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	[RH089 trade name][*]
Manufacturer of Prequalified Product	China Resources Zizhu Pharmaceutical Co Ltd
Active Pharmaceutical Ingredients (API)	Mifepristone and Misoprostol
Pharmaco-therapeutic group (ATC Code)	Mifepristone: Other sex hormone and modulator of the reproductive function/antiprogestogen (G03XB01) Misoprostol: Other gynaecologicals, prostaglandins (G02AD06)
Therapeutic indication	Medical management of induced abortion

1. Introduction

[RH089 trade name] is indicated for the medical management of induced abortion. It should be prescribed and administered in accordance with 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)

Mifepristone (micronized) and misoprostol (HPMC 1% dispersion) have 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 these APIs, used in the manufacture of [RH089 trade name], are 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.

Mifepristone API is of BCS low solubility; hence particle size distribution and polymorphism are considered critical parameters. The API supplier produces polymorphic Form I. Micronized mifepristone is used in the manufacture of the FPP.

Other ingredients

Other ingredients used in mifepristone tablet include corn starch, microcrystalline cellulose, povidone, colloidal silicon dioxide and magnesium stearate. Other ingredients used in misoprostol vaginal tablet include microcrystalline cellulose, sodium starch glycolate, hydrogenated castor oil and hypromellose (HPMC). TSE/BSE free certificates from the suppliers have been provided with regard to all the excipients. None of the excipients are derived from human or animal sources.

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

Finished pharmaceutical product (FPP)

The FPP is a co-blistered product, consisting of one 1 tablet of mifepristone 200 mg and 4 vaginal tablets of misoprostol 200 µg per Alu/Alu blister card.

Mifepristone 200 mg tablets

Pharmaceutical development and manufacture

Mifepristone 200 mg tablets are yellowish, biconvex, round tablets, debossed with M1 on one side; the other side is plain.

The objective of the manufacturer was to develop a stable immediate release tablet, with acceptable characteristics, that would be bioequivalent to the WHO PQTm comparator product, Mifegyne® 200 mg tablets. Following an analysis of the comparator product, a quality target product profile (QTPP) was defined for the multisource product. The composition of the final formulation is qualitatively similar to that of the comparator product. In addition, compatibility studies were conducted between API and proposed excipients which showed that they are compatible. The formula was finalised after a series of formulation optimization studies.

Wet granulation resulted in satisfactory tabletting parameters and similar dissolution profiles to that of the comparator product. Hence the wet granulation method was selected for product development and further optimized. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The product specifications include tests for appearance, identification of API (HPLC, UV), related substances (HPLC), dissolution (HPLC detection), weight variation, loss on drying, assay (HPLC) and microbial limits. The analytical procedures have been adequately validated.

Misoprostol 200 µg vaginal tablets

Pharmaceutical development and manufacture

Misoprostol 200 µg vaginal tablets are hexagonal white tablets, 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. Each tablet contains 200 µg misoprostol as a 1% 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® 200 µg tablets. Following an analysis of the comparator product, a quality target product profile (QTPP) was defined for the multisource product. 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. Optimisation studies included targeting of the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

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.

Co-blistered product

Stability testing

The primary packaging (Alu-Alu blisters) has been selected to protect the co-blistered tablets against moisture, since misoprostol is known to be moisture sensitive.

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions. The product proved to be quite stable at these storage conditions and showed only slight increase in degradation products, 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

This application concerns a co-package of mifepristone 200 mg tablet and 4 misoprostol 200 µg tablets. Two bioequivalence studies were carried out.

Oral administration of mifepristone

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

A randomised, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study of mifepristone 200 mg tablets of Beijing Zizhu Pharmaceutical Co. Ltd, P.R. China (test drug) and Mifegyne® (mifepristone) 200 mg tablets of Exelgyn, France (reference formulation), in healthy human adult male subjects, under fasting conditions (study no. 2719/12). Each subject was assigned to receive each of the following two treatments in a randomised fashion:

Treatment T:	Test – 1 tablets mifepristone 200 mg (mifepristone 200 mg) Batch No. 45130401
Treatment R:	Reference – 1 tablet Mifegyne® (mifepristone 200 mg) Batch No. 11071

A 19-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 72 hours post-dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for mifepristone were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 17 ng/mL for mifepristone.

The study was performed with 84 participants; data generated from a total of 76 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for mifepristone as well as statistical results are summarised in the following table:

Mifepristone

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI** (ANOVAlog)
t_{max} (h)	1.47 ± 2.70	1.69 ± 3.73	–	–
C_{max} (µg/mL)	2.32 ± 0.85 (2.19)	2.20 ± 0.70 (2.09)	104.7	96.1–114.1
$AUC_{0\text{-}72\ h}$ (µg·h/mL)	42.3 ± 17.5 (39.0)	41.1 ± 15.9 (38.0)	102.8	96.3–109.6
$AUC_{0\text{-}inf}$ (µg·h/mL)	39614 ± 14638 (36882)	39073 ± 13608 (36919)	100	94.5–105.6

The results of the study show that preset acceptance limits of 80–125% are met by both AUC and C_{max} values regarding mifepristone. Accordingly, the test tablet mifepristone 200 mg meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Mifegyne® (Exelgyn).

Oral administration of misoprostol

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

A randomised, open-label, single-dose, two-period, two-treatment, crossover study assessed the bioequivalence of reference (R) and test (T) formulations of 2 misoprostol 200 µg tablets administered under fasted condition in healthy male and non-pregnant female subjects (study no. ZZ-2013-001_fasted pivotal).

The objective of the study was to compare the bioavailability of the stated misoprostol 200 µg tablet manufactured for/by China Resources Zizhu Pharm Co. Ltd, China (test drug) with the reference formulation Cytotec® (GD Searle LLC) and to assess bioequivalence. The comparison was performed as a single-centre study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomised fashion:

Treatment T: Test – 2 tablets Misoprostol 200 µg (misoprostol 400 µg) Batch No. 45130301

Treatment R: Reference – 2 tablets Cytotec® (misoprostol 400 µg) 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 hours 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 analysed 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 table:

Misoprostol acid (oral administration)

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI** (ANOVAlog)
t_{max} (minutes)	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·minute/mL)	38508 ± 14476 (36310)	38247 ± 13200 (36344)	100	94.8–105.3
AUC_{0-inf} (pg·minute/mL)	39614 ± 14638 (36882)	39073 ± 13608 (36919)	100	94.5–105.6

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 200 µg 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).

Vaginal administration of misoprostol

To support the vaginal administration, the applicant submitted an additional study in which the tablets were given orally and vaginally. The following bioavailability study has been performed in 2017 according to internationally accepted guidelines.

A randomised, open-label, two-treatment, two-period, two-sequence, single-dose, crossover, pharmacokinetic study of 4 tablets of misoprostol tablets 200 µg (4 × 200 µg) of China Resources Zizhu Pharmaceutical Co. Ltd, given orally and vaginally, in healthy adult female subjects, under fasting conditions (study No. 4039/15).

The objective of the study was to compare the bioavailability of the stated misoprostol 200 µg tablet of China Resources Zizhu Pharm Co. Ltd, China (test drug) after oral and vaginally administration. The comparison was performed as a single-centre study. Each subject was assigned to receive each of the following treatments in a randomised fashion:

Treatment T: Test – 4 tablets misoprostol 200 µg administered orally (misoprostol 800 µg) Batch No. 45170201

Treatment R: Test – 4 tablets misoprostol 200 µg administered vaginally (misoprostol 800 µg) Batch No. 45170201

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 27 samples within 48 hours post-dose for Treatment T and 1 pre-dose sample and 21 samples within 48 hours post-dose for Treatment R) were taken during each study period to obtain the characteristics AUC, C_{max} and t_{max} for bioavailability evaluation. Drug concentrations for misoprostol acid were analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 15 pg/mL for misoprostol acid.

The study was performed with 14 participants; data generated from a total of 13 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioavailability.

Arithmetic mean values of the pharmacokinetic variables for misoprostol acid are summarised in the following table:

Misoprostol acid (oral and vaginal administration)

Pharmacokinetic Parameter	**Test formulation (T)** arithmetic mean ± SD (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional 90% CI** (ANOVAlog)
t_{max} (hours)	0.33 (0.20–0.67)	1.5 (1.0–24)	–	–
C_{max} (pg/mL)	2688 ± 121	1017 ± 611	99	89.6–109.3
AUC_{0-t} (pg·h/mL)	2125 ± 523	5262 ± 3853	100	94.8–105.3
AUC_{0-inf} (pg·h/mL)	2175 ± 530	5976 ± 5648	100	94.5–105.6

According to the WHO guidance, pharmacokinetic data (not necessarily a bioequivalence study) should be submitted, showing that, following vaginal administration, the proposed product produces in vivo misoprostol concentrations with a mean maximal concentration (C_{max}) of at least 200 pg/mL (normalised for a 800 ug dose) and an extent of absorption (AUC) that exceeds that observed following oral administration of the product (on a dose normalised basis).

The mean C_{max} observed in this study after vaginal administration of 800 ug dose was 1017 ± 611 pg/mL, with a minimum C_{max} concentration observed of 348 pg/mL. This mean C_{max} concentration exceeds the 200 pg/mL limit. In addition, the exposure after vaginal administration of 5262 ± 3853 pg·h/mL exceeds the exposure after oral administration i.e. 2125 ± 523 pg·h/mL. This means that the requirements have been fulfilled.

4. Summary of product safety and efficacy

[RH089 trade name] has been shown to conform to the same appropriate standards of quality, efficacy and safety as those required for the innovator products. According to the submitted data on quality and bioavailability of mifepristone and misoprostol tablets in [RH089 trade name] meet the criteria for bioequivalence with regard to rate and extent of absorption and they are therefore bioequivalent to the reference medicines Mifegyne® (Exelgyn) and Cytotec® (GD Searle LLC), respectively.

The clinical safety of this product is considered acceptable when guidance and restrictions presented in the summary of product characteristics are taken into consideration. Reference is made to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

The quality of this product is considered acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Bioequivalence

The mifepristone and misoprostol tablets in [RH089 trade name] have been shown to be bioequivalent to the reference medicines Mifegyne® (Exelgyn) and Cytotec® (GD Searle LLC), respectively.

Efficacy and Safety

[RH089 trade name] is considered effective and safe to use when the guidance and restrictions presented in the summary of product characteristics are taken into consideration.

Benefit Risk Assessment

Based on WHO assessment of data on quality, bioequivalence, safety and efficacy, the team of assessors considered that the benefit–risk profile of [RH089 trade name] was acceptable for the following indication: 'medical management of induced abortion', and has advised that the quality, efficacy and safety of [RH089 trade name] trade name allow inclusion of [RH089 trade name], manufactured at China Resources Zizhu Pharmaceutical Co Ltd, Chaoyang District, Beijing, 100024, China in the list of prequalified medicinal products.