

## Additional Guidance for Submission of the Acceptability Study for Prequalification of Zinc Tablets and Oral Liquid (Solution)

Zinc salt oral preparations have a bitter metallic after-taste, and children will refuse to take them unless this taste is effectively masked. It is therefore essential to assess the acceptability of the zinc tablet or solution to infants, young children, and their parents, as well as the children's adherence to a complete anti-diarrhoeal treatment regimen. As a result, in order for a zinc product for treatment of diarrhoea to be considered for prequalification, an applicant must submit satisfactory results from an appropriately designed and conducted acceptability study.

The 2007 WHO publication *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*<sup>1</sup> provides general information regarding the design of the acceptability study, in Chapters 5 and Annex 8.

The purpose of this document is to address a number of questions that the WHO Prequalification Team: medicines (PQTm) has received from applicants regarding the design and conduct of the acceptability study.

### How should documentation of the Acceptability Study be submitted?

Information regarding the suitably designed and conducted acceptability study should be summarized in the form *Zinc Products: Acceptability Study Summary Form*. Specifically, the applicant should summarize the design, results, and conclusions of the acceptability study. In addition, the complete study protocol and the full study report should both be appended to the form, and the exact location of these documents (Annex number) should be provided.

### Is the acceptability study a clinical trial?

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. ICH E6<sup>2</sup> Good Clinical Practice and the Declaration of Helsinki<sup>2</sup>).

### Where should the acceptability study be conducted?

The study should be conducted in the community, in children with acute diarrhoea. Results from children hospitalized with severe diarrhoea will be of limited validity. However, children may be enrolled at clinics, including hospital facilities, where they present for treatment.

The primary endpoint of the acceptability study is adherence to the treatment regimen. Consequently, children should be prescribed zinc tablets or solution, 10 or 20 mg per day according to age, for 10 (or 14) days, and an in-person visit arranged thereafter, possibly at the home of the child, to assess adherence and palatability, per the published WHO zinc protocol.

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<sup>1</sup> See [http://www.who.int/child\\_adolescent\\_health/documents/9241594942/en/index.html](http://www.who.int/child_adolescent_health/documents/9241594942/en/index.html)

<sup>2</sup> Integrated Addendum to ICH E6 Guideline for Good Clinical Practice R2  
[http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6/E6\\_R2\\_Step\\_4\\_2016\\_1109.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf)

<sup>2</sup> The Declaration of Helsinki, adopted by the World Medical Association, states that biomedical research cannot be done legitimately unless the importance of the objective is in proportion to the risk to the subject.

## What should be the study population?

The study population should consist of children, aged 3–59 months, who present with an acute diarrhoea episode. Based on statistical considerations, 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.<sup>3</sup>

Children should be excluded if they are severely dehydrated (i.e. 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.

## How is adherence measured?

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.

## How is palatability measured?

Palatability is assessed based on the caregiver's report of the child's reaction when given the medicine. The caregiver will assess the child's perception of the taste of the zinc preparation, compared to other medicines, on a five-point scale.

## Can PQTm recommend a contract research organization to conduct the acceptability study?

The applicant may choose to have the acceptability study conducted by a contract research organization (CRO). The PQTm cannot provide recommendations regarding specific CROs. Some guidance for the applicant can be provided by the WHO Public Inspection Reports (WHOPIRs) found on the prequalification website (under Key Resources), which list CROs that have been subject to inspections by the PQTm with a positive outcome. However, other CROs not inspected by WHO but with a record of satisfactory stringent regulatory inspections and/or documented GCP compliance may also be appropriate.

## Is assistance available regarding design of the acceptability study protocol?

Should applicants have unresolved questions with respect to design or conduct of the acceptability study, they are encouraged to contact the PQTm for advice and clarification. It is strongly recommended that a final draft acceptability study protocol conforming to standard clinical trial protocol format is submitted to WHO for review prior to embarking on the study.

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<sup>3</sup> "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)." [http://www.who.int/child\\_adolescent\\_health/documents/9241594942/en/index.html](http://www.who.int/child_adolescent_health/documents/9241594942/en/index.html).