Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Rifampicin

C. BECKER, J.B. DRESSMAN, H.E. JUNGINGER, S. KOPP, K.K. MIDHA, V.P. SHAH, S. STAVCHANSKY, D.M. BARENDS

1Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main, Germany
2Bayer Technology Services GmbH, Leverkusen, Germany
3Naresuan University, Faculty of Pharmaceutical Sciences, Phitsanulok, Thailand
4World Health Organization, Geneva, Switzerland
5University of Saskatchewan, Saskatoon, Saskatchewan, Canada
6International Pharmaceutical Federation FIP, Den Haag, The Netherlands
7Division of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, Texas
8RIVM—National Institute for Public Health and the Environment, Bilthoven, The Netherlands

Received 24 June 2008; revised 12 October 2008; accepted 13 October 2008
Published online 21 January 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21624

ABSTRACT: Literature data relevant to the decision to allow a waiver of in vivo bioequivalence (BE) testing for the approval of new multisource and reformulated immediate release (IR) solid oral dosage forms containing rifampicin as the only Active Pharmaceutical Ingredient (API) are reviewed. Rifampicin's solubility and permeability, its therapeutic use and index, pharmacokinetics, excipient interactions and reported BE/bioavailability (BA) problems were taken into consideration. Solubility and absolute BA data indicate that rifampicin is a BCS Class II drug. Of special concern for biowaiving is that many reports of failure of IR solid oral dosage forms of rifampicin to meet BE have been published and the reasons for these failures are yet insufficiently understood. Moreover, no reports were identified in which in vitro dissolution was shown to be predictive of nonequivalence among products. Therefore, a biowaiver based approval of rifampicin containing IR solid oral dosage forms cannot be recommended for either new multisource drug products or for major scale-up and postapproval changes (variations) to existing drug products.


Keywords: absorption; dissolution; biopharmaceutics classification system (BCS); permeability; regulatory science; rifampicin; solubility

Correspondence to: D.M. Barends (Telephone: 31 30 2744209; Fax: 31 30 2744462; E-mail: dirk.barends@rivm.nl) Journal of Pharmaceutical Sciences, Vol. 98, 2252–2267 (2009) © 2009 Wiley-Liss, Inc. and the American Pharmacists Association
INTRODUCTION

A biowaiver monograph of rifampicin based on literature data, together with additional experimental data, is presented. The risks of basing a BE assessment on \textit{in vitro} rather than \textit{in vivo} study results for the approval of new IR solid oral dosage forms containing rifampicin (“biowaiving”), including both reformulated products and new multisource products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing rifampicin as single API. The purpose and scope of this series of monographs have been previously discussed.\textsuperscript{1} Summarized in few words, 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 in terms of the probability of an incorrect biowaiver decision as well as the consequences of an incorrect 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 is advisable or not. This systematic approach to recommend or advise against a biowaiver decision is referred to in the recently published World Health Organization (WHO) Guideline.\textsuperscript{2} Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),\textsuperscript{3} acetazolamide,\textsuperscript{4} aciclovir,\textsuperscript{5} amitriptyline,\textsuperscript{6} atenolol,\textsuperscript{7} chloroquine,\textsuperscript{7} cimetidine,\textsuperscript{8} diclofenac sodium and diclofenac potassium,\textsuperscript{9} ethambutol dihydrochloride,\textsuperscript{10} ibuprofen,\textsuperscript{11} isoniazid,\textsuperscript{12} metoclopramide,\textsuperscript{13} prednisolone,\textsuperscript{14} prednisone,\textsuperscript{15} propranolol,\textsuperscript{1} pyrazinamide,\textsuperscript{16} ranitidine,\textsuperscript{17} and verapamil.\textsuperscript{1} They are also available online at www.fip.org/bcs.\textsuperscript{18}

EXPERIMENTAL

Literature data was assessed from PubMed,\textsuperscript{19} PubChem,\textsuperscript{20} Medicines Complete,\textsuperscript{21} the WHO search engine WHOLIS,\textsuperscript{22} the BIAM,\textsuperscript{23} ROTE LISTE,\textsuperscript{24} and VIDAL\textsuperscript{25} databases. Key words used for searching were: rifampicin, bioequivalence, bioavailability, biowaiver, solubility, permeability, dissolution, tuberculosis, excipient, toxicity, polymorphism and pharmacokinetics.

GENERAL CHARACTERISTICS

Name

Rifampicin (INN).\textsuperscript{26}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{rifampicin_structure.png}
\caption{Structure of rifampicin, $M_W$ 822.94.}
\end{figure}

3\{[(Methyl-1-piperazinyl)imino]methyl\} rifampicin SV (USAN, USP).\textsuperscript{27}

The structure is shown in Figure 1.

Therapeutic Indications

Rifampicin is a potent antibiotic, active against certain gram positive, gram negative and all populations of tuberculosis (TB) bacilli and other mycobacteria. It is the key API in the combination treatment of TB and leprosy recommended by the WHO.\textsuperscript{29–36}

Therapeutic Index

Rifampicin is administered once daily in a dose of 10 (8–12) mg/kg with a maximum dose of 600 mg.\textsuperscript{23–25,29–37,33,34} Other sources indicate doses of 8–15 mg/kg/day, either once a day or divided into two doses.\textsuperscript{28,37} Rifampicin is relatively non-toxic.\textsuperscript{34,38} At doses up to 75 mg/kg no serious adverse effects have been observed.\textsuperscript{32,38–40}

CHEMICAL PROPERTIES

Polymorphs and Hydrates

Rifampicin exists in two crystalline anhydrous forms (forms I and II) and in two amorphous forms.\textsuperscript{41–44} A monohydrate, a dihydrate and a pentahydrate are also known to exist. The
different forms have different solubilities, see Table 1, and consequently different dissolution behavior.42,45 Solid–state characterization of commercial rifampicin bulk material indicated that it is predominantly a mixture of form II and an amorphous form, in various proportions.41,45 Rifampicin raw materials used by manufacturers of generic rifampicin in South Africa were shown to either contain crystalline form II or a mixture of crystalline form II and the amorphous form.45 However, the pharmacopoeias do not stipulate any specific polymorph.27,46,47

Stability
Rifampicin is stable in the solid state, in sealed containers at room temperature under protection from humidity, light, and oxygen.48–54 In solution, rifampicin decomposes rapidly in acid,43 but its decomposition under neutral conditions is relatively slow.55

Solubility
Several sources report solubility data of rifampicin under non-BCS conditions.42,45,56 Solubility data reported at 37°C in buffered media, that is, as described in the several BCS Guidelines,2,57,58 are summarized in Table 2, together with the Dose/Solubility (D/S) values for the tablet strength according to the WHO Essential Medicines List59 and the highest marketed tablet strengths, see below. No data on the solubility of the pentahydrate were identified. Since rifampicin can be unstable in solution, additional experimental equilibrium solubility determinations were carried out in USP and Pharm. Int. standard Simulated Intestinal Fluids sine pancreatin (SIFsp) pH 6.8 at 37°C, using a standard shake-flask method over 4 h.60,a The pH of the buffers was monitored and readjusted, if necessary, to the initial pH values. A stability-indicating photometric method, previously described in the literature, with simultaneous absorption measurements at 475 and 507 nm was used for quantification of rifampicin.61 Prior to the solubility determinations, stock solutions containing different concentrations of rifampicin were stored and remeasured after 1, 2, 4, 12, and 24 h. At pH 6.8 no appreciable instability was observed within the time-frame used for solubility measurements.62 The results can be found in Table 2. A plot of the D/S values calculated on the basis of the various solubility data versus pH is shown in Figure 2.

Partition Coefficient
A log P of 4.2 was reported for octanol/water, without providing information about temperature and pH.63 Seydel et al. reported a partition coefficient of 15.6 in octanol/aqueous phosphate buffer pH 7.4, also without reporting the temperature.64 Agrawal and Panchagnula65 reported logD values at 37°C in diluted HCl of −1.27 (pH 1.4) and −0.23 (pH 2.36); in citrate buffers of 0.76 (pH 3.0), 0.95 (pH 3.5), 0.83 (pH 4.0), and 0.73 (pH 4.5) and in phosphate buffers of 0.64 (pH 5.2), 0.61 (pH 6.0), 0.42 (pH 6.8), 0.30 (pH 7.4), and 0.09 (pH 8.0). In PubChem, a computed Xlog P of 2.7 is indicated.20

pKₐ
Rifampicin is amphoteric with a pKₐ1 of 1.7 related to the 4-hydroxyl group and a pKₐ2 of 7.9 related to the 3-piperazine nitrogen,43,63,66 with an isoelectric point at pH 4.8 in aqueous solution.67,68

Dosage Form Strengths
The WHO Essential Medicines List describes strengths of 150 and 300 mg rifampicin as either tablet or capsule formulations.59 In most European countries, Marketing Authorizations (MA) exist for 150, 300, 450, and 600 mg tablets and/or capsules; in the USA, MA exist for strengths of 150 and 300 mg, see Table 3.

---

Table 1. Solubility of Different Rifampicin Crystalline Forms and Hydrates at 30°C in Water

<table>
<thead>
<tr>
<th>Reference</th>
<th>Crystalline Form/Hydrate</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Henwood et al.45</td>
<td>Amorph I</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Amorph II</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>Form II</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Monohydrate</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Dihydrate</td>
<td>1</td>
</tr>
</tbody>
</table>

---

The data shown in Table 1 indicate that different forms have different solubilities, which is consistent with the behavior observed in dissolution studies. The solubility of rifampicin is generally low, which can affect its bioavailability and dissolution rate. The higher solubility of the crystalline forms (compared to the amorphous forms) suggests that the crystalline forms are more stable under physiological conditions. The stability of rifampicin in solution is also dependent on pH, with higher pH values leading to increased instability.

The partition coefficient (log P) of rifampicin is lower than many other drugs, indicating that it has a relatively high partitioning into the aqueous phase. This could affect its absorption and distribution in the body. The pKₐ values indicate that rifampicin is amphoteric, with two ionizable groups that influence its interaction with biological systems.

In terms of dosage form strengths, rifampicin is available in a range of strengths, with the WHO Essential Medicines List recommending 150 and 300 mg as standard strengths. The data show that the solubility of rifampicin under non-BCS conditions is relatively low, which may necessitate the use of dissolution-stimulating agents or the formulation of stable solutions to ensure adequate bioavailability.

---

*aExperiments performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany. Standard reference substance from Sigma-Aldrich, Germany, was used, the crystalline form was not specified in the product information.*
Permeability and Absorption

In Vitro/In Silico/In Situ

Biganzoli et al.\textsuperscript{69} investigated the permeability of 13 antibiotics in the Caco-2 model. The reproducibility of the assay conditions as well as the integrity of the cell layer was verified using \textsuperscript{3}H-mannitol. Model drugs, as suggested by the FDA guidance,\textsuperscript{57} were not included in the test set of drugs. An apparent permeability of \(5.79 \pm 0.053 \times 10^{-6} \text{ cm/s}\) was measured for rifampicin.\textsuperscript{69} Since this apparent permeability value is above the critical limit of \(2 \times 10^{-6} \text{ cm/s}\), rifampicin was expected to have a BA over 90\%.\textsuperscript{70–73} Agrawal and Panchagnula\textsuperscript{65} determined the \textit{in situ} permeability of rifampicin in different excised sections of the rat intestine.\textsuperscript{65} Differences in regional effective permeabilities were observed, from \(0.02 \pm 0.02 \text{ cm/s}\) in the stomach up to \(0.62 \pm 0.02 \text{ cm/s}\) in the duodenum. In \textit{in vitro} and \textit{ex vivo} studies, it was concluded that rifampicin is a P-glycoprotein substrate since addition of verapamil, an inhibitor of P-glycoprotein, multidrug resistance associated protein-2

### Table 2. Literature Data and New Experimental Data for the Solubility of Rifampicin at 37°C and the Corresponding Dose/Solubility ratios (D/S) for Two Tablet Strengths

<table>
<thead>
<tr>
<th>References</th>
<th>pH</th>
<th>Medium</th>
<th>Solubility (mg/mL)</th>
<th>D/S (mL)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariappan and Singh\textsuperscript{74}</td>
<td>1.0</td>
<td>HCl, NaCl, H\textsubscript{2}O</td>
<td>127.21</td>
<td>5 2</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>HCl, citric acid, NaOH, NaCl, H\textsubscript{2}O</td>
<td>42.68</td>
<td>14 7</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>HCl, citric acid, NaOH, NaCl, H\textsubscript{2}O</td>
<td>19.21</td>
<td>31 16</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>HCl, citric acid, NaOH, NaCl, H\textsubscript{2}O</td>
<td>3.19</td>
<td>188 94</td>
</tr>
<tr>
<td></td>
<td>5.5</td>
<td>NaCl, Na\textsubscript{2}HPO\textsubscript{4}, H\textsubscript{2}O</td>
<td>0.64</td>
<td>938 469</td>
</tr>
<tr>
<td></td>
<td>7.0</td>
<td>NaCl, Na\textsubscript{2}HPO\textsubscript{4}, H\textsubscript{2}O</td>
<td>0.85</td>
<td>706 353</td>
</tr>
<tr>
<td>Agrawal et al.\textsuperscript{44}</td>
<td>1.4</td>
<td>SGF\textsubscript{sp}</td>
<td>125.5</td>
<td>5 2</td>
</tr>
<tr>
<td></td>
<td>2.36</td>
<td>SGF\textsubscript{sp}</td>
<td>11.4</td>
<td>53 26</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>SGF\textsubscript{sp}</td>
<td>1.15</td>
<td>522 261</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Phosphate buffer</td>
<td>0.99</td>
<td>606 303</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>Phosphate buffer</td>
<td>1.25</td>
<td>480 240</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>Phosphate buffer</td>
<td>1.53</td>
<td>392 196</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Phosphate buffer</td>
<td>1.65</td>
<td>364 182</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>Phosphate buffer</td>
<td>2.54</td>
<td>236 118</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>Acetate buffer</td>
<td>3.35</td>
<td>179 90</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Acetate buffer</td>
<td>5.44</td>
<td>110 55</td>
</tr>
<tr>
<td>Agrawal and Panchagnula\textsuperscript{65}</td>
<td>1.4</td>
<td>HCl solution</td>
<td>125.54</td>
<td>5 2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>HCl solution</td>
<td>11.40</td>
<td>53 26</td>
</tr>
<tr>
<td></td>
<td>2.36</td>
<td>HCl solution</td>
<td>11.40</td>
<td>53 26</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sodium citrate/citric acid buffer</td>
<td>1.15</td>
<td>522 261</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>Sodium citrate/citric acid buffer</td>
<td>0.75</td>
<td>800 400</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Sodium citrate/citric acid buffer</td>
<td>0.99</td>
<td>606 303</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>Sodium citrate/citric acid buffer</td>
<td>1.25</td>
<td>480 240</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>Phosphate buffer</td>
<td>1.53</td>
<td>392 196</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Phosphate buffer</td>
<td>1.65</td>
<td>364 182</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>Phosphate buffer</td>
<td>2.54</td>
<td>236 118</td>
</tr>
<tr>
<td></td>
<td>7.4</td>
<td>Phosphate buffer</td>
<td>3.35</td>
<td>179 90</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Phosphate buffer</td>
<td>5.44</td>
<td>110 55</td>
</tr>
<tr>
<td>New experimental data</td>
<td>6.80</td>
<td>USP SIF\textsubscript{sp}</td>
<td>1.39</td>
<td>432 216</td>
</tr>
<tr>
<td></td>
<td>6.80</td>
<td>Pharm. Int. SIF\textsubscript{sp}</td>
<td>1.39</td>
<td>434 217</td>
</tr>
</tbody>
</table>

\textsuperscript{a}The critical limit for D/S is 250 mL.\textsuperscript{2,57,58}

\textsuperscript{b}Highest strength with an Marketing Authorization (MA) in Germany (DE).\textsuperscript{24}

\textsuperscript{c}Highest strength on the WHO Essential Medicines List.\textsuperscript{59}
and of other exo-transporters increased the net absorption of rifampicin in the jejunum and ileum by two- to threefold and decreased secretion to the lumen about fourfold.74,75 Agrawal and Panchagnula65 obtained similar results using a single-pass perfusion study in rats and excised segments of the rat intestine.

Bioavailability

Rifampicin is readily absorbed from the gastrointestinal (GI) tract.76,77 Nitti et al.78 showed that the pharmacokinetic parameters after intravenous infusion do not differ significantly from those after oral administration of the same doses. Loos et al. reported an absolute BA of 93% after a single oral and intravenous dose of rifampicin at the beginning of the treatment of six adult patients, decreasing to under 70% after repeated dosage due to self-induction of metabolizing enzymes by rifampicin.79–81 Rifampicin was reported to show dose-dependent absorption,33 probably due to saturation of efflux systems in the small intestine.82 Analysis of the absolute BA of rifampicin in a pediatric population revealed that the BA of a freshly prepared oral suspension containing 324 mg/m² rifampicin was only about 50 ± 22% of an intravenous dose of 287 mg/m².83,84 Malabsorption of rifampicin was reported to be common in undernourished patients and patients with AIDS.83,85–89

\[ C_{\text{max}} \text{ and } T_{\text{max}} \text{ values} \]

The \( C_{\text{max}} \) after oral administration of 600 mg rifampicin averages from about 8 to 20 \( \mu \)g/mL.76 \( C_{\text{max}} \) values in healthy volunteers, patients with TB and in children can vary widely from individual to individual.77 Neither \( C_{\text{max}} \) nor \( T_{\text{max}} \) is altered in the elderly.90 Concomitant intake of food delays the absorption, see below.91–95 \( T_{\text{max}} \) values after oral application in various studies were generally about 2 h. In a woman with drug-resistant pulmonary TB receiving rifampicin, para-aminosalicylic acid and levofloxacin via a gastrojejunostomy tube, serum levels after in situ application were compared to published levels after oral administration.96 \( T_{\text{max}} \) after in situ application occurred at 1.5 h compared to 2–3 h after oral administration, indicating faster absorption after direct application, as would be expected on the basis of GI physiology.

Distribution

A plasma protein binding of 80–91% has been reported.33,49 Most of the unbound fraction is not ionized and diffuses freely into most tissues, consistent with the volume of distribution of 70 L.33,49,51 High concentrations can be detected in the cerebrospinal fluid, lung, and skin.97

Metabolism and Elimination

The main metabolic pathway is deacetylation in the liver.76,77 The API itself and its deacetylated metabolite are mainly excreted via the biliary pathway but also renally.34,98 Rifampicin undergoes enterohepatic circulation but its metabolite does not. Within 24 h about 3–30% of a single oral dose is recovered in the feces. The antibiotic shows dose-dependent elimination kinetics. When the biliary route is saturated, that is, at higher doses, the proportion of the dose excreted in the urine and the elimination half-life increases.76,99,100 Up to 30% of the dose is excreted via glomerular filtration and tubular secretion in the urine, with about half of this being unchanged API. Elimination is accelerated in children, resulting in shorter
half-lives in this patient population, but is not altered in the elderly. Rifampicin is a potent enzyme inducer and induces its own metabolism. After 3 weeks of oral and intravenous therapy the absolute BA of rifampicin had decreased to 68%, which was attributed to self-induction of its hepatic first pass metabolism.

### Food and Excipient Interactions

Zent and Smith compared the BA of rifampicin in the fasted state to that after ingestion of a carbohydrate-rich or a fat-rich meal in 27 adult patients with TB. In this study AUC was found not to be altered by either meal compared to the fasted state, $C_{\text{max}}$ was decreased by 15% by a high fat meal.

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Drug Products Containing That Excipient With a MA Granted by the Named Country</th>
<th>Range Present in Solid Oral Dosage Forms With a MA in the USA (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeswax</td>
<td>DE(1,2)</td>
<td>0.44–2</td>
</tr>
<tr>
<td>Calcium stearate</td>
<td>DE(1–3) DK(4,5) ES(6-8) NL(9–11) NO(12,13) SE(14,15)</td>
<td>0.7–43$^a$</td>
</tr>
<tr>
<td>Carmellose sodium</td>
<td>DE(1–3) DK(4) ES(6,8) NL(10,11) NO(13) SE(14)</td>
<td>2.2–160</td>
</tr>
<tr>
<td>Castor oil</td>
<td>DE(1,2)</td>
<td>0.03–3.1</td>
</tr>
<tr>
<td>Castor oil hydrogenated</td>
<td>FI(16)</td>
<td>0.93–37.6$^c$</td>
</tr>
<tr>
<td>Cellulose</td>
<td>DE(1–3,17) ES(6) NL(11)</td>
<td>4.6–1385$^a$</td>
</tr>
<tr>
<td>Cetyl palmitate</td>
<td>DE(1,2)</td>
<td></td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>DE(17)</td>
<td>2–180</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>FI(16)</td>
<td>4.4–792$^c$</td>
</tr>
<tr>
<td>Gelatin</td>
<td>DE(18) DK(5) NL(9,19) NO(12) SE(15) US(20,21)</td>
<td>1–756$^c$</td>
</tr>
<tr>
<td>Glucose</td>
<td>DE(1,2)</td>
<td>157–90$^c$</td>
</tr>
<tr>
<td>Glycerol</td>
<td>FI(16)</td>
<td>0.14–198$^c$</td>
</tr>
<tr>
<td>Hard paraffin</td>
<td>DE(1,2)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypromellose</td>
<td>DE(1,2,17)</td>
<td>0.8–86</td>
</tr>
<tr>
<td>Lactose</td>
<td>DE(1,3) DK(5) ES(6,7) NL(9,11) NO(12) SE(15) US(20,21)</td>
<td>23–1020$^c$</td>
</tr>
<tr>
<td>Macrogol</td>
<td>DE(1,17)</td>
<td>0.12–500$^c$</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>DE(3,17,18) ES(6,22) FI(16) NL(11,19) UK(23) US(20,21)</td>
<td>0.15–401$^c$</td>
</tr>
<tr>
<td>Methyl parahydoxybenzoate</td>
<td>US(21)</td>
<td>0.01–1.8</td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>FI(16)</td>
<td>2.2–418$^c$</td>
</tr>
<tr>
<td>Povidone</td>
<td>DE(1,2) FI(16)</td>
<td>0.17–75</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>DE(1,17)</td>
<td>1.5–52</td>
</tr>
<tr>
<td>Propyl parahydoxybenzoate</td>
<td>US(21)</td>
<td>0.002–0.2</td>
</tr>
<tr>
<td>Silica</td>
<td>DE(1,2,17) US(21)</td>
<td>0.65–99</td>
</tr>
<tr>
<td>Simeticone emulsion</td>
<td>DE(1,2)</td>
<td>0.009–14.4</td>
</tr>
<tr>
<td>Sodium lauryl sulfate</td>
<td>DE(1–3) DK(4) ES(6,8) NL(10,11) NO(13) SE(14) US(21)</td>
<td>0.65–50</td>
</tr>
<tr>
<td>Sorbitol</td>
<td>DE(17)</td>
<td>5–337</td>
</tr>
<tr>
<td>Starch</td>
<td>DE(1–3,18) DK(4) ES(6,8,22) NL(10,11,19) NO(13) SE(14) UK(23) US(20,21)</td>
<td>0.44–1135$^c$</td>
</tr>
<tr>
<td>Sucrose</td>
<td>DE(1,2)</td>
<td>12–900</td>
</tr>
</tbody>
</table>
| Talc                       | DK(1,2,4) ES(8) NL(10) NO(13) SE(14) US(21)                                     | 0.26–220$^c$                                                        

(1), Rifa$^a$ 150/-300 Dragees; (2), Rifa$^a$ 450/-600 Dragees; (3), RifampicinHefa-N 450 mg/-600 mg überzogene Tabletten; (4), Rimactan ovtrukne tabletter 450 mg; (5), Rimactan, kapsel, härda 150/300 mg; (6), RIFALDIN 600 mg Comprimidos recubiertos; (7), Rimactán 300 mg capsulas duras; (8), Rimactán 600 mg comprimidos recubiertos; (9), Rifampicine Sandoz 150/300, capsules 150/300 mg; (10), Rifampicin Sandoz 450/600, omhulde tabletten 450/600 mg; (11), Rifadin, dragees 600 mg; (12), RIMACTAN$^b$ 150/300 mg kapsel, hard; (13), RIMACTAN$^b$ 450/600 mg tabletter, dragee; (14), Rimactan 450/600 mg dragerade tabletter; (15), Rimactan 150 mg härdad kapsel; (16), Rimapen 450/600 mg tabbetti, kalvgaljästeinner; (17), Eremfat$^b$ 150/300/-450/600 Filmtablenten; (18), RifampicinHefa-N 150 mg/-300 mg Hartkapseln; (19), Rifadin, capsules 150/300 mg; (20), Rifadin (rifampin) capsule 150/300 mg; (21), Rifampin (Rifampin) capsule; (22), RIFALDIN 300 mg Cápsulas; (23), Rifadin Capsules 150/300 mg.

$^a$Excipients that could be assumed to be present in the coating/polish/printing ink only were excluded.

$^b$Only single API drug products were included.

$^c$The reported upper range value is unusually high. The authors doubt its correctness.


BIOWAIVER MONOGRAPH FOR RIFAMPICIN 2257
meal and $T_{\text{max}}$ was increased by 21% by a carbohydrate-rich meal. These findings concur partly with the work of Buniva et al.$^{94}$ who observed reduced absorption, with $C_{\text{max}}$ reduced by 40% and $AUC_{0-\text{sh}}$ reduced by 70% compared to the fasted state, after administration of 450 mg of rifampicin with food to four volunteers. In another food-effect study, Polasa and Krishnaswamy$^{95}$ investigated the effect of a typical wheat-based Indian breakfast on the BA of rifampicin in six healthy male volunteers. Compared to the fasted state, AUC and $C_{\text{max}}$ were reduced about 30% and $T_{\text{max}}$ was increased about 30%. Peloquin et al.$^{93}$ investigated the pharmacokinetics of rifampicin in healthy volunteers under fasted conditions and after a high-fat standard FDA breakfast. Food reduced $C_{\text{max}}$ by 36% and nearly doubled $T_{\text{max}}$, but decreased AUC only by 6%. Results are generally in accordance with the effects of slower gastric emptying after food intake, which leads to lower $C_{\text{max}}$ and longer $T_{\text{max}}$ values.

Peloquin et al.$^{93}$ also found that co-administration of rifampicin with an aluminum-magnesium hydroxide antacid did not significantly affect $C_{\text{max}}$, $T_{\text{max}}$, or AUC. This finding contradicts the observations of Khalil et al.$^{103}$ and Buniva et al.$^{94}$ who studied the effect of usual amounts of different antacid preparations on the oral absorption of rifampicin by measuring urinary excretion. In these studies, the BA of a 600 mg dose was significantly reduced when given concomitantly with an antacid preparation with the effect being antacid-dependent: magnesium trisilicate $>$ aluminum hydroxide $>$ sodium bicarbonate. The authors proposed complexation of rifampicin by polyvalent cations as an explanation for this result. In separate in vitro studies, rifampicin was shown to form complexes with di- and trivalent cations such as chromium or aluminum.$^{104,105}$ The Prescribers’ Information for rifampicin products recommends that antacids and dietary supplements should be avoided close to the time of rifampicin administration.$^{48-53}$

Boman et al.$^{106}$ determined the BA of an oral rifampicin solution with and without simultaneous administration of para-aminosalicylate (PAS) granules, placebo granules and Na-PAS tablets in vivo. The PAS and placebo granules contained bentonite as a major excipient; the Na-PAS tablets did not contain bentonite. The PAS and placebo granules significantly decreased the absorption of rifampicin, whereas the Na-PAS tablet had no such effect. In vitro disintegration and dissolution results for PAS granules correlated well with the adsorption of rifampicin by bentonite from the solution.$^{106}$

## DOSAGE FORM PERFORMANCE

### Bioavailability and Bioequivalence Studies

Many reports have been published on the BE of various rifampicin formulations. In 1977, Mannisto$^{107}$ investigated the influence of different dosage forms on the pharmacokinetics of rifampicin. Three 300 mg capsule formulations, two 20 mg/mL syrup formulations and four 600 mg tablet formulations were compared. The rifampicin crystal sizes of all preparations were $<10 \mu m$, the amount of inert excipients was reported to be about 5% (w/w) in the tablet formulations (lactose, starch, cellulose, various pectins etc.) and the syrup suspensions contained small amounts of sucrose and aromatic agents. The two syrup preparations showed very similar serum rifampicin concentrations, whereas the serum level of the best absorbed solid oral rifampicin formulation was only half that of the serum levels achieved with the syrups.

Buniva et al.$^{94}$ compared different experimental lots of licensed and nonlicensed marketed rifampicin capsules formulations with the innovator. Unfortunately, no information about either the composition of the formulations or the drug particle size was provided. Single 600 mg oral doses were administered to fasted healthy volunteers in a balanced, cross-over design. The pharmacokinetic parameters of the innovator appeared to be nearly identical across different batches, storage times and groups of subjects. Comparison of rifampicin products from licensed manufacturers gave similar pharmacokinetic parameters to the innovator with respect to $C_{\text{max}}$, $T_{\text{max}}$, and AUC, whereas $C_{\text{max}}$ and AUC of the nonlicensed manufacturers were significantly lower. In addition, the experimental formulations showed significantly lower $C_{\text{max}}$ and AUC after changes in excipients, modification of the manufacturing process and changes in particle sizes of the API compared to the standard formulation.

Chouchane et al.$^{108}$ investigated the BE of a new 300 mg generic rifampicin capsule formulation in comparison to the innovator in a cross-over study with 12 healthy volunteers. Information about the composition and/or the particle size of the formulations was not provided. Statistical analysis of the different pharmacokinetic parameters, $C_{\text{max}}$, $T_{\text{max}}$, and AUC, showed no sig-
significant differences and hence the BE of the generic capsule formulation was confirmed.

Pahhla et al.\textsuperscript{109} studied the relative BA of two generic rifampicin preparations compared to the innovator \textit{in vitro} and \textit{in vivo}. Neither the composition of the tested formulations nor the particle size of the API was indicated. Each of the nineteen healthy volunteers received a single oral dose of 600 mg as four capsules, each containing 150 mg rifampicin. Significant differences were found between the three formulations with respect to AUC and $T_{\text{max}}$ but not $C_{\text{max}}$. Dissolution testing in 0.1 M HCl at 50 rpm was not able to reveal any differences and hence this test was deemed unsuitable to discriminate among nonequivalent\textsuperscript{b} drug products.

In a meta-analysis of eight \textit{in vivo} BE trials focused on the quality of fixed dose combinations of anti-TB drugs, the authors identified one capsule formulation out of the seven single rifampicin tablet and capsule formulations that was substandard with respect to $C_{\text{max}}$, $T_{\text{max}}$, and AUC.\textsuperscript{82} The composition of the tested formulations was not provided.

Panchagnula et al. postulated various explanations for the variable BA of rifampicin drug products.\textsuperscript{116} Postulated were: differences in raw material characteristics, changes in the crystalline form due to manufacturing processes, influence of excipients on the dosage form performance, instability/degradation in the GI tract and in the presence of light, humidity, and oxygen, inter-individual variability in absorption and metabolism and pH-dependent solubility. The lack of a discriminatory \textit{in vitro} dissolution test to identify substandard formulations was noted as a further problem in comparing rifampicin products.

Excipients

Table 3 shows excipients present in “rifampicin-only” IR solid oral drug products with an MA in Germany (DE),\textsuperscript{24} Denmark (DK),\textsuperscript{111} Finland (FI),\textsuperscript{112} France (FR),\textsuperscript{113} The Netherlands (NL),\textsuperscript{114} Norway (NO),\textsuperscript{115} Spain (SP),\textsuperscript{116} Sweden (SE),\textsuperscript{117} the United Kingdom (UK),\textsuperscript{118} and the USA (US).\textsuperscript{119} In previous monographs, it was hypothesized that drug products with such MAs successfully had passed an \textit{in vivo} BE study. Indeed, rifampicin has not been exempted from \textit{in vivo} BE testing in DE.\textsuperscript{120,121} However, many rifampicin containing drug products were already on the market before BE criteria became effective and were therefore “grandfathered”: clinical efficacy over the years was considered a justification of continuing an MA without requiring an \textit{in vivo} BE study of such an existing drug product.

In Table 3 the ranges of the amounts of excipients present in approved products in the US are also presented.\textsuperscript{122}

\textit{In vitro}, 16–20% rifampicin can be bound by an amount of neutralized magnesium trisilicate usually present in antacid preparations.\textsuperscript{103} Since the amounts of magnesium ions usually present as inert excipients such as fillers, binders and lubricants in oral solid formulations are much lower, the risk of binding reactions of rifampicin to magnesium trisilicate affecting rifampicin absorption appears to be very low.

Further common pharmaceutical excipients utilized in pharmaceutical preparations, such as binders and glidants like bentonite, talc, and kaolin, were reported to rapidly and strongly adsorb the antibiotic and thus reduce the absorbable fraction of the dose.\textsuperscript{106} Granules containing bentonite as a major excipient significantly decreased the absorption of rifampicin \textit{in vivo} and adsorbed rifampicin from solution \textit{in vitro}.\textsuperscript{106} Nevertheless, these granules contained bentonite in an unusually high percentage, 14% (w/w). Since typical amounts of bentonite in tablet formulations are closer to 1%, this effect seems to be of little practical relevance. Additionally, RifampicinHefa-N\textsuperscript{©} 450 mg/-600 mg coated tablets, which has an MA in DE and which contains small amounts of white clay, was shown to be therapeutically equivalent to the innovator, EREM-FAT\textsuperscript{®}.\textsuperscript{48,53}

Dissolution and \textit{In vivo}/\textit{In vitro} Correlation

The current USP specification for “rifampicin-only” formulations is not less than 75% (Q) within 45 min in 900 mL of 0.1 HCl at 37°C in the basket apparatus operated at 50 rpm.\textsuperscript{27} Agrawal and Panchagnula\textsuperscript{123} used this method for comparative \textit{in vitro} dissolution studies of combination anti-TB drug products containing rifampicin, isoniazid, pyrazinamide, and ethambutol dihydrochloride. All tested formulations passed the specification.
with respect to rifampicin, but in the subsequent in vivo BE study, poor BA of some formulations was observed. Therefore, the USP method was judged to be insufficiently discriminating. The authors proposed an alternative dissolution method using 250 mL 0.01 HCl as medium and the paddle apparatus at 50 rpm.

In view of the unsuitability of the USP test, we carried out new experimental dissolution studies under conditions assumed to be more discriminatory with three drug products having an MA in DE and 300 mg pure rifampicin powder, using the Pharm. Int. standard dissolution test for IR solid oral dosage forms containing highly soluble APIs, with 500 mL SIFsp pH 6.8 as the medium and the paddle apparatus operated at 75 rpm. The results, shown in Figure 3, indicate that under these conditions, dissolution is slow and incomplete and the drug products, even though they have MAs, were unable to meet the rapidly dissolving criterion of ≥85% dissolved within 30 min. Increasing the volume of the medium to 900 mL did not lead to better results. As the pure rifampicin powder floated on the surface, the poor wettability of rifampicin was suspected to be a major reason for the slow and incomplete dissolution of the drug products. Indeed, addition of 0.25% SLS to the medium resulted in somewhat faster dissolution.

Only one report identified some kind of correlation of in vitro dissolution data with in vivo data. Rao and Murthy established a Level A correlation of the in vitro release of rifampicin from ethylcellulose coated nonpareil beads in phosphate buffer pH 7.4 with individual plasma levels. However, as this was a modified release product, the results are not germane to IR drug products.

DISCUSSION

Solubility

One prerequisite of the Guidelines is the stability of the API in solution. In our experiments at pH 6.8, no appreciable instability within the time-frames used to determine solubility was observed. But many literature data, in particular at low pH, cannot be considered fully reliable, as the influence of degradation was typically not considered. Additionally, maintenance of constant pH during the solubility determination was not documented. A further source of the variability in the solubility data might be the differences in solubility of the different polymorphic forms. As illustrated in Table 1, the solubility of the amorphous forms is 1.5- to 7.5-fold lower than of the crystalline structures. All three considerations can explain the scatter in the D/S values plotted in Figure 2. According to the current BCS guidelines, an API is highly soluble if D/S ratio is 250 mL over physiological pH range. The scatter of data does not allow a definitive conclusion, indicating that while the 300 mg strength might meet that criterion, the 600 mg strength definitely does not, in line with our own solubility experiments. So, rifampicin narrowly misses the solubility requirements of the WHO for biowaiving of weak acids.

Permeability

Review of available literature data suggest that the fraction of dose absorbed in humans is higher than the cut-off limit of 85% or 90% for highly permeable indicated by the current BCS guidelines. Plasma profiles after intravenous and oral application were shown to be similar, indicating nearly complete absorption.
While it is true that the BA of rifampicin can be reduced in subpopulations with elevated gastric pH, for example, patients with AIDS, and in children,83,85–88,125 the permeability classification of an API is not based on its BA in subpopulations and patients. Cell culture permeability studies consistently report results corresponding to ≥90% absorption.69,126 Results for the partitioning behavior of rifampicin are quite disparate, probably due to the widely varying methodology, and shed little light on the permeability of this API. There are some reports indicating that rifampicin shows dose-dependent, that is, nonlinear absorption, whereas the EMEA Guideline states that linear absorption indicating high permeability reduces the possibility that the dosage form influences the BA.58 However, data on BA in specific subpopulations and permeability in cell lines is of little relevance, as data for the most important determinant of the permeability classification, the fraction of dose absorbed in humans, is available.2,57,58 In conclusion, rifampicin can be classified as highly permeable.

**BCS Classification**

According to all guidances,2,57,58 rifampicin is a BCS Class II API. The recently revised WHO Guideline classified rifampicin also as BCS Class II, as does Lindenberg et al.127 only narrowly missing the solubility requirements for biowaiving of weak acids. Wu and Benet128 assigned rifampicin to Class II in their Biopharmaceutics Drug Disposition Classification System (BDDCS), as it is extensively metabolized and a substrate for efflux transporters.

**Risk of Nonequivalence Caused by Excipients and/or Manufacturing**

Rifampicin is the “problem drug” in fixed dose combination formulations.129–134 Although the rifampicin single drug innovator product shows consistent pharmacokinetics from study to study, many reports of nonequivalence have been reported for multisource drug products, indicating that formulation effects can be important to the BA of rifampicin. Postulated sources of nonequivalence are variations in the amorphous/crystalline/solvate nature of the drug starting material leading to differences in solubility and wettability, as well as excipient and manufacturing influences on solubility and dissolution and degradation in the drug product or in the GI tract.44,45,110 Also, because food effects and interactions with antacids have been documented, different formulations might differ in their interactions with food and/or antacids; this also may be an explanation for the observed nonequivalence of drug products.

**Surrogate Techniques for In Vivo BE Testing**

Nonequivalence of rifampicin formulations has been frequently reported and is therefore relatively likely to occur.82,100,130,132 In view of rifampicin’s high permeability, nonequivalence is most likely to be caused by solubility and/or dissolution problems in vivo rather than by a permeability interaction. In vitro dissolution according to USP, in 0.1 N HCl, has been used in most studies.27 Given the poor stability of rifampicin at low pH, the wisdom of this test condition can be questioned. Even if rifampicin was stable at low pH, this test would not be expected to be discriminat-

**Patient Risks Associated with Nonequivalence**

Nonequivalence, and in a worst case scenario, bioinequivalence of rifampicin IR dosage forms can lead to decreased anti-TB efficacy on the one hand, and in principle to serious, immunologic and dose-dependent hepatic adverse drug reactions (ADRs) on the other hand. If blood levels are sub-therapeutic, rifampicin would not fulfil its key function in the combination treatment of TB, since its bactericidal action is highly dose-dependent.100,135 A further reason to avoid subtherapeutic levels is that a decrease in rifampicin blood levels caused by substandard products could increase the emergence of resistance to rifampicin, which develops in a one-step process.136 Supra-bioavailability of rifampicin products is less of concern, since the serious hepatic or immunologic ADRs only occur at much higher
AUC and/or C\textsubscript{max} values.\textsuperscript{137} Cases of fatal overdose have only been reported after ingestion of doses of at least 14 g, which is about 20 times higher than the usual daily dose.\textsuperscript{138}

CONCLUSIONS

The FDA\textsuperscript{57} and EMEA\textsuperscript{58} guidances currently exclude a biowaiver based approval for BCS Class II APIs. The recently published WHO Guidance allows BCS Class II APIs to be considered for biowaiving if the API is a weak acid and the comparator and the multisource preparations are both rapidly dissolving at pH 6.8.\textsuperscript{2} Although rifampicin only narrowly misses meeting the solubility requirements, rifampicin drug products with an MA in DE fail by far to meet the dissolution criteria. More importantly, many cases of nonequivalence have been documented in the literature and the reasons for these failures are as yet insufficiently understood. In addition, no reliable in vitro surrogate BE test has been identified as yet. Taking all aspects into account, a biowaiver based approval of new multisource IR solid oral products containing rifampicin appears unsuitable and therefore their BE should be established by an in vivo study. For variations (postapproval changes) to existing products, an in vivo BE study is required only for major changes, which are defined in the respective regulatory documents.\textsuperscript{58,139,140} Here, too, a waiver of in vivo BE studies is not recommended for rifampicin containing drug products.\textsuperscript{4} Small variations (postapproval changes) to existing products, as defined in the respective regulatory documents are open to in vitro BE testing, again as defined in the respective regulatory documents.\textsuperscript{9} For these small changes, Table 3 may be helpful.

ACKNOWLEDGMENTS

Dr. M. Flegel, Riemser Arzneimittel AG, Schiessweiler, Germany; Dr. Kunitz, Lungenklinik Heckeshorn, Berlin, Germany; and Kik Groot, RIVM, The Netherlands, are acknowledged for providing literature data, detailed information of the ADRs of rifampicin, and producing Table 2, respectively. Linda Jaffan, Kathrin Nollenberger & Elisabeth Herbert, all Goethe University of Frankfurt, Germany, are acknowledged for their assistance in the experiments.

REFERENCES

48. Wernigerode SP. Fachinformation Rifampicin-Hefa-N® (German).
49. SANOFI-AVENTIS RIFADINE® voie oral, rifampicine (French), VIDALPro (L’intégralité de l’information officielle (issue des RCP de l’Afssaps) sur l’ensemble des médicaments commercialisés en France).
50. SANOFI-AVENTIS RIFADINE® (rifampin capsules USP) and RIFADINE® IV (rifampin for injection USP); Prescribing information US. http://www.sanofi-aventis.us/live/us/en/layout.jsp?scat=BD0DB735-32D7-41C4-898F-74F67D343145.
51. SANDOZ RIMACTANE® 300 mg gélule rifampicine (French), VIDALPro (L’intégralité de l’information officielle (issue des RCP de l’Afssaps) sur l’ensemble des médicaments commercialisés en France).
52. GRÜNENTHAL Fachinformation Rifa® Dragees (German).
53. FATOL Fachinformation EREMFACT® Fatol (German).


