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:	[RH028 trade name][1]
Manufacturer of Prequalified Product:	Shanghai Dahua Pharmaceutical Co. Ltd. 3503 Changzheng Road Chongming County Shanghai China
Active Pharmaceutical Ingredient (API):	Levonorgestrel
Pharmaco-therapeutic group (ATC Code):	Progestogen (G03AD01)
Therapeutic indication:	[RH028 trade name] is a contraceptive method for three years of use.

1. Introduction

[RH028 trade name] provides contraceptive coverage for up to three years. The implants may be removedat the request of the user at any time.

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)

Levonorgestrel used in the manufacturer of [RH028 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 levonorgestrel, used in the manufacture of [RH028 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 dimethylsiloxane/methylvinylsiloxane copolymer core, silicone tubing and polydimethylsiloxane adhesive. The components used in the manufacture in [RH028 trade name] are not of human or animal origin.

[1] Trade names are not prequalified by WHO. This is the national National Medicines Regulatory Authority's responsibility.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

[RH028 trade name] is a set of two flexible, cylindrical, sealed, white or off-white rods. Each implant rodis about 44 mm in length and 2.4 mm in diameter. The two rods are supplied in a sterile primary package. The primary package is a laminated pouch of polyethylene terephthalate and polyethylene designed for pharmaceutical packaging. It has been demonstrated that the primary packaging provides adequate protection against microbial contamination. Ten pouches are packaged in a cardboard box.

[RH028 trade name] was developed as a generic version of Jadelle® with a similar delivery system. The development was initiated by the China State Family Planning Commission (now named National Health and Family Planning Commission, [NHFPC]).

Each implant rod consists of three components:

(1) A dimethylsiloxane/methylvinylsiloxane copolymer medical core containing 75 mg of the progestin levonorgestrel.

(2) The core is enclosed in a thin-walled silicone tubing measuring approximately 2.4 mm in diameter and 44 mm in length.

(3) The implant rod is sealed at the ends with a polydimethylsiloxane adhesive.

The process development focused on the manufacturing of the three major components (core, tubing and seal adhesive), the implant rod assembly process, packaging in pouches, the sterilization process and finished product analysis including performance testing.

Core rods, obtained through a forming and vulcanization process, are inserted into the outer tube, centred and sealed. [RH028 trade name] does not contain antimicrobial preservatives and is terminally sterilized with ethylene oxide. The sterilization process does not affect integrity of the container closure system.

Specifications

The product specifications include tests for appearance; identification (HPLC, TLC); dissolution rate (multipoint with ranges; HPLC detection); assay (HPLC); related substances (HPLC); sterility; content uniformity; heavy metals; endotoxins; platinum; and residue limits of ethylene oxide and organic solvents. The tests with acceptance criteria were justified and the procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH as long-term storage conditions and for six months at 40°C/75%RH as accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at both storage conditions, with no apparent negative trend. 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 Pharmacokinetics

In study 10242 (see also Efficacy and Safety section below), from a subgroup of 50 subjects with body mass index (BMI) below 30 kg/m^2, frequent blood samples were obtained during the first six months after insertion. Data from 22 and 19 subjects in the [RH028 trade name] group and Jadelle® group, respectively, could be included in the levonorgestrel pharmacokinetic analysis. In addition, from 30 out of these 50 subjects (15 in each group) data were available up to 12 months after insertion. Additional sparse sampling data at month 1, 6, 12, 18, 24, 30, 36 and 42 were obtained from a larger group of subjects.

Total levonorgestrel concentrations were measured using a validated LC-MS/MS method. The calibration curve ranged from 50 to 25,000 pg/mL.

The pharmacokinetic results are shown in table PK 1 and the statistical results in table PK 2. The data from the subgroup showed no statistically significant difference in levonorgestrel AUC over the first 12 months after insertion, although the levonorgestrel AUC geometric mean ratio was consistently lower for [RH028 trade name].

Table PK 1. Pharmacokinetic results of levonorgestrel in the pharmacokinetic subgroup.

	[RH028 trade name]		Jadelle®	
*	N	mean ± s.d.	N	mean ± s.d.
Cmax	22	833 ± 367	19	962 ± 366
tmax	22	5.4 ± 5.9	19	4.3 ± 2.1
AUCday7	21	161 ± 67	19	182 ± 67
AUCmonth1	21	621 ± 237	19	685 ± 228
AUCmonth3	21	1445 ± 448	19	1612 ± 505
AUCmonth 6	21	2489 ± 740	17	2862 ± 896
AUCmonth12	15	4335 ± 1378	15	4972 ± 1575

*Cmax (pg/mL); tmax (days); AUC (pg.month/mL); mean as arithmetic mean; s.d.:standard deviation

Table PK 2. Geometric mean (GM) and geometric mean ratio (GMR) of levonorgestrel pharmacokinetic parameters in the pharmacokinetic subgroup.

	[RH028 trade name]		Jadelle®		GMR		
*	N	GM	N	GM	ratio	90%CI	p-value
Cmax	22	761	19	895	0.85	0.68-1.06	0.23
tmax	22	4.1	19	3.8	1.08	0.78-1.50	0.68
AUCday7	21	147	19	170	0.87	0.70-1.08	0.28
AUCmonth1	21	579	19	649	0.89	0.73-1.09	0.33
AUCmonth3	21	1375	19	1536	0.89	0.75-1.07	0.29
AUCmonth 6	21	2377	17	2730	0.87	0.73-1.04	0.19
AUCmonth12	15	4116	15	4754	0.87	0.71-1.06	0.24

*Cmax (pg/mL); tmax (days); AUC (pg.month/mL)

Based upon the sparse sampling data and total levonorgestrel plasma concentration data over up to 42 months of implant, in the Sino-Implant group, average levonorgestrel concentrations decreased from 430 pg/mL one month after insertion to 351, 311, 292, 253, 234, 224 and 229 pg/mL, respectively, at months 6, 12, 18, 24, 30, 36 and 42. In the Jadelle® group, average levonorgestrel concentrations decreased from 451 pg/mL one month after insertion to 369, 312, 326, 305, 315, 273, and 269 pg/mL, respectively, at months 6, 12, 18, 24, 30, 36 and 42 (see table PK 3).

Geometric mean levonorgestrel concentrations were comparable between [RH028 trade name]and Jadelle® up to 12 months after insertion, but differed significantly thereafter, with 14%, 18%, 26%,

21% and 21% lower levonorgestrel concentrations in the [RH028 trade name] group at months 18, 24, 30, 36 and 42.

Table PK 3. Total levonorgestrel concentrations (pg/mL; mean ± sd) by month after insertion.

Month after insertion	[RH028 trade name]	Jadelle®	Geometric mean (90%CI)
1	430 ± 205 (n=488)	451 ± 164 (n=132)	0.93 (0.88 – 0.99)
6	351 ± 210 (n=444)	369 ± 167 (n=114)	0.93 (0.87 – 1.00)
12	311 ± 197 (n=392)	312 ± 114 (n=103)	0.95 (0.88 – 1.03)
18	292 ± 165 (n=349)	326 ± 128 (n=93)	0.86 (0.79 – 0.93)
24	253 ± 124 (n=302)	305 ± 152 (n=80)	0.82 (0.75 – 0.90)
30	234 ± 126 (n=227)	315 ± 179 (n=49)	0.74 (0.66 – 0.82)
36	224 ± 154 (n=200)	273 ± 176 (n=42)	0.79 (0.69 – 0.91)
42	229 ± 170 (n=91)	269 ± 112 (n=19)	0.79 (0.64 – 0.97)

Twenty-nine (5.6%) [RH028 trade name] users had one or more measurements below 100 pg/mL at one or more time points over up to 3.75 years of follow-up, compared to only one (0.7%) Jadelle® user.

In summary, at 36 months after insertion, levonorgestrel (LNG) concentrations were statistically significantly lower in the [RH028 trade name] group compared to Jadelle®, with a GMR of 0.79 (90% CI:0.69-0.91). The pharmacokinetic data raise concern that [RH028 trade name] may have poorer efficacy, due to lower levonorgestrel plasma concentrations. However, 3-year data supported the efficacy and safety of [RH028 trade name]. See Clinical Efficacy and Safety below.

4. Summary of Product Safety and Efficacy

Contraceptive implants with progestins as the active ingredient have been in use worldwide for several decades. There is much low-quality literature on the implant products. In 2015, [RH028 trade name] was added to the list of products in the WHO "Medical eligibility criteria for contraceptive use, Fifth edition." The GRADE assessment of quality of evidence was stated to be "moderate to very low."

The Sponsor has conducted a GCP-compliant, phase 3 clinical trial (Study 10242, n=650) at PROFAMILIA in the Dominican Republic, to assess the effectiveness, safety and acceptability of the product. The study used an allocation ratio of 4:1 of the test product versus the originator product (i.e. Sino-Implant 500/Jadelle® 150).

Women with HIV were excluded from the study.

In compliance with the 2006 EMA "Guideline on clinical investigation of steroid contraceptives in women," the efficacy analyses were both by Pearl Index (number of pregnancies per 100 woman-years) and by life-table analyses.

Three-year data from the pivotal study are at present available.

Regarding efficacy, the Pearl Index for first 3 years combined for [RH028 trade name] is 0.19, for Jadelle® 0.0. These are both in the range of "highly effective" contraceptive products, i.e., with Pearl

Index less than 1.

Regarding safety, there were no significant differences between the 2 products for most of the common AEs (adverse events: irregular menses, headache, dizziness, lower abdominal pain). However, implant breakage rates at or near product removal at 3 years were 13% for [RH028 trade name] versus 3% for Jadelle®. To date this has not been adequately explained by the Sponsor. Labelling in the Summary of Product Characteristics (WHOPAR part 4) and Patient Information Leaflet (WHOPAR part 3) describes how risk of breakage may be minimized in clinical practice. The breakages are considered an annoyance for implant users and healthcare providers, but not a major safety concern.

Possibly-related serious adverse events (SAEs) were not different for [RH028 trade name] versus Jadelle®.

While [RH028 trade name] clinical data were generated from Study 10242 in the Dominican Republic,the indication (contraception) and the labelled safety/efficacy of the product for the user are considered to be applicable to all women, regardless of geographic location/ethnicity.

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 [RH028 trade name] is used in accordance with the SmPC.

Pharmacokinetics

Geometric mean levonorgestrel concentrations were comparable between [RH028 trade name] and Jadelle® up to 12 months after insertion, but differed significantly thereafter. The pharmacokinetic data raise concern that [RH028 trade name] may have poorer efficacy, due to lower levonorgestrel plasmaconcentrations. However, 3-year data supported the efficacy and safety of [RH028 trade name] (see below).

Efficacy and Safety

The 3-year efficacy and safety data from pivotal Study 10242 are considered adequate to support the indication “Contraception” for [RH028 trade name] for that period, in accordance with guidance and restrictions described in the Summary of Product Characteristics and the Patient Information Leaflet. Women with HIV were excluded from the pivotal study, and safety/efficacy conclusions regarding these women cannot be drawn. Although the 13% breakage rate at product removal is high, it is not considered a serious complication. [RH028 trade name] is acceptable for inclusion in the list of WHO prequalified products.

Benefit Risk Assessment

Based on the WHO's assessment of data on quality, pharmacokinetics, safety and efficacy the team of assessors considered that the benefit-risk profile of [RH028 trade name] was acceptable for the following indication: “Contraception for up to three years” and has advised that the quality, efficacy and safety of [RH028 trade name] allow inclusion of [RH028 trade name], manufactured at Shanghai Dahua Pharmaceutical Co. Ltd., 3503 Changzheng Road, Chongming County, Shanghai, China, in the list of prequalified medicinal products.