cause the formation of additional dust and the occasional spill over onto the sealing tools is likely to interfere with the proper functioning of the machine. It is therefore advisable to plan the purchase of an automatic dosing/filling/sealing machine with appropriate feeding systems. The automatic equipment, with its sensitive mechanical and

electronic parts, performs to full satisfaction only if installed in ambient conditions of about 24°C and a maximum of 60% relative humidity. The installation of an appropriate air conditioning system is therefore imperative where an automatic machine is planned. Where voltage fluctuations are common, the procurement of an adequate voltage stabilizer must also be considered.

CAUTION

Intentional excess filling/dosing to compensate for any product that might remain in the packet at the time of use should be strictly avoided as it may result in a higher sodium concentration in the solution and ultimately lead to hypernatraemia, particularly in infants.

6.6.5 Weight/dosage control

Whether done by hand, semi-automatically, or automatically, in all cases the dosing must be controlled by weighing some random samples at intervals of 10-15 minutes. The results are permanently recorded in order to evaluate the production yield and observe the performance of the machine in general.

6.6.6 Leak test

Where an aluminium laminate is used, the packets must be submitted to an air leak test at intervals of 10-20 minutes.

6.7 Packing/labeling

Once the ORS has been filled and sealed and the batch number printed or embossed on the packets, these are packed directly into collecting boxes, and then into cartons for transportation. The boxes and cartons must be provided with labels indicating the following:

- name of product
- quantity
- batch number (date of manufacture)
- expiry date
- name of manufacturer

The batch number and the date of manufacture can be incorporated in a single code number, which should be stamped or written by hand on the printed label.

6.8 Quarantine

All batches are kept in a separate quarantine area until they have passed the quality control tests (see section 7). When released by the quality control laboratory, the cartons are moved to the storage area for dispatch. The production records and a box of packets from each batch are retained for one year longer than the shelf life of the product as reference samples.

7 Quality control of finished product

ORS, because of its specific nature (tendency to absorb moisture), demands rapid analysis and release after mixing for final packing. It is therefore recommended that a quality control/in-process control laboratory be established and linked directly to the mixing/production room. For reasons of economy, responsibility, investment, and staffing, the functions of such a laboratory should, where possible, be limited specifically to analysis of the final ORS product (uniformity). The receipt, analysis, and release of raw materials for production should be handled by a central /main quality control laboratory, where one exists. The analytical methods described in this document have been selected and adapted for use in developing countries and situations where more sophisticated methods cannot be considered. The methods have been field-tested, but may need further adaptation to local conditions (depending, for example, on the temperature and quality of the water, room temperature and relative humidity, available chemicals). Any other analytical methods that give reliable and accurate results may be applied.

7.1 Physical properties

7.1.1 Appearance of product

A white, crystalline powder, odorless.

7.1.2 Storage

Oral Rehydration Salts should be kept in a sealed packet; if a free-flowing powder is required, it should be kept in an air-tight packet, preferably made of aluminium laminate.

7.1.3 Uniformity of mass (standard dose for a solution of 1000 ml)

Weigh the contents of 20 packets selected at random every 10 to 15 minutes and determine the average mass. Not more than two of the individual masses should deviate from the average mass by more than 5% and none should deviate by more than 10%.

If one or more of the packets exceed the above limits, reject the batch or weigh every packet in the batch (for gross weight).

7.1.4 Labeling

The designation on the packet of Oral Rehydration Salts should state: (1) the total net mass and the mass of the contents of each constituent, both expressed in grams, (2) the required volume of water to reconstitute the solution, (3) directions for the preparation of the solution and its administration, and (4) a warning that any solution that remains unused 24 hours after preparation is to be discarded.

Check 10 packets for completeness and legibility of the label. If 2 or more packets are unacceptable, reject the batch, or check every packet in the batch.

7.1.5 Seal (only if packed in aluminium laminate)

Check 10 packets every 10 to 20 minutes. Bundle up the packets and submerge them under water in a vacuum desiccator or equivalent device. Draw a vacuum of about 18kPa (15 cm of mercury or -0.8 bar) and hold for one minute. Examine for air leakage indicated by a fine stream of bubbles. Re-establish normal pressure and open packets to examine for water penetration.

If water penetration (leakage) is observed, search for the reason (e.g., dirty sealing jaws, wrinkles, pinholes in laminate, product sealed with laminate), and reject the batch if necessary.

7.1.6 Moisture content (only if packed in aluminium laminate)

Limits: maximum 2%

Check two packets by drying the contents to constant mass at 50°C. This means that the drying process should be continued until the results of two consecutive weighings do not differ by more than 0.5 mg, the second weighing being made after an additional hour of drying under the prescribed conditions. They should not lose more than 20 mg/g. If the limit is exceeded in one packet, check another 18 packets.

If two or more packets are found to exceed the limit, reject the batch, and investigate the source of moisture absorption during the production operation.

7.1.7 Appearance of solution

Dissolve the entire contents of one packet of ORS or about 20.5 g of the mixture in 1000 ml of water. The solution should be clear and odorless, or should have only a faint yellow stain.

7.1.8 pH of solution

Check the pH of the solution reconstituted as directed on the label. It should be within the range of 7.0 - 8.8.

7.2 Chemical composition/identification (basic tests)

7.2.1 Melting behaviour

Heat gently a small quantity of the test substance; it melts. The melt first becomes yellow, then brown, swells up and burns, evolving an odor of burnt sugar.

7.2.2 Identity tests

Dissolve the entire content of one packet of ORS, or about 20.5 g of the mixture, in 250 ml of water. The solution is slightly alkaline when tested with a pH indicator paper R.

7.2.2.1 Glucose

Add a few drops of the solution prepared above to 5 ml of hot potassio-cupric tartrate TS; a copious red precipitate is produced (glucose).

7.2.2.2 Sodium

Apply one of the following alternatives:

(a) introduce the solution prepared above into a non-luminous flame using a magnesia stick or a nichrome or platinum wire sealed to a glass rod; a strong yellow colour can be observed.

(b) dissolve 2.5 g of ORS mixture in 5 ml of water and add 5 ml of potassium pyroantimonate (13 g/l) TS. A white, crystalline precipitate is formed. If necessary, heat the solution to obtain a precipitate.

7.2.2.3 Chlorides

To 5 ml of the solution prepared above add 0.5 ml of nitric acid (130 g/l) TS and 0.5 ml of silver nitrate (40 g/l) TS; a white, curdy precipitate is formed. Separate the precipitate, wash it with water, and add an excess of ammonia (100 g/l) TS; the precipitate dissolves.

7.2.2.4 Potassium

To 5 ml of the solution prepared above add 4 drops of sodium cobaltinitrite (100 g/l) TS; a yellow-orange precipitate is produced.

7.2.2.5 Citrate

To 5 ml of the solution prepared above add 3 ml of mercuric chloride (65 g/l) TS and heat to boiling. If turbid, filtrate the hot solution, heat again, and add a few drops of potassium permanganate (10 g/l) TS; the violet colour is immediately discharged and a white precipitate is produced (citrate).

7.3 Chemical composition

Oral Rehydration Salts contain not less than 90.0% and not more than 110.0% of the equivalent amounts of sodium (Na^+), potassium (K^+), chlorides (Cl^-), citrate ($C_6H_5O_7^{3-}$) of the relevant constituents stated on the label, and not less than 90.0% and not more than 110.0% of the amount of anhydrous glucose ($C_6H_{12}O_6$) stated on the label.

Limits: 18.45 - 22.55 g (90% - 110%)

In addition to the samples taken after mixing, random samples of the packed finished product should be taken and analyzed for uniformity (for example, at the beginning, middle, and end of the dosing process). In view of the fact that a single dose may represent a complete treatment, the content of each packet should comply with the given requirements. The concentrations and acceptable limits, calculated for the standard weight of 20.5 g dissolved in 1000 ml of water, are as follows:

Na^+	74.1 mmol/l	limits	66.7 - 81.5 mmol/l	(90% - 110%)
Cl^-	64.6 mmol/l	limits	58.1 - 71.1 mmol/l	(90% - 110%)
K^+	20.1 mmol/l	limits	18.1 - 22.1 mmol/l	(90% - 110%)
$Citrate^{-3}$	9.9 mmol/l	limits	8.9 - 10.9 mmol/l	(90% - 110%)
Glucose	74.9 mmol/l	limits	67.4 - 82.4 mmol/l	(90% - 110%)

All the assays should be carried out on quantities taken from a single packet. If the quantity of one packet is insufficient to carry out all the assays, take another packet for the assay for citrates and for the assay for glucose from the same batch.

7.3.1 Sodium and potassium

For the assays of sodium, potassium and chlorides prepare the "solution A" by dissolving 8 g of ORS, accurately weighted, in sufficient water to produce 500 ml.

7.3.1.1 Sodium

a) Solutions

Test solution: Dilute 3 ml of solution A to 500 ml with water.

Standard solution "100%": Use a standard solution prepared by dissolving sodium chloride R, previously dried to constant mass, in 1000 ml of water to contain 508.4 mg of NaCl (0.2 mg of Na^+ per ml). For the preparation of the reference solution, dilute 2 ml of standard solution "100%" with water to 50 ml.

Standard solution "90%": Use a standard solution prepared by dissolving sodium chloride R, previously dried to constant mass, in 1000 ml of water to contain 457.6 mg of NaCl (0.18 mg of Na^+ per ml). For the preparation of the reference solution, dilute 2 ml of the standard solution "90%" with water to 50 ml.

Standard solution "110%": Use a standard solution prepared by dissolving sodium chloride R, previously dried to constant mass, in 1000 ml of water to contain 559.2 mg of NaCl (0.22 mg of Na^+ per ml). For the preparation of the reference solution, dilute 2 ml of the standard solution "110%" solution with water to 50 ml.

Each g of sodium chloride and of trisodium citrate dihydrate is equivalent to 0.3934 g and 0.2345 g of Na^+, respectively.

b) Assays

Select the filter of the flame-photometer for the determination of sodium a wavelength of 589 nm.

Aspirate water as blank solution and calibrate the zero.

Aspirate the reference solution and adjust the sensitivity for a correct reading.

Recheck the zero.

Aspirate the reference solutions and record the results: r_{100}, r_{90} and r_{110}

Aspirate the test solution and record the result: t

Calculate $\dfrac{t \times 74.1}{r_{100}}$ = mmol of Na^+ per dose

The mixture should contain 66.7 - 81.5 mmol/l of sodium per unit dose. The result (t) should not be below the reference of "90%" (r_{90}) or above the reference of "110%" (r_{110}).

7.3.1.2 Potassium

a) Solutions

Test solution: Dilute 3 ml of solution A to 500 ml with water.

Standard solution "100%": Use a standard solution prepared by dissolving potassium chloride R, previously dried to constant mass, in 1000 ml of water to contain 234.1 mg of KCl (0.122 mg of K^+ per ml). For the preparation of the reference solution, dilute 3 ml of the standard solution "100%" with water to 100 ml.

Standard solution "90%": Use a standard solution prepared by dissolving potassium chloride R, previously dried to constant mass, in 1000 ml of water to contain 210.7 mg of KCl (0.110 mg of K^+ per ml). For the preparation of the reference solution, dilute 3 ml of the standard solution "90%" with water to 100 ml.

Standard solution "110%": Use a standard solution prepared by dissolving potassium chloride R, previously dried to constant mass, in 1000 ml of water to contain 257.5 mg of KCl (0.134 mg of K^+ per ml). For the preparation of the reference solution, dilute 3 ml of the standard solution "100%" with water to 100 ml.

Each g of potassium chloride is equivalent to 0.5245 g of K^+.

b) Assays

Select the filter of the flame-photometer for the determination of sodium at a wavelength of 767 nm.

Aspirate water as blank solution and calibrate the zero.

Aspirate the reference solution and adjust the sensitivity for a correct reading.

Recheck the zero.

Aspirate the reference solutions and record the results: r_{100}, r_{90} and r_{110}

Aspirate the test solution and record the result: t

Calculate $\dfrac{t \times 20.1}{r_{100}}$ = mmol of K^+ per dose

The mixture should contain 18.1 - 22.1 mmol/l of potassium per unit dose. The result (t) should not be below the reference of "90%" (r_{90}) or above the reference of "110%" (r_{110}).

7.3.2 Chloride

Titrate 20 ml of solution A (containing 35.75 mg of chloride) with silver nitrate (0.1 mol/l) VS, using potassium chromate (100 g/l) TS as indicator.

Each ml of silver nitrate (0.1 mol/l) VS is equivalent to 3.545 mg of Cl^-.

Calculate: ml AgNO3 x 6.4 = X mmol chloride per ORS packet.

Each g of sodium chloride and of potassium chloride is equivalent to 0.6066 g and 0.4756 g of Cl^-, respectively.

7.3.3 Citrate

Disperse 2.8 g of ORS, accurately weighted, in 80 ml of glacial acetic acid R1, heat to about 50°C, and allow to cool to room temperature. Then dilute to 100 ml with glacial acetic acid R1, and allow to stand for 10 minutes..

Titrate 20 ml of the above solution with perchloric acid (0.1 mol/l) VS, using 0.25 ml of 1-naphtholbenzeine/acetic acid TS as indicator (ml $_1$), as described in the 4th edition of the International Pharmacopoeia (2.6 - Non-aqueous titration. Method A).

Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 6.303 mg of $C_6H_5O_7^{3-}$.

Calculate: ml perchloric acid (0.1 mol/l) x 1.23 = X mmol citrate per ORS packet.

Each g of sodium citrate is equivalent to 0.6430 g of $C_6H_5O_7^{3-}$.

7.3.4 Glucose

Dissolve 8 g of ORS, accurately weighed, in 40 ml of water, add 0.2 ml of ammonia (~100 g/l) TS, and dilute to 50 ml with water. Mix and allow to stand for 30 minutes. Determine the "Optical rotation" and calculate the quantity, in g, of anhydrous glucose $C_6H_{12}O_6$ by multiplying the observed rotation in degrees by 0.9477.

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Estimating the demand for ORS

ORS requirements are calculated for each year of the national programme, which is aimed primarily at children under 5 years of age. The estimates are based on epidemiological statistics (national average of diarrhoea episodes per child per year) and on the objectives and targets set in the plan of operations of the programme. The following questions represent a simplified procedure for obtaining the number of ORS packets required for one year.

1. How many cases of acute diarrhoea will receive treatment with oral rehydration salts (ORS) in the year in question?[1]

   (This figure is normally available in the plan of operations of the national programme)

   If this figure is not available, the following calculation can be made made:

   A. Total population of children under 5 years?

   B. National average of diarrhoea episodes per child per year? (Normally based on results obtained in a special study. It is known that children under 5 years age in developing countries have an average of about 2 episodes of diarrhoea per year.)

   C. Percentage of diarrhoea episodes (in children under 5 years) expected to be treated with ORS during the year in question?[1] The given figure will need to be expressed in decimal terms for calculation (e.g., 50%=0.5). The answer to Question Number 1 can now be calculated as follows:

1			A		x	B		x	C		=	1	

2. How many ORS packets are required to treat one case of diarrhoea) (Normally an average of 2 packets)[2]

3. How many packets will be required for the year in question?

1		x	2		=	3	

[1] This refers only to the pre-packed complete WHO-recommended formula. Before answering this question, it is necessary to consider what proportion of cases will receive "salt and sugar" and "household food" solutions.

[2] Each for one litre of solution

Checklist for assessing the feasibility of local production of ORS

1. General

1.1. Total population of the country: .....

1.2 Total population to be supplied with ORS from the planned production facility .....

1.3 Source, dose and quantities of ORS supplied to national authorities:

	Quantity	Dose	Price per packet
■ UNICEF	.....	.....	.....
■ WHO	.....	.....	.....
■ Other bilateral agencies	.....	.....	.....
■ Local government production	.....	.....	.....
■ Local commercial production	.....	.....	.....
■ Others	.....	.....	.....

1.4 How many packets were used last year? .....

1.5 How many packets are there at present in storage? .....

1.6 Proportion of planned ORS requirements for the preparation of ORS solutions (a) in health facilities and (b) for individual use:

	Health facilities	Individual use
In 20....	.....	.....
In 20....	.....	.....
In 20....	.....	.....
In 20....	.....	.....
In 20....	.....	.....

1.7 What has been identified as the appropriate and ideal standard dose

- for use in health centres .....
- for individual use .....

1.8 What is the desired presentation

Powder	O
Tablet	O
Liquid	O

1.9 What are the average climatic conditions in the country or region where ORS is produced and used?

C° .....

Rh .....

1.10 Is any particular type of packaging material preferred - e.g., International standard using laminated aluminium foil? .....

Is any type of packaging material acceptable, provided that it is locally produced and available in the required quantities? .....

1.11 Are the necessary funds for local production (or purchase) of ORS available or foreseen in the budget of the national programme? .....

2. Raw material

2.1 Are any of the ingredients of ORS locally produced or available through importation:

	Imported	**Locally**	**Produced**	**Price per kg**
Glucose anhydrous	.....	.....	.....	.....
Sodium chloride	.....	.....	.....	.....
Potassium chloride	.....	.....	.....	.....
Sodium bicarbonate	.....	.....	.....	.....
Trisodium citrate, dihydrate	.....	.....	.....	.....

2.2 Is aluminium foil (laminate) locally produced? .....

If yes, by whom? .....

2.3 Is polyethylene locally produced? .....

If yes, by whom? .....

3. Production facilities/infrastructure

3.1 Is there a pharmaceutical laboratory/factory in the country belonging to the Ministry of Health/Government? .....

If yes, specify .....

3.2 How many commercial pharmaceutical companies exist in the country? .....

3.3 Is any drug or food produced in powder form and packed in sachets in the country, e.g., lemonade, soup)? .....

If yes, specify .....

3.4 Could ORS production be integrated in any existing government-owned or commercial facility? .....

If yes, are the WHO-recommended good manufacturing practices (GMP) applied? .....

Is a quality control laboratory available? .....

Are additional equipment and instruments required

for ORS production? .....

Are skilled production and quality control staff available for ORS production? .....

3.5 Is ORS production to be handled as a separate, idependent and autonomous unit? .....

If yes:

- is the basic infrastructure such as road access, water supply, sewerage, electricity, etc. available? .....
- are basic facilities such as warehouse, production rooms, toilets, lockers, quality control laboratory, etc. available .....
- are the necessary equipment, machinery and instruments for quality control facilities available? .....
- is trained staff for the warehouse, production and quality control facilities available? .....

4. Logistics

4.1 What is the normal delivery time for the goods in question?

Raw materials, locally produced .....

Raw materials, imported .....

Packaging material, locally produced .....

Packaging material, imported .....

4.2 Is the supply limited to certain season (road conditions)? .....

4.3 Is the available storage space for this material sufficient to cover the delivery cycles (normal delivery time) specified in paragraph 4.1 above? .....

4.4 Is the infrastructure (water, power, etc.) adequate, regular, stable? .....

4.5 Are the finished goods to be stored (before distribution) in the factory? .....

4.6 Does the Government at present distribute drugs, vaccines, etc? .....

If yes, is the distribution efficient and satisfactory? .....

If not, state reasons why .....

Procedure for evaluating the cost of locally produced ORS

A. Requirements of ORS (see section 3.2) based on the plan of operation of the national programme:

1	Expected demand for ORS in one year (N°. of packets) .....

B. Cost of raw materials and packaging material, including seafreight, land transport, import duties, and handling charges for the expected requirements of ORS:

Item	Quantity*	Unit price	Total price
GLUCOSE SODIUM CHLORIDE SODIUM CITRATE POTASSIUM CHLORIDE PACKAGING MATERIAL			
Total cost of ingredients and packaging material		2	

C. Cost of raw materials and packaging material for ONE packet:

2		:	1		=	3	

D. Fixed assets and depreciations:

	Initial costs	Expected life	Annual costs
Buildings Infrastructure equipment Production equipment Maintenance of building and equipment			
Total fixed annual costs of ORS production		4	

E. Fixed annual costs of personnel

Type of employment	Number required	Annual salary	Annual cost
Manager/Supervisor Technician/Chemist Laboratory assistant Operator Packer Labourer			
Total annual cost of personnel		5	

F. Summary of costs of local production:

Raw material for present year	2	
Fixed assets	4	
Personnel	5	
Administration (estimation)	6	
Contingencies/profit	7	
	8	

G. Cost per packet of locally produced ORS:

8		:	1		=	9	

H. Cost of imported packet, including freight:

10	

Good manufacturing practices for pharmaceutical products: main principles

Annex 4

Annex 4 is copied from the document “WHO Technical Report Series, No 908”, 2003. Thus, pagination does not correspond with the current document.

WHO Technical Report Series. No 908, 2003

Annex 4
Good Manufacturing Practices for pharmaceutical products: main principles

Introduction

The first WHO draft text on good manufacturing practices (GMP) was prepared in 1967 by a group of consultants at the request of the Twentieth World Health Assembly (resolution WHA20.34). It was subsequently submitted to the Twenty-first World Health Assembly under the title "Draft requirements for good manufacturing practice in the manufacture and quality control of drugs and pharmaceutical specialities" and was accepted.

The revised text was discussed by the WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1968 and published

as an annex to its twenty-second report. The text was then reproduced (with some revisions) in 1971 in the Supplement to the second edition of *The International Pharmacopoeia*.

In 1969, when the World Health Assembly recommended the first version of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce in resolution WHA22.50, it accepted at the same time the GMP text as an integral part of the Scheme. Revised versions of both the Certification Scheme and the GMP text were adopted in 1975 by resolution WHA28.65. Since then, the Certification Scheme has been extended to include the certification of:

— veterinary products administered to food-producing animals;
— starting materials for use in dosage forms, when they are subject to control by legislation in both the exporting Member State and the importing Member State;
— information on safety and efficacy (resolution WHA41.18, 1988).

In 1992, the revised draft requirements for GMP were presented in three parts, of which only Parts One and Two are reproduced in this document (*1*).

"Quality management in the drug industry: philosophy and essential elements", outlines the general concepts of quality assurance as well as the principal components or subsystems of GMP, which are joint responsibilities of top management and of production and quality control management. These include hygiene, validation, self-inspection, personnel, premises, equipment, materials and documentation.

"Good practices in production and quality control", provides guidance on actions to be taken separately by production and by quality control personnel for the implementation of the general principles of quality assurance.

These two parts were subsequently supplemented by further guidelines which are integral parts of these good manufacturing practices for pharmaceutical products. All these texts are available on the

web page of the World Health Organization. (http.www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpcover.html)

Considerable developments in GMP have taken place in the intervening years, and important national and international documents, including new revisions, have appeared (*2*, *3*, *4*, *5*). Thus the necessity to revise the main principles and incorporate the concept of validation.

General considerations

Licensed pharmaceutical products (marketing authorization) should be manufactured only by licensed manufacturers (holders of a manufacturing authorization) whose activities are regularly inspected by competent national authorities. This guide to GMP shall be used as a standard to justify GMP status, which constitutes one of the elements of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce, through the assessment of applications for manufacturing authorizations and as a basis for the inspection of manufacturing facilities. It may also be used as training material for government drug inspectors, as well as for production, quality control and quality assurance personnel in the industry.

The guide is applicable to operations for the manufacture of drugs in their finished dosage forms, including large-scale processes in hospitals and the preparation of supplies for use in clinical trials.

The good practices outlined below are to be considered general guides[1], and they may be adapted to meet individual needs. The equivalence of alternative approaches to quality assurance, however, should be validated. The guide as a whole does not cover safety aspects for the personnel engaged in manufacture or environmental protection: these are normally governed by national legislation. A new concept of hazard analysis related to the risks in production and personnel safety is also newly recommeded (Annex 7). The manufacturer should assure the safety of workers and take the necessary measures to prevent pollution of the external environment. International Nonproprietary Names (INNs) for pharmaceutical substances designated by WHO should be used when available, together with other designated names.

Glossary

The definitions given below apply to the terms used in this guide. They may have different meanings in other contexts.

active pharmaceutical ingredient (API)
Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

[1] The word "should" in the text means a strong recommendation

airlock
An enclosed space with two or more doors, which is interposed between two or more rooms, e.g. of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

authorized person
The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

batch (or lot)
A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number)
A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

batch records
All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

bulk product
Any product that has completed all processing stages up to, but not including, final packaging.

calibration
The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding

known values of a reference standard. Limits for acceptance of the results of measuring should be established.

clean area
An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

consignment (or delivery)
The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

contamination
The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

critical operation
An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

cross-contamination
Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

finished product
A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling.

in-process control
Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

intermediate product
Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

large-volume parenterals
Sterile solutions intended for parenteral application with a volume of 100 ml or more in one container of the finished dosage form.

manufacture
All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

manufacturer
A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

marketing authorization (product licence, registration certificate)
A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

master formula
A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

master record
A document or set of documents that serve as a basis for the batch documentation (blank batch record).

packaging
All operations, including filling and labelling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

packaging material
Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

pharmaceutical product
Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production
All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

qualification
Action of proving that any premises, systems and items of equipment work correctly and actually lead to the expected results. The meaning of the word "validation" is sometimes extended to incorporate the concept of qualification.

quality assurance
See Part One (pp. 7–35).

quality control
See Part One (pp. 7–35).

quarantine
The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

reconciliation
A comparison between the theoretical quantity and the actual quantity.

recovery
The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

reprocessing
Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk

product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

reworking
Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

self-contained area
Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

specification
A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (SOP)
An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

starting material
Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

validation
Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Quality management in the drug industry: philosophy and essential elements[1]

In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the "quality policy", i.e. the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management.

The basic elements of quality management are:

— an appropriate infrastructure or "quality system", encompassing the organizational structure, procedures, processes and resources;
— systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance".

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

The concepts of quality assurance, GMP and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. Quality assurance

1.1 *Principle.* "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that:

(a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other

[1] Good manufacturing practices for pharmaceutical products, Part One In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-second report* Geneva, World Health Organization. 1992, Annex 1 (WHO Technical Report Series, No 823)

associated codes such as those of good laboratory practice (GLP)[1] and good clinical practice (GCP);

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) managerial responsibilities are clearly specified in job descriptions;

(d) arrangements are made for the manufacture, supply and use of the correct starting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;

(f) the finished product is correctly processed and checked, according to the defined procedures;

(g) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 & 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control and release of pharmaceutical products;

(h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf-life;

(i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

(j) deviations are reported, investigated and recorded;

(k) there is a system for approving changes that may have an impact on product quality;

(l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the

[1] This is a code governing the testing of chemicals to obtain data on their properties and ensuring safety with respect to human health and the environment It is different from that described in "Good laboratory practices in governmental drug control laboratories" in the Thirtieth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series. No 748. 1987, Annex 1)

company, the company's suppliers, and the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

2. Good manufacturing practices for pharmaceutical products (GMP)

2.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMP are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP:

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
(b) qualification and validation are performed;
(c) all necessary resources are provided, including:
    (i) appropriately qualified and trained personnel;
    (ii) adequate premises and space;
    (iii) suitable equipment and services;
    (iv) appropriate materials, containers and labels;
    (v) approved procedures and instructions;
    (vi) suitable storage and transport;
    (vii) adequate personnel, laboratories and equipment for in-process controls;
(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
(e) operators are trained to carry out procedures correctly;
(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;

(h) the proper storage and distribution of the products minimizes any risk to their quality;
(i) a system is available to recall any batch of product from sale or supply;
(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

3. Sanitation and hygiene

3.1 A high level of sanitation and hygiene should be practised in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive programme of sanitation and hygiene. (For *personal hygiene* see section 11, and for *sanitation* see section 12, "Premises".)

4. Qualification and validation

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.

4.2 The key elements of a qualification and validation programme of a company should be clearly defined and documented in a validation master plan.

4.3 Qualification and validation should establish and provide documentary evidence that:

(a) the premises, supporting utilities, equipment and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
(b) the premises, supporting utilities and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
(c) the premises, supporting utilities and equipment operate in accordance with their design specifications (operational qualification or OQ);
(d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation or PV, also called performance qualification or PQ).

4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.

4.5 Qualification and validation should not be considered as one-off exercises. An on-going programme should follow their first implementation and should be based on an annual review.

4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.

4.7 The responsibility of performing validation should be clearly defined.

4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.

4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.

4.11 It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems and cleaning procedures.

5. Complaints

5.1 *Principle.* All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.

5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation or recall.

5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

5.4 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.

5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular,

other batches that may contain reprocessed product from the defective batch should be investigated.

5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.

5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.

5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting or any other serious quality problems with a product.

6. Product recalls

6.1 *Principle.* There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.

6.2 The authorized person should be responsible for the execution and coordination of recalls. He/she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.

6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.

6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.

6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.

6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.

6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.

6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7 Contract production and analysis

7.1 *Principle.* Contract production and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.

7.3 The contract should permit the contract giver to audit the facilities of the contract accepter.

7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The contract giver

7.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.

7.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

7.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person.

The contract accepter

7.8 The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

7.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analysed for the contract giver.

The contract

7.11 There must be a written contract between the contract giver and the contract accepter which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of

complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8 Self-inspection and quality audits

8.1 *Principle.* The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection programme should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, e.g. in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up programme.

Items for self-inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) personnel;
(b) premises including personnel facilities;
(c) maintenance of buildings and equipment;
(d) storage of starting materials and finished products;
(e) equipment;
(f) production and in-process controls;
(g) quality control;
(h) documentation;
(i) sanitation and hygiene;
(j) validation and revalidation programmes;
(k) calibration of instruments or measurement systems;
(l) recall procedures;
(m) complaints management;
(n) labels control;
(o) results of previous self-inspections and any corrective steps taken.

Self-inspection team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of self-inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-inspection report

8.5 A report should be made at the completion of a self-inspection. The report should include:

(a) self-inspection results;
(b) evaluation and conclusions;
(c) recommended corrective actions.

Follow-up action

8.6 There should be an effective follow-up programme. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract production and analysis").

Suppliers' audits and approval

8.8 The person responsible for quality control should have responsibility together with other relevant departments for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved supplier's list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

9. Personnel

9.1 *Principle.* The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3. All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key personnel

9.6 Key personnel include the head of production, the head of quality control and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by

national legislation. Their education should include the study of an appropriate combination of:

(a) chemistry (analytical or organic) or biochemistry;
(b) chemical engineering;
(c) microbiology;
(d) pharmaceutical sciences and technology;
(e) pharmacology and toxicology;
(f) physiology;
(g) other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. 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 pharmaceutical products.

9.8 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations:

(a) authorization of written procedures and other documents, including amendments;
(b) monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of quality assurance;
(f) approval and monitoring of suppliers of materials;
(g) approval and monitoring of contract manufacturers;
(h) designation and monitoring of storage conditions for materials and products;
(i) performance and evaluation of in-process controls;
(j) retention of records;
(k) monitoring of compliance with GMP requirements;
(l) inspection, investigation and taking of samples in order to monitor factors that may affect product quality.

9.9 The head of the production generally has the following responsibilities:

(a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;

(b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
(c) to ensure that the production records are evaluated and signed by a designated person;
(d) to check the maintenance of the department, premises, and equipment;
(e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available;
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.10 The head of the quality control generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk and finished products in relation with their specifications;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;
(d) to approve sampling instructions, specifications, test methods and other quality control procedures;
(e) to approve and monitor analyses carried out under contract;
(f) to check the maintenance of the department, premises and equipment;
(g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out;
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

9.12 The authorized person will also be involved in other activities, including the following:

(a) implementation (and, when needed, establishment) of the quality system;

(b) participation in the development of the company's quality manual;
(c) supervision of the regular internal audits or self-inspections;
(d) oversight of the quality control department;
(e) participation in external audit (vendor audit);
(f) participation in validation programmes.

9.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

9.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:

(a) the marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned;
(b) the principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed;
(c) the principal manufacturing and testing processes have been validated, if different;
(d) all the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records;
(e) any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority;
(f) any additional sampling, inspection, tests and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations;
(g) all necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines;
(h) appropriate audits, self-inspections and spot-checks are carried out by experienced and trained staff;
(i) approval has been given by the head of quality control;
(j) all relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g. subdivision of output batches from a common input, factors associated with continuous production runs).

10. Training

10.1 The manufacturer should provide training in accordance with a written programme for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programmes should be available. Training records should be kept.

10.3 Personnel working in areas where contamination is a hazard, e.g. clean areas or areas where highly active, toxic, infectious or sensitizing materials are handled, should be given specific training.

10.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. Personal hygiene

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials,

in-process materials or drug products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines should not be permitted in production, laboratory and storage areas, or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or non-employees, e.g. contractors' employees, visitors, senior managers, and inspectors.

12. Premises

12.1 *Principle.* Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g. during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals. There should be a procedure for rodent and pest control.

12.10 Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished products, products in quarantine, and released, rejected, returned or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently

lit and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, controlled, monitored and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire or explosion should be stored in safe and secure areas.

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labelling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example with provisions for dust control. Such areas may be part of either storage or production areas.

Production areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances and certain non-pharmaceutical products, should not be conducted in the same facilities. In exceptional cases,

the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

12.28 Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent back-flow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken and to the external environment. These areas should be regularly monitored during both production and non-production periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

12.32 Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

12.33 Quality control laboratories should be separated from production areas. Areas where biological, microbiological or radioisotope test methods are employed should be separated from each other.

12.34 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture and other external factors, or where it is necessary to isolate the instruments.

13. Equipment

13.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.

13.4 All service pipings and devices should be adequately marked and special attention paid to the provision of non-interchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labelled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Non-dedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.

14. Materials

14.1 *Principle.* The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents and labelling materials.

General

14.3 No materials used for operations such as cleaning, lubrication of equipment and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly

fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6. Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labelling and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labelled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing and release.

14.13 Starting materials in the storage area should be appropriately labelled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference where applicable;
(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
(c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled);

(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the quality control department and within their shelf-life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labelled as such.

Packaging materials

14.19 The purchase, handling and control of primary and printed packaging materials should be as for starting materials.

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity and conformity with the packaging instructions.

Intermediate and bulk products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good practices in quality control".

Rejected, recovered, reprocessed and reworked materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf-life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

Recalled products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabelling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Reagents and culture media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labelled. The label should indicate the concentration, standardization factor, shelf-life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labelled with at least the following information:

(a) name of the material;
(b) batch or lot number and control number;
(c) date of preparation;
(d) shelf-life;
(e) potency;
(f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials or finished products.

15. Documentation

15.1 *Principle.* Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control; to ensure that all personnel concerned with manufacture know what to do and when to do it; to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review and statistical analysis. The design and use of documents depend upon the manufac-

turer. In some cases some or all of the documents described below may be brought together, but they will usually be separate.

General

15.2 Documents should be designed, prepared, reviewed and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed and dated by the appropriate responsible persons. No document should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up to date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently

checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper print-outs or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents required

Labels

15.10 Labels applied to containers, equipment or premises should be clear, unambiguous and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colours to indicate status (e.g. quarantined, accepted, rejected, clean).

15.11 All finished drug products should be identified by labelling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;
(b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g. number of dosage units, weight, volume);
(c) the batch number assigned by the manufacturer;
(d) the expiry date in an uncoded form;
(e) any special storage conditions or handling precautions that may be necessary;
(f) directions for use, and warnings and precautions that may be necessary;
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions and control number, as appropriate.

Specifications and testing procedures

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents and reagents (e.g. acids and bases) used in production should be included.

15.15 Each specification should be approved, signed and dated, and maintained by quality control, quality assurance unit or documentation centre. Specifications for starting materials, intermediates, and bulk, finished products and packaging meterials are referred to in sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for starting and packaging materials

15.18 Specifications for starting, primary and printed packaging materials should provide, if applicable, a description of the materials, including:

(a) the designated name (if applicable, the INN) and internal code reference;
(b) the reference, if any, to a pharmacopoeial monograph;
(c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice other data may be added to the specification, such as:

(a) the supplier and the original producer of the materials;
(b) a specimen of printed materials;
(c) directions for sampling and testing, or a reference to procedures;
(d) storage conditions and precautions;
(e) the maximum period of storage before re-examination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for re-assaying each starting material, as determined by its stability.

Specifications for intermediate and bulk products

15.20 Specifications for intermediate and bulk products should be available. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for finished products

15.21 Specifications for finished products should include:

(a) the designated name of the product and the code reference, where applicable;
(b) the designated name(s) of the active ingredient(s) (if applicable, with the INN(s));
(c) the formula or a reference to the formula;
(d) a description of the dosage form and package details;
(e) directions for sampling and testing or a reference to procedures;
(f) the qualitative and quantitative requirements, with acceptance limits;
(g) the storage conditions and precautions, where applicable;
(h) the shelf-life.

Master formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include:

(a) the name of the product, with a product reference code relating to its specification;
(b) a description of the dosage form, strength of the product and batch size;
(c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
(d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
(e) a statement of the processing location and the principal equipment to be used;
(f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, e.g. cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
(g) detailed step-wise processing instructions (e.g. checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
(h) the instructions for any in-process controls with their limits;
(i) where necessary, the requirements for storage of the products, including the container, the labelling, and any special storage conditions;
(j) any special precautions to be observed.

Packaging instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size and type. These should normally include, or make reference to:

(a) the name of the product;
(b) a description of its pharmaceutical form, strength and, where applicable, method of application;
(c) the pack size expressed in terms of the number, weight or volume of the product in the final container;
(d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types, with the code or reference number relating to the specifications for each packaging material;
(e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
(f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used;
(h) details of in-process controls with instructions for sampling and acceptance limits.

Batch processing records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:

(a) the name of the product;
(b) the number of the batch being manufactured;

(c) dates and times of commencement, of significant intermediate stages, and of completion of production;
(d) the name of the person responsible for each stage of production;
(e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
(f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(g) any relevant processing operation or event and the major equipment used;
(h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
(i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield;
(j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch packaging records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programmes are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and work station are clear of previous products, documents or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:

(a) the name of the product, the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;
(b) the date(s) and time(s) of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;

(d) the initials of the operators of the different significant steps;
(e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
(f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
(g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
(h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Standard operating procedures (SOPs) and records

15.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for:

(a) equipment assembly and validation;
(b) analytical apparatus and calibration;
(c) maintenance, cleaning and sanitization;
(d) personnel matters including qualification, training, clothing and hygiene;
(e) environmental monitoring;
(f) pest control;
(g) complaints;
(h) recalls;
(i) returns.

15.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include:

(a) the name of the material on the delivery note and the containers;
(b) the "in-house" name and/or code of material if different from (a);
(c) the date of receipt;
(d) the supplier's name and, if possible, manufacturer's name;

(e) the manufacturer's batch or reference number;
(f) the total quantity, and number of containers received;
(g) the batch number assigned after receipt;
(h) any relevant comment (e.g. state of the containers).

15.34 There should be standard operating procedures for the internal labelling, quarantine and storage of starting materials, packaging materials and other materials, as appropriate.

15.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g. use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include:

(a) the method of sampling and the sampling plan;
(b) the equipment to be used;
(c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
(d) the amount(s) of sample(s) to be taken;
(e) instructions for any required subdivision of the sample;
(f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labelling;
(g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk or finished product is identified with a specific batch number.

15.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, e.g. in a logbook. The record should include at least the date of allocation, product identity and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:

(a) the name of the material or product and, where applicable, dosage form;
(b) the batch number and, where appropriate, the manufacturer and/or supplier;
(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and reference to any specifications (limits);
(e) date(s) and reference number(s) of testing;
(f) the initials of the persons who performed the testing;
(g) the date and initials of the persons who verified the testing and the calculations, where appropriate;
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, e.g. to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used and facilities and equipment to be cleaned. Such written procedures should be followed.

16. Good practices in production

16.1 *Principle.* Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labelling, dispensing, processing, packaging and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labelled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases it may be useful to record also the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, non-medicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g. cross-contamination or mix-up).

Prevention of cross-contamination and bacterial contamination during production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g. supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapours, sprays or organisms from materials and products in process, from residues on equipment, from intruding insects, and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example:

(a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations and certain other biologicals);
(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
(c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
(d) minimizing the risk of contamination caused by recirculation or re-entry of untreated or insufficiently treated air;
(e) wearing protective clothing where products or materials are handled;
(f) using cleaning and decontamination procedures of known effectiveness;
(g) using a "closed system" in production;
(h) testing for residues;
(i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g. for microbiological monitoring and particulate matter where appropriate).

Processing operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free

from any starting materials, products, product residues, labels or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of eqiupment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging operations

16.25 When the programme for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups or substitutions. Different products should

not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines and other equipment are clean and free from any products, materials or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labelling. If labelling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabelling can occur.

16.29 The correct performance of any printing (e.g. of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. On-line verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular on-line control of the product during packaging should include at least checks on:

(a) the general appearance of the packages;
(b) whether the packages are complete;
(c) whether the correct products and packaging materials are used;
(d) whether any overprinting is correct;
(e) the correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

17. Good practices in quality control

17.1 Quality control is the part of GMP concerned with sampling, specifications and testing, and with the organization, documentation and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

17.2 The independence of quality control from production is considered fundamental.

17.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be independent of other departments and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

(a) adequate facilities, trained personnel and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
(b) samples of starting materials, packaging materials, intermediate products, bulk products and finished products must be taken by methods and personnel approved of by the quality control department;
(c) qualification and validation must be performed;
(d) records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting

and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated;

(e) the finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labelled;

(f) records must be made of the results of inspecting and testing the materials and intermediate, bulk and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures;

(g) no batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control;

(h) sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 Quality control as a whole will also have other duties, such as to establish, validate and implement all quality control procedures, to evaluate, maintain, and store the reference standards for substances, to ensure the correct labelling of containers of materials and products, to ensure that the stability of the active pharmaceutical ingredients and products is monitored, to participate in the investigation of complaints related to the quality of the product, and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

17.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of starting materials and intermediate, bulk and finished products

17.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should

be checked by the supervisor before the material or product is released or rejected.

17.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.12 Each sample container should bear a label indicating:

(a) the name of the sampled material;
(b) the batch or lot number;
(c) the number of the container from which the sample has been taken;
(d) the number of the sample;
(e) the signature of the person who has taken the sample;
(f) the date of sampling.

17.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test requirements

Starting and packaging materials

17.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity and other quality parameters.

17.15 An identity test should be conducted on a sample from each container of starting material (see also section 14.14).

17.16 Each batch (lot) of printed packaging materials must be examined following receipt.

17.17 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15). Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information (*6*):

(a) identification (name and address) of the issuing supplier;
(b) signature of the competent official, and statement of his or her qualifications;
(c) the name of the material tested;
(d) the batch number of the material tested;
(e) the specifications and methods used;
(f) the test results obtained;
(g) the date of testing.

In-process control

17.18 In-process control records should be maintained and form a part of the batch records (see section 15.25).

Finished products

17.19 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.20 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch record review

17.21 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one

year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full re-examinations.

Stability studies

17.23 Quality control should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.24 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25 A written programme for ongoing stability determination should be developed and implemented to include elements such as:

(a) a complete description of the drug involved in the study;
(b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
(c) provision for the inclusion of a sufficient number of batches;
(d) the testing schedule for each drug;
(e) provision for special storage conditions;
(f) provision for adequate sample retention;
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

17.26 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

References

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3 *Good manufacturing practice for medicinal products in the European Community* Brussels, Commission of the European Communities, 1992

4 Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme (PIC/S) In: *Guide to good manufacturing practice for medicinal plants*, Geneva, PIC/S Secretariat, 2000

5 *Quality assurance of pharmaceuticals A compendium of guidelines and related materials Volume 2 Good manufacturing practices and inspection* Geneva, World Health Organization, 1999

6 Model certificate of analysis In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations Thirty-sixth report* Geneva, World Health Organization, 2002, Annex 10 (WHO Technical Report Series, No 902)