

# Production of Zinc Tablets and Zinc Oral Solutions

Guidelines for Programme Managers and Pharmaceutical Manufacturers

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# Definitions

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

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# Introduction

WHO and UNICEF have released revised recommendations for the management of diarrhoea aimed at dramatically reducing the number of deaths due to diarrhoea. These new recommendations take into account two significant recent advances: demonstration of the increased efficacy of a new formulation for ORS containing lower concentrations of glucose and salt, and success in using zinc supplementation in addition to rehydration therapy in the management of diarrhoeal diseases<sup>1</sup>.

In order to ensure that these recommendations become effective, it is essential that the industry be encouraged to prepare zinc formulations which contain only zinc as active ingredient. Many vitamin products and other nutritional supplements containing zinc are available commercially. However, it is uncommon for these products to have the recommended dosage of zinc. Therefore a product containing only zinc is required. The product should be formulated in such a way as to mask the strong metallic aftertaste of zinc to enhance acceptability to children. Zinc salt formulations for administration to children could take the form of oral solution or tablets. The specifications of zinc products for use in the management of diarrhoea are listed in Annex 1.

For all organizations involved in the procurement of zinc tablets or zinc oral solutions, the procurement should be made from trusted sources, such as those companies pre-qualified for zinc tablets and oral solutions in the UNICEF suppliers list and those with a proven record of quality products. When organizations make a tender to purchase zinc products, the tender should clearly state the quality specifications required as mentioned in Annex 1. In addition, zinc sulfate tablets and zinc sulfate oral solutions should comply with the specifications as detailed in the relevant pharmacopoeial monographs for zinc sulfate tablets and/or zinc sulfate oral solution (see USP monographs in Annexes 2 and 3). Relevant monographs on zinc sulfate tablets and zinc sulfate oral solutions are also under development for inclusion in the International Pharmacopoeia.

These guidelines were prepared to assist policy makers and programme managers in the selection and procurement of quality zinc products (zinc tablets and zinc oral solutions) for use in the prevention and treatment of diarrhoea in children under the age of five. These guidelines can also be used by pharmaceutical manufacturers to develop quality zinc products.

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<sup>1</sup> WHO/UNICEF. Joint Statement - Clinical Management of Acute Diarrhoea. WHO/FCH/CAH/04.7, May 2004. [http://www.who.int/child-adolescent-health/New\\_Publications/CHILD\\_HEALTH/Acute\\_Diarrhoea.pdf](http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/Acute_Diarrhoea.pdf)

# 2

## Specifications common to tablets and oral solutions

Zinc tablets and zinc oral solutions should be manufactured according to recognized principles of Good Manufacturing Practices (GMP) using ingredients that comply with specifications designed to ensure that the final products meet the requirements of the compendial monographs (see Annexes 2 and 3). 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, [http://whqlibdoc.who.int/trs/WHO\\_TRS\\_908.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf). 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://whqlibdoc.who.int/trs/WHO\\_TRS\\_908.pdf](http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf).

### Box 1: Safety concern

Many developing countries are wholly dependent on the importation of starting materials for use in the local production of essential and generic medicines. Starting materials often change hands many times before reaching the manufacturer or assembler of the final marketed product and there are many opportunities for the material to undergo re-labelling along the distribution and trade chain. As a result, chemicals and materials required for production of pharmaceutical products can become contaminated or undergo a change in identity, either accidentally or as a result of negligence, and sometimes fraud.

The most documented incidents of contamination involve diethylene glycol, which is now held responsible for hundreds of unnecessary deaths throughout the world<sup>1</sup>. Ingestion of diethylene glycol often leads to death through kidney failure. In Haiti in 1996, some 100 children died after taking paediatric syrup containing glycerol contaminated with diethylene glycol. Further incidents have occurred in 1998 in Gurgaon, India, and in 2006 in Panama.

<sup>1</sup> Jagvir Singh, A.K. Dutta, Shashi Khare, N.K. Dubey, A.K. Harit, N.K. Jain, T.C. Wadhwa, S.R. Gupta, A.C. Dhariwal, D.C. Jain, Rajesh Bhatia, Jotna Sokhey. Diethylene glycol poisoning in Gurgaon, India, 1998. *Bulletin of the World Health Organization*, 2001, 79: 88-95.

### 2.1 Ingredients and process

#### 2.1.1 Starting materials

Starting materials are defined as those materials which are used in the manufacture of a pharmaceutical product or those which come into contact with the product during its manufacture. They may include raw materials, active and inactive ingredients, excipients, propellants, containers, and packaging material. An important aspect of good manufacturing practices (GMP) for pharmaceutical products is assuring the quality of all the starting materials used. The need for analytical testing to check the quality of starting materials is explained in detail in section 14 of the WHO GMP guidelines referred to above. Failure to ensure that starting materials are of the required quality can have very serious consequences (see box entitled Safety concerns).

#### 2.1.2 Zinc

Zinc in zinc tablets and zinc oral solutions can be in the form of zinc sulfate, zinc gluconate, or zinc acetate, all water-soluble zinc salts. The most widely used zinc salt is zinc sulfate, essentially because it is the cheapest of the three zinc salts mentioned above. Clinical trials that have evaluated the efficacy of zinc supplementation in the management of diarrhoea have used these three zinc salts and no difference in efficacy has been shown. Therefore, they are considered equally effective. However, because zinc sulfate is the most widely used salt of zinc, this document is focusing on zinc products containing zinc sulfate.

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- **Zinc sulfate, monohydrate**

Molecular formula	$\text{ZnH}_2\text{SO}_4 \cdot \text{H}_2\text{O}$
Relative molecular mass	179.46
Chemical name	zinc sulfate, monohydrate

The quality of the active ingredient should comply with the relevant substance monograph<sup>1</sup>.

### 2.1.3 Sweetening and flavouring agents

Zinc tablets and zinc oral solutions may contain one or more suitable flavours and sweeteners for greater acceptability. The label should indicate the name(s) and amount(s) of any added substances(s). Such added substances —

- Should be harmless in the amounts used,
- Should not exceed the minimum quantity required for providing their intended effect,
- Should not impair the bioavailability or the therapeutic efficacy or safety of the preparation, and
- Should not interfere with the assays and tests used to determine compliance with the pharmacopoeial standards.

## 2.2 Strength

Strength indicates the prescribed amount of active ingredient in a single tablet or in a specified volume of an oral solution. This amount can be verified by using the assay as described below.

Tablets may contain either 10 or 20 mg of zinc and the concentration of zinc in oral solutions may be 10mg/5mL. Decisions about the best strength to be used should depend on better adherence to treatment by patient, taking into consideration other issues as well, such as price, medicine delivery, and duration of treatment (10- or 14-day treatment). Preferably, in any given country, only one strength of tablets or oral solution should be available to avoid dosing errors. If 10-mg zinc tablets are chosen, it will mean that older children will have to take two tablets each day; if 20-mg zinc tablets are chosen, it will mean that for younger infants only half a tablet will be given each day and therefore tablets will have to be scored to facilitate this.

With oral solutions, because it is difficult to accurately measure half a teaspoon of solution, it is recommended that oral solution of zinc contain 10mg of elemental zinc per 5 mL, that is to say per one teaspoon. It means that infants below 6 months of age will receive one teaspoon, while older children will need 2 teaspoons of oral solution per day.

It is very important to specify the dosage needed during procurement.

## 2.3 Identification

Identification (ID) test verifies the identity of the substance as described in the labelling. As described in the *USP* monographs (Annexes 2 and 3), the identity of zinc sulfate is verified by simple and rapid colorimetric reactions, using the two tests described in sections 2.3.2.1 and 2.3.2.2.

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<sup>1</sup> Zinc sulfate. The United States Pharmacopeia USP 26, 2003. pp 1958-59.

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### 2.3.1 Solutions

- *Test solution* — Dissolve a portion of powdered tablets in water, or dilute a small quantity of oral solution in water to obtain a solution containing about 0.05 g of zinc sulfate per mL.
- *Glycerine Solution* — a mixture of glycerine and water (85:15).
- *Sodium Sulfide Solution* — Dissolve 12 g of sodium sulfide with heating in 45 mL of a mixture of water and glycerine solution (10:29), allow to cool, and dilute to 100 mL with the same mixture of solvents. The solution should be colourless.
- *Hydrochloric Acid Solution* — Transfer 20 g of hydrochloric acid to a 100-mL volumetric flask and dilute to volume with water and mix.
- *Barium Chloride Solution* — Transfer 61 g of barium chloride to a 1000-mL volumetric flask, dissolve in water, and dilute to volume with the same solvent and mix.
- *Sodium Hydroxide Solution* — Transfer 42 g of sodium hydroxide to a 100-mL volumetric flask, and dilute to volume with water and mix.
- *Ammonium Chloride Solution* — Transfer 107 g of ammonium chloride to a 1000-mL volumetric flask, and dilute to volume with water and mix.

### 2.3.2 Identification tests

#### 2.3.2.1 Sulfate

To 5 mL of the *Test solution* add 1 mL of *Hydrochloric Acid Solution* and 1 mL of *Barium Chloride Solution*. A white precipitate is formed.

#### 2.3.2.2 Zinc

To 5 mL of the *Test solution* add 0.2 mL of *Sodium Hydroxide Solution*. A white precipitate is formed. Add an additional 2 mL of *Sodium Hydroxide Solution* and the precipitate dissolves. Add 10 mL of *Ammonium Chloride Solution* and the solution remains clear. Add 0.1 mL of *Sodium Sulfide Solution* and a white precipitate is formed.

## 2.4 Assay

Assays are conducted to confirm the content claimed in the labelling. For example, if the labelling on the package indicates 20 milligram (mg) elemental zinc tablets or oral solutions containing 10mg/5 mL of elemental zinc, the assay test should confirm that the value obtained is between the limits of not less than 95 percent and not more than 105 percent for tablets or between the limits of not less than 90 percent and not more than 110 percent for oral solution.

### 2.4.1 Assay for tablets

Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about **90 mg of zinc** to a 200-mL volumetric flask. Dissolve in 15 mL of dilute acetic acid, and sonicate for 15 minutes. Dilute with water to volume, and mix. Add 50 mg of xylene orange triturate to the solution, and mix. Neutralize the solution with about 2 g of methenamine until the solution is a violet-pink colour. Titrate with 0.1 M edetate disodium VS (EDTA) **until the solution is yellow**.

Each mL of 0.1 M edetate disodium VS is equivalent to 17.946 mg of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ) or 6.53 mg of elemental zinc.

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### 2.4.2 Assay for oral solutions

Transfer an accurately measured volume of zinc oral solution, equivalent to about **99 mg of zinc** to a 250-mL flask. Add 50 mL of water and 10 mL of ammonia–ammonium chloride buffer TS and 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS until the solution is green.

Each mL of 0.05 M edetate disodium is equivalent to 8.973 mg of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ) or 3.27 mg of elemental zinc.

## 2.5 Packaging and storage

Zinc sulfate tablets and zinc oral solutions should be kept in a well-closed container. A well-closed container is by definition a container that must protect the product from extrinsic solids and from loss of the article when subjected to ordinary or customary conditions of handling, shipment, storage, and distribution.

Because dispersible tablets are water sensitive, blister packing appears to be the most suitable presentation for this formulation. The zinc tablets should not be packaged in bottles or other similar multi-dose containers because they will be subjected to humidity each time the container is opened and may start to disintegrate. Zinc sulfate tablets should be stored in accordance with the directions given by the manufacturer.

Zinc sulfate oral solution should be kept in a well-closed container. In addition, it should be protected from light and stored in accordance with the directions given by the manufacturer.

Zinc solutions are less stable than solid dosage forms, and therefore in developing countries the proper storage of oral solutions is more difficult than the storage of tablets. Stability studies of zinc oral solutions must be conducted at room temperature in order to demonstrate that zinc oral solutions can be stored at such a temperature.

## 2.6 Labelling

Labelling refers to all labels and other written or graphic material printed upon the container of an article, or upon any package or wrapper in which the article is enclosed. The label on the package should include the name and amount of the active ingredient, batch number, expiry date, manufacturer's name and address, number of units per package, and dosage form. The package insert and/or the package should include relevant information, such as directions for use, content of all ingredients, adverse effects, contraindications, storage conditions, etc. When drawings or any other designs are added to facilitate adherence to treatment and intake of the medicine, the required GMP information, such as expiry date, batch number, strength, number of units, and dosage form should still be clearly printed in the secondary package.

Zinc tablets and zinc oral solutions should be labelled in terms of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ) and in terms of elemental zinc.

# 3

## Additional specifications for zinc tablets

### 3.1 Dispersibility of zinc tablets

Because this treatment is intended for infants and young children, zinc tablets should be dispersible. The disintegration of a zinc tablet in a small volume (5 mL) of water or breast milk should occur in **less than one minute**. Disintegration is complete when there is no solid part of the tablet left. Because the zinc salts recommended above are all highly soluble in water, when tablets are fully disintegrated the zinc salt can be considered as fully dissolved in the water. Therefore, zinc tablets should be tested for disintegration time, and procurement agencies should check the certificate of analysis for disintegration data.

According to the *USP* monograph, disintegration time of zinc tablets should be complete in less than one minute. Disintegration time can be determined following the methodology described in the *USP* document in Annex 4, which also describes all the specifications of the apparatus necessary for this test and presents schematic descriptions of its dimensions.

For uncoated tablets, the test is carried out as follow:

- 1 dosage unit is placed in each of the six tubes of the disintegration apparatus, using water at  $37\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ ;
- After one minute, the basket is lifted from the water and the tablets are observed;
- All six tablets should disintegrate completely within one minute;
- If one or two tablets fail to disintegrate completely within one minute, the test should be repeated on an additional 12 tablets;
- The results of the test are considered satisfactory if not fewer than 16 out of the total of 18 tablets tested are disintegrated completely within one minute.

### 3.2 Uniformity of content

Dosage forms, such as tablets, are evaluated for their uniformity of content — meaning that the amount of active ingredients contained in all tablets should be within acceptable limits of the average content. The Assay result for the content, determined on a bulked sample of 20 tablets (see section 2.4), has to be within acceptable limits of the labelled claim. The uniformity limits below relate the zinc content in a single tablet to the average content.

In the case of zinc sulfate tablets, the uniformity of content is determined by measuring the content of each of 10 individual tablets using the titration method of the assay described above. While in the assay, not fewer than 20 tablets are powdered, and only a portion of this powder is used to make a zinc sulfate solution; in the uniformity of content test, each tablet is powdered and used separately to make a solution of zinc sulfate. The content of each tablet is then estimated using EDTA coloured titration described in section 2.4.1. After titration the amount of zinc in each tablet should be within  $\pm 15\%$  of the average amount of the active ingredient. However, if

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one individual tablet deviates by more than  $\pm 15\%$ , but is within  $\pm 25\%$  of the average amount of the active ingredient, examine a further 20 tablets drawn from the same original sample as the first 10 tablets. The preparation under test complies only if the amount of zinc found in no more than one out of 30 tablets deviates by more than  $\pm 15\%$  of the average amount. None should deviate by more than  $\pm 25\%$  of the average amount.

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# 4

## Additional specifications for zinc oral solutions

### 4.1 pH

The pH is a measure of the acidity or alkalinity of a solution. A pH value of 7 is considered neutral. Values below 7 indicate acidity, while those higher than 7 indicate alkalinity. The pH of zinc sulfate oral solution should be between 2.5 and 4.5 as specified in the *USP* monograph. The method to measure the pH of pharmaceutical preparation and the instruments required are described in details in Annex 5. This test is widely used by drug quality control laboratories. The pH is determined by using a suitable and properly standardized potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity. The pH should be measured at temperature of  $25\text{ }^{\circ}\text{C} \pm 2^{\circ}$ . The pH meter should be standardized using certified commercial pH buffers with a pH value accurate to 0.01 pH unit. If the pH of zinc solution is outside the range indicated by the monograph, the stability as well as the taste of the product could be affected.

### 4.2 Specific gravity

Specific gravity is the heaviness of a substance compared to the same volume of water. The specific gravity of zinc sulfate oral solution is between 1.18 and 1.24 as specified in the *USP* monograph (see Annex 6). The specific gravity of a liquid, unless otherwise stated, is the ratio of the weight of the liquid in air at  $25\text{ }^{\circ}\text{C}$  to that of an equal volume of water at the same temperature. The measurement could be done by weighing the tested liquid and a similar volume of water in a special recipient (like a flask) called a pycnometer at constant temperature.

- Select a scrupulously clean, dry pycnometer that has been calibrated previously by determining its weight empty and after it is completely filled with recently boiled water whose temperature is maintained at  $25\text{ }^{\circ}\text{C}$ . Subtract the weight of the empty pycnometer from the weight of the pycnometer containing water to obtain the weight of the water at  $25\text{ }^{\circ}\text{C}$  ( $W_w$ ).
- Adjust the temperature of the liquid to be tested to about  $20\text{ }^{\circ}\text{C}$ , and completely fill the pycnometer with it.
- Then, adjust the temperature of the filled pycnometer to  $25\text{ }^{\circ}\text{C}$ , and remove any excess of liquid and weigh the filled pycnometer. Subtract the weight of the empty pycnometer from the weight of the filled pycnometer with the tested liquid to obtain the weight of the tested liquid at  $25\text{ }^{\circ}\text{C}$  ( $W_l$ ).
- The specific gravity of the liquid is determined by dividing the weight of the tested liquid contained in the pycnometer by the weight of water contained in it both determined at  $25\text{ }^{\circ}\text{C}$ :

$$sp = W_l / W_w.$$

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# Acceptability of zinc tablet and zinc oral solutions

## 5.1 Evaluation of taste masking

Water-soluble zinc salts have a strong bitter metallic after-taste, and children will refuse to take the medicine if this metallic after-taste is not completely masked.

However, this organoleptic characteristic of medicines is not a usual specification required by pharmacopoeial monographs, because taste can be assessed only by taking the medicine. A short guide on how to evaluate the taste of a medicine has been published by the European Medicines Agency Committee for Medicinal Products for Human Use (see Annex 7). This guide can be useful to manufacturers intending to develop zinc products for treatment of diarrhoea in children.

During the procurement process, the candidate zinc products (tablets or oral solutions) should be evaluated for taste-masking by having them tasted by mothers and some children to make sure that the taste masking is effective and the zinc products acceptable. Acceptance of the product by mothers first is critical to adherence to treatment by children.

Taste masking is often done by adding fruit flavours to the product. The procuring entities should bear in mind, however, that the product will be used by children and the taste of certain fruit would not be accepted by children unfamiliar with that fruit. The flavours or sweeteners must be common to the areas where the product will be used.

Procurement agencies must also review data about any taste trials conducted by the manufacturer of the zinc tablets or oral solution.

## 5.2 Evaluation of acceptability and adherence to treatment

Adherence to the treatment regimen for 10 to 14 days is essential to ensure the full effect of zinc for the prevention and treatment of diarrhoea. However, adherence to treatment can be obtained only if the zinc products promoted for use in the management of diarrhoea are acceptable to infants and young children.

So, it is strongly advised that all zinc products considered for use in the management of diarrhoea be tested for acceptability using a standard methodology. Such a methodology (Annex 8) should allow one to precisely determine the proportion of children receiving zinc for a duration considered satisfactory. As a general guideline, a treatment may be considered to have good acceptability if 80% of the prescribed treatment is taken by at least 70% of the children.

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# 6

## Other considerations

### 6.1 Product formulation and production

It is recommended for the management of diarrhoea to use a product containing **only** zinc. It is especially important not to use zinc formulation also containing **iron**, because iron may interfere with zinc absorption.

The zinc dosage form, whether produced locally or imported, should be manufactured according to the WHO standards of GMPs as mentioned before. The stability studies should be performed according to the WHO guidelines entitled “Guidelines for stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms, Annex 5, WHO Technical Report Series, No. 863, 1996, as amended, see page 12, WHO Technical Report Series, No 937, 2006<sup>1</sup> and these data should be available during the procurement.

### 6.2 Product registration

Zinc tablets and oral solutions should be registered as medicines to be sold over the counter (OTC). Medicine registration procedures and requirements are different from country to country; however, the following are the minimum guarantees a drug regulatory authority should require in order to register zinc tablet or oral solution:

- Certificate showing that the product was manufactured in a GMP facility,
- Certificate of analysis showing that the product conforms to an appropriate pharmacopoeial monograph,
- Assurance that the dispersibility, dosage, disintegration time, and masking of the taste are correct, and
- Complete information about the manufacturing process, the ingredients and their origin, the quality control data, the stability, the packaging, and the labelling that is up to standard.

More information on this topic can be found in the document entitled “Implementing the new recommendation for the management of diarrhoea — Guidelines for policy makers and programme managers”<sup>2</sup>, and on the WHO web page entitled “Medicines Policy and Standards, Technical Cooperation for Essential Drugs and Traditional Medicine” at <http://www.who.int/medicines/en>.

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<sup>1</sup> WHO Expert Committee on Specifications for Pharmaceutical Preparations - Fortieth Report - Technical Report Series, No 937. WHO/Geneva, 2006 (ISBN-13 9789241209373).

<sup>2</sup> Implementing the new recommendation for the management of diarrhoea - Guidelines for policy makers and programme managers. World Health Organization, 2006 (ISBN 92 4 159421 7) [http://www.who.int/child-adolescent-health/New\\_Publications/CHILD\\_HEALTH/ISBN\\_92\\_4\\_159421\\_7.pdf](http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/ISBN_92_4_159421_7.pdf).

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### 6.3 Inclusion of zinc in the National Essential Medicines List

According to the World Health Organization, essential medicines are “those that satisfy the primary health care needs of the population”. Zinc sulfate tablets and oral solution in 10 mg per unit dosage forms are included in the 14<sup>th</sup> Edition of the WHO Model List of Essential Medicines (<http://www.who.int/entity/medicines/services/expertcommittees/essentialmedicines/TRS933SelectionUseEM.pdf>).

It is important to update national EML to include zinc products, as the EML guides the selection of medicines for national procurement and for the standard treatment guidelines (STGs). As most countries have not automatically adopted the new WHO EML that was revised in March 2005 (see above), submission of an application to the national EML committee for the inclusion of the new ORS and zinc will be necessary. It is not necessary to specify the particular salt of zinc in the EML; it is sufficient to mention 10 mg and 20 mg elemental zinc.

### 6.4 Post-marketing surveillance and adverse drug reaction (ADR) monitoring<sup>1</sup>

As should be the case when any new medicine is introduced to the country, post-marketing surveillance and adverse drug reaction (ADR) pilot programmes should be put in place. Such programmes will help check the quality of the new product in the market and prevent any widespread harmful reaction to it. A systematic surveillance programme ensures that samples are randomly collected from the market and tested at scheduled intervals by the quality control laboratory in the country. An ADR programme will monitor the safety of the newly introduced medicine. Product labels and package inserts should be checked against those approved for registration. A system of product complaints regarding quality should also be in place.

#### 6.4.1 Adverse drug reactions

To date there has been no report of severe adverse reaction from any form of zinc supplementation for the treatment of diarrhoea. Trials have included more than 9,100 children who have participated in efficacy trials in both the placebo and zinc study arms and nearly 12,000 child-years of observation from one large effectiveness trial. The zinc doses have ranged from 5 to 45 mg per day and have been well-tolerated in diverse settings. Trials have found no differences in adverse reactions based on the different zinc salts (sulfate, acetate, and gluconate) used in supplementation trials. Presently, the only reported side effect of zinc supplementation has been vomiting. Of the seven trials that have reported on incidences of vomiting, only two reported more vomiting in the children who received the zinc than in the placebo group. One trial reported higher vomiting in the zinc versus the control group when zinc was given with multiple micronutrients but not when given alone. Copper status has been evaluated in four trials. Three of the four trials did not find a difference in serum copper status after supplementation. One trial did find a significant trend of decreased copper level when comparing zinc supplemented children to non-zinc supplemented children. However, these children were malnourished with persistent diarrhoea at baseline. Overall, there is no substantial evidence of short-term zinc supplementation for diarrhoea management adversely affecting copper status. In addition to trials treating diarrhoea, there have been several

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<sup>1</sup> Adverse Drug Reactions Monitoring (WHO). [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/advdrugreactions/en/index.html](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/advdrugreactions/en/index.html).

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trials assessing the efficacy of zinc for the treatment of pneumonia, malaria, measles, and the common cold. Treatments have typically included approximately 20 mg per day for the duration of the illness, which is typically less than two weeks. There have been no serious adverse events linked to zinc supplementation reported in these studies.

The human body has efficient homeostatic mechanisms that regulate the absorption and retention of zinc, which decreases the likelihood of toxic build up and adverse effects in the body. Ingesting too much zinc at once can cause gastric distress and the typical signs and symptoms that are often associated with food poisoning. High doses of zinc for long periods of time may lead to a lower concentration of plasma lipoproteins and decrease copper absorption, yet this is easily corrected by adjusting the intake levels of zinc and copper accordingly. There have been only a few reported cases of adverse effects due to excessive zinc intake. The majority of these cases occurred in adults who knowingly ingested many times a normal daily dose of zinc over a long period of time. Even in the most extreme cases of more than 1 gram of zinc taken daily for many months, the majority of patients recovered from all signs and symptoms, including fatigue, gastrointestinal discomfort, and anaemia as soon as zinc intake was decreased and serum zinc returned to within normal range. In a report by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, there was only 1 reported case in a child where the likelihood of causation by zinc was “certain” (side effect: epistaxis). There were only 4 reports of possible adverse responses to zinc ingestion among children less than 10 years of age.

#### 6.4.2 Reporting of adverse drug reactions

Despite the absence of serious adverse effects linked to the use of the new ORS or to the use of zinc in the literature, once treatment becomes more widespread, mechanisms should be in place for active reporting of adverse events associated with their use. This may be ensured by the establishment of a regular reporting system through the health facilities and/or through special studies. This system for monitoring adverse events must be developed within the systems for monitoring adverse events for other medicines. Forms for recording adverse events should be provided to the health facilities. At each level of the health system, a point person must be appointed to collate the data, and a system for reporting back to the central level should be developed.

Reporting quality and safety data to international bodies, e.g., WHO, UNICEF, and others, will both help other countries and establish a history of the new zinc dosage forms.

### 6.5 Quality assurance for the procurement of zinc tablets and oral solutions<sup>1</sup>

While good procurement practices are the first line of defence in assuring the quality of medicines used in the country, product quality surveillance must be integrated at all levels of the health system to ensure that zinc oral solutions and/or tablets available in the market are of the appropriate quality. A comprehensive system includes ensuring quality during medicine registration, procurement, and distribution through the public and private sectors. It also includes a mechanism for removing from the supply chain any products found to be of inappropriate quality. Sections 2, 3, and 4 of this document are intended to provide suitable specifications for use in situations when quality control testing is required.

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<sup>1</sup> A model quality assurance system for procurement agencies (Recommendations for quality assurance systems focusing on pre-qualification of products and manufacturers, purchasing, storage and distribution of pharmaceutical products). Annex 6, WHO Technical Report Series 937, 2006.

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# Specifications of zinc products for use in the management of diarrhoea

## 1. Dosage

- Each individual dose of zinc should contain 10 mg or 20 mg of elemental zinc.
- For oral solutions, the concentration of elemental zinc should be either 10 mg/5 mL or 20 mg/5 mL.
- For tablets, each tablet should contain either 10 mg or 20 mg of elemental zinc. Tablets containing 20 mg of elemental zinc should be scored.

## 2. Type of zinc salt

The zinc salt used to prepare oral solutions or tablets for use in the management of diarrhoea should be soluble in water. Therefore, only the following zinc salts should be used:

- Zinc sulfate
- Zinc acetate
- Zinc gluconate.

## 3. Type of tablets

As the zinc tablets will be used in infants and young children, it is essential that the tablets be dispersible. This means that the tablets should completely disaggregate in less than 60 seconds in 5 mL of tap water or breast milk.

## 4. Taste-masking

Zinc salts have a bad metallic taste that led to the use of zinc as a vomiting agent until the beginning of the twentieth century. To get infants and young children to take zinc tablets or zinc oral solution repeatedly every day for 10–14 days, it is essential that this metallic taste be totally masked.

## 5. Packaging

Tablets and oral solutions should be packaged to provide a full treatment of 10–14 daily doses of zinc (i.e., for oral solutions containing 20 mg/5 mL, bottles should contain 50–75 mL of oral solution; for tablets, a blister should contain 10–14 tablets).

## 6. Shelf life

The zinc product should have a shelf life of at least two years.

# USP monograph for zinc sulfate tablets

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Zinc Sulfate Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labelled amount of  $ZnSO_4 \cdot H_2O$ . It may contain one or more suitable flavours and sweeteners.

**Packaging and storage:** Preserve in well-closed containers, and store at controlled room temperature.

**Labelling:** Label the Tablets in terms of zinc sulfate ( $ZnSO_4 \cdot H_2O$ ) and in terms of elemental zinc.

**Identification:**

- Test solution* — Dissolve a portion of powdered Tablets in water to obtain a solution containing about 0.05g of zinc sulfate per mL.
- Glycerine Solution* — a mixture of glycerine and water (85:15).
- Sodium Sulfide Solution* — Dissolve 12 g of sodium sulfide with heating in 45 mL of a mixture of water and glycerine solution (10:29), allow to cool, and dilute to 100 mL with the same mixture of solvents. The solution should be colourless.
- Hydrochloric Acid Solution* — Transfer 20g of hydrochloric acid to a 100-mL volumetric flask and dilute to volume with water and mix.
- Barium Chloride Solution* — Transfer 61 g of barium chloride to a 1000-mL volumetric flask, dissolve in water, and dilute to volume with the same solvent and mix.
- Sodium Hydroxide Solution* — Transfer 42 g of sodium hydroxide to a 100-mL volumetric flask, and dilute to volume with water and mix.
- Ammonium Chloride Solution* — Transfer 107 g of ammonium chloride to a 1000-mL volumetric flask, and dilute to volume with water and mix.

**A:** To 5 mL of the *Test solution* add 1 mL of *Hydrochloric Acid Solution* and 1 mL of *Barium Chloride Solution*. A white precipitate is formed.

**B:** To 5 mL of the *Test solution* add 0.2 mL of *Sodium Hydroxide Solution*. A white precipitate is formed. Add an additional 2 mL of *Sodium Hydroxide Solution*, and the precipitate dissolves. Add 10 mL of *Ammonium Chloride Solution* and the solution remains clear. Add 0.1 mL of *Sodium Sulfide Solution* and a white precipitate is formed.

**Disintegration:** 60 seconds.

**Uniformity of dosage units:** Meet the requirements.

**Residual solvents:** Meet the requirements.

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**Assay:** Weigh and finely powder not fewer than 20 tablets. Transfer an accurately weighed portion of the powder, equivalent to about 90 mg of zinc, to a 200-mL volumetric flask. Dissolve in 15 mL of dilute acetic acid, and sonicate for 15 minutes. Dilute with water to volume, and mix. Add 50 mg of xylene orange triturate to the solution, and mix. Neutralize the solution with about 2 g of methenamine until the solution is a violet-pink colour. Titrate with 0.1 M edetate disodium VS until the solution is yellow. Each mL of 0.1 M edetate disodium VS is equivalent to 17.946 mg of  $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ .

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# USP monograph for zinc sulfate oral solution

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Zinc Sulfate Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labelled amount of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ). It may contain one or more suitable flavours and sweeteners.

**Packaging and storage:** Preserve in well-closed containers protected from light, and store in a cool, dry place.

**Labelling:** Label the Oral Solution in terms of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ) and in terms of elemental zinc.

**Identification:** The Oral Solution responds to the tests for *Zinc* and for *Sulfate*.

**pH:** Between 2.5 and 4.5.

**Specific gravity:** Between 1.18 and 1.24.

**Residual solvents:** Meets the requirements.

**Assay:** Transfer an accurately measured volume of Oral Solution, equivalent to about 99 mg of  $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$  to a 250-mL flask. Add 50 mL of water and 10 mL of ammonia–ammonium chloride buffer TS and 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS to a green endpoint. Each mL of 0.05 M edetate disodium is equivalent to 8.973 mg of zinc sulfate ( $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ ).

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# Disintegration

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This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troche, or are to be chewed, or are designed as modified-release dosage forms. Determine the type of units under test from the labelling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

## Apparatus

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 138 to 155 mm in height and having an inside diameter of 97 to 110 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35 °C and 39 °C, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 1.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

**Basket-Rack Assembly** — The basket-rack assembly consists of six open-ended transparent tubes, each  $77.5 \pm 2.5$  mm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plastic plates, each 8.8 to 9.2 cm in diameter and 5 to 8.5 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the centre of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.57 to 0.66 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat, provided the specifications for the glass tubes and the screen mesh size are maintained.

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**Disks** — The use of disks is permitted only where specified or allowed in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk  $9.5 \pm 0.15$  mm thick and  $20.7 \pm 0.15$  mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel  $2 \pm 0.1$  mm holes extend between the ends of the cylinder. One of the holes is centred on the cylindrical axis. The other holes are centred  $6 \pm 0.2$  mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centres of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of  $1.6 \pm 0.1$  mm, and its bottom edges lie at a depth of  $1.6 \pm 0.1$  mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of  $9.4 \pm 0.2$  mm, and its centre lies at a depth of  $2.6 \pm 0.1$  mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph, add a disk to each tube, and operate the apparatus as directed under *Procedure*.

## **Procedure**

**Uncoated Tablets** — Place 1 dosage unit in each of the six tubes of the basket and, if prescribed, add a disk. Operate the apparatus, using water or the specified medium as the immersion fluid, maintained at  $37 \pm 2$  °C. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not fewer than 16 of the total of 18 tablets tested are disintegrated.

# pH

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For compendial purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity, the glass electrode, and a suitable reference electrode. The instrument should be capable of sensing the potential across the electrode pair and, for pH standardization purposes, applying an adjustable potential to the circuit by manipulation of “standardization,” “zero,” “asymmetry,” or “calibration,” control, and should be able to control the change in millivolts per unit change in pH reading through a “temperature” and/or “slope” control. Measurements are made at  $25 \pm 2$  °C, unless otherwise specified in the individual monograph or herein.

The pH scale is defined by the equation:

$$\text{pH} = \text{pH}_s + (E - E_s) / k,$$

in which  $E$  and  $E_s$  are the measured potentials where the galvanic cell contains the solution under test, represented by pH, and the appropriate *Buffer Solution for Standardization*, represented by  $\text{pH}_s$ , respectively. The value of  $k$  is the change in potential per unit change in pH and is theoretically  $[0.05916 + 0.000198 (t - 25 \text{ °C})]$  volts at any temperature  $t$ .

It should be emphasized that the definitions of pH, the pH scale, and the values assigned to the *Buffer Solutions for Standardization* are for the purpose of establishing a practical, operational system so that results may be compared between laboratories. The pH values thus measured do not correspond exactly to those obtained by the definition,  $\text{pH} = -\log a_{H^+}$ . So long as the solution being measured is sufficiently similar in composition to the buffer used for standardization, the operational pH corresponds fairly closely to theoretical pH. Although no claim is made with respect to the suitability of the system for measuring hydrogen-ion activity or concentration, the values obtained are closely related to the activity of the hydrogen ion in aqueous solutions.

Where a pH meter is standardized by use of an aqueous buffer and then used to measure the “pH” of a nonaqueous solution or suspension, the ionization constant of the acid or base, the dielectric constant of the medium, the liquid-junction potential (which may give rise to errors of approximately 1 pH unit), and the hydrogen-ion response of the glass electrode are all changed. For these reasons, the values so obtained with solutions that are only partially aqueous in character can be regarded only as apparent pH values.

## Buffer Solutions for Standardization of the pH Meter

*Buffer Solutions for Standardization* are to be prepared as directed in the accompanying table.<sup>1</sup> Buffer salts of requisite purity can be obtained from the National Institute of Standards and Technology. Solutions may be stored in hard glass or polyethylene bottles fitted with a tight closure or carbon dioxide-absorbing tube (soda lime). Fresh solutions should be prepared at intervals not to exceed 3 months using carbon dioxide-free water. The table indicates the pH of the buffer solutions as a function of temperature. The instructions presented here are for the preparation of solutions having the designated molal (*m*) concentrations. For convenience, and to facilitate their preparation, however, instructions are given in terms of dilution to 1000 mL volume rather than specifying the use of 1000 g of solvent, which is the basis of the molality system of solution concentration. The indicated quantities cannot be computed simply without additional information.

### pH Values of buffer solutions for standardization

Temperature °C	Potassium Tetraoxalate 0.05 m	Potassium Biphthalate 0.05 m	Equimolal Phosphate 0.05 m	Sodium Tetraborate 0.01 m	Calcium Hydroxide Saturated at 25°
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.68	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.69	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.70	4.05	6.83	9.04	11.84
50	1.71	4.06	6.83	9.01	11.71
55	1.72	4.08	6.83	8.99	11.57
60	1.72	4.09	6.84	8.96	11.45

**Potassium Tetraoxalate, 0.05 m** — Dissolve 12.61 g of  $\text{KH}_3(\text{C}_2\text{O}_4)_2 \cdot 2\text{H}_2\text{O}$  in water to make 1000 mL.

**Potassium Biphthalate, 0.05 m** — Dissolve 10.12 g of  $\text{KHC}_8\text{H}_4\text{O}_4$ , previously dried at 110 °C for 1 hour, in water to make 1000 mL.

**Equimolal Phosphate, 0.05 m** — Dissolve 3.53 g of  $\text{Na}_2\text{HPO}_4$  and 3.39 g of  $\text{KH}_2\text{PO}_4$ , each previously dried at 120 °C for 2 hours, in water to make 1000 mL.

**Sodium Tetraborate, 0.01 m** — Dissolve 3.80 g of  $\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$  in water to make 1000 mL. Protect from absorption of carbon dioxide.

<sup>1</sup> Commercially available buffer solutions for pH meter standardization, standardized by methods traceable to the National Institute of Standards and Technology (NIST), labeled with a pH value accurate to 0.01 pH unit may be used. Solutions prepared from ACS reagent grade materials or other suitable materials, in the stated quantities, may be used provided the pH of the resultant solution is the same as that of the solution prepared from the NIST certified material.

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**Calcium Hydroxide, saturated at 25 °C**—Shake an excess of calcium hydroxide with water, and decant at 25 °C before use. Protect from absorption of carbon dioxide.

Because of variations in the nature and operation of the available pH meters, it is not practicable to give universally applicable directions for the potentiometric determinations of pH. The general principles to be followed in carrying out the instructions provided for each instrument by its manufacturer are set forth in the following paragraphs. Examine the electrodes and, if present, the salt bridge prior to use. If necessary, replenish the salt bridge solution, and observe other precautions indicated by the instrument or electrode manufacturer.

To standardize the pH meter, select two *Buffer Solutions for Standardization* whose difference in pH does not exceed 4 units and such that the expected pH of the material under test falls between them. Fill the cell with one of the *Buffer Solutions for Standardization* at the temperature at which the test material is to be measured. Set the “temperature” control at the temperature of the solution, and adjust the calibration control to make the observed pH value identical with that tabulated. Rinse the electrodes and cell with several portions of the second *Buffer Solution for Standardization*, then fill the cell with it, at the same temperature as the material to be measured. The pH of the second buffer solution is within  $\pm 0.07$  pH unit of the tabulated value. If a larger deviation is noted, examine the electrodes and, if they are faulty, replace them. Adjust the “slope” or “temperature” control to make the observed pH value identical with that tabulated. Repeat the standardization until both *Buffer Solutions for Standardization* give observed pH values within 0.02 pH unit of the tabulated value without further adjustment of the controls. When the system is functioning satisfactorily, rinse the electrodes and cell several times with a few portions of the test material, fill the cell with the test material, and read the pH value. Use carbon dioxide-free water ... for solution or dilution of test material in pH determinations. In all pH measurements, allow a sufficient time for stabilization.

Where approximate pH values suffice, indicators and test papers may be suitable.

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## Specific gravity

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Unless otherwise stated in the individual monograph, the specific gravity determination is applicable only to liquids, and, unless otherwise stated, is based on the ratio of the weight of a liquid in air at 25 °C to that of an equal volume of water at the same temperature. Where a temperature is specified in the individual monograph, the specific gravity is the ratio of the weight of the liquid in air at the specified temperature to that of an equal volume of water at the same temperature. When the substance is a solid at 25 °C, determine the specific gravity at the temperature directed in the individual monograph, and refer to water at 25 °C.

### Method 1

**Procedure** — Select a scrupulously clean, dry pycnometer that previously has been calibrated by determining its weight and the weight of recently boiled water contained in it at 25 °C. Adjust the temperature of the liquid to about 20 °C, and fill the pycnometer with it. Adjust the temperature of the filled pycnometer to 25 °C, remove any excess of the liquid, and weigh. Subtract the tare weight of the pycnometer from the filled weight of the pycnometer. When the monograph specified a temperature different from 25 °C, filled pycnometers must be brought to the temperature of the balance before they are weighed. Subtract the tare weight of the pycnometer from the filled weight.

The specific gravity of the liquid is the quotient obtained by dividing the weight of the liquid contained in the pycnometer by the weight of the water contained in it, both determined at 25 °C, unless otherwise directed in the individual monograph.

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# Qualitative evaluation of the taste by a taste panel<sup>1</sup>

Consumer testing is acknowledged as the best population to assess a product. Consumers are regarded as individuals who are pre-screened to be actual users of the product tested with particular interest to product quality. In line with this definition and taking into consideration the sensory differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of paediatric formulations.

## 1. Quantitative evaluation of the taste on the basis of analytical methods

The analytical method utilized is very similar to that for determination of the drug release and is mainly based on the detection of drug substance within a short period of time in aqueous medium (e.g., artificial saliva). It is regarded as an indirect method for assessing taste masking since it does not contribute in the evaluation of taste and sweetness of the drug product. It is commonly used for measuring the effectiveness of coating and complexation within formulation. Taste masking is achieved when in the frame of 1–2 min drug substance is either not detected or the detected amount is below the threshold for identifying its bad taste.

## 2. Quantitative evaluation of the taste using a taste sensor

The taste sensor (electronic tongue, e-tongue) can detect taste in a manner similar to human gustatory sensation. Taste substances cause changes in electric charge density of the lipid/polymer membrane surface and/or ion distribution near the surface of the membrane of the sensor. The total electric change is given as the response membrane electric potential for the substance tested. The response electric potential is different for substances possessing different taste qualities in each membrane and differs from one membrane to the other. Thus, taste information is acquired as a pattern of membrane potentials (*I*). The output of the electronic tongue is the taste quality of the formulations tested and their intensity compared either to established standards (eg., assessment of bitterness using quinine hydrochloride or caffeine solution at different concentration levels) or other references (e.g., the formulation containing the active compound to be tested without any tasting masking agents). The methodology may be applicable to many paediatric dosage forms (2,3). The procedure is comparatively inexpensive and easy to conduct. In addition to taste evaluation during drug product development, taste sensors would also be useful in screening new substances for bitterness and monitoring the stability of taste over time.

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<sup>1</sup> Reflection paper: Formulation of choice for the paediatric formulation. EMEA/CHMP/PEG/194810/2005.  
<http://www.emea.eu.int/pdfs/human/peg/19481005en.pdf>.  
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### 3. Qualitative evaluation of the taste by a taste panel

Consumer testing is acknowledged as the best population to assess a product. Consumers are regarded as individuals who are pre-screened to be actual users of the product tested with particular interest to product quality. In line with this definition and taking into consideration the sensory differences between adults and children, it is evident that the children as a target population are regarded as the most suitable panel for taste assessment of paediatric formulations.

#### 3.1 Recommendations for performing taste trials in children

To design a palatability study in children the following parameters need to be considered as key elements:

- The test should be short in order to match children's attention span.
- As children are easily distracted, the test has to be intrinsically motivating and "fun" to do.
- The procedure has to be as easy as possible so that even very young children (e.g., pre-schoolers) could understand it.
- In order to ensure reliable assessment preventing confusion by the children and taste fatigue, the number of variants to be tested should be limited to a maximum of four.

Palatability studies are not described in any regulatory guidance but must be considered as clinical studies performed by qualified personnel with Ethical Committee approval and informed consent from parents or guardians and assent from the child as appropriate. There may be ethical difficulties in designing suitable safe studies in which children can easily participate.

#### 3.2 Participation and test performance

Generally, children aged 4 years and older are considered to be able to participate in taste trials. Younger children are very often shy and reluctant. Furthermore, their ability to understand and follow the guidance is sometimes limited; they also lose their interest or have difficulty concentrating during the entire testing period. The failure rate varies up to 50% depending on the design and duration of the test. In addition, they are often unable to communicate their feeling and preferences (4,5). In order to increase children's understanding and motivation it is recommended to start off with either high concentrations of the testing agent to be assessed (flavour or sweetener) or with known compounds (e.g., commonly used flavours) followed by the more specific, unusual one (e.g., strawberry or cherry followed by passion fruit). In some cases to begin the test with high concentrations of testing agent (e.g., sweetener) would be inappropriate due to the unpleasant sweet taste or the bitter aftertaste. Procedures to remove the previous taste may include repeated rinsing of the mouth, eating of salty crackers, and a sufficiently long interval between sessions.

#### 3.3 Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective i.e., what exactly should be determined. The test objective will determine the type and age of subjects and the methodology to design, conduct, and interpret the study and its outcome (6).

- Affective testing includes acceptance/preference testing. Typical questions addressed are "which sample do you prefer", "how much do you like it", and "what don't you like".
- Analytical testing requires the use of objective sensory methodologies aiming to determine the characteristics/properties of the test item, without defining acceptance/preference measures. Analytical testing answers questions such as "which sample is more bitter" or

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“which sample is different”. Analytical methods help define the sensory properties of the medicinal product preparation and differentiate between variants but will not directly predict how much a variant will be liked. It is often used as a technical tool to support development/optimization purposes.

- Ranking is a very straightforward method that can be used for preference or analytical assessment (“please rank samples in order of your personal preference” or “please rank samples in increasing order of bitterness”, respectively). The advantage of this method is its simple procedure. However, the study results may be biased due to limited memory and attention of the tester during the entire testing period. This limitation may be more pronounced depending on the age of the subjects participating.

### 3.4 Evaluation principles

In most cases smell, texture, taste, and aftertaste, and sometimes also appearance (e.g., if coloured) are addressed. The language used in the questionnaire has to be simple, intelligible, and plain for all participants independent of their age, social skills, and developmental level. It is recommended to utilize commonly used terms relevant to the age of the participants to describe these properties:

- sweet, salty, sour, and bitter characterizing the taste
- thin, thick, viscous, gritty aiming to portray the texture of the testing item
- sweet, salty, sour, and bitter but also astringent, numbness, or freshness for the aftertaste

The following two principles for taste evaluation are established in palatability studies with children: verbal judgment and facial hedonic scale (7).

- Verbal judgement followed by scoring in a scale of e.g., 1 to 5 (score 1 corresponds to very good and score 5 to very bad) facilitates the statistical evaluation of the data obtained (8)
- While the facial hedonic scale allows the expression of preferences using a pictorial scale.

Children below 5–6 years are not considered to be able to express differences in taste perception by use of the preferential method. A reliable estimation of differences particularly in this age group (< 5 years) might be achieved using the child’s own spontaneous verbal judgements following a control question. The facial hedonic scale can not be used solely to discriminate between the tastes of tested formulations in the lowest age group. Young children may link the figures with things other than taste (e.g., happy face = I will not stay longer in hospital, sad face = pain or discomfort). Facial expressions and behaviour pattern of the subject itself (wry faces, shrug shoulders, vomit, or spit the formulation out) may also reflect the acceptance of the tested formulation (4,5). In order to assure reliable outcome of a palatability study with young children it is suggested to involve parents, guardians, or health providers in the study, asking about any discomfort or other observations in relation to the acceptance of the study medicine. Since older children judge more critically than younger ones, they are able to discriminate between the formulations using both the verbal judgment and hedonic scale.

Independent of the age of the children and the evaluation principle selected, it is suggested to include in the questionnaire concluding questions to the overall taste evaluation of the formulation such as “which formulation was the best” or “which formulation tasted worst”. Similar approaches may be followed for the assessment of the flavour used: “which of the tested flavours did you like the most” or “which one did you dislike the most”.

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# Design of the acceptability study

Acceptability tests must be considered as clinical studies performed by qualified personnel with Ethical Committee approval and informed consent from parents or guardians.

This acceptability studies should be conducted in communities, in children with acute diarrhoea, who have been prescribed dispersible zinc tablet (one 20-mg tablet per day for 10 days). Blister packs of zinc tablets are given to selected drug-sellers and healthcare providers in the community. A visit to the home of the children prescribed zinc dispersible tablets is arranged 2 weeks after to assess acceptability of and adherence to the instructions for zinc treatment.

The study population should include children aged 3–59 months with an acute diarrhoea episode, whose caretakers sought assistance from one of the selected drug-sellers or healthcare providers and are provided with the zinc blister pack.

## Sample size

To identify a  $\pm 7.5\%$  minimal difference in acceptability between children aged over and below 18 months with an anticipated 70% acceptability ( $p$ ), setting the level of confidence at 95% ( $z = 1.95$ ), the resulting sample size estimate is 140 children per group. To adjust for potential drop-outs, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age-group).

## Measurement

The definitions used for acceptability and adherence are:

**Acceptability:** Acceptability is measured on the basis of a caretaker's report of his/her child's behaviour when given the medicine. The caretakers are asked about their perception of taste of the zinc tablet given to their children compared to other medicines. The response options are better, same, or worse than other medicines.

**Adherence:** Adherence is defined in relation to the dose given, frequency of daily administration, duration of treatment, and preparation (dispersion) of the tablets.

