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:	[RH074 trade name][1]
Manufacturer of Prequalified Product:	Mylan Laboratories Limited Plot No. 20 & 21, Pharmez The Pharmaceutical Special Economic Zone Sarkhej – Bavla National Highway No. 8-A Nr. Village – Matoda Tal- Sanand Dist. – Ahmedabad Postal code: 382213 India
Active Pharmaceutical Ingredient (API):	Medroxyprogesterone acetate
Pharmaco-therapeutic group (ATC Code):	Progestogens, ATC Code G03AC06
Therapeutic indication:	[RH074 trade name] is used for long-term contraception in women aged over 18 years. [RH074 trade name] may be used in adolescents aged over 12 years if there is compelling reason for contraception and other methods are unsuitable or unacceptable.

1. Introduction

[RH074 trade name] is used for long-term contraception in women aged over 18 years (see Part 4 for full indications).

[RH074 trade name] should be initiated by a health care provider experienced in the management of female contraception.

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)

The API manufacturer supplies micronized, sterile medroxyprogesterone acetate for manufacture of the finished product. Medroxyprogesterone acetate (sterile) used in the manufacture of [RH074 trade name] 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

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

Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that medroxyprogesterone acetate (sterile), used in the manufacture of Medroxyprogesterone acetate 150mg/mL suspension for injection, 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.

The API is of BCS low solubility and formulated as a suspension, hence particle size distribution (PSD) is considered a critical parameter and forms part of the FPP manufacturer's API specification, with acceptance criteria set on the information of the API lot used in the FPP biobatch. Polymorphic forms are not known.

Other ingredients

Other ingredients used in the suspension for injection include polysorbate 80, macrogol 3350, methyl paraben (E218), propyl paraben (E216), sodium chloride, hydrochloric acid and/or sodium hydroxide for the pH adjustment and water for injection, all being pharmacopoeial controlled. There are no excipients of animal or human origin. A BSE/TSE compliance declaration was provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off- white sterile suspension, filled in 2 mL type I clear tubular glass vial with grey bromobutyl rubber stopper and white flip-off aluminium seal.

The *Additional Guidance on Submission Requirements for Medroxyprogesterone Acetate Depot Injection Products Using the Common Technical Document (CTD) Format* (WHO Guidance) posted on the WHO PQTm website was used extensively as guidance during development of the product. The WHO Guidance recommends that a first approach to deal with the rather complex situation in targeting the QTPP of the comparator product would be adoption of the composition of the comparator product. The qualitative and quantitative composition of the excipients selected for this multisource product is actually the same as listed for the WHO recommended comparator product, Depo-Provera® Contraceptive Injection obtained from the US market. As part of the pharmaceutical development studies, the comparator product was characterized in terms of critical attributes such as pH, rheological properties, dissolution, polymorphic form and PSD. Detailed studies on redispersibility / resuspendability, syringeability, injectability and sedimentation rate of the proposed finished product were performed in accordance with the WHO Guidance.

The manufacturing process includes the steps of compounding, filtration, filling and stoppering, sealing and terminal sterilization. It was demonstrated that the suspension for injection is stable towards the terminal sterilization process and that this process has no impact on critical quality attributes, including the solid-state properties. Studies such as autoclave suitability, hold times of the various bulk solutions, tubing compatibility, rubber closure compatibility, filter validation, photostability and freeze-thaw were performed during the development of the manufacturing process.

For selection of a dissolution method Test 1 (USP Apparatus IV, flow through cell) and Test 2 (paddle) of the USFDA OGD recommended dissolution methods were investigated in light of the extended release properties of the depot injection. Apparatus IV showed the desired discriminatory power and was selected and optimised as QC test. As per the WHO Guidance the discriminatory power of the selected dissolution method was tested in relation to PSD variation, varying of polyethylene glycol grade and varying of polyethylene glycol 3350 quantity was studied. The discrimination power with respect to PSD was demonstrated.

Specifications

The finished product specifications include tests for description, identification of the API (IR, HPLC)

and the parabens (HPLC), specific gravity, pH, sedimentation volume, resuspendability / redispersibility, syringeability and injection volume, viscosity, osmolality, sodium chloride content, sterility, bacterial endotoxins, dissolution (USP type IV apparatus, HPLC detection), uniformity of dosage units, assay (HPLC), content of methyl and propyl paraben (HPLC), related substances (HPLC), PSD and particulate matter.

These tests are regarded acceptable for the suspension for injection as per the WHO Guidance. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition. A decrease in pH was noted at both storage conditions, though it stayed within limits, accompanied by a decreasing trend in viscosity. The other parameters did not show any atypical trend. The PSD and dissolution data do not suggest particle growth or agglomeration. Photostability studies demonstrated that protection from light is not necessary. Based on the available stability data, the proposed shelf-life and storage conditions 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 2017 according to internationally accepted guidelines.

An open label, balanced, randomized, three-treatment, one-period, single dose, parallel, bioequivalence study of [RH074 trade name] manufactured by Jai Pharma Ltd., India with that of 'Depo-Provera® Contraceptive Injection' (medroxyprogesterone acetate injectable suspension, USP) 150 mg/mL distributed by Pharmacia & Upjohn Company, USA administered intramuscularly in healthy adult female subjects under fasting conditions (study no. 551-15).

The objective of the study was to compare the bioavailability of the stated [RH074 trade name] manufactured by/for Jai Pharma Ltd., India (test drug) with the reference formulation Depo-Provera® (Pharmacia & Upjohn Company) and to assess bioequivalence. The suspension was administered by the intramuscular route either on the left/right side of the deltoid muscle or on the left/right side of the gluteal muscle.

The comparison was performed as an open label, randomized, three-treatment, one period, single-dose parallel study in healthy subjects. Each subject was assigned to receive one of the following treatments:

Treatment T1: Test – 1 injection [RH074 trade name]
(medroxyprogesterone 150 mg)
Batch no. 6488A002.
Treatment T2: Test – 1 injection [RH074 trade name]
(medroxyprogesterone 150 mg)
Batch no. 6475A003.
Treatment R: Reference – 1 injection Depo-Provera®
(medroxyprogesterone 150 mg)
Batch no. L82823.

Treatment T2 is the to be marketed formulation.

Serial blood samples (1 pre-dose sample and 41 samples within 140 days post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for medroxyprogesterone were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 pg/ml for medroxyprogesterone.

The study was performed with 429 participants; data generated from a total of 396 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for medroxyprogesterone (treatment T2 and Reference) as well as statistical results are summarised in the following table:

Medroxyprogesterone

Pharmacokinetic Parameter	Test formulation (T2) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	156 (24 – 2522)	133 (2 – 1849)	-	-
C_{max} (pg/ml)	2709 ± 1276 (2820)	3027 ± 1343 (2766)	88.6	82.1 – 95.6
AUC_{0-90d} (ng.h/ml)	3015 ± 1182 (2743)	3017 ± 1014 (2809)	97.7	91.7 – 104.2
AUC_{0-140d} (ng.h/ml)	3483 ± 1069 (3244)	3462 ± 910 (3306)	99.8	94.6 – 105.4
AUC_{0-inf} (ng.h/ml)	4245 ± 1428 (3766)	4029 ± 1035 (3871)	103.6	98.0 – 109.6

*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 medroxyprogesterone. Accordingly, the test [RH074 trade name] meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Depo-Provera® (Pharmacia & Upjohn Company).

4. Summary of Product Safety and Efficacy

[RH074 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, [RH074 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Depo-Provera® (Pharmacia & Upjohn Company) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of this product is considered 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 [TB327 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH074 trade name] has shown to be bioequivalent with Depo-Provera® (Pharmacia & Upjohn Company,USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH074 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [TB327 trade.name] was acceptable for the following indication: **'[RH074 trade name] is used for long-term contraception in women aged over 18 years'** and has advised that the quality, efficacy and safety of [RH074 trade name] allow inclusion of [RH074 trade name], manufactured at Mylan Laboratories Limited, Plot No. 20 & 21, Pharmaceutical Special Economic Zone, Sarkhej- Bavla National Highway No. 8-A, Matoda, Tal-Sanand, Ahmedabad 382213, India, in the list of prequalified medicinal products.