

COMMENTARY

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Efavirenz

RODRIGO CRISTOFOLETTI,^{1,2} ANITA NAIR,³ BERTIL ABRAHAMSSON,⁴ D. W. GROOT,⁵ SABINE KOPP,⁶ PETER LANGGUTH,⁷
JAMES E. POLLI,⁸ VINOD P. SHAH,⁹ JENNIFER B. DRESSMAN³

¹Brazilian Health Surveillance Agency (Anvisa), Division of Bioequivalence, Londrina State University, Londrina, Brazil

²Department of Pathology, Clinical Analysis and Toxicology, Londrina State University, Londrina, Brazil

³Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany

⁴AstraZeneca R&D, Mölndal, Sweden

⁵RIVM—National Institute for Public Health and the Environment, Bilthoven, The Netherlands

⁶World Health Organization, Geneva, Switzerland

⁷Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg University, Mainz, Germany

⁸Department of Pharmaceutical Sciences, University of Maryland, Baltimore

⁹International Pharmaceutical Federation FIP, The Hague, The Netherlands

Received 3 September 2012; revised 12 October 2012; accepted 30 October 2012

Published online 22 November 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23380

ABSTRACT: Literature data pertaining to the decision to allow a waiver of *in vivo* bioequivalence testing for the approval of immediate-release (IR) solid oral dosage forms containing efavirenz as the only active pharmaceutical ingredient (API) are reviewed. Because of lack of conclusive data about efavirenz's permeability and its failure to comply with the "high solubility" criteria according to the Biopharmaceutics Classification System (BCS), the API can be classified as BCS Class II/IV. In line with the solubility characteristics, the innovator product does not meet the dissolution criteria for a "rapidly dissolving product." Furthermore, product variations containing commonly used excipients or in the manufacturing process have been reported to impact the rate and extent of efavirenz absorption. Despite its wide therapeutic index, subtherapeutic levels of efavirenz can lead to treatment failure and also facilitate the emergence of efavirenz-resistant mutants. For all these reasons, a biowaiver for IR solid oral dosage forms containing efavirenz as the sole API is not scientifically justified for reformulated or multisource drug products. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association *J Pharm Sci* 102:318–329, 2013

Keywords: efavirenz; absorption; Biopharmaceutics Classification System (BCS); permeability; regulatory science; solubility

Correspondence to: Jennifer B. Dressman (Telephone: +49-69-79829680, Fax: +49-69-79829724; E-mail: dressman@em.uni-frankfurt.de)

This article reflects the scientific opinion of the authors and not necessarily the policies of regulating agencies, the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO), nor the Brazilian Health Surveillance Agency (Anvisa).

A project of the International Pharmaceutical Federation FIP, Focus Group BCS & Biowaiver, www.fip.org/bcs.

Rodrigo Cristofolletti and Anita Nair have contributed equally to this article.

Journal of Pharmaceutical Sciences, Vol. 102, 318–329 (2013)

© 2012 Wiley Periodicals, Inc. and the American Pharmacists Association

INTRODUCTION

A biowaiver monograph on efavirenz is presented, based on literature and some additional laboratory data. This monograph reviews the biopharmaceutical properties of efavirenz and the risks associated with waiving *in vivo* bioequivalence (BE) testing for the approval of new immediate-release (IR) solid oral dosage forms containing this active pharmaceutical ingredient (API), for both reformulated products and new multisource drug products. This evaluation refers to drug products containing efavirenz as the only API and not to combination products. The purpose and

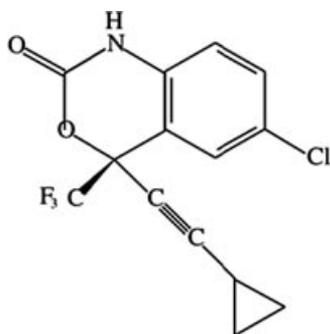


Figure 1. Structure of efavirenz

scope of this series of monographs have been previously discussed.¹ Quoting Vogelpoel et al.,¹ “the aim is to evaluate all pertinent data available from literature sources for a given API to assess the risks associated with a biowaiver. For these purposes, risk is defined as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver approval is advisable or not. This systematic approach to recommend or advise against a biowaiver decisions is referred to in the recently published World Health Organization (WHO) Guideline.² These monographs do not intend to simply apply the WHO,² United States Food and Drug Administration (US FDA),³ and/or European Medicine Agency (EMA)⁴ Guidances, but aim also as a critical evaluation of these and other countries’ regulatory documents.” Biowaiver monographs have already been published for over 30 APIs, and these are also available online at www.fip.org/bcs.⁵

EXPERIMENTAL

Literature data were obtained from Web of Science, PubMed, and Micromedex databases up to June 2011. The keywords used for searching were efavirenz, intestinal absorption, linear pharmacokinetics (PK), absolute bioavailability (BA), BE, log *P*, solubility, permeability, and lipophilicity. Information was also obtained from regulatory documents published by the WHO,² the US FDA,³ and the EMA.⁴ Additional experimental data were generated at the Goethe University to complete the evaluation of efavirenz’s solubility and dissolution characteristics.

GENERAL CHARACTERISTICS

INN: Efavirenz.⁶ Its structure is shown in Figure 1.

Therapeutic Indication

Efavirenz is an antiretroviral, non-nucleoside reverse transcriptase inhibitor (NNRTI) used specifically in the treatment of HIV-1 infection.^{7–10} It is used along with other antiretrovirals for combination therapy of HIV-1 patients. Efavirenz can be considered as the NNRTI of choice in patients with tuberculosis co-infection but is contraindicated in pregnant women because of its teratogenic effects.¹¹

Therapeutic Index and Toxicity

The most common adverse events reported in the safety and tolerability studies of efavirenz are central nervous system symptoms and skin rash. Almost 53% of the patients reported at least one central nervous system symptom (which include dizziness, insomnia, and hallucinations among others), of which 2% were classified as severe and resulted in discontinuation of treatment. Also, 26% of adults and 45% of pediatric patients developed maculopapular skin eruptions of some grade, warranting discontinuation of treatment in 1.7% of adults and 8.8% of children.¹²

Empiric PK–pharmacodynamic (PD) relationships have been established for adult patients taking efavirenz. Treatment failure is more likely to occur when drug plasma levels are lower than 1 µg/mL, whereas central nervous system toxicity tends to be more prevalent in patients with plasma concentrations of efavirenz higher than 4 µg/mL.¹³ PK–PD approaches have also been applied to therapy of pediatric patients with efavirenz. According to these studies, a threshold area under the plasma concentration–time curve (AUC) of around 50 µg h/mL should be achieved to avoid therapeutic failure.^{14,15}

PHYSICOCHEMICAL PROPERTIES

Solubility

Efavirenz is reported to be practically insoluble in water. An aqueous solubility of below 10 µg/mL has been reported, but the temperature at which the tests were performed was not stated.^{12,16,17} Rabel et al.¹⁸ reported an intrinsic solubility of 8.3 µg/mL by calculating the solubility of efavirenz in the pH range of 1–8. The solubility tests were carried out at various pH by addition of hydrochloric acid or sodium hydroxide solution to deionized water.¹⁸ Gao et al.¹⁹ reported the solubility of efavirenz in biorelevant media, which was found to be higher than in aqueous buffer. Because of the absence of Biopharmaceutics Classification System (BCS)-conform solubility data in the literature, additional solubility studies were performed on the API according to the WHO Guidelines.²

Table 1. Solubility of Efavirenz in Different Buffered Media at 37°C and the Corresponding Dose/Solubility (*D/S*) Ratio Based on the Maximum Dose Strength of 600 mg

Medium	pH	Solubility (mg/mL)	<i>D/S</i> ratio (mL)
Water	6.4	0.0115	52,173
SGF _{sp} ^a	1.2	0.0117	51,282
Acetate buffer	4.5	0.0089	67,415
SIF _{sp}	6.8	0.0093	64,516
SIF _{sp} ^b	7.5	0.0107	56,074

SGF_{sp}, simulated gastric fluid *sine* pepsin; SIF_{sp}, simulated intestinal fluid *sine* pancreatin.

^aSame composition as SGF_{sp} with pH adjusted to 1.0.

^bSame composition as SIF_{sp} with pH adjusted to 7.0 and 7.5.

Solubility studies based on the shake-flask method were performed in Uniprep[®] (Whatman Inc., New Jersey, USA) vials in buffers with pH values in the range 1.2–7.5 at 37 ± 0.5°C. Approximately 10 mg of API was weighed into the vials, and 3 mL of medium was added. After incubating the vials on an orbital shaker for 24 h, the filter plunger was pushed through the Uniprep[®] vial (Whatman Inc.), and the resulting filtrate was analyzed for dissolved efavirenz. All tests were performed in triplicate. Table 1 shows the solubility and the dose–solubility ratio of efavirenz over the pH range of 1.2–7.5.

The dose–solubility ratio across the tested pH range was far in excess of 250 mL, indicating that efavirenz cannot be classified as “highly soluble” according to the BCS.

Stereochemistry and Polymorphism

Efavirenz possesses a chiral carbon atom at position 4. The 4S enantiomer is used in commercially available formulations. A 3 mg/mL solution in methanol shows a specific optical rotation of 89°–100° at 20°C.⁹ No polymorphs of efavirenz have been reported in the open literature.

pKa

Rabel et al.¹⁸ reported a pKa of 10.1 ± 0.1 for efavirenz.

Partition Coefficient (log *P*)

A log *P* value of 2.07 ± 0.12 was determined by the *n*-octanol–water shake-flask method,²⁰ although the temperature at which this value was obtained was not reported. Rowe et al.²¹ reported a higher value of log *P*, 5.4, but no information regarding the experimental conditions was given.

Available Dosage Form Strengths

Efavirenz is available as single API and fixed-dose combination products in the form of capsules, tablets, and oral solutions. IR dosage forms containing single API are available in 50, 100, 200, and 600 mg

dosage strengths.^{8,22,23} The highest dose strength of efavirenz recommended in the 17th edition of the WHO Model List of Essential Medicine is 600 mg for tablets and 200 mg for capsules.²⁴

PHARMACOKINETIC PROPERTIES

Absorption and Bioavailability

Efavirenz is absorbed after oral doses with peak plasma concentrations being achieved after about 2–5 h.⁸ Its PK is dose related, with the increase in maximum plasma concentration (*C*_{max}) being less than proportional after single oral administration of doses ranging from 100 to 1600 mg.²⁵ This behavior has been attributed to the limited aqueous solubility of efavirenz on one hand or to dose-related delayed gastric emptying on the other hand.²⁶ As it has a high log *P* value [higher than that of metoprolol (log *P* 1.88), a BCS Class I standard], it seems likely that uptake by passive diffusion, rather than saturable absorption, is its main absorption process.

No human absolute oral BA data have been reported for efavirenz. However, its absolute BA after administration of an oral suspension prepared in 0.5% aqueous methylcellulose is reported to be 16% in rats and 42% in monkeys.²⁷ A mass balance study in humans showed a mean total recovery of radioactivity of 66 ± 27% of the administered dose over 21 days.²⁸ No clinically significant difference was reported with respect to the PK parameters in healthy individual and HIV-infected patients.²⁸ Coadministration of food and efavirenz increases its AUC and *C*_{max} by 17%–28% (reduced fat meal) and 39%–79% (normal caloric meal). Alteration of gastric pH does not seem to affect efavirenz absorption because neither coadministration of antacid nor famotidine altered the *C*_{max} or AUC of efavirenz.²⁸

Permeability

In Caco-2 cell studies, using albumin to maintain sink conditions in the receptor compartment, an apparent permeability (*P*_{app}) of 12.7 × 10⁻⁶ cm/s at pH 6.5 was measured for efavirenz. However, no highly or poorly permeable standard was assayed together with efavirenz to validate the result. Despite this, the authors concluded that efavirenz is a highly permeable drug.²⁹ Other authors reported a *P*_{app} of 40 × 10⁻⁶ cm/s for efavirenz, but no further information regarding the experimental conditions was provided.²⁸

No study evaluating the direct relevance of intestinal uptake transporters on the absorption of efavirenz has been reported. Several studies corroborate that efavirenz is not a P-glycoprotein (P-gp) substrate. Janneh et al.³⁰ reported that the intracellular accumulation of efavirenz in lymphoblastic cell line (CEM) which overexpresses P-gp, was not different from that

of normal CEM cells. Similarly, a further study found no significant differences between plasma levels of efavirenz in three MDR1 C3435T genotypes (CC, TT, and heterozygotes).³¹ Additionally, efavirenz did not show a significant difference between the apical or basolateral influx clearance in Caco-2 cells and its P_{app} value was not affected by verapamil,³² also implying that efavirenz is not a P-gp substrate.

Distribution, Metabolism, and Elimination

Efavirenz is widely distributed, with a volume of distribution around 280–500 L, which is consistent with its high lipophilicity.³³ Nevertheless, it is highly bound to plasma protein (>99%), primarily to albumin.²⁵

Metabolism seems to be the main process in the clearance of efavirenz because in a mass balance study after intaking an oral dose of 400 mg of ¹⁴C-efavirenz, no quantifiable concentration of labeled parent drug was detected in urine.³⁴ Also, the 8-hydroxy efavirenz glucuronide metabolite was responsible for 86% of radioactivity found in urine,³⁴ and after administering ¹⁴C-efavirenz intravenously to bile-duct-cannulated rats, more than 80% of radioactivity was recovered as metabolites in the bile, whereas no parent labeled drug was detected.²⁶ Efavirenz is mainly metabolized by CYP2B6 and CYP3A4.³⁵ Some pharmacogenomics studies showed that efavirenz plasma levels are affected by the polymorphism of CYP2B6.^{36–39} The mean elimination half-life of efavirenz was determined to be 64 and 48 h after single and multiple dose administration,²⁵ respectively. The shorter half-life observed in the multiple-dose studies was attributed to autoinduction of hepatic CYP3A4.^{40,41}

DOSAGE FORM PERFORMANCE

Bioequivalence Studies

One report in literature has demonstrated BE of a generic capsule formulation of efavirenz 200 mg with the Sustiva® (Bristol-Meyers Squibb GmbH & Company KGaA, Uxbridge, UK) 200 mg (innovator) capsule. In this study, 42 healthy volunteers (34 men and eight women) were enrolled and the 90% confidence intervals (CIs) for log-transformed C_{max} and AUC_{0-72h} were within 80%–125%, meeting the current BE criteria. The composition of the generic formulation was not reported.⁴²

On the US FDA web site, two BE studies supporting the new drug application for Sustiva® capsules (Bristol-Meyers Squibb GmbH & Company KGaA) and for Sustiva® tablets (Bristol-Meyers Squibb GmbH & Company KGaA), a new dosage form, have been reported.^{28,34} The first BE study was a three-period study designed to compare the 200 mg mi-

cronized clinical trial formulation and two (100 and 200 mg) commercial wet granulation formulations. In this report, each one of the 28 enrolled healthy volunteers (20 men and eight women) received a single 200 mg dose; however, no further information regarding sampling time or composition of formulation was given. The 90% CIs for log-transformed AUC_{0-t} for both test formulations fell within the limits of 80%–125%, but the 90% CIs for C_{max} for both tests (112%–136% and 110%–134%) failed to meet the current BE criteria. No dissolution test results were reported, so it is not known whether dissolution testing could have predicted the BE failure. In a subsequent clinical trial in 261 patients (test formulation) and 107 patients (commercial formulation), no significant differences were observed in the incidence of adverse effects.

The second BE study reported on the US FDA web site was a three-period BE study designed to compare the commercial Sustiva® (Bristol-Meyers Squibb GmbH & Company KGaA) 200 mg capsules with two (300 and 600 mg) tablet formulations. In this report, 21 healthy volunteers received a single 600 mg dose and plasma samples were collected up to 504 h. The 90% CIs for C_{max} (92.73%–115.46% and 98.65%–122.82%) and AUC_{0-504h} (96.02%–109.16% and 95.61%–108.69%) were within the current BE limits. The compositions of formulations were not reported. The dissolution profiles of these formulations were similar under experimental conditions recommended by the United States Pharmacopoeia (USP)^{43,44}: 1000 mL of water with sodium lauryl sulfate (SLS; 1% for capsules and 2% for tablets) at 37°C and a paddle speed of 50 rpm.³⁴

Table 2 encompasses the details of five BE studies conducted on efavirenz products (single API) prequalified by the WHO.⁴⁵ All the products were reported to demonstrate BE when compared with the WHO-approved comparator. However, efavirenz tablets from Ranbaxy Laboratories Limited, Sirmour, Himachal Pradesh, India (WHOPAR HA306), failed to conform to the presently applicable 90% CI BE criteria of 80%–125% for C_{max} .⁴⁵ Instead, a wider limit of 75%–133% was applied and the product was deemed bioequivalent with the comparator based on the “additional data” provided to support a wider limit. Nevertheless, the plasma concentrations at 12 and 24 h [C_{12} (90% CI: 96.6–118.7) and C_{24} (90% CI: 111.5–113.8)] were within the 80%–125% limits. No information about the “additional data” was available in the public report.⁴⁵

Dissolution and *In Vitro/In Vivo* Correlation

The USP recommends dissolution testing of efavirenz solid oral dosage forms in 900 mL medium using apparatus 2 (paddle) at an agitation speed of 50 rpm.

Table 2. Bioequivalence Study Results of Efavirenz Products Reported in the WHO Public Assessment Reports of the WHO Prequalification Program

References	Dose	Subjects	Formulation	Composition	Prandial	Study Design	Pharmacokinetic Parameters	Bioequivalence Criteria, Statistics	Results	In vitro Tests
WHO public assessment reports (HA352) ⁴³	600 mg Efavirenz	Data of 28 healthy male volunteers were analysed	Efavir 600 (Cipla Ltd., Mumbai, India), Sustiva 600 (Bristol Myers Squibb, Princeton, USA)	Efavir 600 tablet excipients: lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, sodium glycolate, and colorant	Fasted state	Randomized, open-label, crossover design	C_{max} , t_{max} , AUC_{0-t} , $AUC_{0-\infty}$, $t_{1/2}$	90% confidence intervals, ANOVA	Bioequivalent	Not reported
WHO public assessment reports (HA390) ⁴³	600 mg Efavirenz	Data of 32 healthy subjects were analyzed	Efavirenz tablets 600 (Strides Arcolab Ltd., Bangalore, Karnataka India.), Sustiva 600 (Bristol Myers Squibb)	Efavirenz 600 tablet excipients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate (SLS), PEG 400, hypromellose, titanium dioxide, and colorants	Fasted state	Randomized, single-dose, open-label, crossover design	$AUC_{0-\infty}$, C_{max} , and T_{max}	90% confidence intervals, ANOVA	Bioequivalent	Not reported
WHO public assessment reports (HA399) ⁴³	600 mg Efavirenz	Data of 33 healthy male subjects were analyzed	Estiva-600 (Hetero Drugs Ltd., Ranga Reddy Dist. Hyderabad, India), Sustiva 600 (Bristol Myers Squibb, USA)	Estiva 600 tablet excipients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, SLS, PEG 400, hypromellose, titanium dioxide, and colorants	Fasted state	Randomized, single-dose, open-label, crossover	AUC , C_{max} , and T_{max}	90% confidence intervals, ANOVA	Bioequivalent	Not reported

(Continued).

Table 2. Continued

References	Dose	Subjects	Formulation	Composition	Prandial	Study Design	Pharmacokinetic Parameters	Bioequivalence Criteria, Statistics	Results	In vitro Tests
WHO Public assessment reports (HA438) ⁴³	200 mg ×3 Efavirenz	Data of 59 healthy male and female subjects were analyzed	Efavir-200 capsules (Cipla Ltd., Goa, India), Sustiva 200 capsules (Bristol Myers Squibb)	Efavir 200 capsule excipients: lactose monohydrate, magnesium stearate, sodium starch glycolate; capsule shell contains gelatin, SLS, titanium dioxide, and colorants	Fasted state	Randomized, single-dose, open-label, crossover	AUC, C _{max}	90% confidence intervals, ANOVA	Bioequivalent	Not reported
WHO Public assessment reports (HA306) ⁴³	600 mg Efavirenz	Data of 36 healthy male and female subjects were analyzed	Efavirenz tablets 600 (Ranbaxy Laboratories Ltd. Sirmour, Himachal Pradesh, India), Sustiva 600 (Bristol Myers Squibb, USA)	Efavirenz 600 tablets excipients: microcrystalline cellulose, croscarmellose sodium, hydroxyl propyl cellulose, SLS, lactose monohydrate, magnesium stearate, hypromellose, titanium dioxide, and colorant	Fasted state	Open labeled, balanced, randomized, two-treatment, two-period, two-sequence, single-dose crossover study	AUC ₀₋₉₆ ; C _{max}	90% confidence intervals, ANOVA	90% CI (108–133) for C _{max} and AUC ₀₋₉₆ 90% CI (103–115); considered bioequivalent when additional data for wider limits (75%–133%) were submitted; however, no information about the submitted data was provided	Not reported

However, the medium and tolerance limits specified for the dissolution of efavirenz tablets and capsules differ considerably. The USP recommends 2% SLS in water as the dissolution medium for tablets but 1% SLS solution for capsules. Similarly, the *Q* limit (amount of dissolved active ingredient) specification is not less than 80% of the labeled amount of efavirenz dissolved in 30 min for tablets but somewhat longer, 45 min, for capsules.^{43,44}

As the compendial quality control methods differ from the biowaiver methods, additional BCS-conform dissolution studies were performed on the innovator product (Sustiva[®]; Bristol-Meyers Squibb GmbH & Company KGaA; 100 mg capsules; batch #0B56702) and a test product (Efavir[®]; Cipla Ltd., Goa, India; 200 mg capsules; batch #X01221) in pH 1.2, 4.5, and 6.8 according to the WHO guidelines for biowaiver procedure. The study indicated less than 12% release of the API from the test or comparator products in all three media, over a period of 1 h (Fig. 2).

The dissolution profiles of the comparator product, obtained from BCS-conform tests, were also compared with its dissolution profiles in the compendial media. Figure 3 indicates that although the capsules demonstrated more than 85% drug release within 15 min in a simple 1% SLS solution in water, less than 12% of the labeled API was dissolved in the aqueous buffers in the same time period.

The ability of the USP dissolution method to discriminate appropriately among batches was also challenged in two studies. In the first study, two batches (A and B) of Sustiva[®] (Bristol-Meyers Squibb GmbH & Company KGaA) 200 mg capsules showed dissimilar ($f_2 \sim 28$) dissolution profiles using the experimental conditions described in the USP. However, despite *in vitro* dissimilarity, these products were found to be bioequivalent, C_{\max} (95.1%–111.7%) and AUC_{0-t} (96.0%–103.2%),³⁴ suggesting overdiscrimination by the compendial test.

In the second study, Gao et al.¹⁹ compared the *in vitro* and *in vivo* behavior of three efavirenz formulations (capsule, tablet A, and tablet B). Although the author found good agreement between the *in vitro* and *in vivo* disintegration times, the *in vitro* dissolution rate in 1000 mL of 1% SLS at 37°C, stirring with the paddle at 50 rpm, failed to correlate with the *in vivo* behavior. Tablet A showed a significantly slower absorption rate and reduced extent of efavirenz absorption compared with tablet B, even though it showed a faster drug release in the dissolution studies run according to the USP method.¹⁹ Thus, the latter two examples suggest that the *in vitro* dissolution test recommended by the USP for efavirenz is unable to accurately predict differences in the rate or extent of efavirenz absorption.

Excipients

Table 3 indicates the commonly used excipients in efavirenz IR solid oral dosage forms having Marketing Authorization in Canada, Switzerland, European Union, and United States. Single API products listed on the WHO list of prequalified medicinal products are also included. Search for efavirenz products in Japan, on the Japan Pharmaceutical Reference (http://www.e-search.ne.jp/~jpr/jpr_db/eindex.html), returned no hits.

Studies by Gao et al.¹⁹ on two tablet formulations of efavirenz (tablet A containing croscarmellose sodium and sodium starch glycolate and tablet B containing croscarmellose sodium) demonstrated that the rate and extent of drug absorption were influenced by the type and amount of superdisintegrants used.

Similarly, Rajesh et al.⁴⁶ studied the impact of superdisintegrants, namely crospovidone, croscarmellose sodium, and sodium starch glycolate, on the release of efavirenz from tablet formulations. The study reported that the mode of addition of disintegrant (intragranular or extragranular) did not affect efavirenz release in crospovidone containing tablets. By contrast, in the case of formulations containing croscarmellose sodium and sodium starch glycolate, intragranular addition decreased the API release from the products appreciably.⁴⁶ However, no *in vivo* studies with these formulations were performed.

The innovator product lists SLS as one of the excipients in the capsule and tablet formulations. Dissolution tests of the product were also performed in simulated gastric fluid *sine* pepsin (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid *sine* pancreatin (pH 6.8) to determine whether the SLS in the formulation improved the dissolution of the API in the medium. However, Figure 3 reveals that the surfactant in the formulation does not play any significant role in improving drug dissolution.

No other reports addressing the impact of excipients on efavirenz dissolution were found in the literature survey.

DISCUSSION

Solubility

Biopharmaceutics Classification System conform solubility studies revealed dose/solubility (*D/S*) ratio values greater than 250 mL across the pH range 1.2–7.5 at 37°C for efavirenz. Consequently, efavirenz fails to comply with the “highly soluble” API criteria according to the biowaiver guidelines.^{2–4} Because of its poor solubility characteristics, efavirenz could belong to either Class II or Class IV of the BCS.

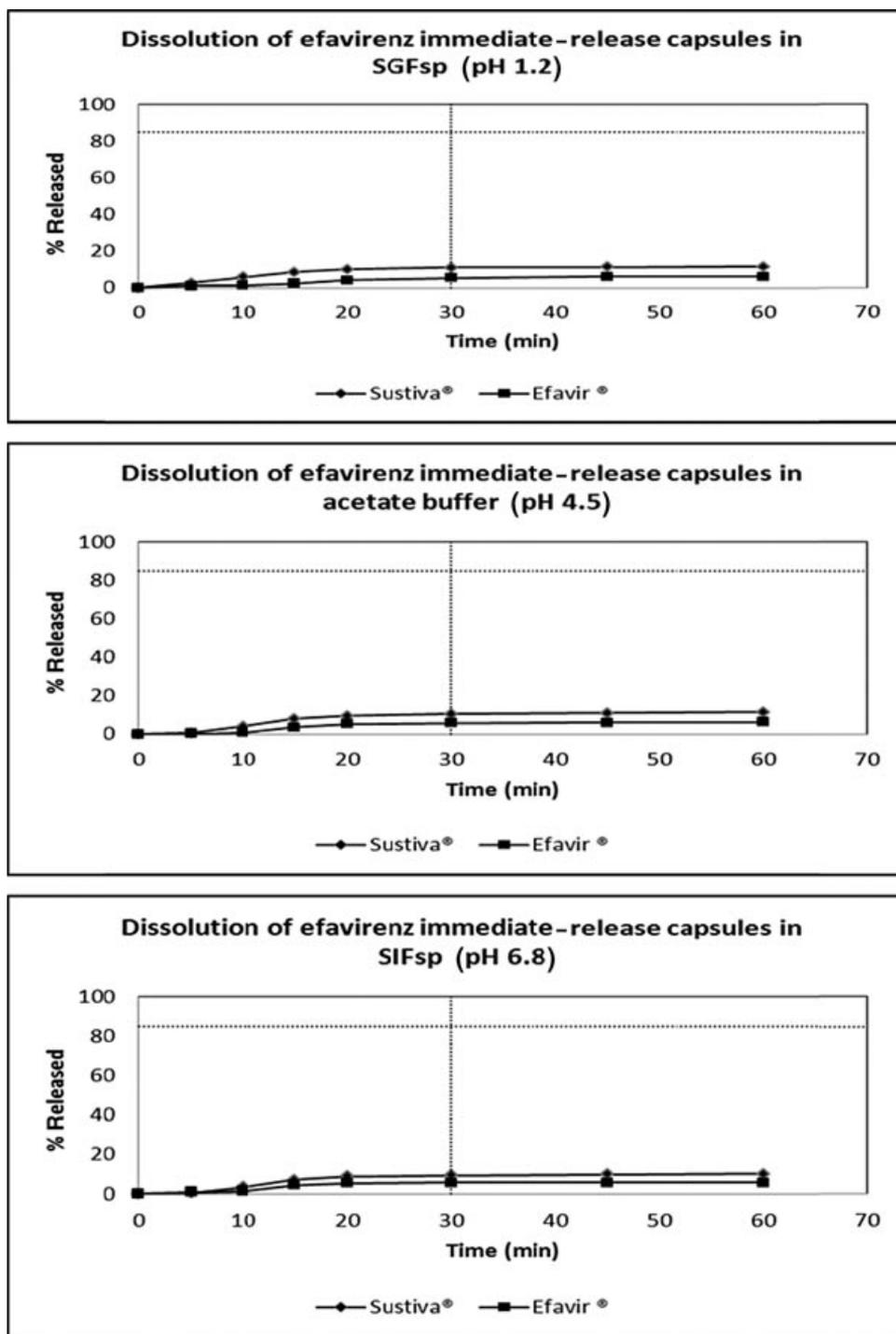


Figure 2. Dissolution profiles of efavirenz immediate release capsules (comparator: Sustiva[®], test product: Efavir[®]) in pH 1.2, 4.5, and 6.8 according to the BCS guidelines. Data points are mean values (*n* = 6). The horizontal and vertical dotted lines represent the EMA³/WHO² criterion of “rapidly dissolving” products.

Permeability

There is no human data clearly demonstrating that the fraction absorbed of efavirenz is higher than 85%. In the mass balance study, the mean urinary recovery of total radioactivity was 25 ± 8.3%, and the fecal recovery was 41 ± 20.1%, so the total recovery was

66 ± 27% of the administered dose over 21 days.³⁴ The variability appears to be very high, but the study enrolled only six healthy male volunteers. In any case, the results are not consistent with high permeability, which would require a recovery of 85% or more (WHO and EMA) or 90% (US FDA) of the administered dose, noting also that a substantial part of the

Table 3. Excipients* Present in Efavirenz IR Solid Oral Drug Products with a Marketing Authorization (MA) in Canada (CA), Switzerland (CH), European Union (EU)**, the United States (US), and on the WHO List of Prequalified Medicinal Products***, and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a MA in the US****

Excipient	Drug Products Containing that Excipient with a MA Granted by the Named Country or Products on the WHO List of Prequalified Medicinal Products ^a	Range Present in Solid Oral Dosage Forms with a MA in the US (mg)
Cellulose, microcrystalline	CA (1), CH (2), EU (3–5), US (6), WHO (7–11)	4.6–1385 ^b
Croscarmellose sodium	CA (1), CH (2), EU (4,5), US (6), WHO (7–11)	2–180
Hydroxypropylcellulose	CA (1), CH (2), EU (3–5), US (6), WHO (7–11)	1.6–132
Lactose	CA (1,12), CH (2), EU (4,5,13,14), US (6,15), WHO (7–11,16–19)	23–1020 ^e
Magnesium stearate	CA (1,12) CH (2) EU (3–5,13,14) US (6,15) WHO (7–11,16–19)	0.15–401 ^e
Poloxamers	EU (3)	3.2–110
Povidone	WHO (18)	0.17–80
Sodium lauryl sulfate	CA (1,12) CH (2) EU (3–5,13,14) US (6,15) WHO (7–11,16,17)	0.65–52
Sodium starch glycolate	CA (12) EU (3,13,14) US (15) WHO (16–19)	2–876 ^b
Starch, pregelatinized	WHO (18)	4.2–600

*Colorants and ingredients present in the coating/shell and/or the printing ink are not included.

**Products are authorized in Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and United Kingdom.

***Sources of data: CA, www.hc-sc.gc.ca (accessed June 11, 2012); CH, www.kompodium.ch (accessed June 13, 2012); EU, www.ema.europa.eu (accessed June 11, 2012); US, <http://dailymed.nlm.nih.gov/dailymed/about.cfm> (accessed June 18, 2012); WHO, http://apps.who.int/prequal/whopar/whoparproducts/whopar_index.htm (accessed June 26, 2012).

****US FDA's Inactive Ingredient Database, <http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm> (version date March 2012).

^aFootnote by WHO: "Trade names are not prequalified by WHO. This is under local DRA responsibility. Throughout this WHOPAR, the proprietary name is given as an example only."

^bThe upper range value reported is unusually high for solid oral dosage forms and the authors doubt its correctness.

- ^{Pr}SUSTIVA (efavirenz) tablets, 300 and 600 mg.
- Stocrin[®], Filmtabletten 50/200/600 mg.
- Efavirenz Teva 600 mg film-coated tablets.
- STOCRIN 50/200/600 mg film-coated tablets.
- SUSTIVA 600 mg film-coated tablets.
- SUSTIVA[®] (efavirenz) tablet, film-coated (600 mg).
- Efavirenz 600 mg Tablets (Ranbaxy).
- Efavirenz 600 mg tablets (MSD Interpharma).
- Efavirenz tablets 200/600 mg (Strides Arcolab Ltd.).
- Estiva-600[®] 600 mg tablet (Hetero Drugs Ltd.).
- Efavirenz 600 mg tablet (Matrix Ltd.).
- ^{Pr}SUSTIVA (efavirenz) capsules, 50 and 200 mg.
- STOCRIN 50/100/200 mg hard capsules.
- SUSTIVA 50/100/200 mg hard capsules.
- SUSTIVA[®] (efavirenz) capsule, gelatin coated (50/200 mg).
- Efavirenz 200 mg capsules (Ranbaxy).
- Efavirenz 50/200 mg hard capsules (MSD Interpharma).
- Efavir 600[®] 600 mg tablet (Cipla Ltd.).
- Efavirenz 200 mg capsules (Cipla Ltd.).

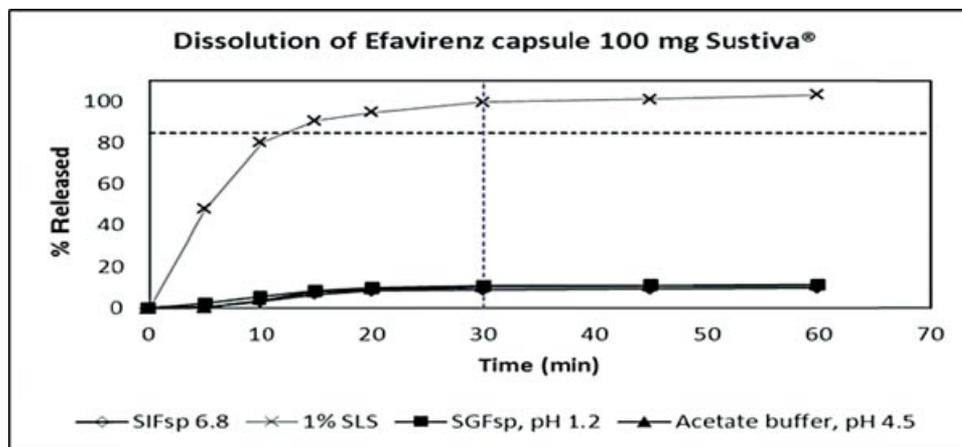


Figure 3. Dissolution of Sustiva[®] 100 mg capsule: paddle apparatus at 75 rpm, 37°C, 900 mL. (◇) Simulated intestinal fluid without pancreatin (pH 6.8); (■) simulated gastric fluid without pepsin (pH 1.2); (▲) acetate buffer (pH 4.5); and (x) paddle apparatus at 50 rpm, 37°C, medium: 1% SLS solution. Data points are mean values ($n = 6$). The horizontal and vertical dotted lines represent the EMA³/WHO² criterion of "rapidly dissolving" products.

dose was recovered in the feces. Although two studies in cell monolayers classified efavirenz as a highly permeable drug,^{29,34} no highly or poorly permeable standards were assayed together with efavirenz to validate the results. Instead, efavirenz was classified as a well absorbed compound based on the range defined by Yee⁴⁷ ($P_{app} > 10 \times 10^{-6}$ cm/s) for compounds with BA lying in the range from 70% to 100%. Although efavirenz has been classified as BCS Class II on the basis of its metabolic and solubility behavior using the Biopharmaceutical Drug Disposition Classification System (BDDCS) principles,⁴⁸ this way of classifying APIs is not yet recognized by the various regulatory authorities. All results taken together, it appears that the permeability of efavirenz has not yet been conclusively determined.

BCS Classification and Eligibility for the Biowaiver

Because of the absence of conclusive data on intestinal permeability of efavirenz, it is not possible to assign a definite class to this API. Instead, efavirenz can be regarded as BCS Class II/IV. This classification corroborates that of Lindenbergh et al.,⁴⁹ whereas according to BDDCS⁴⁸ and Kasim et. al.¹⁶ it had been assigned to BCS Class II. Efavirenz is a weak acid, in which the carbamate group undergoes deprotonation at high pH values. According to the WHO guidelines, a biowaiver can be granted to Class II APIs provided they fulfill the *D/S* criteria of 250 mL or less at pH 6.8 (weak acids). Because efavirenz fails to comply with this requirement (see Table 1), the API is not an appropriate candidate for a biowaiver, even if it were to be shown conclusively to be a Class II API. Also, to be eligible for a biowaiver, both the test and the comparator dosage forms must be rapidly dissolving ($Q > 85\%$ in 30 min or less) at pH 6.8 without surfactant. On the basis of the dissolution data (Fig. 2), it can be concluded that efavirenz would not be eligible for a biowaiver as the comparator (innovator) product failed to comply with the “rapidly dissolving” product criterion at pH 6.8.

Risks with Respect to Excipient and/or Manufacturing Variations

Gao et al.¹⁹ evaluation of the influence of two superdisintegrants on the absorption of efavirenz tablet A, formulated with croscarmellose sodium and sodium starch glycolate, showed a significantly slower absorption rate and reduced extent of efavirenz absorption compared with tablet B, which was formulated with croscarmellose sodium as the only superdisintegrant. The authors attributed this result to the formation of a viscous gel layer, due to sodium starch glycolate, hindering efavirenz's diffusion.¹⁹ Furthermore, the *in vitro* dissolution results (1000 mL of 1% SLS at 37°C and paddle 50 rpm) do not correlate with the

in vivo results because the dissolution rate of tablet A was faster than that of tablet B. Hence, this *in vitro* dissolution test, which was more restrictive than the compendial dissolution method for efavirenz tablets⁴³ and which was able to differentiate between formulations, was still unable to correctly predict the *in vivo* results.

Moreover there are two reports of non-BE seen in the literature (see Table 2).^{28,45} These results point out that variations in composition, even when using common excipients such as sodium starch glycolate,¹⁹ or in the manufacturing process (micronized vs. wet granulation),³⁴ can indeed have an impact on the rate and extent of efavirenz absorption. This is not unexpected for poorly soluble drugs of indeterminate permeability because the *in vivo* dissolution may not be the sole rate-controlling step in drug absorption.⁵⁰

Surrogate Techniques for *In Vivo* BE Testing

The *in vitro* dissolution recommended by the USP does not seem to be predictive because *in vitro* differences were not confirmed *in vivo* and vice versa.^{19,34} A possible reason for this is that the USP method employs 2% SLS to ensure sink conditions for tablets (1% SLS for capsules), and is thus far from the composition of the gastrointestinal fluids. On the basis of data presented in this review, compendial *in vitro* dissolution tests for efavirenz cannot be regarded as a sufficiently reliable surrogate for an *in vivo* BE test. Dissolution studies performed on the comparator and generic product according to the BCS-conform methods clearly indicated its inability to discriminate between the two products. The API in the test product attained the plateau concentration in the dissolution medium around the same time as the comparator. However, for both Sustiva[®] (Bristol-Meyers Squibb GmbH & Company KGaA) 100 mg and Efavir[®] (Cipla Ltd.) 200 mg, the percentage released was so low that application of the f_2 test (which tests for an absolute difference of 10% in profiles) would be meaningless. Thus, it can be concluded that neither the compendial method nor the BCS-conform dissolution tests can be used as a surrogate technique for *in vivo* BE testing of efavirenz IR products.

Patient Risks Associated with Bioinequivalence

Because there is a difference of fourfold between the minimum toxic dose (4 µg/mL) and the minimum effective dose (1.0 µg/mL), efavirenz cannot be considered as a narrow therapeutic index drug according to the Code of Federal Regulations.⁵¹ Furthermore, efavirenz is not on the list of Narrow Therapeutic Range Drugs of the Japanese Health Authorities or Health Canada.^{52,53}

It has been reported that a bioinequivalence with respect to C_{max} (supra-BA) had no clinical relevance.³⁴

Subtherapeutic concentrations of efavirenz, on the contrary, can lead to treatment failure (more likely to occur when drug plasma levels are lower than 1.0 µg/mL) as well as facilitating the emergence of efavirenz-resistant mutants.¹³

CONCLUSIONS

Owing to inconclusive permeability evidence and poor solubility, efavirenz is assigned to BCS Class II/IV. The US FDA³ and EMA⁴ guidelines do not allow the BCS-based biowaiver approval of products containing Class II APIs. The WHO² guidance only allows a BCS Class II APIs to be considered for biowaiving if they fulfill the *D/S* criteria of 250 mL or less at pH 6.8 (weak acids), and that the test and comparator products are both rapidly dissolving (*Q* > 85% in 30 min or less) with similar profiles at pH 6.8 and similar at pH 1.2 and 4.5 (all tests without surfactant). Efavirenz failed by far to meet the solubility boundary at pH 6.8, and the innovator product also failed to comply with the dissolution criteria. BCS Class IV APIs are not eligible for biowaivers in any of these jurisdictions. A biowaiver for IR solid oral dosage forms containing efavirenz is therefore not scientifically justified for multisource drug product registration or after extensive reformulation of an existing product. Instead, BE should be tested using appropriately designed PK studies.

REFERENCES

- Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Moller H, Olling M, Shah VP, Barends DM. 2004. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: Verapamil hydrochloride, propranolol hydrochloride, and atenolol. *J Pharm Sci* 93(8):1945–1956.
- World Health Organization (WHO). 2006. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Accessed January 10, 2011, at: http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf#page=403.
- U. S. Department of Health and Human Services: Food and Drug Administration Center for Evaluation and Research (CDER). 2000. Guidances for Industry: Waiver of *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on Biopharmaceutics Classification System. Accessed January 10, 2011, at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070246.pdf>.
- European Medical Agency. 2010. Committee for Medicinal Products for Human Use: Guideline on the investigation of bioequivalence. Accessed January 10, 2011, at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf.
- International Pharmaceutical Federation (FIP). 2011. Special Interest Group on BCS and Biowaiver. Accessed May 20, 2011, at: http://www.fip.org/bcs_monographs.
- World Health Organization (WHO). 2006. The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances. Accessed June 30, 2011, at: <http://apps.who.int/medicinedocs/index/assoc/s14147e/s14147e.pdf>.
- Vrouenraets SM, Wit FW, van Tongeren J, Lange JM. 2007. Efavirenz: A review. *Expert Opin Pharmacother* 8(6):851–871.
- Sweetman S, Ed. 2009. Martindale: The complete drug reference. 36th ed. London UK: Pharmaceutical Press.
- Maggiolo F. 2009. Efavirenz: A decade of clinical experience in the treatment of HIV. *J Antimicrob Chemother* 64(5):910–928.
- Hardman JG, Limbird LE, Gilman AG, Eds. 2001. Goodman & Gilman's The pharmacological basis of therapeutics. 10th ed. New York: McGraw-Hill Medical Publishing Division.
- World Health Organization. 2004. Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach. Accessed August 2, 2011, at: http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf.
- United States Food and Drug Administration (US FDA). 2011. Sustiva label. Accessed June 15, 2011, at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020972s0361bl.pdf.
- Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. 2001. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 15(1):71–75.
- Fletcher CV, Brundage RC, Fenton T, Alvero CG, Powell C, Mofenson LM, Spector SA. 2008. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther* 83(2):300–306.
- Hirt D, Urien S, Olivier M, Peyriere H, Nacro B, Diagbouga S, Zoure E, Rouet F, Hien H, Msellati P, Van De Perre P, Treluyer JM. 2009. Is the recommended dose of efavirenz optimal in young West African human immunodeficiency virus-infected children? *Antimicrob Agents Chemother* 53(10):4407–4413.
- Kasim NA, Whitehouse M, Ramachandran C, Bermejo M, Lennernas H, Hussain AS, Junginger HE, Stavchansky SA, Midha KK, Shah VP, Amidon GL. 2004. Molecular properties of WHO essential drugs and provisional biopharmaceutical classification. *Mol Pharm* 1(1):85–96.
- Moffat AC, Osselton DM, Widdop B, Eds. 2004. Clarke's analysis of drugs and poisons. 3rd ed. London, UK: Pharmaceutical Press.
- Rabel SR, Maurin MB, Rowe SM, Hussain M. 1996. Determination of the pKa and pH-solubility behavior of an ionizable cyclic carbamate, (S)-6-chloro-4-(cyclopropylethynyl)-1,4-dihydro-4-(trifluoromethyl)-2H-3,1-benzoxazin-2-one (DMP 266). *Pharm Dev Technol* 1(1):91–95.
- Gao J, Hussain MA, Motheram R, Gray DA, Benedek IH, Fiske WD, Doll WJ, Sandefer E, Page RC, Digenis GA. 2007. Investigation of human pharmacoscintigraphic behavior of two tablets and a capsule formulation of a high dose, poorly water soluble/highly permeable drug (efavirenz). *J Pharm Sci* 96(11):2970–2977.
- Almond LM, Hoggard PG, Edirisinghe D, Khoo SH, Back DJ. 2005. Intracellular and plasma pharmacokinetics of efavirenz in HIV-infected individuals. *J Antimicrob Chemother* 56(4):738–744.
- Rowe S, Fontalbert L, Rabel S, Maurin M. 1999. Physical chemical properties of efavirenz. Accessed June 15, 2011, at: http://www.aapsj.org/abstracts/AM_1999/1005.htm.
- U.S. Department of Health and Human Services: Food and Drug Administration. Drugs@FDA. Accessed August 2, 2011, at: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>.
- Rote Liste Service GmbH. 2011. Rote Liste. Accessed August 2, 2011, at: http://www.rote-liste.de/Online/jsearch_stoffe?WIRKSTOFF.

24. World Health Organization. 2011. WHO Model List of Essential Medicines 17th. Accessed June 1, 2012, at: http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf.
25. Smith PF, DiCenzo R, Morse GD. 2001. Clinical pharmacokinetics of non-nucleoside reverse transcriptase inhibitors. *Clin Pharmacokinet* 40(12):893–905.
26. Balani SK, Kauffman LR, deLuna FA, Lin JH. 1999. Nonlinear pharmacokinetics of efavirenz (DMP-266), a potent HIV-1 reverse transcriptase inhibitor, in rats and monkeys. *Drug Metab Dispos* 27(1):41–45.
27. Young SD, Britcher SF, Tran LO, Payne LS, Lumma WC, Lyle TA, Huff JR, Anderson PS, Olsen DB, Carroll SS, et al. 1995. L-743, 726 (DMP-266): A novel, highly potent non-nucleoside inhibitor of the human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob Agents Chemother* 39(12):2602–2605.
28. United States Food and Drug Administration (US FDA). 2011. Sustiva approval history: Application number 20-360. Accessed June 15, 2011, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-360_Efavirenz_biopharmr.pdf.
29. Aungst BJ. 1999. P-glycoprotein, secretory transport, and other barriers to the oral delivery of anti-HIV drugs. *Adv Drug Deliv Rev* 39(1–3):105–116.
30. Jannet O, Chandler B, Hartkoorn R, Kwan WS, Jenkinson C, Evans S, Back DJ, Owen A, Khoo SH. 2009. Intracellular accumulation of efavirenz and nevirapine is independent of P-glycoprotein activity in cultured CD4 T cells and primary human lymphocytes. *J Antimicrob Chemother* 64(5):1002–1007.
31. Winzer R, Langmann P, Zilly M, Tollmann F, Schubert J, Klinker H, Weissbrich B. 2003. No influence of the P-glycoprotein genotype (MDR1 C3435T) on plasma levels of lopinavir and efavirenz during antiretroviral treatment. *Eur J Med Res* 8(12):531–534.
32. Stormer E, von Moltke LL, Perloff MD, Greenblatt DJ. 2002. Differential modulation of P-glycoprotein expression and activity by non-nucleoside HIV-1 reverse transcriptase inhibitors in cell culture. *Pharm Res* 19(7):1038–1045.
33. Best BM, Goicoechea M. 2008. Efavirenz—still first-line king? *Expert Opin Drug Metab Toxicol* 4(7):965–972.
34. United States Food and Drug Administration (US FDA). 2011. Sustiva approval history: Application number 20-972. Accessed June 15, 2011, at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20972biopharm_review.pdf.
35. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. 2003. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: Implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. *J Pharmacol Exp Ther* 306(1):287–300.
36. Cabrera SE, Santos D, Valverde MP, Dominguez-Gil A, Gonzalez F, Luna G, Garcia MJ. 2009. Influence of the cytochrome P450 2B6 genotype on population pharmacokinetics of efavirenz in human immunodeficiency virus patients. *Antimicrob Agents Chemother* 53(7):2791–2798.
37. Haas DW, Gebretsadik T, Mayo G, Menon UN, Acosta EP, Shintani A, Floyd M, Stein CM, Wilkinson GR. 2009. Associations between CYP2B6 polymorphisms and pharmacokinetics after a single dose of nevirapine or efavirenz in African Americans. *J Infect Dis* 199(6):872–880.
38. Leger P, Dillingham R, Beauharnais CA, Kashuba AD, Rezk NL, Fitzgerald DW, Pape JW, Haas DW. 2009. CYP2B6 variants and plasma efavirenz concentrations during antiretroviral therapy in Port-au-Prince, Haiti. *J Infect Dis* 200(6):955–964.
39. Mukonzo JK, Roshamar D, Waako P, Andersson M, Fukasawa T, Milani L, Svensson JO, Ogwal-Okeng J, Gustafsson LL, Aklillu E. 2009. A novel polymorphism in ABCB1 gene, CYP2B6*6 and sex predict single-dose efavirenz population pharmacokinetics in Ugandans. *Br J Clin Pharmacol* 68(5):690–699.
40. Berruet N, Sentenac S, Auchere D, Gimenez F, Farinotti R, Fernandez C. 2005. Effect of efavirenz on intestinal p-glycoprotein and hepatic p450 function in rats. *J Pharm Pharm Sci* 8(2):226–234.
41. Mouly S, Lown KS, Kornhauser D, Joseph JL, Fiske WD, Benedek IH, Watkins PB. 2002. Hepatic but not intestinal CYP3A4 displays dose-dependent induction by efavirenz in humans. *Clin Pharmacol Ther* 72(1):1–9.
42. Marier JF, Morin I, Al-Numani D, Stiles M, Morelli G, Tippabhotla SK, Vijan T, Singla AK, Garg M, Di Marco M, Monif T. 2006. Comparative bioavailability of a generic capsule formulation of the reverse transcriptase inhibitor efavirenz and the innovator product. *Int J Clin Pharmacol Ther* 44(4):180–184.
43. U.S. Department of Health and Human Services: Food and Drug Administration. 2009. Efavirenz tablets: Authorized USP pending monograph. Accessed August 2, 2011, at: <http://www.usp.org/pdf/EN/pendingStandards/m3428.pdf>.
44. U.S. Department of Health and Human Services: Food and Drug Administration. 2009. Efavirenz capsules: Authorized USP pending monograph. Accessed August 2, 2011, at: <http://www.usp.org/pdf/EN/pendingStandards/m4047.pdf>.
45. World Health Organization. Overview of WHO public assessment report. Accessed June 1, 2012, at: http://apps.who.int/prequal/WHOPAR/WHOPARPRODUCTS/WHOPAR_Index.htm.
46. Rajesh YV, Balasubramaniam J, Bindu K, Sridevi R, Swetha M, Rao VU. 2010. Impact of superdisintegrants on efavirenz release from tablet formulations. *Acta Pharm* 60(2):185–195.
47. Yee S. 1997. In vitro permeability across Caco-2 cells (colonic) can predict in vivo (small intestinal) absorption in man—Fact or myth. *Pharm Res* 14(6):763–766.
48. Benet LZ, Broccatelli F, Oprea TI BDDCS applied to over 900 drugs. *AAPS J* 13(4):519–547.
49. Lindenberger M, Kopp S, Dressman JB. 2004. Classification of orally administered drugs on the World Health Organization Model List of Essential Medicines according to the biopharmaceutics classification system. *Eur J Pharm Biopharm* 58(2):265–278.
50. Amidon GL, Lennernas H, Shah VP, Crison JR. 1995. A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res* 12(3):413–420.
51. United States Food and Drug Administration (US FDA). 2011. Title 21—Food and drugs, Chapter I—Subchapter D—drugs for human use—Part 320—bioavailability and bioequivalence requirements. Accessed June 2, 2011, at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=320&showFR=1>.
52. Health Canada. 2009. Critical dose drugs. Accessed June 2, 2011, at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/prodpharma/applic-demande/guide-ld/bio/critical.dose.critique-eng.pdf.
53. National Institute of Health Sciences (NIHS). 2010. Guideline for bioequivalence studies for different strengths of oral solid dosage forms. Accessed June 2, 2011, At: [http://www.nihs.go.jp/drug/be-guide\(e\)/strength/strength.html](http://www.nihs.go.jp/drug/be-guide(e)/strength/strength.html).