Q&A for submission of applications for prequalification of Zinc Sulfate tablets and Zinc Sulfate oral liquid (solution)

This document should not be treated as a comprehensive guideline; it serves as a complement to other guidances by summarizing some of the basic requirements for the prequalification of zinc sulfate products and in particular highlighting some exemptions and special requirements that are applicable specifically for these products. Applicants are encouraged to familiarize themselves with the 2007 WHO publication entitled "Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Program Managers and Pharmaceutical Manufacturers"¹ and the WHO PQP quality guideline (WHO TRS 970, Annex 4, 2012).

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"², zinc supplementation "…can be given as syrup or dispersible tablet, whichever is available or affordable…" However, as the Ph.Int. and USP monographs for zinc sulfate tablets require a disintegration time of 60 seconds or less (very fast disintegrating), applicants should submit applications for either zinc tablets that meet the above disintegration time specification or oral zinc solutions.

Is evidence of compliance with 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 Active Pharmaceutical Ingredient (API)? Information on the API can be submitted to WHO in one of the following four options:

- As a confirmation of API prequalification document, or
- As a valid European Certificate of Suitability (CEP) with all Annexes; or
- As an API Master File as described in WHO’s "Guidelines on active pharmaceutical ingredient master file procedure" (WHO TRS 948, Annex 4, 2008); or
- 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 WHO PQP 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., Ph.Eur./BP, 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 (6) months accelerated and six (6) months long-term stability studies conducted on at least two (2) 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 (3) consecutive production scale batches should be submitted.
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 PQP. However, any requirements for national registration will need to be considered after prequalification.

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.

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 GI status or the availability of the zinc through interactions such as complexation.¹ 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 (1) 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.¹ 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 Program 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.” Therefore, 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 the Prequalification Programme.

**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 (1) 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 (1) minute without any agitation. After the one (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≥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 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.

**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 Sulfate Products: Biowaiver Application Form [MS Word PDF]).

**Are there any FPP specification requirements for Zinc sulfate formulations?**

In view of the requirements of the WHO Guidance "Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Program Managers and Pharmaceutical Manufacturers", the following are preferable for the PQP:

- 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)

**Any specific packaging and labelling requirements?**

On the basis of the above 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.

**Is an acceptability study required for each specific formulation?**

Yes. 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. Zinc products considered for use in the management of diarrhoea should therefore be tested for acceptability using a standard methodology and the study results summarized in a separate form (Zinc Sulfate Products: Acceptability Study Summary Form [MS Word PDF]). Refer to Annex 8 of "Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Program Managers and Pharmaceutical Manufacturers" for more information.

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5 Zinc sulfate monohydrate is used in the manufacture of tablets (Ph.Int., BP and USP), whereas the monohydrate (Ph.Int, USP) or heptahydrate (Ph.Int) are used in the oral solution.

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