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	[RH054 trade name]*
Manufacturer of Prequalified Product	Bayer de México S.A. de C.V. Orizaba, Ojo de Agua S/N 94450 Ixtaczoquitlán, Veracruz Mexico
Active Pharmaceutical Ingredients (APIs)	Estradiol valerate /Norethisterone enantate
Pharmaco-therapeutic group (ATC Code)	Progestogens and estrogens, fixed combinations (G03AA)
Therapeutic indication	[RH054 trade name] is indicated in women for hormonal contraception

1. Introduction

[RH054 trade name] is indicated in women for hormonal contraception, as detailed in the summary of product characteristics.

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 Ingredients (APIs)

Estradiol valerate

A CEP (Certificate of Suitability) issued by the EDQM was submitted for estradiol valerate ensuring good manufacturing control and applicability of the Ph.Eur monograph to control the quality of the API.

Norethisterone enantate

The norethisterone enantate API is partially supported by a CEP. The CEP covers pure norethisterone API. Norethisterone is subsequently esterified to norethisterone enantate.

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

Norethisterone enantate is a white to creamy white crystalline powder. It is insoluble in water, freely soluble in acetone, methanol, dehydrated ethanol, dioxan and ether and slightly soluble in light petroleum.

The API specifications include tests for appearance, identification, appearance of solution (clarity and colour), melting range, specific optical rotation, sulphated ash, a limit for enantic acid, loss on drying, residual solvents, related substances, assay, microbial purity, bacterial endotoxins and elemental impurities.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packaging.

Other ingredients

Other ingredients include benzyl benzoate and castor oil for injection. No excipient with the risk of transmitting TSE/BSE is used.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a clear, oily solution, free of particles, filled in brown glass type I OPC (one point cut) colour coded ampoules. The solution for injection is always administered by the intramuscular route.

The manufacturing process is a standard process – conducted under appropriate aseptic conditions – including the steps of preparation of the solution, aseptic filtration, filling of the solution in ampoules and sealing. Finally, thermal treatment of the filled and sealed ampoules in an autoclave is performed. Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture. Process validation have been conducted on 3 consecutive batches.

Specifications

The finished product specifications include tests for description, colour of OPC spot/coding ring of the ampoule, appearance of the solution /visible particles, identification of the APIs (HPLC and UV/DAD), identification of castor oil (HPLC), extractable volume, colour, particulate contamination (sub-visible particles), degradation products (HPLC), assay (HPLC), bacterial endotoxins and sterility.

Stability testing

Stability studies have been conducted at 30°C/65%RH (zone IVa) as long-term storage condition and for six months at 40°C/75%RH as accelerated conditions. The product proved to be quite stable at both long term and accelerated 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 bioequivalence

A bioequivalence study was not conducted as [RH054 trade name] is the comparator.

4. Summary of product safety and efficacy

The benefits of [RH054 trade name] have been proven in terms of clinical efficacy. The clinical safety of [RH054 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 [RH054 trade name] is used in accordance with the SmPC.

Bioequivalence

A bioequivalence study was not conducted as [RH054 trade name] is the comparator.

Efficacy and Safety

Regarding clinical efficacy and safety, [RH054 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 WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [RH054 trade name] was acceptable for the following indication: **'hormonal contraception for women'**, and has advised that the quality, efficacy and safety of [RH054 trade name] allow inclusion of [RH054 trade name], manufactured at Bayer de México S.A. de C.V., Orizaba, Ojo de Agua S/N, 94450 Ixtaczoquitlán, Veracruz, Mexico, in the list of prequalified medicinal products.