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

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| **Name of the Finished Pharmaceutical Product:** | [HA658 trade name]* |
| **Manufacturer of Prequalified Product:** | Shanghai Desano Bio-Pharmaceutical Co., Ltd.<br>1479 Zhangheng Road<br>China (Shanghai) Pilot Free Trade Zone<br>Shanghai 201203<br>P.R. China |
| **Active Pharmaceutical Ingredient (API):** | Efavirenz |
| **Pharmaco-therapeutic group (ATC Code):** | Non-nucleoside reverse transcriptase inhibitor (J05AG03) |
| **Therapeutic indication:** | [HA658 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents. |

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

## 1. Introduction

[HA658 trade name] is indicated for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents.

For use of antiretroviral agents for post-exposure prophylaxis consult the most recent official treatment guidelines (e.g. those by WHO).

[HA658 trade name] should be prescribed by a health care provider experienced in the management of HIV infection.

## 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)

Efavirenz 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 the API, used in the manufacture of Efavirenz 600mg Tablets, 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 inspection of the sites of API manufacture to verify compliance with WHO GMP requirements.

The solid state attributes of the API were considered to be critical for the FPP manufacturer since the API is regarded critically insoluble (of BCS low solubility across the physiological pH range). Efavirenz shows polymorphism and Form I is consistently produced. PSD limits were set on the data obtained for the API batch used in the manufacture of the FPP biobatch. PSD is also a retest parameter.

### Other ingredients

Other ingredients used in the core tablet formulation include lactose monohydrate, sodium starch glycolate, polyvinylpyrrolidone, sodium lauryl sulfate, microcrystalline cellulose and magnesium stearate. Magnesium stearate is from plant origin. A TSE/BSE free attestation has been provided for lactose monohydrate. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, polyethylene glycol and iron oxide yellow.

### Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a yellow, film-coated, modified capsule-shaped, biconvex tablet debossed with "D03" on one side and plain on the other side. The tablets are packaged in HDPE bottles with child resistant polypropylene closure.

The strategy of the product development was to obtain immediate release tablets that would be bioequivalent to the WHO recommended comparator product, Sustiva® Tablets 600mg. The excipients selected are well established, commonly used in the manufacture of immediate release tablets and supported by API-excipient compatibility studies.

Due to the poor aqueous solubility of efavirenz across the physiological pH range, micronized substance was chosen to obtain dissolution profiles similar to those of the comparator product. Considering the high API content and poor powder flowability of micronized efavirenz, direct compression was considered not feasible and an aqueous wet granulation process was proposed for manufacture of the core tablets. Stress studies showed that polymorphic Form I of efavirenz is stable to moisture and heat, rendering wet granulation feasible.

The selected manufacturing process is standard and includes the steps of wet granulation, drying, sizing, blending, compression and coating. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

*Specifications*

The finished product specifications are pharmacopoeial based and include tests for description, identification of the API (IR, HPLC), assay (HPLC), dissolution (HPLC detection), uniformity of dosage units (by mass variation), organic impurities (HPLC), loss on drying and microbial limits.

*Stability testing*

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated condition in the packaging proposed for marketing of the product. The product was shown to be very stable at these 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 2015 according to internationally accepted guidelines.

Study title: A randomized, balanced, open label, two treatment, two period, two sequence, single dose, truncated, crossover, bioequivalence study of Efavirenz tablets 600 mg of Shanghai Desano Bio-Pharmaceutical Co., Ltd., 1479 Zhangheng Road, Zhangjiang Hi-Tech Park, Shanghai 201203, China, with Sustiva tablets 600 mg of Bristol-Myers Squibb Company in normal, healthy, adult male and female human subjects under fasting conditions (study no. ARL/14/692).

The objective of the study was to compare the bioavailability of the stated Efavirenz 600 mg tablets manufactured for/by Shanghai Desano Bio-Pharmaceutical Co., Ltd., China (test drug) with the reference formulation Sustiva® (Bristol-Myers Squibb Company) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following treatments in a randomized fashion:

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| Treatment T: | Test – 1 tablet Efaviranz 600 mg (efavirenz 600 mg) Batch no. BJE14001 |
| Treatment R: | Reference – 1 tablet Sustiva® (efavirenz 600 mg) Batch no. 2M51995B |

A 28 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 18 samples within 72 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, $C_{max}$ and $t_{max}$ for bioequivalence evaluation. Drug concentrations for efavirenz were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 51 ng/ml for efavirenz.

The study was performed with 36 participants; data generated from a total of 29 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

**Efavirenz**

| 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) | 3.22 ± 1.55 | 3.30 ± 1.00 | - | - |
| $C_{max}$ (ng/mL) | 2417 ± 726 (2326) | 2768 ± 772 (2665) | 87.3 | 80.2 – 95.0 |
| $AUC_{0-t}$ (ng.h/mL) | 54749 ± 19035 (52563) | 59163 ± 19516 (56136) | 93.6 | 88.1 – 99.5 |

* 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 efavirenz. Accordingly, the test Efavirenz 600 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Sustiva® (Bristol-Myers Squibb Company).

## 4. Summary of product safety and efficacy

[HA658 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 [HA658 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sustiva® tablets 600 mg for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HA658 trade name] is considered to be acceptable when guidance and restrictions stated in the Summary of Product Characteristics 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 [HA658 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HA658 trade name] has shown to be bioequivalent with Sustiva® tablets 600 mg (Bristol – Myers Squibb, USA).

**Efficacy and Safety**

Regarding clinical efficacy and safety, [HA658 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 [HA658 trade name] was acceptable for the following indication: **"for the treatment of HIV-1 infection in combination with other antiretroviral agents in adults and adolescents"** and would allow inclusion of [HA658 trade name], manufactured at Shanghai Desano Bio-Pharmaceutical Co., Ltd., 1479 Zhangheng road, China (Shanghai) Pilot Free Trade Zone, Shanghai 201203, P.R. China in the list of prequalified medicinal products.