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	[RH106 trade name]*
Manufacturer of Prequalified Product	Incepta Pharmaceuticals Ltd Unit-10, Injectable Potent Drug (IPD), Krishnapura, Sahabelishor, Dhamrai, Dhaka, Bangladesh
Active Pharmaceutical Ingredient(s) (API)	Medroxyprogesterone acetate
Pharmaco-therapeutic group (ATC Code)	**G03AC06:** Progestogens, used in hormonal contraceptives.
Therapeutic indication	Contraception

1. Introduction

[RH106 trade name] is used for long-term contraception in women

[RH106 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 [RH106 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 Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that medroxyprogesterone acetate (sterile), used in the manufacture of [RH106 trade name], 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:

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

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 methyl paraben, propyl paraben, sodium chloride, polyethylene glycol 3350, polysorbate 80, povidone, L-methionine, disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide and/or hydrochloric acid (for adjustment of pH) and water for injection, all being pharmacopoeial controlled. There are no excipients of animal or human origin. BSE/TSE compliance declarations were provided for all excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off- white suspension for injection, filled in in a single-dose pre-filled injection injector called uniject. Each uniject injector comprises a linear low-density polyethylene laminate reservoir with a siliconized stainless steel, thin wall needle attached via a low-density polyethylene port and valve. Each uniject injector is enclosed in an aluminium foil pouch.

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 PQT/MED 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, Sayana Press® 104mg/0.65mL suspension for injection. As part of the pharmaceutical development studies, the comparator product was characterized in terms of critical attributes such as pH, viscosity 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 is a standard aseptic process, conducted under appropriate conditions, including the steps of compounding (vehicle and final suspension preparation), followed by filling into uniject injector and sealing. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on three consecutive batches.

For selection of a dissolution method, Test 1 (USP Apparatus IV, flow through cell method) and Test 2 (USP Apparatus II modified, paddle method) of the USFDA OGD recommended dissolution methods were investigated in light of the release properties of the subcutaneous injection. Test 2 showed 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 and viscosity (varying of polyethylene glycol grade/quantity). The discrimination power with respect to PSD and viscosity was demonstrated.

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 include tests for description, identification of the API (IR, HPLC) and parabens (HPLC), extractable volume, particle size distribution, pH, specific gravity, content of methyl and propyl paraben (HPLC), dissolution (USP type II apparatus, UV detection), related substances (HPLC), uniformity of dosage units (content uniformity), assay (HPLC), content of L-methionine, syringeability, resuspendability, clumping, sodium chloride content , viscosity, osmolality, sedimentation rate, sub-visible particulate matter, bacterial endotoxins and sterility. 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 at 25°C/60%RH (zone II) and 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at 40°C/75%RH as accelerated storage condition. The data showed slight to no variability for all parameters at the storage conditions. 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 2023 according to internationally accepted guidelines.

A randomized, single dose, single-period, parallel group, subcutaneous bioavailability/ bioequivalence study of the Medroxyprogesterone Acetate suspension (104 mg/0.65 ml) for injection manufactured by Incepta Pharmaceuticals Ltd, Bangladesh (test), with Sayana Press®, manufactured by Pfizer Ltd, UK (reference) in healthy, adult, premenopausal female subjects (study no. IPL-MPSC-102).

The objective of the study was to compare the bioavailability of the stated Medroxyprogesterone acetate 104 mg/0.65 ml suspension for injection manufactured by/for Incepta Pharmaceuticals Ltd, Bangladesh (test drug) with the reference formulation Sayana Press® (Pfizer) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, parallel study in healthy premenopausal female subjects under fasting conditions. Each subject was assigned to receive one of the following two treatments in a randomized fashion:

Treatment T: Test – 1 injection Medroxyprogesterone acetate suspension 104 mg/0.65 ml

(medroxyprogesterone acetate 104 mg)
Batch no. 23003.

Treatment R: Reference – 1 injection Sayana Press® 104 mg/0.65 ml

(medroxyprogesterone acetate 104 mg)

Batch no. FJ6772.

Serial blood samples (1 pre-dose sample and 33 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 acetate were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 25 pg/ml for medroxyprogesterone acetate.

The study was performed with 220 participants; data generated from a total of 213 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Medroxyprogesterone acetate

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} (h)	144 ± 203	204 ± 335	-	-
C_{max} (ng/ml)	1.178 ± 0.422 (1.111)	1.096 ± 0.396 (1.037)	107.2	99.7 – 115.2
$AUC_{0\text{-}91d}$ (ng.h/ml)	1154 ± 367 (1095)	1207 ± 402 (1143)	95.8	89.3 – 102.7
$AUC_{0\text{-}140d}$ (ng.h/ml)	1486 ± 452 (1413)	1589 ± 499 (1509)	93.6	87.4 – 100.3

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding medroxyprogesterone acetate. Accordingly, the test Medroxyprogesterone acetate 104 mg/0.65 ml suspension for injection meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Sayana Press® (Pfizer).

4. Summary of product safety and efficacy

[RH106 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, [RH106 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sayana Press® (Pfizer). for which benefits have been proven in terms of clinical efficacy. The clinical safety of [RH106 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 [RH106 trade name] is used in accordance with the SmPC.

Bioequivalence

[RH106 trade name] has been shown to be bioequivalent with Sayana Press® (Pfizer).

Efficacy and Safety

Regarding clinical efficacy and safety, [RH106 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 [RH106 trade name] was acceptable for the use in long term contraception, and would allow inclusion of [RH106 trade name], manufactured at Incepta Pharmaceuticals Ltd, Krishnapura, Sahabelishor, Dhamrai, Dhaka, Bangladesh, in the list of prequalified medicinal products.