Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Rifampicin

C. BECKER,[1,2] J.B. DRESSMAN,[1] H.E. JUNGINGER,[3] S. KOPP,[4] K.K. MIDHA,[5] V.P. SHAH,[6] S. STAVCHANSKY,[7] D.M. BARENDS[8]

[1]Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main, Germany

[2]Bayer Technology Services GmbH, Leverkusen, Germany

[3]Naresuan University, Faculty of Pharmaceutical Sciences, Phitsanulok, Thailand

[4]World Health Organization, Geneva, Switzerland

[5]University of Saskatchewan, Saskatoon, Saskatchewan, Canada

[6]International Pharmaceutical Federation FIP, Den Haag, The Netherlands

[7]Division of Pharmaceutics, College of Pharmacy, University of Texas at Austin, Austin, Texas

[8]RIVM—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. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 98:2252–2267, 2009

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

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

This article reflects the scientific opinion of the authors and not necessarily the policies of Bayer Technology Services; regulatory agencies; the International Pharmaceutical Federation (FIP) and the World Health Organization (WHO).

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)

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 *in vitro* rather than *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.[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.[2] Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),[3] acetazolamide,[4] aciclovir,[5] amitriptyline,[6] atenolol,[1] chloroquine,[7] cimetidine,[8] diclofenac sodium and diclofenac potassium,[9] ethambutol dihydrochloride,[10] ibuprofen,[11] isoniazid,[12] metoclopramide,[13] prednisolone,[14] prednisone,[15] propranolol,[1] pyrazinamide,[16] ranitidine,[17] and verapamil.[1] They are also available online at www.fip.org/bcs.[18]

EXPERIMENTAL

Literature data was assessed from PubMed,[19] PubChem,[20] Medicines Complete,[21] the WHO search engine WHOLIS,[22] the BIAM,[23] ROTE LISTE,[24] and VIDAL[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).[26]

3[[(Methyl-1-piperazinyl)imino]methyl] rifamycin SV(USAN, USP).[27]

(12Z,14E,24E-2S,16S,17S,18R,19R,20R,21S, 22R,23S)-5,6,9,17,19-Pentahydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-8-(4-methylpiperazin-1-yliminomethyl)-1,11-dioxo-1,2-dihydro-2,7-(epoxypentadeca[1.11.13]trienimino)naphto [2,1-b]furan-21-yl acetate.[28]

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.[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.[23–25,29–31,33,34] Other sources indicate doses of 8–15 mg/kg/day, either once a day or divided into two doses.[28,37] Rifampicin is relatively nontoxic.[34,38] At doses up to 75 mg/kg no serious adverse effects have been observed.[34,38–40]

CHEMICAL PROPERTIES

Polymorphs and Hydrates

Rifampicin exists in two crystalline anhydrous forms (forms I and II) and in two amorphous forms.[41–44] A monohydrate, a dihydrate and a pentahydrate are also known to exist. The

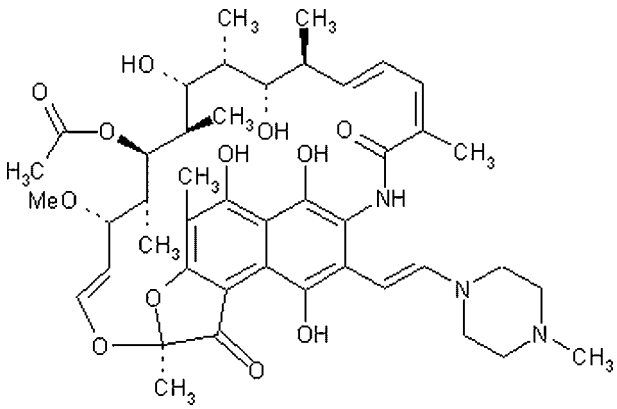

Figure 1. Structure of rifampicin, M_W 822.94.

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

Reference	Crystalline Form/Hydrate	Solubility (mg/mL)
Henwood et al.[45]	Amorph I	0.9
	Amorph II	0.2
	Form II	1.5
	Monohydrate	0.9
	Dihydrate	1

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 Guidances,[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 List[59] 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 (SIF_{sp}) 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 Panchagnula[65] reported $\log D$ 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 $X\log P$ of 2.7 is indicated.[20]

pK_a

Rifampicin is amphoteric with a pK_{a1} of 1.7 related to the 4-hydroxyl group and a pK_{a2} 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 (MAs) exist for 150, 300, 450, and 600 mg tablets and/or capsules; in the USA, MAs exist for strengths of 150 and 300 mg, see Table 3.

[a]Experiments 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.

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

References	pH	Medium	Solubility (mg/mL)	D/S (mL)[a] 600 mg Tablet[b]	D/S (mL)[a] 300 mg Tablet[c]
Mariappan and Singh[74]	1.0	HCl, NaCl, H_2O	127.21	5	2
	1.5	HCl, citric acid, NaOH, NaCl, H_2O	42.68	14	7
	2.0	HCl, citric acid, NaOH, NaCl, H_2O	19.21	31	16
	2.5	HCl, citric acid, NaOH, NaCl, H_2O	3.19	188	94
	5.5	NaCl, Na_2HPO_4, H_2O	0.64	938	469
	7.0	NaCl, Na_2HPO_4, H_2O	0.85	706	353
Agrawal et al.[44]	1.4	SGF_{sp}	125.5	5	2
	2.36	SGF_{sp}	11.4	53	26
	3	SGF_{sp}	1.15	522	261
	4	Phosphate buffer	0.99	606	303
	4.5	Phosphate buffer	1.25	480	240
	5.2	Phosphate buffer	1.53	392	196
	6	Phosphate buffer	1.65	364	182
	6.8	Phosphate buffer	2.54	236	118
	7.4	Acetate buffer	3.35	179	90
	8	Acetate buffer	5.44	110	55
Agrawal and Panchagnula[65]	1.4	HCl solution	125.54	5	2
	2	HCl solution	11.40	53	26
	2.36	HCl solution	11.40	53	26
	3	Sodium citrate/citric acid buffer	1.15	522	261
	3.5	Sodium citrate/citric acid buffer	0.75	800	400
	4	Sodium citrate/citric acid buffer	0.99	606	303
	4.5	Sodium citrate/citric acid buffer	1.25	480	240
	5.2	Phosphate buffer	1.53	392	196
	6	Phosphate buffer	1.65	364	182
	6.8	Phosphate buffer	2.54	236	118
	7.4	Phosphate buffer	3.35	179	90
	8	Phosphate buffer	5.44	110	55
New experimental data	6.80	USP SIF_{sp}	1.39	432	216
	6.80	Pharm. Int. SIF_{sp}	1.39	434	217

[a]The critical limit for D/S is 250 mL.[2,57,58]
[b]Highest strength with an Marketing Authorization (MA) in Germany (DE).[24]
[c]Highest strength on the WHO Essential Medicines List.[59]

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

In Vitro/In Silico/In Situ

Biganzoli et al.[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 ^{3}H-mannitol. Model drugs, as suggested by the FDA guidance,[57] were not included in the test set of drugs. An apparent permeability of $5.79 \pm 0.053 \times 10^{-6}$ cm/s was measured for rifampicin.[69] Since this apparent permeability value is above the critical limit of 2×10^{-6} cm/s, rifampicin was expected to have a BA over 90%.[70–73] Agrawal and Panchagnula[65] determined the *in situ* permeability of rifampicin in different excised sections of the rat intestine.[65] Differences in regional effective permeabilities were observed, from 0.02×10^{-4} cm/s in the stomach up to 0.62×10^{-4} cm/s in the duodenum. In *in vitro* and *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

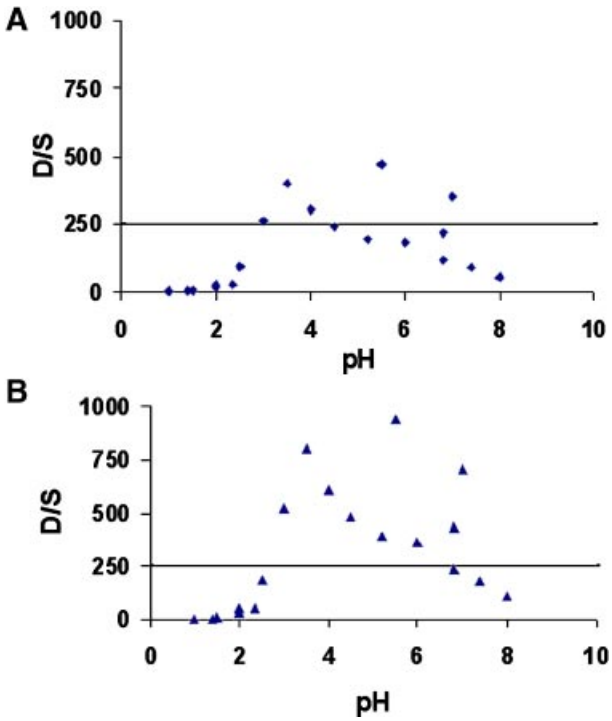

Figure 2. Dose/Solubility (D/S) values (mL) of rifampicin at 37°C as a function of pH, for 300 mg dosage forms (A) and for 600 mg dosage forms (B). The critical D/S value is 250 mL (black line).

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 Panchagnula[65] 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/m^2 rifampicin was only about $50 \pm 22\%$ of an intravenous dose of 287 mg/m^2.[83,84] Malabsorption of rifampicin was reported to be common in undernourished patients and patients with AIDS.[83,85–89]

C_{max} and T_{max} values

The C_{max} after oral administration of 600 mg rifampicin averages from about 8 to 20 μg/mL.[76] C_{max} values in healthy volunteers, patients with TB and in children can vary widely from individual to individual.[77] Neither C_{max} nor T_{max} is altered in the elderly.[90] Concomitant intake of food delays the absorption, see below.[91–95] T_{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_{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

Table 3. Excipients[a] Present in Rifampicin[b] Containing IR Solid Oral Drug Products With an Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), Norway (NO), Spain (ES), Sweden (SE), United Kingdom (UK) and the United States (US), and the Minimal and Maximal Amount of that Excipient Present Pro Dosage Unit in Solid Oral Drug Products with a MA in the USA

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

(1), Rifa® 150/-300 Dragees; (2), Rifa® 450/-600 Dragees; (3), RifampicinHefa-N 450 mg/-600 mg überzogene Tabletten; (4), Rimactan overtrukne tabletter 450 mg; (5), Rimactan, kapsler, hårde 150/300 mg; (6), RIFALDIN 600 mg Comprimidos recubiertos; (7), Rimactán 300 mg cápsulas duras; (8), Rimactán 600 mg comprimidos recubiertos; (9), Rifampicine Sandoz 150/300, capsules 150/300 mg; (10), Rifampicine Sandoz 450/600, omhulde tabletten 450/600 mg; (11), Rifadin, dragees 600 mg; (12), RIMACTAN® 150/300 mg kapsel, hard; (13), RIMACTAN® 450/600 mg tabletter, drasjerte; (14), Rimactan 450/600 mg dragerade tabletter; (15), Rimactan 150 mg hårda kapslar; (16), Rimapen 450/600 mg tabletti, kalvopäällysteinen; (17), Eremfat® 150/-300/-450/-600 Filmtabletten; (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.

half-lives in this patient population, but is not altered in the elderly.[90] Rifampicin is a potent enzyme inducer and induces its own metabolism.[101,102] 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.[79,80,99]

Food and Excipient Interactions

Zent and Smith[92] 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_{max} was decreased by 15% by a high fat

meal and T_{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_{max} reduced by 40% and AUC_{0-8h} 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_{max} were reduced about 30% and T_{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_{max} by 36% and nearly doubled T_{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_{max} and longer T_{max} values.

Peloquin et al.[93] also found that co-administration of rifampicin with an aluminum-magnesium hydroxide antacid did not significantly affect C_{max}, T_{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 μm, 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_{max}, T_{max}, and AUC, whereas C_{max} and AUC of the nonlicensed manufacturers were significantly lower. In addition, the experimental formulations showed significantly lower C_{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_{max}, T_{max}, and AUC, showed no sig-

nificant differences and hence the BE of the generic capsule formulation was confirmed.

Pahkla et al.[109] studied the relative BA of two generic rifampicin preparations compared to the innovator *in vitro* and *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_{max} but not C_{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[b] drug products.

In a meta-analysis of eight *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_{max}, T_{max}, and AUC.[82] The composition of the tested formulations was not provided.

Panchagnula et al. postulated various explanations for the variable BA of rifampicin drug products:[110] 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, interindividual variability in absorption and metabolism and pH-dependent solubility. The lack of a discriminatory *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);[24] Denmark (DK);[111] Finland (FI);[112] France (FR);[113] The Netherlands (NL);[114] Norway (NO);[115] Spain (SP);[116] Sweden (SE);[117] the United Kingdom (UK);[118] and the USA (US).[119] In previous monographs, it was hypothesized that drug products with such MAs successfully had passed an *in vivo* BE study. Indeed, rifampicin has not been exempted from *in vivo* BE testing in DE.[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 *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.[122]

In vitro, 16–20% rifampicin can be bound by an amount of neutralized magnesium trisilicate usually present in antacid preparations.[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.[106] Granules containing bentonite as a major excipient significantly decreased the absorption of rifampicin *in vivo* and adsorbed rifampicin from solution *in vitro*.[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® 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, EREMFAT®.[48,53]

Dissolution and *In vivo*/*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.[27] Agrawal and Panchagnula[123] used this method for comparative *in vitro* dissolution studies of combination anti-TB drug products containing rifampicin, isoniazid, pyrazinamide, and ethambutol dihydrochloride. All tested formulations passed the specification

[b]In many situations, it is not clear if the products were truly bio*in*equivalent. Bio*in*equivalence implies that the whole 90% confidence interval of one, or more, BE attributes (AUC, C_{max}, T_{max}) fall outside of their acceptance range, whereas failure to meet BE criteria implies that the 90% confidence interval of one, or more, BE attributes not fully fall inside their acceptance range. In this paper the expressions "non-equivalence" and "non-equivalent" should be taken to mean: bioinequivalence and/or not meeting BE criteria.

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[c] 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,[46] with 500 mL SIF_{sp} 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 $\geq$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.[62]

Only one report identified some kind of correlation of *in vitro* dissolution data with *in vivo* data. Rao and Murthy[124] 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 Guidances[2,57,58] 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

[c]Experiments performed at the Institute of Pharmaceutical Technology, Goethe University, Frankfurt am Main, Germany.

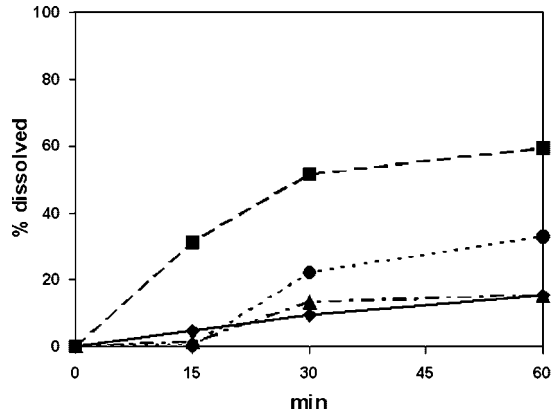

Figure 3. Dissolution of 300 mg rifampicin powder (◆); Eremfat® 300 coated tablets (■); RifampicinHefa-N 300 mg capsules (▲) and Rifa® 300 sugar coated tablets (●). Paddle apparatus, 75 rpm, medium: SIF_{sp} pH 6.8. Error bars not shown.

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 guidances, an API is *highly soluble* if D/S ratio is $\leq$250 mL over physiological pH range.[2,57,58] Figure 2 indicates that that criterion is not met for either strength in the range pH 3–7. Therefore, rifampicin cannot be classified as *highly soluble* according to the current criteria.[2,57,58]

The recently published WHO Guidance also 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.[2] 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%[2] or 90%[57] for *highly permeable* indicated by the current BCS guidances.[2,57,58] Plasma profiles after intravenous and oral application were shown to be similar, indicating nearly complete absorption.[76,78,79,99]

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 $\geq$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 Benet[128] 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.[82,109,130,132] 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 discriminating, since rifampicin is highly soluble in very acidic solution. Dissolution testing at a pH closer to Rifampicin's iso-electric point, pH 4.8, where the solubility is lower, may provide a higher discriminatory power, but this has yet not been explored in terms of *in vitro–in vivo* relationships. At pH 6.8, dissolution is slow and incomplete. Our experiments indicated that the poor wettability of rifampicin is at least partially causing the erratic *in vitro* dissolution. In summary, on the basis of current evidence, comparative *in vitro* dissolution testing in three media at pH 1.2, 4.5, and 6.8, as recommended by the Guidances[2,57,58] cannot be regarded as a sufficiently reliable surrogate test for an *in vivo* BE study.

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 sub-therapeutic 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_{max} values.[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.[138]

CONCLUSIONS

The FDA[57] and EMEA[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.[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.[58,139,140] Here, too, a waiver of *in vivo* BE studies is not recommended for rifampicin containing drug products.[d] 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.[9] For these small changes, Table 3 may be helpful.

[d]Previous monographs on APIs of BCS Class II, fullfilling the criterion of *rapidly dissolving* at pH 6.8, arrived at a "positive" biowaiver recommendation, but for rifampicin, which only narrowly misses meeting these solubility requirements, we arrived at a "negative" recommendation. This sheds light on the limitations of the BCS concept. For ibuprofen, we reached a "positive" recommendation, despite reports of nonequivalence of ibuprofen containing drug products, because evidence led us to assume that *in vitro* dissolution would be able to detect such non-equivalence.[11] For diclofenac, not one single report of nonequivalence was identified. In addition, for ibuprofen and diclofenac, the patient risks associated with an inadvertently accepted nonequivalent drug product were considered acceptable. The different outcomes for these three BCS Class II APIs show that the BCS classification of an API is only one aspect to be taken into account in a biowaiver decision. The BCS solely considers solubility and permeability, whereas rifampicin case shows that further factors can be assumed as critical in the absorption process, most probably wettability. In particular when a biowaiver outside BCS Class I is considered, a positive biowaiver decision needs evidence of a low risk for non-equivalence of drug products. Also, positive evidence is needed for predictive power of surrogate BE techniques for that particular API. In all biowaiver decisions the patient risks associated with an inadvertently accepted non-equivalent drug product need to be considered. This biowaiver monograph series follows that line of reasoning.

ACKNOWLEDGMENTS

Dr. M. Flegel, Riemser Arzneimittel AG, Schiffweiler, 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

1. 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 93:1945-L 1956.
2. WHO. 2006. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. Technical Report Series, No 937, 40th Report, Annex 8 of WHO Expert committee on specifications for pharmaceutical preparations. http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf.
3. Kalantzi L, Reppas C, Dressman JB, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky SA, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Acetaminophen (paracetamol). J Pharm Sci 95:4–14.
4. Granero GE, Longhi MR, Becker C, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Acetazolamide. J Pharm Sci 97: 3691–3699.
5. Arnal J, Gonzalez-Alvarez I, Bermejo M, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid

oral dosage forms: Aciclovir. J Pharm Sci 97:5061–5073.
6. Manzo RH, Olivera ME, Amidon GL, Shah VP, Dressman JB, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Amitriptyline hydrochloride. J Pharm Sci 95:966–973.
7. Verbeeck RK, Junginger HE, Midha KK, Shah VP, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms based on biopharmaceutics classification system (BCS) literature data: Chloroquine phosphate, chloroquine sulfate, and chloroquine hydrochloride. J Pharm Sci 94:1389–1395.
8. Jantratid E, Prakongpan S, Dressman JB, Amidon GL, Junginger HE, Midha KK, Barends DM. 2006. Biowaiver monographs for immediate release solid oral dosage forms: Cimetidine. J Pharm Sci 95:974–984.
9. Chuasuwan B, Binjesoh V, Polli JE, Zhang H, Amidon GL, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Diclofenac sodium and diclofenac potassium. J Pharm Sci, published online: August, 27, 2008.
10. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Ethambutol dihydrochloride. J Pharm Sci 97:1350–1360.
11. Potthast H, Dressman JB, Junginger HE, Midha KK, Oeser H, Shah VP, Vogelpoel H, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms: Ibuprofen. J Pharm Sci 94:2121–2131.
12. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Isoniazid. J Pharm Sci 96:522–531.
13. Stosik AG, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Metoclopramide hydrochloride. J Pharm Sci 97:3700–3708.
14. Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Prednisolone. J Pharm Sci 96:27–37.
15. Vogt M, Derendorf H, Kramer J, Junginger HE, Midha KK, Shah VP, Stavchansky S, Dressman JB, Barends DM. 2007. Biowaiver monographs for immediate release solid oral dosage forms: Prednisone. J Pharm Sci 96:1480–1489.
16. Becker C, Dressman JB, Amidon GL, Junginger HE, Kopp S, Midha KK, Shah VP, Stavchansky S, Barends DM. 2008. Biowaiver monographs for immediate release solid oral dosage forms: Pyrazinamide. J Pharm Sci 97:3709–3720.
17. Kortejarvi H, Yliperttula M, Dressman JB, Junginger HE, Midha KK, Shah VP, Barends DM. 2005. Biowaiver monographs for immediate release solid oral dosage forms: Ranitidine hydrochloride. J Pharm Sci 94:1617–1625.
18. http://www.fip.org/www/index.php?page=ps_sig_bcs.
19. National Libary of Medicine (NLM) and the National Institutes of Health, NCBI, PubMed http://www.pubmed.gov. 2007.
20. National Libary of Medicine (NLM). NCBI PubChem Compound http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pccompound.
21. Medicines Complete. 2007. Pharmaceutical Press, London. http://www.medicinescomplete.com/mc/.
22. World Health Organization (WHO). Library & Information Networks for Knowledge Database (WHOLIS). http://dosei.who.int/uhtbin/cgisirsi/Mon+Jan+10+13:45:18+MET+2005/0/49.
23. VIDAL BIAM database: Rifampicine (French). http://www.biam2.org.
24. Rote Liste® Service GmbH Frankfurt/Main:ROTE LISTE® Arzneimittelsverzeichnis für Deutschland (einschließlich EU-Zulassungen und bestimmter Medizinprodukte) (German) (accessed 03-03-2008). http://www.rote-liste.de/Online.
25. VIDAL L'information de référence sur les produits de santé (French). http://www.vidal.fr.
26. World Health Organization (WHO). 1997. Guidance on INN. http://www.who.int/medicines/services/inn/innquidance/en/.
27. 2008. U.S., Pharmacopeia (USP31-NF26).
28. The Merck Index, 2005. 13th edition.
29. World Health Organization (WHO). 2003. Revision approved June 2004. Treatment of Tuberculosis: Guidelines for national programmes. http://www.emro.who.int/stb/media/pdf/Guidelines2003. pdf.
30. Treatment of Tuberculosis, American Thoracic Society, CDC, and Infectious Diseases Society of America—United States, 2003. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.
31. World Health Organization (WHO). 2004. Toman's Tuberculosis. Case Detection, Treatment and Monitoring. Second Edition. http://whqlibdoc.who.int/publications/2004/9241546034.pdf, http://whqlibdoc.who.int/publications/2004/9241546034_1.pdf, http://whqlibdoc.who.int/publications/ 2004/9241546034_2.pdf, http://whqlibdoc.who.int/publications/2004/9241546034_3.pdf, http://whqlibdoc.who.int/publications/2004/9241546034_4.pdf.
32. WHO Pharmaceuticals Newsletter No.1. 2002. Excerpts from the report of the 24th Annual Meeting of the National Centres participating in the

WHO Programme for International Drug Monitoring. World Health Organization (WHO). http://www.who.int/medicines/publications/newsletter/en/news2002_1.pdf.
33. Martindale. 2007. The complete drug reference, electronic version. London: Pharmaceutical Press. http://www.medicinescomplete.com/mc/martindale/2006/.
34. AHFS Drug Information. 2007. Electronic version. London: Pharmaceutical Press. http://www.medicinescomplete.com/mc/ahfs/current/.
35. Venkatesan K. 1989. Clinical pharmacokinetic considerations in the treatment of patients with leprosy. Clin Pharmacokinet 16:365–386.
36. Saerens EJ. 1975. The use of rifampicin in the treatment of leprosy. Lepr Rev 46:125–128.
37. Pharm. Eur. Kommentar (German), 20. Lieferung, Vol. 6 2005.
38. Update: Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection—United States, 2003. &&&http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed &dopt=Citation&list_uids=12904741.
39. Flageul B, Wagner L, Cottenot F. 2001. Immunoallergic accidents with rifamipcin. Acta Leprol 12:71–78.
40. Namisato M, Ogawa H. 2000. Serious side effects of rifampin on the course of WHO/MDT: A case report. Int J Lepr Other Mycobact Dis 68:277–282.
41. Cavenaghi R. 1989. Rifampicin raw material characteristics and their effect on bioavailability. Bull Int Union Tuberc Lung Dis 64:36–37, 40–32 discussion.
42. Henwood SQ, Liebenberg W, Tiedt LR, Lotter AP, de Villiers MM. 2001. Characterization of the solubility and dissolution properties of several new rifampicin polymorphs, solvates, and hydrates. Drug Dev Ind Pharm 27:1017–1030.
43. Pelizza G, Nebuloni M, Ferrari P, Gallo GG. 1977. Polymorphism of rifampicin. Farmaco [Sci] 32:471–481.
44. Agrawal S, Ashokraj Y, Bharatam PV, Pillai O, Panchagnula R. 2004. Solid-state characterization of rifampicin samples and its biopharmaceutic relevance. Eur J Pharm Sci 22:127–144.
45. Henwood SQ, de Villiers MM, Liebenberg W, Lotter AP. 2000. Solubility and dissolution properties of generic rifampicin raw materials. Drug Dev Ind Pharm 26:403–408.
46. World Health Organization (WHO). 2007. The International Pharmacopoeia. General Methods of Analysis, Quality specifications for Pharmaceutical Substances, Excipients and Dosage Forms. 4th Edition 1. Suppl. &&&http://www.who.int/bookorders/anglais/detart1.jsp?sesslan=1&codlan=1&codcol=15&codcch=4091.
47. European Pharmacopoeia 2008. (6th Edition 2008).
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 EREMFAT® Fatol (German).
54. Singh S, Bhutani H, Mariappan TT, Kaur H, Bajaj M, Pakhale S. 2002. Behavior of uptake of moisture by drugs and excipients under accelerated conditions of temperature and humidity in the absence and the presence of light. 1. Pure antituberculosis drugs and their combinations. Int J Pharm 245:37–44.
55. Prankerd RJ. 2000. Stability of rifampicin in dissolution medium. Int J Pharm 199:111–112.
56. Gallo GG. 1977. Analytical profiles of drug substances and excipients, K. Florey's/H.G. Brittain: Oxford University Press, 5: 467–513.
57. 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 a Biopharmaceutics Classification System. http://www.fda.gov/CDER/GUIDANCE/3618fnl.pdf.
58. European Medicines Evaluation Agency (EMEA). Committee for Proprietary Medicinal Products (CPMP). 2001. Note for Guidance on the Investigation of Bioavailability and Bioequivalence. http://www.emea.eu.int/pdfs/human/ewp/140 198en. pdf.
59. World Health Organization (WHO). 2007. Essential Medicines WHO Model List (EML). 15th edition, (revised version March 2007). http://www.who.int/medicines/publications/08_ENGLISH_indexFINAL_EML15.pdf.
60. Glomme A, Marz J, Dressman JB. 2005. Comparison of a miniaturized shake-flask solubility method with automated potentiometric acid/base

titrations and calculated solubilities. J Pharm Sci 94:1–16.
61. Shishoo CJ, Shah SA, Rathod IS, Savale SS, Kotecha JS, Shah PB. 1999. Stability of rifampicin in dissolution medium in presence of isoniazid. Int J Pharm 190:109–123.
62. Becker CDJB. 2006. Biopharmaceutical Characterisation of Rifampicin (Poster). World Meeting on Pharmaceutics Biopharmaceutics and Pharmaceutical Technology, Geneva, March 2006.
63. Clarke's Analysis of Drugs and Poisons, Pharmaceutical Press, London: Electronic version. 2007. Pharmaceutical Press, London, http://www.medicinescomplete.com/mc/clarke/2006/.
64. Seydel JK. 1970. Physico-chemical studies on rifampicin. Antibiot Chemother 16:380–391.
65. Agrawal S, Panchagnula R. 2005. Implication of biopharmaceutics and pharmacokinetics of rifampicin in variable bioavailability from solid oral dosage forms. Biopharm Drug Dispos 26:321–334.
66. Oppolzer W, Prelog V. 1973. The constitution and configuration of rifamycins B, O, S. and SV. Helv Chim Acta 56:2287–2314.
67. Maggi N, Pasqualucci CR, Ballotta R, Sensi P. 1966. Rifampicin: A new orally active rifamycin. Chemotherapy 11:285–292.
68. Maggi N, Pallanza R, Sensi P. 1965. New derivatives of rifamycin SV. Antimicrobial Agents Chemother 5:765–769.
69. Biganzoli E, Cavenaghi LA, Rossi R, Brunati MC, Nolli ML. 1999. Use of a Caco-2 cell culture model for the characterization of intestinal absorption of antibiotics. Farmaco 54:594–599.
70. Artursson P, Borchardt RT. 1997. Intestinal drug absorption and metabolism in cell cultures: Caco-2 and beyond. Pharm Res 14:1655–1658.
71. Artursson P, Karlsson J. 1991. Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells. Biochem Biophys Res Commun 175:880–885.
72. Artursson P, Magnusson C. 1990. Epithelial transport of drugs in cell culture. II: Effect of extracellular calcium concentration on the paracellular transport of drugs of different lipophilicities across monolayers of intestinal epithelial (Caco-2) cells. J Pharm Sci 79:595–600.
73. Artursson P. 1990. Epithelial transport of drugs in cell culture. I: A model for studying the passive diffusion of drugs over intestinal absorptive (Caco-2) cells. J Pharm Sci 79:476–482.
74. Mariappan TT, Singh S. 2003. Regional gastrointestinal permeability of rifampicin and isoniazid (alone and their combination) in the rat. Int J Tuberc Lung Dis 7:797–803.
75. Mariappan TT, Singh S. 2004. Evidence of efflux-mediated and saturable absorption of rifampicin in rat intestine using the ligated loop and everted gut sac techniques. Mol Pharm 1:363–367.
76. Acocella G. 1978. Clinical pharmacokinetics of rifampicin. Clin Pharmacokinet 3:108–127.
77. Holdiness MR. 1984. Clinical pharmacokinetics of the antituberculosis drugs. Clin Pharmacokinet 9:511–544.
78. Nitti V, Virgilio R, Patricolo MR, Iuliano A. 1977. Pharmacokinetic study of intravenous rifampicin. Chemotherapy 23:1–6.
79. Loos U, Musch E, Jensen JC, Mikus G, Schwabe HK, Eichelbaum M. 1985. Pharmacokinetics of oral and intravenous rifampicin during chronic administration. Klin Wochenschr 63:1205–1211.
80. Loos U, Musch E, Jensen JC, Schwabe HK, Eichelbaum M. 1987. Influence of the enzyme induction by rifampicin on its presystemic metabolism. Pharmacol Ther 33:201–204.
81. Zhang JN, Liu XG, Zhu M, Chiu FC, Li RC. 1998. Assessment of presystemic factors on the oral bioavailability of rifampicin following multiple dosing. J Chemother 10:354–359.
82. Agrawal S, Singh I, Kaur KJ, Bhade S, Kaul CL, Panchagnula R. 2004. Bioequivalence trials of rifampicin containing formulations: Extrinsic and intrinsic factors in the absorption of rifampicin. Pharmacol Res 50:317–327.
83. Koup JR, Williams-Warren J, Viswanathan CT, Weber A, Smith AL. 1986. Pharmacokinetics of rifampin in children. II. Oral bioavailability. Ther Drug Monit 8:17–22.
84. Koup JR, Williams-Warren J, Weber A, Smith AL. 1986. Pharmacokinetics of rifampin in children. I. Multiple dose intravenous infusion. Ther Drug Monit 8:11–16.
85. Berning SE, Huitt GA, Iseman MD, Peloquin CA. 1992. Malabsorption of antituberculosis medications by a patient with AIDS. N Engl J Med 327:1817–1818.
86. Peloquin CA, Nitta AT, Burman WJ, Brudney KF, Miranda-Massari JR, McGuinness ME, Berning SE, Gerena GT. 1996. Low antituberculosis drug concentrations in patients with AIDS. Ann Pharmacother 30:919–925.
87. Choudhri SH, Hawken M, Gathua S, Minyiri GO, Watkins W, Sahai J, Sitar DS, Aoki FY, Long R. 1997. Pharmacokinetics of antimycobacterial drugs in patients with tuberculosis, AIDS, and diarrhea. Clin Infect Dis 25:104–111.
88. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, Rajasekaran S, Padmapriyadarsini C, Swaminathan S, Bhagavathy S, Venkatesan P, Sekar L, Mahilmaran A, Ravichandran N, Paramesh P. 2004. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. Antimicrob Agents Chemother 48:4473–4475.

89. Douglas JG, McLeod MJ. 1999. Pharmacokinetic factors in the modern drug treatment of tuberculosis. Clin Pharmacokinet 37:127–146.
90. Advenier C, Gobert C, Houin G, Bidet D, Richelet S, Tillement JP. 1983. Pharmacokinetic studies of rifampicin in the elderly. Ther Drug Monit 5:61–65.
91. Panchagnula R, Rungta S, Sancheti P, Agrawal S, Kaul CL. 2003. In vitro evaluation of food effect on the bioavailability of rifampicin from antituberculosis fixed dose combination formulations. Farmaco 58:1099–1103.
92. Zent C, Smith P. 1995. Study of the effect of concomitant food on the bioavailability of rifampicin, isoniazid and pyrazinamide. Tuber Lung Dis 76:109–113.
93. Peloquin CA, Namdar R, Singleton MD, Nix DE. 1999. Pharmacokinetics of rifampin under fasting conditions, with food, and with antacids. Chest 115:12–18.
94. Buniva G, Pagani V, Carozzi A. 1983. Bioavailability of rifampicin capsules. Int J Clin Pharmacol Ther Toxicol 21:404–409.
95. Polasa K, Krishnaswamy K. 1983. Effect of food on bioavailability of rifampicin. J Clin Pharmacol 23:433–437.
96. Reid J, Marciniuk D, Peloquin CA, Hoeppner V. 2002. Pharmacokinetics of antituberculosis medications delivered via percutaneous gastrojejunostomy tube. Chest 121:281–284.
97. Forgan-Smith R, Ellard GA, Newton D, Mitchison DA. 1973. Pyrazinamide and other drugs in tuberculous meningitis. Lancet 2:374.
98. Brechbuhler S, Fluehler H, Riess W, Theobald W. 1978. The renal elimination of rifampicin as a function of the oral dose. A convenient way to assess relative bioavailability. Arzneimittelforschung 28:480–483.
99. Acocella G, Bonollo L, Mainardi M, Margaroli P, Tenconi LT. 1977. Serum and urine concentrations of rifampicin administered by intravenous infusion in man. Arzneimittelforschung 27:1221–1226.
100. Ellard GA, Fourie PB. 1999. Rifampicin bioavailability: A review of its pharmacology and the chemotherapeutic necessity for ensuring optimal absorption. Int J Tuberc Lung Dis 3:S301–S308, discussion S317–S321.
101. Schuetz EG, Schinkel AH, Relling MV, Schuetz JD. 1996. P-glycoprotein: A major determinant of rifampicin-inducible expression of cytochrome P4503A in mice and humans. Proc Natl Acad Sci USA 93:4001–4005.
102. Schuetz EG, Beck WT, Schuetz JD. 1996. Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells. Mol Pharmacol 49:311–318.
103. Khalil SAH, Elkhordagui LK, Elgholmy ZA. 1984. Effect of antacids on oral absorption of rifampicin. Int J Pharm 20:99–106.
104. Sadeghi S, Karimi E. 2006. Spectrophotometric determination of rifampicin through chelate formation and charge transfer complexation in pharmaceutical preparation and biological fluids. Chem Pharm Bull (Tokyo) 54:1107–1112.
105. Ganescu I, Bratulescu G, Lilea B, Ganescu A, Barbu A. 2002. Chromium anion complexes and drug analysis—Quantitative determination of rifampicin. Acta Chim Slov 49:339–345.
106. Boman G, Lundgren P, Stjernstrom G. 1975. Mechanism of the inhibitory effect of PAS granules on the absorption of rifampicin: Adsorption of rifampicin by an excipient, bentonite. Eur J Clin Pharmacol 8:293–299.
107. Mannisto P. 1977. Absorption of rifampin from various preparations and pharmaceutic forms. Clin Pharmacol Ther 21:370–374.
108. Chouchane N, Barre J, Toumi A, Tillement JP, Benakis A. 1995. Bioequivalence study of two pharmaceutical forms of rifampicin capsules in man. Eur J Drug Metab Pharmacokinet 20:315–320.
109. Pahkla R, Lambert J, Ansko P, Winstanley P, Davies PD, Kiivet RA. 1999. Comparative bioavailability of three different preparations of rifampicin. J Clin Pharm Ther 24:219–225.
110. Panchagnula R, Agrawal S. 2004. Biopharmaceutic and pharmacokinetic aspects of variable bioavailability of rifampicin. Int J Pharm 271:1–4.
111. Laegemiddel Styrelson Danish Medicines Agency (accessed 03-03-2008). http://www.dkma.dk.
112. National Agency for Medicines, Helsinki, Finland: The National Agency for Medicines responsibilities are to maintain and promote the safety and safe use of medicinal products, medical devices and blood products. (accessed 03-03-2008). www.nam.fi.
113. Thériaque (Centre National Hospitalier d'Information sur le Médicament) (accessed 04-03-2008). http://www.theriaque.org.
114. College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board of The Netherlands (accessed 04-03-2008). www.cbg-meb.nl.
115. Statens legemiddelverk, Norvegian Medicines Agency (accessed 04-03-2008). www.legemiddelverket.no.
116. Agencia Española de Medicamentos y Productos Sanitarios (accessed 03-03-2008). http://www.agemed.es.
117. Läkemedelsverket. Medical Product Agency Sweden (accessed 04-03-2008). http://www.lakemedelsverket.se.
118. The medicines information web site provided by Datapharm Communications Ltd. (accessed 04-03-2008). www.medicines.org.uk.

119. DailyMed Current Medication Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894. National Institutes of Health, Health & Human Services (accessed 04-03-2008). www.dailymed.nlm.nih.gov.
120. Gleiter CH, Gundert-Remy U. 1994. Bioinequivalence and drug toxicity. How great is the problem and what can be done? Drug Saf 11:1–6.
121. Gleiter CH, Klotz U, Kuhlmann J, Blume H, Stanislaus F, Harder S, Paulus H, Poethko-Muller C, Holz-Slomczyk M. 1998. When are bioavailability studies required? A German proposal. J Clin Pharmacol 38:904–911.
122. The Inactive Ingredients Database, U.S. Food and Drug Administration Center for Drug Evaluation and Research (accessed 04-03-2008). http://www.fda.gov/cder/iig/iigfaqWEB.htm#purpose.
123. Agrawal S, Panchagnula R. 2004. Dissolution test as a surrogate for quality evaluation of rifampicin containing fixed dose combination formulations. Int J Pharm 287:97–112.
124. Rao BS, Murthy KV. 2002. Studies on rifampicin release from ethylcellulose coated nonpareil beads. Int J Pharm 231:97–106.
125. McColl KE. 1996. Helicobacter pylori, gastric acid, and duodenal gastric metaplasia. Gut 39:615–616.
126. 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 14:763–766.
127. Lindenberg 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 58:265–278.
128. Wu CY, Benet LZ. 2005. Predicting drug disposition via application of BCS: Transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res 22:11–23.
129. Agrawal S, Panchagnula R. 2004. In vitro evaluation of fixed dose combination tablets of antituberculosis drugs after real time storage at ambient conditions. Pharmazie 59:782–785.
130. Agrawal S, Singh I, Kaur KJ, Bhade SR, Kaul CL, Panchagnula R. 2004. Comparative bioavailability of rifampicin, isoniazid and pyrazinamide from a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm 276:41–49.
131. Agrawal S, Singh I, Kaur KJ, Bhade SR, Kaul CL, Panchagnula R. 2002. Bioequivalence assessment of rifampicin, isoniazid and pyrazinamide in a fixed dose combination of rifampicin, isoniazid, pyrazinamide and ethambutol vs. separate formulations. Int J Clin Pharmacol Ther 40:474–481.
132. Agrawal S, Kaur KJ, Singh I, Bhade SR, Kaul CL, Panchagnula R. 2002. Assessment of bioequivalence of rifampicin, isoniazid and pyrazinamide in a four drug fixed dose combination with separate formulations at the same dose levels. Int J Pharm 233:169–177.
133. Panchagnula R, Sancheti P, Rungta S, Agrawal S, Kaul CL. 2003. Evaluation of bioequivalence of isoniazid and pyrazinamide in three and four drugs fixed dose combinations using WHO simplified protocol. Pharmacol Res 48:383–387.
134. Gurumurthy P, Ramachandran G, Vijayalakshmi S, Kumar AK, Venkatesan P, Chandrasekaran V, Vjayasekaran V, Kumaraswami V, Prabhakar R. 1999. Bioavailability of rifampicin, isoniazid and pyrazinamide in a triple drug formulation: Comparison of plasma and urine kinetics. Int J Tuberc Lung Dis 3:119–125.
135. Jindani A, Aber VR, Edwards EA, Mitchison DA. 1980. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 121:939–949.
136. Telenti A, Imboden P, Marchesi F, Lowrie D, Cole S, Colston MJ, Matter L, Schopfer K, Bodmer T. 1993. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. Lancet 341:647–650.
137. Agal S, Baijal R, Pramanik S, Patel N, Gupte P, Kamani P, Amarapurkar D. 2005. Monitoring and management of antituberculosis drug induced hepatotoxicity. J Gastroenterol Hepatol 20: 1745–1752.
138. Holdiness MR. 1989. A review of the Redman syndrome and rifampicin overdosage. Med Toxicol Adverse Drug Exp 4:444–451.
139. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), September 1997, CMC 8; Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation. ed. http://www.fda.gov/CDER/GUIDANCE/1214fnl.pdf.
140. U.S. Department of Health and Human Services Food and Drug Administration Center for Evaluation and Research (CDER).1995. Guidances for industry: Immediate Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation. http://www.fda.gov/CDER/GUIDANCE/cmc5.pdf.