Guidance on the Submission of Applications for Prequalification of Zinc Tablets and Zinc Oral Liquid (Solution)

This document should not be treated as a comprehensive guideline but, as a document that serves as a complement to other guidance by summarizing some of the basic requirements for the prequalification of zinc sulfate products and highlighting some exemptions and special requirements that are applicable specifically for these products. Although this document refers mainly to zinc sulfate products, the principles discussed are also applicable for the other invited zinc salts, i.e., gluconate, acetate, and citrate.

Applicants are encouraged to familiarize themselves with the 2007 WHO publication entitled *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers* and the WHO PQT/MED quality guideline (WHO TRS 970, Annex 4, 2012).

This document addresses general application issues, Quality-related issues, bioavailability / biowaiver-related issues, and clinical acceptability study-related issues in a question-and-answer format.

1. Application Issues

What dosage forms for zinc sulfate are being sought for prequalification?

According to the WHO guidance for *Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers* zinc supplementation "…can be given as syrup or dispersible tablet, whichever is available or affordable…" However, as the International Pharmacopoeia (Ph. Int.) for zinc sulfate tablets require a disintegration time of 60 seconds or less (very fast disintegrating) when tested at 25°C, applicants should submit applications for either zinc tablets that meet the above disintegration time specification or oral zinc solutions.

Is evidence of Marketing Authorization required to demonstrate that the product is registered or approved for sale in accordance with national requirements?

No such evidence is required at the time of submission of the dossier to PQT/MED, however, any requirements for national registration will need to be considered after prequalification.

Are there any specific packaging and labelling requirements?

On the basis of the information summarized below and in consideration of the formulation and posology from the treatment guidelines:

- Zinc sulfate tablets should be stored in blister packaging (not bottles or multi-dose containers).
- Zinc formulations should be distributed in quantities sufficient for treatment for 10-14 days i.e., at least 5–14 tablets per blister packaging or 50–140 mL as oral solution.
- The strength of the formulation on the labelling should always be in terms of zinc sulfate and elemental zinc, e.g., zinc (as sulfate monohydrate) 20mg tablets. If the USP standard is claimed, the composition in the SmPC and PIL should include the strength in terms of the API form, e.g., “Each tablet contains 54.9 mg zinc sulfate monohydrate equivalent to 20 mg of zinc.”
- As specified in the Ph.Int. monograph, “Liquid Preparations for Oral Use”, oral solutions in multi-dose containers are required to have a device capable of uniformly dispensing the required range of doses (5 to 10 ml for 10mg/5ml solution). A sample of the device must be provided, along with (1) specifications (with IR identification of the material); (2) data to demonstrate the uniformity of mass of doses delivered by the measuring device at the lowest intended dose, as outlined in the monograph referenced above; and (3) the “Instructions on Use and Handling” should provide clear instructions.
- A one-time study of extractables (e.g., USP <661> and <671>), 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) and water loss (e.g., USP <671>) is required for oral solutions in plastic bottles.

2. Quality-related Issues

Is evidence of compliance with Good Manufacturing Practices (GMP) required for the active pharmaceutical ingredient (API) manufacturer?

All manufacturers of APIs used in prequalified medicinal products are expected to comply with GMP. If available, a certificate of GMP compliance should be submitted.

What information is required regarding the API?

Information on the API can be submitted to WHO in one of the following four options:

- as a confirmation of API prequalification document
- as a valid European Certificate of Suitability (CEP) with all Annexes
- as an API Master File as described in WHO's Guidelines on active pharmaceutical ingredient master file procedure (WHO TRS 948, Annex 4, 2008)
- full details provided in the product dossier.

In addition, data on the API is required for each of the above options as outlined in the quality guideline (WHO TRS 970, Annex 4, 2012).

Are there any API specification requirements for zinc sulfate?

API specifications should be in line with a pharmacopoeial monograph (Ph. Int., European/British Pharmacopoeia (Eur./BP), Japanese Pharmacopoeia (JP) or USP) with additional tests/limits for arsenic; 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, JP, or USP).

Is analytical validation information for the assay of the API required to be submitted with the dossier?

Information on validation is required if an in-house method is used. Such information is not required if the assay method is pharmacopoeial (Ph.Int., Ph.Eur./BP, JP or USP).

Is analytical validation information required for the assay of the API in the FPP?

If assay is pharmacopoeial (Ph.Int., USP, JP or BP), only evidence of specificity (with respect to effects of placebo) and method precision should be submitted. Additional validation data is required if an in-house method is used.

What are the minimum stability requirements for the API and FPP?

The minimum data required at the time of submitting the dossier should be from six months accelerated and six months long-term stability studies conducted on at least two batches, not less than one batch of at least pilot scale and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 to 50,000 tablets or capsules). For oral solutions in plastic containers, the parameters studied should include water loss.

How much evidence is required as proof of validation of the manufacturing process of the FPP?

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, then full validation data for the production of at least three consecutive production scale batches should be submitted.

Is evidence of compliance with GMP required for the FPP manufacturer?

Yes, a copy of a valid manufacturing license and/or GMP certificate for the FPP manufacturer is required.

Are there any FPP specification requirements for zinc sulfate formulations?

In view of the requirements of the WHO guidance document, *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*, the following are preferable for the PQT/MED:

- Treatment is recommended as 10 or 20mg as a single dose and procurers are encouraged to purchase either the 10mg or 20mg tablet strength, not both. Therefore, it is expected that any tablet formulation containing 20mg elemental zinc per tablet should be scored to facilitate breaking. A demonstration of the weight uniformity of tablet halves is required for scored tablets. The Applicant should carry out a subdivision test as per Section 3.2.P.2.2.1 of the WHO PQP quality guideline to demonstrate that the tablets can be divided into equal halves.
- Specifications should be in line with the Ph.Int. monographs for paediatric zinc sulfate oral solution and paediatric zinc sulfate tablets, as appropriate.
- Additional specifications should include fineness of dispersion and uniformity of dosage units for tablets. Oral solutions should include visual inspection (clear and free from any precipitate). See also the notes on disintegration in this document.
- Evaluation of taste masking or taste acceptability for both formulations should be conducted during product development (see below).

3. Bioavailability / Biowaiver-related Issues

Is a bioequivalence study report required?

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 and
- 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 (see for example, Zinc sulfate. In: Martindale. The Complete Drug Reference. Sean C Sweetman, Editor. 37th Edition, Pharmaceutical Press, (p. 2161)). While typical tablet diluent *(e.g.,* microcrystalline cellulose) and disintegrant (e.g., colloidal anhydrous silica or crospovidone) excipients are not expected to have a significant impact on absorption due to either minimal reactivity or being present in limited quantities, sweeteners are a significant concern. As is indicated in the 2007 WHO publication entitled *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers*, products may contain one or more suitable flavours 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, applicants 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 assessment if sufficient information concerning the excipients(s) and their impact on zinc absorption is not available to WHO PQT/MED.

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 demonstrating efficacy of the proposed product in the treatment of acute diarrhoea or in vivo bioavailability data demonstrating that administration of the proposed product produces adequate plasma levels of zinc within a 72-hour administration period, is required.

Advice on the Selection of Excipients

The potential impact of interactions between zinc ions and pharmaceutical excipients on absorption is very difficult to predict. As mentioned above, there is particular concern with respect to the potential impact of sweeteners and flavours on the in vivo absorption of zinc. For this reason, applicants to prequalification must provide evidence that the sweeteners/flavours present in their zinc sulfate products do not negatively impact the absorption of zinc.

As an aid to the development of zinc sulfate formulations, WHO PQT/MED has determined that the following pharmaceutical sweeteners and flavours can be employed as excipients in zinc sulfate formulations, without having to provide additional evidence to WHO PQT/MED that the ingredient does not negatively impact the absorption of zinc:

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

It is important that these excipients be employed in the smallest quantities possible to achieve the desired sweetening/flavouring 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 we have confidence that their impact will be negligible, additional information on the impact of that quantity of excipient on zinc absorption may be requested.

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

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 one 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≥6) should be conducted.

Oral syrups

The same principles are applicable to oral syrup products. In order 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.

A form is available for submission of information in support of a biowaiver application for a zinc sulfate product (*Zinc products: biowaiver application form*).

4. Clinical Acceptability Study-related Issues

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* provides general information regarding the design of the acceptability study, in Chapters 5 and Annex 8.

Is a waiver from the requirement to conduct an Acceptability Study possible?

Based on the information available to PQT/MED, if the proposed product employs the sweeteners and flavours as described above in the section, *Advice on the Selection of Excipients*, then a waiver from the requirement to conduct an Acceptability Study can be considered. If the sweeteners and flavours contained in the proposed product differ qualitatively or quantitatively from those described in the above section, *Advice on the Selection of Excipients*, then an Acceptability Study must be submitted in support of an application to PQT/MED.

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 Guideline E6 Good Clinical Practice and the Declaration of Helsinki).

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.

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 in-person or virtual visits arranged thereafter, possibly at the home of the child, to assess adherence and palatability, per the published WHO PQT/MED zinc protocol. All records of the assessment visits should be retained for inspection by WHO staff. (Efficacy assessment is not required, as this is considered well-established.)

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.

To identify a ± 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 dropouts, it is necessary to add 10 children in each group, for a final target sample of 300 children (150 in each age group).

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 PQT/MED 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 PQT/MED 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 PQT/MED 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 PQT/MED 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.