This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[DI010 trade name]*
Manufacturer of Prequalified Product	PharmEvo (Private) Limited A-29, North Western Industrial Zone Port Qasim Karachi -75020. Pakistan
Active Pharmaceutical Ingredient (API)	Zinc sulfate monohydrate
Pharmaco-therapeutic group (ATC Code)	Mineral supplements ATC code: A12CB01
Therapeutic indication	[DI010 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years.

1. Introduction

[DI010 trade name] is indicated for the treatment of acute and persistent diarrhoea in infants and children aged up to 5 years.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

Zinc sulfate monohydrate has been prequalified by WHO according to WHO's Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that the API, used in the manufacture of [DI010 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

Other ingredients

Other ingredients include sodium benzoate, sorbitol solution, citric acid anhydrous, sodium citrate, aspartame, sodium saccharin, orange trusil flavour and purified water, all of which are controlled by acceptable specifications. None of the excipients are of animal or human origin.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a clear transparent, orange- flavoured solution. It is presented in an amber type III glass bottle containing 60 mL of solution. The bottle is fitted with a plastic (LDPE) U-plug and closed with an aluminium cap. The product is supplied with a plastic (HDPE) graduated measuring spoon. Each bottle is packed in a carton.

The objective of the development programme was to obtain a stable and optimized formulation of Zinc (as sulfate) 10 mg/5 mL oral solution that would comply with the pharmacopoeial requirements of zinc (as sulfate) oral solution, and with acceptable taste properties. These properties are required by the 2007 WHO publication entitled *Production of Zinc Tablets and Zinc Oral Solutions: Guidelines for Programme Managers and Pharmaceutical Manufacturers* to be used in infant treatment programmes. Since adherence to the treatment regimen will be affected if the product is not acceptable to infants, young children and their mothers or caregivers, zinc preparations should be formulated as palatable and in such a way as to mask the strong bitter metallic aftertaste of zinc in order to enhance acceptability. The excipients selected were based on the excipients used in the WHO comparator product ZinCfant® 20 mg tablets (M/S Laboratories Pharmaceutiques Rodael, Fierne, France) and API-excipient compatibility studies. Aspartame and sodium saccharin were used as sweeteners; orange trusil flavour was added as a flavouring agent. Sufficient evidence was provided with respect to the acceptability of the product in accordance with the above-mentioned guidance.

The manufacturing process involves the following steps: preparation of preservative solution, addition of excipients, addition of zinc sulfate monohydrate to solution, addition of flavour, pH adjustment, volume make up, filtration and filling. Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

According to a risk evaluation by the applicant, the FPP has no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications are pharmacopoeial based and include tests for appearance, identification (zinc and sulfate), pH, specific gravity, deliverable volume, assay (sodium benzoate and zinc) and microbial limits.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at accelerated storage conditions in the packaging proposed for marketing of the product. The product proved to be stable at both storage conditions. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage period after first opening of the bottle is based on in-use stability data. The product should be protected from light.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

[DI010 trade name] meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc formulations.

4. Summary of product safety and efficacy

[DI010 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [DI010 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product ZinCfant® 20 mg tablets (M/S Laboratories Pharmaceutiques Rodael, Fierne, France) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [DI010 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [DI010 trade name] is used in accordance with the SmPC.

Bioequivalence

[DI010 trade name] meets the criteria for a biowaiver in accordance with the WHO guidance and criteria for zinc formulations.

Efficacy and Safety

Regarding clinical efficacy and safety, [DI010 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [DI010 trade name] was acceptable for the following indication: 'treatment of acute and persistent diarrhoea in infants and children aged up to 5 years', and would allow inclusion of [DI010 trade name], manufactured at PharmEvo (Private) Limited, A-29, North Western Industrial Zone Port Qasim, Karachi-75020, Pakistan in the list of prequalified medicinal products.