Recommendations on Zinc and Low Osmolarity Oral Rehydration Salts Product Specifications for the Treatment of Acute Pediatric Diarrhea

This document provides guidance on specifications for 1) zinc and 2) Oral Rehydration Salts (ORS) in order to assist organizations involved in the procurement of zinc/ORS in making decisions related to product selection. The guidance provided below is preliminary and is not intended to serve as a definitive or comprehensive standard on product specification and therefore is not a replacement for the detailed WHO published guidelines referenced below.

Zinc supplementation along with ORS is recommended in the management of pediatric diarrhea.[1] A child with uncomplicated diarrhea should be treated with low-osmolarity ORS, given 1L of fluid per day for 2 consecutive days. In addition to the ORS, a child 1-5 months of age should receive 10mg of zinc per day, for 10-14 days, and children 6-59 months of age should receive 20mg of zinc per day for 10-14 days. This treatment is administered by caregivers to the children, most often in the home.

In order to facilitate adoption of treatment guidelines and widespread scale-up of zinc, it is important that the pharmaceutical industry prepare formulations that contain only zinc at the recommended dosage.[2] The drug product must be formulated to mask the strong metallic taste of zinc. Zinc salts for household administration to children may take the form of dispersible tablets or oral solutions. The development of alternate, affordably priced dosage forms that are more appealing to children is encouraged provided international standards of quality and clinical efficacy are met.

Organizations involved in the procurement of zinc/ORS should carefully consider product ease of administration across pediatric age groups, ease of accurate dosing by the caregiver as the drug is administered at home, patient adherence, cost, and quality as factors guiding their choice of product. If tendering for zinc/ORS products, organizations should specify required quality assurance and quality control requirements; in addition to compliance with product specifications as detailed in relevant published pharmacopeial monographs.

For further information please refer to the following WHO Documents:

1. Production of Zinc Tablets and Oral Solutions, available at: http://whqlibdoc.who.int/publications/2007/9241594942_eng.pdf
2. Oral Rehydration Salts: Production of the New ORS, available at: http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf
3. Joint WHO/UNICEF recommendation on diarrhea management http://whqlibdoc.who.int/hq/2004/WHO_FCH_CAH_04.7.pdf

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[1] WHO/UNICEF. Joint Statement - Clinical Management of Acute Diarrhea. WHO/FCH/CAH/04.7, May 2004. http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/Acute_Diarrhoea.pdf

[2] It is important to note that zinc is considered to be a medicine and regulatory agencies, procurement organizations, manufacturers, and international bodies should apply pharmaceutical standards of quality assurance and quality control.

Zinc Dispersible Tablets and Zinc Oral Solutions

Composition

Zinc Sulfate, Zinc Gluconate, and Zinc Acetate are all water soluble zinc salts which have shown **no difference in efficacy, therefore are considered equally effective**.

- Zinc Sulfate is the most commonly used and is generally the least expensive amongst the three zinc salts.

Presentation

- **Dosage Forms and Strength:**
    - 20mg Dispersible Scored Tablets and/or 10mg Dispersible Tablets are possible. It may be preferable to only have one strength of tablet available to simplify the supply chain and training for the health providers.
        - If procuring both strengths of dispersible tablets, it is important to note that the incidence of diarrhea is much higher in children over the age of 6 months, and the relative quantities of both types of tablets should reflect this.[3]
        - In the case of the 20mg dispersible scored tablets, children under six months of age will be given half a tablet per day, and children over six months of age will be given a full one. This is the most common choice.
        - If 10mg dispersible tablets are chosen instead, children over six months of age will be required to take two tablets, thereby increasing pill burden.
        - The disintegration of dispersible zinc tablets should occur in less than one minute in a small volume (5ml, a teaspoon) of water or breast milk. The certificate of analysis should include the disintegration data to ensure compliance (refer to pharmacopeial monographs for further detail).

    - Zinc Oral Solutions at Concentration of 10mg/5ml or 20mg/5ml are possible. As with the tablets, both concentrations may be procured or it may be preferable to only have one strength of oral solution available to simplify the supply chain and training for the health providers.
        - If procuring both concentrations of syrups, it is important to note that the incidence of diarrhea is much higher in children over the age of 6 months, and the relative quantities of both types of syrups should reflect this.[4]

[3] Estimates suggest that children between the age of 0 – 5months account for approximately 10% of the global diarrhea incidence for children between the ages of 0 – 59 months.
[4] Ibid.

- Manufacturers should include a measuring device such as a graduated plastic cup or graduated spoon along with each bottle, allowing for accurate measuring and administration at the household level.
    - In the case of the 20mg/5ml syrups, children under six months of age will be given 2.5ml per day, and children over six months of age will be given 5ml per day. This is the most common choice.
    - In the case of the 10mg/5ml syrup, children under six months of age will be given 5ml per day, and children over six months of age will be given 10ml per day.

- **Taste Masking**
    - Zinc tablets and oral solutions must be suitably taste masked and may contain sweetening and flavoring agents to ensure palatability and acceptance by end-users. The agents used should not compromise the therapeutic efficacy and bioavailability of zinc, should be harmless in the quantity used, and should not interfere with quality control procedures to test compliance with pharmacopeial standards.

Packaging and Storage

- **Dispersible Tablets**
    - Blister packaging of sufficient quality to protect the dispersible tablets from humidity in 1 x 10 or 1 x 14 tablets strips is suggested; decisions on the number of tablets per strip should be made on the basis of whether national guidelines recommend a ten or fourteen day treatment course.
        - Dispersible tablets are water sensitive and multi-dose containers would subject the tablets to humidity each time the container is opened.
        - The treatment protocol requires either the 10mg or 20mg age-appropriate dose to be given once a day for ten to fourteen days. The 1 x 10 or 1 x14 strips allows for one strip to be provided per episode of diarrhea, and a visual cue for the caregiver to continue the treatment until completed.

- **Zinc Oral Solutions:**
    - 50ml or 70ml (for 20mg/5ml solutions) / 100ml or 140ml (for 10mg/5ml solutions) well closed glass or plastic containers, which offer a degree of protection from ambient light are suggested. As with the tablets, decisions on the bottle size should be made on the basis of whether national guidelines recommend a ten or fourteen day treatment course.

- **Shelf Life:**
    - Zinc dispersible tablets and Zinc Oral Solutions with a shelf life of two years or longer are recommended.
    - Stability studies at Zone 4 conditions of 30 degrees Celsius and 70% relative humidity should demonstrate appropriate stability at the indicated shelf life.

Low Osmolarity Oral Rehydration Salts (L-ORS) Powder

ORS is a balanced glucose-electrolyte mixture that has been used in varying compositions since 1969 for the treatment of clinical dehydration from diarrhea. During this period, numerous studies have been undertaken to develop an improved ORS. One approach consisted in reducing the osmolarity of ORS solution; this was done by reducing the solution's glucose and salt concentrations. Studies to evaluate the safety and efficacy of reduced osmolarity ORS in children with acute non-cholera diarrhea, and in adults and children with cholera were carried out. These studies showed that the efficacy of ORS solution for treatment of children with acute non-cholera diarrhea is improved by reducing ORS' sodium concentration to 75 mEq/l, its glucose concentration to 75 mmol/l, and its total osmolarity to 245 mOsm/l. The studies also showed a decrease in the need for unscheduled supplemental IV therapy in children, a reduction in stool output, and in the incidence of vomiting.[5] This "third generation" ORS is commonly referred to as "New ORS" or "Low Osmolarity ORS (L-ORS)".

Because of the improved effectiveness of L-ORS solution WHO and UNICEF now recommend it for diarrhea of all etiologies and in all age groups.

Composition

The following table outlines the composition of the L-ORS formulation with a total osmolarity of 245 mOsmol/l.[6]

L-ORS	Grams/Liter	%		L-ORS	mmol/liter
Sodium chloride	2.6	12.683%		Sodium	75
Glucose, anhydrous	13.5	65.854%		Chloride	65
Potassium chloride	1.5	7.317%		Glucose, anhydrous	75
Trisodium citrate, dihydrate	2.9	14.146%		Potassium	20
				Citrate	10
Total	20.5	100%		Total	245

Presentation

- **Dosage Form**
  - Powder form of ORS is currently the most widely used as it is the simplest to manufacture and also the least costly. The development of cost competitive ready-to-use liquid dosage forms, that meet the WHO specifications, is also encouraged.

- **Flavoring and Coloring**
  - Flavoring and coloring ORS may create greater acceptability and consequently increased use. However, several considerations must be employed.
    - Flavored and colored ORS may be marginally more expensive

[5] Refer to http://whqlibdoc.who.int/hq/2006/WHO_FCH_CAH_06.1.pdf for further information.

[6] It is important to note that L-ORS is considered to be a medicine and regulatory agencies, procurement organizations, manufacturers, and international bodies should apply pharmaceutical standards of quality assurance and quality control.

- Several flavoring agents may change the stability profile and/or required storage conditions of ORS, hence demonstrating stability and equivalent safety and efficacy is required.

Dosing Size, Packaging Material, and Shelf Life

- **Dosing / Pack Size**
  - It is recommended that efforts be made to establish a national standard pediatric pack size to avoid confusion in the field and reduce the risk of under or over concentrating due to varying pack sizes. The standard dose corresponds to a one liter solution of ORS, as indicated in the composition table above. However, alternate pack sizes are permissible depending on local conditions. Decisions should be made on the basis of an economic justification and consumer preferences.

- **Packaging and Shelf Life**
  - Packing in hermetically sealed aluminum laminate is recommended in order to ensure the ORS product remains "free flowing" in a range of ambient conditions. 7
  - A shelf life of 2-3 years in a range of storage conditions is recommended. Stability studies at Zone 4 conditions of 30 degrees Celsius and 70% relative humidity should demonstrate appropriate stability at the indicated shelf life.

Co-packaging Zinc and ORS

- **Co-packing "bundling" of Zinc and ORS**
  - Zinc and ORS are jointly indicated in the management of acute pediatric diarrhea. Hence co-packing the products may result in improved uptake of commodities, improved treatment adherence, and potential for promotion of a "treatment kit" in the private sector. Several considerations must be taken into account however:
    - Regulatory permission to co-package such products
    - Cost consideration of additional packaging materials and labeling, which may be minimal if suitably designed
    - Quality control and batch tracking implications
    - Net shipping cost/savings
    - In the private sector:
      - Consumer ability to pay for a co-packaged kit
      - Co-package retail pricing vs. the sum of the individual components
      - Consumer preference for a treatment kit versus individual components or competing dosage forms, e.g. syrups
      - Incentives for distributors and retailers

- **Zinc and ORS must *NOT BE* Co-formulated at this time**
  - The addition of Zinc to ORS has not been shown to improve the solution's efficacy at this time.[8]

[7] For further information refer to: WHO: Production of the New ORS, p.28

[8] For further information refer to:

a) WHO: Production of the New ORS, p.5

b) Bahl R, Bhandari N, Saksena M, Strand T, Kumar GT, Bhan MK, Sommerfelt H. Efficacy of zinc-fortified oral rehydration solution in 6- to 35-month-old children with acute diarrhea

c) Wadhwa N, Natchu UC, Sommerfelt H, Strand TA, Kapoor V, Saini S, Kainth US, Bhatnagar S. ORS containing zinc does not reduce duration or stool volume of acute diarrhea in hospitalized children. J Pediatr Gastroenterol Nutr. 2011 Aug;53(2):161-7