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	[RH048 trade name][*]
Manufacturer of Prequalified Product	China Resources Zizhu Pharmaceutical Co., Ltd. No. 27, Chaoyang North Road Chaoyang District, Beijing 100024 P. R. China
Active Pharmaceutical Ingredient(s) (API)	Misoprostol
Pharmaco-therapeutic group (ATC Code)	Uterotonics, Prostaglandins (G02AD06)
Therapeutic indication	[RH048 trade name] is indicated for prevention of post-partum haemorrhage when oxytocin is not available, induction of labour, incomplete abortion as well as spontaneous and induced abortion (preferably with mifepristone)

1. Introduction

[RH048 trade name] is indicated for prevention of post-partum haemorrhage when oxytocin is not available, induction of labour, incomplete abortion as well as spontaneous and induced abortion (preferably with mifepristone).

[RH048 trade name] should be prescribed and administered in accordance with countries' national laws and regulations.

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)

Misoprostol Dispersion (1:100 in HPMC) used in the manufacturer of Misoprostol 0.2 mg Tablets 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 SeriesNo. 953, 2009, Annex 4). This procedure provides an assurance that Misoprostol Dispersion (1:100 in HPMC), used in the manufacture of Misoprostol 0.2 mg Tablets, is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). 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.

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

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil and hypromellose (HPMC). None of the excipients are derived from human or animal sources.

Finished Pharmaceutical Product (FPP)

Pharmaceutical development and manufacture
The multisource product is a hexagonal white tablet, debossed with M and 3 at each side of a score line on the flat side, the other side is slightly convex. The score line is not intended for breaking the tablet. The tablets are presented in cold form aluminium (Alu-Alu) blister packs.

Each tablet contains 0.2 mgmisoprostol as a 1:100 dispersion in HPMC.

The objective of the manufacturer was to develop an immediate release tablet that would be bioequivalent to the WHO PQTm comparator product, Cytotec® 0.2 mg tablets. Following an analysis of the comparator product, a quality target product profile (QTPP) was defined for multisource tablets. The composition of the final formulation is qualitatively similar to that of the comparator product. Reverse engineering of the comparator product was conducted to establish the concentration of each excipient. In addition, API/excipient compatibility studies demonstrated that the API is compatible with the excipients selected for the final formulation.
The manufacturing process entails direct compression, which is regarded an appropriate choice due to the moisture sensitivity of the product. Optimization studies included targeting of the dissolution profiles of the comparator product. The primary packaging (Alu-Alu blisters) has been selected for protection of the tablet against moisture. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Product specifications
The product specifications include tests for tablet description, identification of API (HPLC, UV), related substances (HPLC), dissolution (by HPLC), content uniformity, water content, assay (HPLC) and microbial limits. The analytical procedures have been adequately validated.

Stability testing
Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product is chemically not very stable; the data showed an increase of degradation with time at accelerated and long-term storage conditions, though within justified limits. Based on the available stability data, the proposed shelf life and storage conditions of the FPP as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2013 according to internationally accepted guidelines.

Study title: A randomized, open-label, single-dose, two-period, two- treatment, crossover study to assess the bioequivalence of Reference (R) and Test (T) formulations of Misoprostol tablet 0.2 mg × 2 administered under fasted condition in healthy male and nonpregnant female subjects (study no. ZZ-2013-001_fasted pivotal).

The objective of the study was to compare the bioavailability of the stated Misoprostol 0.2 mg tablet manufactured for/by China Resources Zizhu Pharm Co, Ltd (test drug) with the reference formulation

Cytotec® (GD Searle LLC) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

Treatment T: Test – 2 tablets Misoprostol 0.2 mg (misoprostol 0.4 mg) Batch no. 45130301
Treatment R: Reference – 2 tablets Cytotec® (misoprostol 0.4 mg) Batch no. C111611

A 14 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 19 samples within 12 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for misoprostol acid were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 pg/ml for misoprostol acid.

The study was performed with 40 participants; data generated from a total of 40 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for misoprostol acid as well as statistical results are summarised in the following tables:

Misoprostol acid

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (min)#	12.0 (7.5 – 60)	15.0 (7.5 – 45)	-	-
C_{max} (pg/ml)	1080 ± 431 (995)	1104 ± 515 (1005)	99	89.6 – 109.3
AUC_{0-t} (pg.min/ml)	38508 ± 14476 (36310)	38247 ± 13200 (36344)	100	94.8 – 105.3
AUC_{0-inf} (pg.min/ml)	39614 ± 14638 (36882)	39073 ± 13608 (36919)	100	94.5 – 105.6

* geometric mean; # median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max}values regarding misoprostol acid. Accordingly, the test Misoprostol 0.2 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Cytotec® (GD Searle LLC).

4. Summary of product safety and efficacy

[RH048 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [RH048 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Cytotec® (GD Searle LLC) tablets for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. Reference is made 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 [RH048 trade name] is used in accordance with the SmPC.

Biowaiver

[RH048 trade name] has been shown to have similar dissolution characteristics with Cytotec® 200 µg tablet (GD Searle LLC).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH048 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [RH048 trade name]was acceptable for the following indication: **"prevention of postpartum haemorrhage when oxytocin is not available, for induction of labour, for incomplete abortion as well as spontaneous and induced abortion (preferably with mifepristone)"** and has advised that the quality, efficacy and safety of [RH048 trade name]allow inclusion of [RH048 trade name], manufactured at China Resources Zizhu Pharmaceutical Co., Ltd, No. 27, Chaoyang North Road, Chaoyang District, Beijing 100024, P.R. Chinain the list of prequalified medicinal products.