

MODULE III

ZINC



Manual for Procurement & Supply of
Quality-Assured MNCH Commodities

ZINC

SULFATE, GLUCONATE, ACETATE, AND CITRATE
DISPERSIBLE TABLETS 10 MG, 20 MG
ORAL SOLUTION 10 MG PER UNIT DOSAGE

GENERAL PRODUCT INFORMATION

The use of zinc supplements in addition to ORS is recommended by WHO and UNICEF in the management of acute diarrhea in children.^{1,2} Zinc is also considered to be a lifesaving drug by the UN Commission on Life-Saving Commodities for Women and Children.

Zinc in zinc supplements can be in the form of zinc sulfate, zinc gluconate, zinc acetate, or zinc citrate, all water-soluble zinc salts. The most widely used zinc salt is zinc sulfate, essentially because it is the cheapest of the four zinc salts mentioned above. Clinical trials that have evaluated the efficacy of zinc supplements in the management of diarrhea have used different zinc salts, and no difference in efficacy and safety has been shown. Therefore, all are considered acceptable. However, because zinc sulfate is the most widely used salt of zinc, this document focuses on zinc products containing zinc sulfate. Zinc sulfate is also included in the WHO Model List of Essential Medicines.

Zinc supplements for administration to children could take the form of dispersible tablets or oral solution (syrup). However, because the burden of diarrheal disease is in early childhood, especially among children less than 2 years of age, dispersible tablets are the preferred formulation for the ease of administration and logistics.

¹ WHO. 2005. *The Treatment of Diarrhea: A Manual for Physicians and Other Senior Health Workers*. Geneva: WHO. Available at http://www.who.int/maternal_child_adolescent/documents/9241593180/en/.

² WHO. 2006. *Implementing the New Recommendations on the Clinical Management of Diarrhea: Guidelines for Policy Makers and Programme Managers*. Geneva: WHO. Available at http://www.who.int/maternal_child_adolescent/documents/9241594217/en/.

A strong safety profile allows the potential classification of zinc as an over-the-counter drug, without requiring a prescription.

KEY CONSIDERATIONS IN PROCUREMENT

1. Procured products should contain only zinc as an active ingredient to support the effective prevention and treatment of diarrhea in children. Many vitamin products and other nutritional supplements containing zinc that are available commercially, do not have the recommended dosage of zinc. It is especially important not to use zinc formulations containing iron because iron may interfere with zinc absorption.
2. Procurement should be made from trusted sources. This includes manufacturers prequalified by WHO and those with a proven record of quality products. Zinc products must comply with the quality specifications as detailed in the “[Product Specifications](#)” module below.
3. Procurers need to focus on product quality to ensure that it is safe for patient use as.

KEY QUALITY CONSIDERATIONS

Product specification

Zinc tablets should be procured only in dispersible form as treatment is intended for use in infants and young children. Tablets should disaggregate completely in less than 60 seconds in 5 mL of normal drinking water or breast milk. Therefore, zinc tablets must be tested for disintegration time according to the compendial monograph. Procurers should check the certificate of analysis for disintegration data.

Packaging and labeling

Procure only zinc dispersible tablets that are packaged in blisters as they are water-sensitive. Zinc tablets packaged in bottles or other similar multidose containers should not be procured because they will be subjected to humidity each time the container is opened and may start to disintegrate.

Only one strength of tablets should be procured to avoid dosing errors. Zinc dispersible tablets may contain either 10 or 20 mg of zinc. If 10-mg zinc tablets are procured, 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 one-half tablet will be given each day, and therefore the 20-mg zinc tablets will need to be scored to facilitate this. Data demonstrating the weight uniformity of tablet halves should be provided for 20-mg scored tablets.

For zinc oral solutions, a concentration of 10 mg of elemental zinc per 5 mL (per 1 teaspoon) should be procured, because it is difficult to accurately

measure one-half teaspoon of solution. It means that infants younger than 6 months of age will receive 1 teaspoon, while older children will need 2 teaspoons of oral solution per day.

Note: The method by which parents and caregivers measure liquid medications for children has long been identified as potentially problematic. Measuring devices used to administer liquid medications have included a variety of implements, including household teaspoons, dosing cups, droppers, cylindrical spoons, and oral syringes. Despite the common use, it has been demonstrated that household teaspoons do not accurately measure the 5-mL volume intended in dosing medications. For this reason, the use of dispersible tablets is preferable once the final product contains the correct dosage for the patient.^{3,4}

Additional information about the packaging and labeling can be found in the Annex.

Storage, transportation, and distribution

Procurers need to verify from manufacturers there is satisfactory stability data to support shelf life and storage conditions.

Procurers need to verify the stability data to ensure that the zinc product has a shelf life of at least 2 years when stored at room temperature. Zinc oral solutions are less stable than tablet dosage forms; therefore, their shelf life may be shorter than the shelf life of tablets. In low- and middle-income countries, the proper storage of oral solutions can also be more difficult than the storage of tablets. When considering whether zinc oral solutions should be procured, cost must be considered. This includes not just the price of the product but also the cost of storage and transportation.

Preference should be given to formulations with long-term stability studies conducted under zone IVa or zone IVb conditions (30°C/65%RH/75%RH).

Additional information about the finished product storage requirement can be found in Section 3.

Other specific requirements

During the procurement process, procurers should review data about the acceptability study conducted by the manufacturer of the zinc tablets or oral solution. Adherence to the treatment regimen for 10–14 days is essential to ensure the full effect of zinc for the prevention and treatment of diarrhea. However, adherence to treatment can be obtained only if the zinc products are acceptable to infants and young children. A short guide on how to conduct an acceptability study is described in the Annex.

Procurers should ensure the candidate zinc products (tablets or oral solutions) have been evaluated for taste masking during the procurement

³ Johnson, A., and R. Meyers, 2016. "Evaluation of Measuring Devices Packaged With Prescription Oral Liquid Medications." *Journal of Pediatric Pharmacology and Therapeutics* 21(1): 75–80.

⁴ Batchelor, H. K., and J. F. Marriott. 2015. "Formulations for Children: Problems and Solutions." *British Journal of Clinical Pharmacology* 79(3): 405–18.

process. Water-soluble zinc salts have a strong, bitter, metallic aftertaste, and children will refuse to take the medicine if the metallic aftertaste is not completely masked. Taste masking is often done by adding fruit flavors to the

product. Added flavors or sweeteners must be common to the areas where the product will be used. Acceptance of the product first by mothers is critical to adherence to treatment by children. A short guide on how to evaluate the taste is described in the Annex.

Name of the Medicinal Product

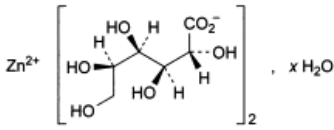
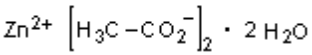
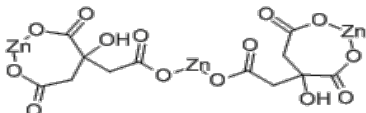
Zinc (sulfate, gluconate, acetate, citrate)

Chemical Name

ZINC PRODUCT	CHEMICAL NAME
Zinc sulfate*	Zinc sulfate monohydrate, zinc sulfate heptahydrate
Zinc gluconate	Zinc bis(D-gluconate) hydrate; D-Gluconic acid, zinc salt, hydrate (2:1:?)
Zinc acetate	Zinc acetate dihydrate; Acetic acid, zinc salt, hydrate (2:1:2)
Zinc citrate	Zinc citrate; Trizinc dicitrate; Citric acid, zinc salt

*Zinc sulfate contains one or seven molecules of water of hydration. Zinc sulfate monohydrate is used in the manufacture of tablets, whereas the monohydrate or heptahydrate are used in the oral solution.

Chemical Structure

ZINC PRODUCT	CHEMICAL STRUCTURE
Zinc sulfate	$ZnSO_4, H_2O$ (monohydrate); $ZnSO_4, 7H_2O$ (heptahydrate)
Zinc gluconate	$C_{12}H_{22}O_{14}Zn, xH_2O$ 
Zinc acetate	$C_4H_6O_4Zn, 2H_2O$ 
Zinc citrate	$C_{12}H_{10}O_{14}Zn_3$ 

Pharmaceutical Form

- Dispersible tablet
- Oral solution

Advantages of dispersible tablets versus oral solutions include:

- Easier to produce and production costs are less, which make them more affordable than standard liquid formulations
- More easily transportable and incurring lower handling and transportation costs for the same amount of active ingredient (less volume, less weight)
- Can be used in very young children (0–6 months)
- Can be dispersed in breast milk after pumping
- Easy to dispense and requiring minimal manipulation by health professionals and parents prior to use, which minimizes the risk of errors
- Requiring a small amount of water for administration

Qualitative and Quantitative Composition

Zinc sulfate dispersible tablet: Each tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of elemental zinc.

List of typical excipients⁵:

- Aspartame
- Colloidal anhydrous silica
- Magnesium stearate
- Microcrystalline cellulose
- Crospovidone
- Other sweeteners
- Flavors

Zinc sulfate oral solution: Each 5 mL contains 27.5 mg zinc sulfate monohydrate equivalent to 10 mg of elemental zinc.

Packaging and Presentation

Zinc dispersible tablets should be stored in blister packaging (usually available in PVC/PVDC-aluminum foil blister).

Zinc oral solutions are packed in glass or plastic bottles. Oral solutions in multidose containers require a device capable of uniformly dispensing the required range of doses (5–10 mL for 10 mg/5 mL solution).

WHO guidelines for the treatment of diarrhea recommend that zinc (10–20 mg/day) be given for 10–14 days to all children with diarrhea. Therefore, zinc tablets and oral solution should be packaged in quantities sufficient to provide a full treatment of 10–14 daily doses of zinc (e.g., at least 14 tablets per blister packaging or 140 mL as oral solution).

WHO recommends using zinc and ORS together to ensure the effective treatment of diarrhea; a co-package of ORS and zinc in accordance with WHO treatment protocol guidelines is offered by some manufacturers to improve treatment regimen adherence.

The packaging configurations procured by UNICEF are:

- ORS low osmolarity, 2 sachets for 1 L + zinc 20-mg dispersible tablets, blister of 10, packed together in a kit
- ORS low osmolarity, 4 sachets for 0.5 L + zinc 20-mg dispersible tablets, blister of 10, packed together in a kit

⁵ Based on the formulation of the WHO-prequalified products.

SUPPLY



Generally, products prequalified by the WHO PQP and/or approved by an SRA are considered quality-assured and highly recommended for procurement. In the absence of WHO-prequalified, SRA-approved, or ERP-recommended products, medicines from trusted sources, such as manufacturers approved by UN agencies, can be considered for procurement. Alternatively, the procurement agency may conduct its own quality assessment as described in [Module II](#).

WHO-prequalified products

As of February 2018, there are three zinc sulfate products prequalified by the WHO PQP, as shown below. All of them are in the dispersible tablet dosage form. It is recommended to check the updated information at the time of procurement, which can be found at <https://extranet.who.int/prequal/content/prequalified-lists/medicines>.

Table Z-I. List of WHO-Prequalified Zinc Sulfate Dispersible Tablets

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
DI002	Nutriset, BP 35, le Bois Ricard, Malaunay, 76770, France	FPP manufacturing site: Laboratoires Pharmaceutiqu es Rodael, 1 route de SOCX, Bierne, 59380, France API manufacturing site: Dr Paul Lohmann GmbH KG, Hauptstrasse 2, Emmerthal, 31860, Germany	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	4-Dec-12	36 months	Do not store above 30°C, protect from moisture.
DI004	Alkem Laboratories Ltd, Alkem House, "Devashish" Senapati Bapat Marg, Lower Parel, Mumbai, 400 013, India	FPP manufacturing site: Alkem Laboratories Ltd, 167/2 Mahatma Ghandi Udyog Nagar, Amaliya, Dhabel, Daman, 396 210, India API manufacturing site: Canton Laboratories Pvt Ltd, Survey No. 350, Mujpur, Taluka: Padra, Vadodara, Gujarat, 391440, India	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC: 10 x 10's	19-Feb-14	36 months	Do not store above 30°C, protect from moisture, protect from light.

WHO REF. NUMBER	MARKETING AUTHORIZATION HOLDER	MANUFACTURING SITE	DOSAGE FORM AND STRENGTH	PACKAGING AND PRESENTATION	DATE OF PRE-QUALIFICATION	SHELF LIFE	STORAGE CONDITION
D1005	Macleods Pharmaceuticals Ltd, 304 Atlanta Arcade, Marol Church Road, Anheri-Kurla Road, Anheri (E), Mumbai, 400 059, India	FPP manufacturing site: Macleods Pharmaceuticals Ltd, Block No. N2, Village Theda, P.O. Lodhi Majra, Tehsil Baddi, District Solan, Himachal Pradesh, 174 101, India	Tablet, dispersible 20 mg	Blister Alu/PVC/PVdC; 10 x 10's	7-Dec-16	36 months	Do not store above 30°C, protect from moisture, protect from light.
		API manufacturing site: Dr Paul Lohmann GmbH KG, Hauptstrasse 2, 31860 Emmerthal, Germany;					
		Canton Laboratories Pvt Ltd, Survey No. 350, Mujpur, Taluka: Padra, Vadodara, Gujarat, 391440, India					

SRA-approved products

As of February 2018, there are no SRA-approved zinc supplements for use in treatment of diarrhea in children,⁶ probably because the disease is much rarer and is treated differently in high-income countries.

When manufacturers claim products are approved by an SRA, they should provide the following information/documents to prove the SRA approval:

- A copy of the marketing authorization issued by the reference SRA
- The approved product information (e.g., Summary of Product Characteristics, product information leaflet, and the labeling by the reference SRA).
- A statement confirming the FPP—including but not limited to composition/formulation, strength, manufacturing, specifications, packaging, and product information—will in all respects be the same as the product approved by the reference SRA
- Product sample

The procurer may cross check the submitted information with the corresponding NMRA websites:

- US FDA: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
- EU regulatory authorities: https://ec.europa.eu/health/documents/community-register/regca_en
- Swissmedic: <https://www.swissmedic.ch/swissmedic/en/home/services/authorized-medicines/human-and-veterinary-medicines.html>
- Health Canada: <https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>
- TGA Australia: <https://www.tga.gov.au/australian-register-therapeutic-goods>

Trusted sources

Apart from the WHO-prequalified products listed in Table Z-I above, zinc sulfate 20 mg dispersible tablets from the following manufacturers are listed by UNICEF as approved sources for procurement⁷:

- CHI Pharmaceuticals, Nigeria
- FDC Ltd, India
- Square Pharmaceuticals, Bangladesh
- Universal Corporation Ltd, Kenya

It is recommended to check for updated information on the UNICEF website at the time of procurement.

⁶ Zinc supplements approved and marketed in SRA countries are of different strengths and to be used for the treatment of zinc deficiency.

⁷ Available at https://www.unicef.org/supply/files/ORS_and_Zinc_Supply_Update.pdf

Related products

Zinc oral solution may be available at a concentration of 20 mg/5 mL. The recommended zinc dosage is 10–20 mg/day given for 10–14 days to all children with diarrhea. As it is difficult to accurately measure one-half teaspoon of solution, it is recommended that oral solution in the concentration of 10 mg/5 mL be procured for convenient use and avoidance of dosing errors.

STORAGE, STABILITY, AND DEGRADATION



Zinc products have no cold chain storage complications.

Shelf life: 36 months, depending on the manufacturer. It is recommended to check the product label before use.

Storage conditions: Do not store above 30°C. Do not freeze. Protect from moisture and light.

PRODUCT SPECIFICATIONS

The product must meet pharmacopoeial specifications,⁸ such as those of USP and BP, depending on the quality assurance policy of the procurement agency, or the equivalent thereof.

In view of the requirements of the WHO guidance document on production of zinc tablets and zinc oral solutions,⁹ the following specifications are also recommended:

- Treatment is recommended as 10 or 20 mg as a single dose. Therefore, it is expected that any tablet formulation containing 20 mg elemental zinc per tablet should be scored to facilitate breaking. A subdivision test should be carried out to demonstrate tablets can be divided into equal halves. The uniformity of dose in the tablet halves should be demonstrated.
- Since adherence to the treatment regimen will be affected if the product is not acceptable to infants, young children, and their mothers, zinc preparations should be formulated in such a way as to mask the strong, bitter metallic aftertaste of zinc in order to enhance acceptability. Evaluation of taste masking and taste acceptability for both tablet and oral solution formulations should be conducted during product development using a standard methodology as described in the WHO guidance document on production of zinc tablets and zinc oral solutions, which is summarized in the Annex.

⁸ As of February 2018, there are no monographs of zinc tablets and zinc oral solutions published in the International Pharmacopoeia. Updated information should be checked at <http://apps.who.int/phint/en/p/about/>

⁹ World Health Organization. 2007. *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*. Geneva: WHO. Available at http://www.who.int/maternal_child_adolescent/documents/9241594942/en/

Zinc

Table Z-2. US Pharmacopoeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	A white precipitate is formed. When an additional 2 mL of <i>sodium hydroxide solution</i> is added, the precipitate dissolves. When 10 mL of <i>ammonium chloride solution</i> is added, the solution remains clear. When 0.1 mL of <i>sodium sulfide solution</i> is added, a white precipitate is formed.	As per USP monograph of zinc sulfate tablets
Identification b) Sulfate	A white precipitate is formed.	As per USP monograph of zinc sulfate tablets
Assay (zinc sulfate monohydrate)	95.0–105.0%	Titration, USP<541>
Disintegration	Not more than 60 seconds	USP<701>
Uniformity of dosage units	Meet the requirements	USP<905>

Table Z-3. British Pharmacopoeia Specifications for Zinc Sulfate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Yields the reactions characteristics of zinc and zinc salts.	Appendix VI
Identification b) Sulfate	Yields the reactions characteristics of sulfates	Appendix VI
Assay (zinc sulfate monohydrate)	95.0–105.0%	Titration, Appendix VIII D
Disintegration	Not more than 60 seconds	Appendix XII A
Uniformity of dosage units	Meet the requirements	Appendix XII C

Table Z-4. US Pharmacopoeia Specifications for Zinc Sulfate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meet the requirements	USP<191>
Identification b) Sulfate	Meet the requirements	USP<191>
pH	2.5–4.5	USP<791>
Specific gravity	1.18–1.24	USP<841>
Assay (zinc sulfate monohydrate)	90.0–110.0%	Titration, USP<541>

Zinc

Table Z-5. US Pharmacopoeia Specifications for Zinc Gluconate Tablets

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) TLC	The principal spot from <i>sample solution</i> corresponds in color, size, and Rf value to that from the <i>standard solution</i> .	As per USP monograph of zinc gluconate tablets
Identification b) Chemical reaction	A white precipitate is formed after the first addition of <i>sodium hydroxide solution</i> . The precipitate dissolves after the second addition of <i>sodium hydroxide solution</i> . The solution remains clear after addition of <i>ammonium chloride solution</i> , and a white precipitate forms after addition of <i>sodium sulfide solution</i> .	As per USP monograph of zinc gluconate tablets
Assay (zinc gluconate)	93.0–107.0%	Titration, USP monograph
Disintegration	Not more than 60 seconds	USP<701>
Disintegration and dissolution of dietary supplements	Not less than 75% of the labeled amount of zinc gluconate is dissolved.	USP<2040>
Uniformity of dosage units	Meet the requirements	USP<905>

Table Z-6. US Pharmacopoeia Specifications for Zinc Acetate Oral Solution

TEST	ACCEPTANCE CRITERIA	ANALYTICAL METHOD
Identification a) Zinc	Meet the requirements	USP<191>
Identification b) Acetate	Meet the requirements	USP<191>
pH	5.7–6.3	USP<791>
Assay (zinc acetate dihydrate)	90.0–110.0%	Titration, USP<541>
Microbial enumeration test	The total aerobic microbial count does not exceed 10^2 cfu/mL. The total molds and yeasts count does not exceed 10^1 cfu/mL.	USP<61>
Tests for specified microorganisms	Absence of <i>Escherichia coli</i>	USP<62>

WHO guidance on the study for the scored tablets¹⁰

When the tablet is functionally scored to facilitate the breaking, a study should be undertaken to ensure the uniformity of dose in the tablet halves. The manufacturer should provide a description of the test method, individual values, mean and relative standard deviation (RSD) of the results.

The content uniformity testing should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (e.g., the splits) would be 10 halves for bisected tablets (one-half of each tablet is retained for the test). The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g., manually split by hand). The uniformity of content is determined by measuring the content of each of 10 halves using the assay method described in the US or British Pharmacopoeia. While in the assay, no 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 half is powdered and used separately to make a solution of zinc sulfate. The content of each half is then determined and used for calculating the acceptance value.

The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the routine finished product specifications.

¹⁰ Refer to World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 to *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 46th report. Technical Report Series No. 970. Geneva: WHO.

PART I: CLINICAL PARTICULARS

Therapeutic indications

Zinc (as sulfate) 20-mg dispersible tablets is indicated for the treatment of acute and persistent diarrhea in infants and children up to 5 years of age.

Posology, method, and duration of administration

For children below 6 months of age: ½ tablet once daily for 10–14 days

For children 6 months–5 years of age: 1 tablet once daily for 10–14 days

The tablet (or half tablet) should be dispersed completely in 1 teaspoon (5 mL) of clean water or breast milk and the entire amount administered orally to the infant or child.

It is recommended that doses be administered between meals, and a repeat dose given if vomiting occurs within 30 minutes.

For missed doses, the missing dose can be taken as soon as possible, unless there is less than 6 hours remaining until the next dose.

Contraindications

Hypersensitivity to the active substances or to any of the excipients.

Special warnings and precautions for use

Drugs that may inhibit zinc absorption, such as penicillamine, sodium valproate, and ethambutol, should not be co-administered with zinc (as sulfate) 20-mg dispersible tablets, unless the risks of discontinuation of the drug are judged to outweigh the benefit of zinc in treatment of the child's diarrhea.

Excipients

Zinc (as sulfate) 20-mg dispersible tablets contain aspartame, a source of phenylalanine. This should be considered when prescribing the product to patients with phenylketonuria.

Interaction with other medicinal products and other forms of interaction

Antibiotics

When taken together, zinc may reduce the absorption of tetracyclines (but not doxycycline), and quinolone antibiotics. In addition, zinc may also interfere with the absorption of cephalexin or ceftibuten. An interval of at least 3 hours should be allowed between administration of zinc and any of these medicines.

Pregnancy and Lactation

Pregnancy

The safety of zinc (as sulfate) 20-mg dispersible tablets in pregnancy has not been established.

Lactation

Zinc crosses the placenta and is present in breast milk. The safety of zinc (as sulfate) 20-mg dispersible tablets in lactation has not been established.

Effects on ability to drive and use machines

There is no evidence regarding the effect of zinc on the ability to drive or use machinery, however zinc (as sulfate) 20-mg dispersible tablets is not expected to have any effect on these abilities.

Undesirable effects

In clinical trials in children, administration of zinc (as sulfate) 20-mg dispersible tablets was associated with vomiting or regurgitation. In one study, vomiting attributed to the tablet was reported very commonly ($\geq 10\%$) and regurgitation was reported commonly ($\geq 1\%$ to $<10\%$)—in 5.2% in 14% and 5.2% of children, respectively. In most cases, vomiting or regurgitation occurred shortly after administration of the first dose (within 10 minutes) and was not recurrent. Zinc salts may also cause abdominal pain and dyspepsia (frequency unknown).

Overdose

Symptoms

High doses of zinc cause emesis. In addition, zinc sulfate is corrosive at high doses, and may cause irritation and corrosion of the gastrointestinal tract, including ulceration of the stomach and possible perforation. Overdosage with zinc has also been associated with acute renal tubular necrosis and interstitial nephritis. Prolonged high dose zinc supplementation may result in copper deficiency.

Treatment

In cases of acute zinc overdose, treatment is primarily supportive; however, induced emesis, gastric lavage, or activated charcoal may be useful in cases of substantial ingestions of zinc tablets. Chelating agents such as calcium disodium EDTA may be useful.

PART 2: SPECIAL CONSIDERATIONS IN QUALITY ASSESSMENT

Information contained in this annex is intended to assist procurement agencies that plan to perform the full prequalification of zinc products. When assessing the complete quality/CMC documentation, assessors should consider the following particular information on zinc tablets and oral solutions.

API

Any soluble zinc salts (e.g., sulfate, gluconate, acetate, or citrate) may be used for the formulation of the tablets and oral solutions.

As of February 2018, there are two zinc sulfate APIs prequalified by the WHO PQP.

Manufacturers of WHO-Prequalified Zinc Sulfate API

WHO REF. NUMBER	APPLICANT	API MANUFACTURING SITE	STORAGE CONDITION	RETEST PERIOD OR SHELF LIFE	DATE OF PRE-QUALIFICATION
WHOAPI-146	Canton Laboratories Pvt Ltd	Canton Laboratories Pvt Ltd, Survey No. 350 Mujpur Taluka: Padra Vadodara Gujarat 391440, India	Do not store above 25°C.	60 months	12/7/2016
WHOAPI-232	Dr Paul Lohmann GmbH KG	Dr Paul Lohmann GmbH KG, Hauptstrasse 2 31860 Emmerthal Germany	Do not store above 30°C; protect from moisture.	36 months	7/3/2014

Two manufacturers of zinc have obtained a certificate of suitability to monographs of the European Pharmacopoeia (CEP), confirming its suitable quality for use in medicinal product.

Manufacturers of Zinc with CEP Certificate

SUBSTANCE	CERTIFICATE HOLDER	CERTIFICATE NUMBER	ISSUE DATE	TYPE
Zinc sulfate heptahydrate (monograph number 111)	Macco Organiques, SRO CZ 792 01 Bruntál, Czech Republic	R0-CEP 2015-375-Rev 00	2/1/2017	Chemistry
Zinc gluconate (monograph number 2164)	Givaudan-Lavirotte FR, 69008 Lyon, France	R0-CEP 2012-221-Rev 00	2/7/2014	Chemistry

Other manufacturers of zinc should provide evidence for GMP compliance and API quality documentation as per WHO guidelines.¹

API specifications of zinc should be in line with a pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP) with additional tests/limits for arsenic; as well as for lead, alkalies, and alkaline earths and iron if not included in that monograph. Such additional tests may be based on another pharmacopoeial monograph (Ph.Int., Ph.Eur./BP, or USP).

Zinc salts (sulfate, gluconate, acetate, citrate) should be kept in a well-closed, non-metallic container.

Zinc gluconate is a hygroscopic material, and should be protected from atmospheric moisture .

Excipients

The excipients of zinc sulfate tablets include typical tablet diluent (e.g., microcrystalline cellulose), disintegrant (e.g., colloidal anhydrous silica or croscopovidone), and lubricant (e.g., magnesium stearate). Furthermore, the tablets may contain one or more suitable flavors and sweeteners for greater acceptability.

The potential impact of interactions between zinc ions and excipients on absorption is very difficult to predict. The typical tablet diluent, disintegrant, and lubricant excipients are not expected to have a significant impact on absorption due to either minimal reactivity or being present in limited quantities. There is particular concern with respect to the potential impact of sweeteners and flavors on the in vivo absorption of zinc. For this reason, as indicated in the WHO prequalification guidance document *Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution)*,² manufacturers must provide evidence that sweeteners/flavors present in their zinc products do not negatively impact the absorption of zinc. The principles are applicable for all zinc salts (e.g., sulfate, gluconate, acetate, and citrate).

¹ World Health Organization. 2012. "Guidelines on Submission of Documentation for a Multisource (Generic) Finished Pharmaceutical Product for WHO Prequalification: Quality Part." Annex 4 in: *WHO Expert Committee on Specifications for Pharmaceutical Preparations*. 46th report. WHO Technical Report Series, No. 970. Geneva: WHO.

² World Health Organization/Prequalification Team. 2016. *Q&A: Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution)*. Geneva: WHO/PQT. Available at https://extranet.who.int/prequal/sites/default/files/documents/50%20Q%26A%20zinc%20sulfate%20tablets_Nov2016.pdf

As an aid to the development of zinc formulations, WHO PQP has determined that the following pharmaceutical sweeteners and flavors can be employed as excipients in zinc formulations, without providing additional evidence that the ingredient does not negatively impact the absorption of zinc:

- Aspartame
- Ethyl vanillin (in quantities < 1 mg per 20-mg zinc sulfate tablet)
- Mannitol
- Mono ammonium glycyrrhizinate*
- Saccharin sodium (in quantities < 1 mg per 20-mg zinc sulfate tablet)
- Sorbitol
- Trusil flavors*

It is important that these excipients are employed in the smallest quantities possible to achieve the desired sweetening/flavoring effect. In particular, the identified excipients (*) should be employed in quantities of no more than approximately 2% of the formulation by mass. If it is judged that the above-noted excipients are employed in quantities above the limit for which there is confidence and their impact will be negligible, additional information on the impact of that quantity of excipient on zinc absorption may be requested for assessment.

It is important to note that the above WHO PQP advice does not indicate that other sweetening/flavoring excipients are not acceptable; it indicates that the use of other sweetening/flavoring excipients must be justified with supporting information on their impact on zinc absorption.

Manufacturing process

Zinc tablets and zinc oral solutions should be manufactured according to recognized principles of GMP using ingredients that comply with specifications designed to ensure the final products meet the requirements of the compendial monographs.

The uniformity of the batch used in biowaiver or bioavailability studies should be provided. In addition, a manufacturing process validation protocol for the validation of the first three production-scale batches should be submitted. In the case where the manufacturer is already manufacturing production-scale batches, the full validation data for the production of at least three consecutive production scale batches should be submitted.

Packaging

Zinc tablets are usually packed in PVC/PVDC-aluminum foil blister.

Zinc oral solutions are packed in glass or plastic bottles.

Suitability of container should be demonstrated, including:

Safety

- Blister: declarations as to compliance with appropriate food additive regulations (e.g., USFDA or EU regulations)

- Glass/plastic bottles: food grade declaration and tests as per USP<660>/Ph.Eur. 3.2.1 (Glass); USP<661>/Ph.Eur. 3.1.10 (Plastics)

Protection

- Blister: water vapor permeation (WVTR) and light transmission (LT) rate as per USP<671>
- Glass/plastic bottles: plastics: WVTR (weight loss) and LT as per USP<671>

Compatibility

- Accelerated and long-term stability data for the packaged finished products
- A one-time study of extractables (e.g., USP<661> and USP<671>) and leachables (either a study or certification that the materials of construction for packaging components in contact with the product meet the requirements for indirect food additives: e.g., 21 CFR 174–186) is required for oral solutions in plastic bottles.

Oral solutions in multidose containers are required to have a device capable of uniformly dispensing the required range of doses (5–10 mL for 10 mg/5 mL solution). A sample of the device must be provided, along with (1) specifications (with infrared identification of the material); (2) data to demonstrate the uniformity of mass of doses delivered by the measuring device at the lowest intended dose; and (3) the “Instructions on use and handling” should provide clear instructions.

Bioequivalence requirements

As there is currently no comparator product available, a bioequivalence study is not possible. The primary pathway to approval of the safety and efficacy portion of a dossier for most products will be via a biowaiver application. A biowaiver from the requirement to conduct in vivo studies is possible if adequate supporting documentation is provided. The requirements for a biowaiver are described below.

Tablets (dispersible)

The absorption of zinc is sensitive to many factors that affect either gastrointestinal status or the availability of the zinc through interactions such as complexation. For this reason, a waiver from the requirement to provide in vivo study data on the proposed product can be considered under specific circumstances as follows:

- Evidence is provided to demonstrate that the excipients do not negatively impact the absorption of zinc.
- The zinc from the proposed product is proven to be completely in solution after one minute using the solubility test described below.

Effects of excipients on zinc absorption

The potential impact of interactions between zinc ions and excipients on absorption is very difficult to predict. Sweeteners are a significant concern. As is indicated in the WHO guidance document on production of zinc tablets and zinc oral solutions, products may contain one or more suitable flavors and sweeteners in order to improve acceptability but these substances “should not impair the bioavailability or the therapeutic efficacy or safety of the preparation.” In order for a waiver from in vivo studies to be considered, manufacturers must provide evidence that the sweeteners employed would not negatively affect the

absorption of zinc from the formulation. Such evidence can come from either literature or in vitro studies, such as comparative absorption data from cells or infused intestines.

Similar information concerning other excipients may be requested during the product assessment if sufficient information concerning the excipients(s) and their impact on zinc absorption is not available.

Solubility testing

The solubility test should be conducted using tablets from a representative commercial or pilot batch. The percentage of zinc in solution should be assessed under the following conditions:

- One tablet should be immersed in 5.0 mL water at room temperature. The vessel containing the tablet in water should be allowed to sit for one minute without any agitation. After the 1 minute, the solution should be filtered immediately (e.g., using a syringe filter, and subsequently analyzed for zinc content).
- The quantity of zinc in solution should be calculated as a percentage of the total zinc in the tablet. It is expected that the reported percentage value will be close to the label claim (with tolerance for content and analytical variations).
- A sample size of at least six measurements ($n \geq 6$) should be conducted.

If it cannot be established that the excipients present in the proposed product formulation do not significantly negatively impact the absorption of zinc, clinical study data are required demonstrating efficacy of the proposed product in the treatment of acute diarrhea or in vivo bioavailability data demonstrating that administration of the proposed product produces adequate plasma levels of zinc within a 72-hour administration period.

Oral solution

The same principles are applicable to oral solution products. For a waiver from the requirement to conduct in vivo studies to be considered, evidence must be provided that the excipients present in the proposed product formulation do not significantly negatively impact the absorption of zinc. If this cannot be established, in vivo study data as described above will be required.

WHO guidance on the evaluation of taste marking³

Qualitative evaluation of the taste by a taste panel⁴

Consumer testing is acknowledged as the best method for assessing a product. Consumers are regarded as individuals who are prescreened 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 pediatric formulations.

³ Refer to Annex 7 of World Health Organization. 2007. Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers. Geneva: WHO,.

⁴ European Medicines Agency. 2005. *Reflection Paper: Formulation of Choice for the Paediatric Formulation*. EMA/CHMP/PEG/194810/2005. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

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., preschoolers) could understand it.
- In order to ensure a reliable assessment, to prevent 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.

Participation and test performance

Generally, children aged 4 years and older are considered 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 may have difficulty concentrating during an entire testing period. The failure rate varies up to 50% depending on the design and duration of the test. In addition, young children are often unable to communicate their feelings and preferences.

In order to increase children’s understanding and motivation it is recommended to start with either high concentrations of the testing agent to be assessed (flavor or sweetener) or with known compounds (e.g., commonly used flavors) 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 a 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.

Sensory evaluation: affective and analytical testing, and ranking

Probably the most critical item in sensory evaluation is defining the objective. The test objective will determine the type and age of subjects and the methodology for design, conduct, and interpretation of the study and its outcome. Considerations include the following:

- 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 with the aim of determining the characteristics/properties of the test item, without defining acceptance/preference measures. Analytical testing answers questions such as “which sample is more bitter” or “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.

Evaluation principles

In most cases smell, texture, taste and aftertaste, and sometimes also appearance (e.g., if colored) are addressed. Language used in the questionnaire should be simple, intelligible, and plain for all participants independent of their age, social skills, and developmental level. It is recommended to use common, familiar terms relevant to the age of the participants to describe these properties, such as:

- Sweet, salty, sour, and bitter for characterizing the taste
- Thin, thick, viscous, gritty, for describing the texture of the testing item
- Sweet, salty, sour, and bitter but also astringent, numbness, or freshness, for describing the aftertaste

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

- Verbal judgment followed by scoring in a scale of, for example, 1–5, with a score of 1 corresponding to very good and a score 5 to very bad, facilitates the statistical evaluation of the data obtained
- By contrast, the facial hedonic scale allows the expression of preferences using a pictorial scale.

Children younger than 5–6 years are not considered 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 judgments following a control question. The facial hedonic scale cannot 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 behavior pattern of the subject (making wry faces, shrugging shoulders, vomiting, or spitting the formulation out) may also reflect the acceptance of the tested formulation. 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 flavor used: “which of the tested flavors did you like the most” or “which one did you dislike the most.”

WHO guidance on the acceptability study⁵

The acceptability study is considered a clinical trial, and therefore should be performed by qualified personnel, following ethical committee approval, and with the informed consent of parents or guardians. Study conduct must therefore conform to accepted ethical standards (i.e., ICH2 Good Clinical Practices and the Declaration of Helsinki).

The study should be conducted in the community, in children with acute diarrhea. Results from children hospitalized with severe diarrhea will be of limited validity. However, children may be enrolled at clinics, including hospital facilities, where they present for treatment, and this may provide a favorable setting for assessment of the taste acceptability of the tablets or solution, due to the availability of trained personnel, for example.

An essential component of the acceptability study is assessment of adherence to a complete treatment regimen. Consequently, children should be prescribed zinc tablets or solution, 10 or 20 mg per day according to age, for 10–14 days, and a visit is arranged for 2 weeks later, possibly at the home of the child, to assess acceptability of and adherence to the zinc treatment.

The study population should consist of children, aged 3–59 months, with an acute diarrhea episode. Based on statistical considerations,⁶ the study should aim to recruit 300 subjects, including 150 children up to the age of 18 months, and 150 children older than 18 months.

Children should be excluded if they are severely dehydrated (e.g., require hospitalization); have taken any other prescription drugs during the preceding 24 hours; have known food or drug allergies to any of the constituents of the test product; or have a medical condition that could interfere with the ability to discriminate taste, for example the common cold, or a sinus or bronchial infection.

Acceptability is assessed based on the caregiver's report of the child's behavior when given the medicine. The caregiver is asked about his or her perception of the taste of the zinc preparation given to the child, compared to other medicines. The possible responses are better, same, or worse than other medicines.

Adherence is assessed by the number of doses of medication taken by each child.

A treatment is generally considered to have good acceptability if 80% of the prescribed treatment is taken by at least 70% of the children.

⁵ Refer to Annex 8 of World Health Organization. 2007. *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*. Geneva: WHO.

⁶ 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 confidence level at 95% ($z = 1.95$), the resulting sample size estimate is 140 children per group. To adjust for potential dropouts, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age group).