

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Pyrazinamide

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ABSTRACT: Literature data relevant to the decision to allow a waiver of *in vivo* bioequivalence (BE) testing for the approval of immediate release (IR) solid oral dosage forms containing pyrazinamide as the only active pharmaceutical ingredient (API) are reviewed. Pyrazinamide is BCS Class III, with linear absorption over a wide dosing range. The risk of bioequivalence is estimated to be low. Depending on the definition used, pyrazinamide can be classified as a narrow therapeutic index (NTI) drug, which is usually a caveat to biowaiving but may be deemed acceptable if the Summary of Product Characteristics (SmPCs) of the test product stipulates the need for regular monitoring of liver function. It is concluded that a biowaiver can be recommended for IR solid oral dosage only when the test product (a) contains only excipients present in pyrazinamide IR solid oral drug products approved in ICH or associated countries, (b) these excipients are present in amounts normally used in IR solid oral dosage forms, (c) the test product is *very rapidly dissolving*, (d) the SmPC of the test product indicates the need for monitoring of the patient's liver function. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3709–3720, 2008

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

INTRODUCTION

A biowaiver monograph of pyrazinamide based on literature data together with some additional experimental data is presented. The risks of basing a bioequivalence (BE) assessment on *in vitro* rather than *in vivo* study results for the approval of new immediate release (IR) solid oral

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This article reflects the scientific opinion of the authors and not the policies of regulating agencies.

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dosage forms containing pyrazinamide (“biowaivering”), including both reformulated products and new multisource drug products, are evaluated under consideration of its biopharmaceutical and clinical properties. This evaluation refers to drug products containing pyrazinamide as the only active pharmaceutical ingredient (API) and not to combination products.

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 as the probability of an incorrect biowaiver decision as well as the consequences of the decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation can be made as to whether a biowaiver approval is advisable or not. This systematic approach to recommend or advise against a biowaiver decisions is referred to in the recently published World Health Organization (WHO) Guideline.² It is pointed out that these monographs do not simply apply this WHO Guideline, nor the FDA and/or EMEA Guidance, but also want to serve as a critical validation of these regulatory documents. Biowaiver monographs have already been published for acetaminophen (INN: paracetamol),³ amitriptyline,⁴ atenolol,¹ chloroquine,⁵ cimetidine,⁶ ethambutol,⁷ ibuprofen,⁸ isoniazid,⁹ prednisolone,¹⁰ prednisone,¹¹ propranolol,¹ ranitidine,¹² and verapamil.¹ They are also available online at the website of the International Pharmaceutical Federation FIP.¹³

EXPERIMENTAL

Literature data from PubMed,¹⁴ PubChem,¹⁵ Medicines Complete,¹⁶ WHO search engine WHOLIS,¹⁷ the BIAM,¹⁸ ROTE LISTE,¹⁹ and VIDAL²⁰ databases was assessed. Key words used were: pyrazinamide, BE, bioavailability, biowaiver, solubility, permeability, dissolution, tuberculosis, excipient, toxicity, polymorphism, and pharmacokinetics.

GENERAL CHARACTERISTICS

Name

Pyrazinamide (INN), pyrazinecarboxamide.^{21,22} The structure is shown in Figure 1.

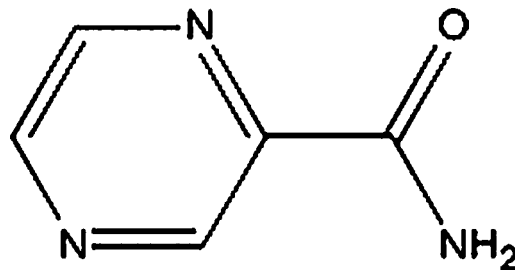


Figure 1. Structure of pyrazinamide, Mw 123.113.

Therapeutic Indications

Pyrazinamide is one of the key APIs used in the combination treatment of tuberculosis recommended by the WHO.²³ The standard regime currently calls for initial therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months, followed by a continuation phase comprising isoniazid and rifampicin which lasts 4 months. Pyrazinamide is used in the initial phase of the treatment for its bactericidal activity against slowly metabolizing bacilli, which results in a low incidence of bacteriological relapse after completion of the chemotherapy regimen.^{23–25}

The mechanism of action of pyrazinamide is not fully elucidated.^{25,26} The antimicrobial activity of this synthetic analogue of nicotinamide appears to depend partly on a conversion to its primary metabolite, pyrazinoic acid, in an acidic environment. The metabolite interacts with mycobacterial pyrazinamidase present in *in vitro* susceptible strains of *Mycobacterium tuberculosis*.²⁷

Therapeutic Index and Toxicity

The WHO,²³ the Martindale,²⁸ and the British and American Thoracic Society^{24,29} recommend standard daily doses of 25 (20–30), 20–35 (maximum 3 g), and 18.2–26.3 mg/kg (maximum 2 g) of pyrazinamide, respectively. Generally, pyrazinamide has been used in doses ranging from 15 to 40 mg/kg/day.^{30–32} After an oral dose of 1.5 g, peak serum concentrations of 33 μg/mL were reported,²⁸ after an oral dose of 27 mg/kg to healthy volunteers a peak serum concentration of 39 μg/mL was reported.³³ Different dosing schemes are recommended for children and HIV positive patients.^{23,24,29,34,35}

The most common serious adverse drug reaction (ADR) is drug-induced hepatitis.³⁶ Toxic effects of pyrazinamide are related to dose and duration of treatment but may occur at any time during

therapy.³⁷ At doses higher than 3 g/day the incidence of hepatitis increases to 15%;^{24,38,39} a dose of 3 g was reported to give a peak serum concentration of 59 $\mu\text{g/mL}$.²⁸ The incidence of side effects seems to be increased in subpopulations like females, the elderly, those of Asian heritage, patients with renal impairment and HIV patients.⁴⁰ Toman's Tuberculosis recommends that a basic examination of liver function should be conducted before starting treatment with pyrazinamide.³⁴ According to the current WHO guideline, the onset of acute liver failure should be managed by immediate interruption of pyrazinamide treatment.²³ Therefore, patients should be educated to detect the clinical signs of impending acute liver failure.^{41,42} Because of its liver toxicity, pyrazinamide is also contraindicated in patients with latent tuberculosis who are concomitantly taking other potentially liver-toxic drugs, who drink excessive amounts of alcohol, or who have underlying liver disease or a history of isoniazid-associated liver injury.^{23,28,43–45} In these cases the benefits of pyrazinamide therapy should be weighed against possible hepatic ADRs.²⁴

Pyrazinamide inhibits the renal excretion of urates, resulting in gout in predisposed patients.²⁷ If hyperuricemia is severe or is accompanied by acute gouty arthritis, pyrazinamide should be discontinued.^{23,24,29} The Prescribers' Information, also known as the Summary of Product Characteristics (SmPCs), for most drug products having a marketing authorization (MA)

contains appropriate cautionary statements as well as instructions for monitoring of hepatic function.^{37,43,46}

CHEMICAL PROPERTIES

Polymorphs

Pyrazinamide occurs in four polymorphic forms with different crystal structures: α -, β -, γ -, and δ -pyrazinamide, depending on the solvent and the temperature used in the manufacturing process.^{47–50} Differences in solubility of the four polymorphic forms have not been reported. The pharmacopoeias do not stipulate any specific polymorph.

Solubility

A summary of the literature solubility data, as well as additional experimental solubility data under physiological conditions and corresponding dose/solubility (D/S) ratios are presented in Table 1.

Partition Coefficient (log *P*)

log *P* values of 0.2⁵¹ at 30°C and 0.6⁵² have been reported for the system octanol/water. However, no detailed information was provided about the

Table 1. Literature Data and New Experimental Solubility Data (mg/mL) for Pyrazinamide and the Corresponding Dose/Solubility Ratios (D/S) for Two Tablet Strengths

Medium, pH	USP	Merck Index	New Experimental Data (37°C)	Florey's (38°C)	D/S Ratio ^a (mL)	
					500 mg Tablet ^b	400 mg Tablet ^c
Water	14.9				33.6	26.8
Water		15			33.3	26.7
Water				26.5	18.9	15.1
Water					78.1	62.5
Water ^d			20.3		24.7	19.7
SGF _{sp} , pH 1.2 ^d			22.7		22.0	17.6
Phosphate buffer, pH 4.5 ^d			21.6		23.2	18.6
SIF _{sp} , pH 6.8 ^d			22.3		22.5	18.0

^aCriterion is ≤ 250 mL.

^bHighest strength on the DE, DK, FI, FR, NL, and USA market.

^cHighest strength on the WHO Essential Medicines List.

^dThe solubility of pyrazinamide (batch 062K1334 Sigma-Aldrich Chemie GmbH, obtained from Steinheim, DE) at 37°C was determined in buffers pH 1.2, pH 4.5, and pH 6.8, using the standard shake-flask method over 24 h. The pH of the buffers was monitored and readjusted to the initial pH values. Experiments performed at the Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main, DE.

test conditions such as the temperature and pH. A log *P* of 1 was observed for the system (butanol/water) at 30°C.⁵¹ A computed *X*log *P* of -1.884 is indicated in the PubChem database.¹⁵ Kasim et al.⁵³ obtained a log *P* of -0.68 and a ClogP[®] of -1.41 using fragmentation methods based on atomic contributions to lipophilicity and the ClogP[®] program (version 3.0, Biobyte Corp, Claremont, CA, <http://www.biobyte.com>).

p*K*_a

Pyrazinamide is an extremely weak base. A p*K*_a value of 0.5 (no temperature specified) has been reported in the literature.⁵⁴

Dosage Form Strengths

The WHO Essential Medicines List specifies a 400 mg tablet dosage form of pyrazinamide.⁵⁵ Single API dosage forms with an MA in Germany (DE),⁵⁶ Denmark (DK),⁵⁷ Finland (FI),⁵⁸ France (FR),⁵⁹ The Netherlands (NL),⁶⁰ and the USA (USA)⁶¹ contain 500 mg pyrazinamide.

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

No studies investigating the *in situ* or *ex vivo* intestinal permeability, absolute bioavailability (BA) or Caco-2 cell studies could be identified in the literature.

It is widely believed that pyrazinamide is nearly fully absorbed from the gut.^{18,28,62} In a study carried out by Ellard³² as early as 1969, a urinary recovery of about 40% after 48 h was measured after administration of an oral dose of 1500 and 3000 mg to healthy subjects. In another leg of this study, referred to as the Nairobi "crossover study," 34–35% of an oral dose of 500 mg administered three times a day, 1500 mg once a day or 3000 mg once a day were recovered in the urine of patients with tuberculosis after 24 h.³² In the same study, using extraction with subsequent coupling color reaction and measurement of the optical density as the analytical method, no API could be detected in the aqueous acetone extracts of feces. Lacroix et al.⁶³ found a cumulative urinary excretion of 73% of the ingested oral dose of pyrazinamide and its metabolites 72 h after administration of a single oral dose of 27 mg/kg to healthy subjects. On the basis of this information

the authors hypothesized that pyrazinamide possesses a high BA.^{27,63} In children, the absorption of pyrazinamide appears to be delayed and sometimes reduced.⁶⁴

*T*_{max} values of 1–2 h were reported after oral application, values consistent with a moderate to fast rate of absorption.^{65,66} However, rapid absorption does not necessarily indicate that absorption is complete.

Wilkins et al.⁶⁷ studied the population pharmacokinetics of three pooled studies encompassing 227 South African patients with tuberculosis. Using NONMEM[®] (version V), a one-compartment model with first-order absorption including a zero-order component describing the release from the formulation, the absorption of pyrazinamide was estimated to be bimodally distributed in approximately even portions between two distinct subgroups: those who absorb the compound quickly and those with slow absorption.

Zhu et al.⁶⁸ showed an increase of drug concentration in the blood proportional to administered dose in the range from 0.2 to 3.6 g/day suggesting that absorption in this dosing range is not dose-dependent. In the "Nairobi Cross-over" study, peak serum concentrations of pyrazinamide and urinary excretion of pyrazinamide and pyrazinoic acid were proportional to the given dose within the investigated range of 500–3000 mg. In the "Extended East African" study Ellard³² showed that serum pyrazinamide concentrations were inversely proportional to the body weights of 19 African patients receiving 1500 mg pyrazinamide daily or 3000 mg on alternate days.

Distribution, Metabolism and Excretion

Pyrazinamide is distributed to most body tissues including lung, kidney, liver, crosses the blood brain barrier^{18,46,69} and penetrates across the membrane of macrophages.⁷⁰

In early studies, pyrazinamide was found to be not bound to plasma proteins in humans, rabbits, and dogs⁵¹ whereas recent literature indicates a plasma protein binding of about 50% without specifying the assay conditions.³⁷ Woo et al.⁷¹ determined the plasma protein binding of the API to α-1-acid glycoprotein (15%), albumin and whole plasma (40%) *in vitro*. Pyrazinamide is metabolized to its active metabolite, pyrazine-2-carboxylic acid, and subsequently hydroxylated to 5-hydroxypyrazine-2-carboxylic acid.^{27,72} Pyrazinamide metabolism has a moderate interpatient

variability in adults but median clearance is higher in children and results in a 43% shorter half-life.⁷³ The parent drug, but not its metabolites, are filtered and afterwards actively reabsorbed by the kidneys.^{27,63} Within 24 h, the urinary recovery is about 30–40% of an oral dose.^{32,65,72,74} The API was not detected in the stools after oral administration.³²

Food and Other Gastrointestinal Interactions

Peloquin et al.⁷³ investigated the influence of food and antacids on the pharmacokinetics of oral pyrazinamide in healthy volunteers. The study design consisted of a randomized, four-period, crossover study. Single oral doses of 30 mg/kg of pyrazinamide were administered twice under fasting conditions, once with an aluminum–magnesium antacid and once with a high-fat meal and standard dosages of isoniazid, rifampicin, and ethambutol. In all four treatments, a single dose of 30 mg/kg was administered orally using 500 mg scored tablets (Wyeth-Lederle, Philadelphia, PA) and 240 mL of tap water. Serum was collected over 48 h and analyzed by gas chromatography with a mass selective detector. In the fasted state, the variability in AUC, C_{\max} and t_{\max} across the 14 subjects was low. Since the fasted treatment was repeated, intra-subject variability in the pharmacokinetic parameters could be assessed and was found to be low. In the fed versus fasted part of the study, significantly different values for C_{\max} (–12%) and delayed absorption (t_{\max} +80%) were measured after administration of a standard, high fat breakfast (792 kcal) compared to the fasted state. Zent et al. compared the BA of pyrazinamide in the fasted state to its BA after ingestion of a carbohydrate-rich or a high fat meal in 27 adult patients with tuberculosis.⁶⁸ In this study, neither C_{\max} , AUC nor t_{\max} were found to be altered by either diet.

Pyrazinamide was shown to be stable in different suspensions: a “simple syrup” mixture and methylcellulose “simple syrup” mixture, both containing a dose of 100 mg/mL and in a mixture of Pyrazinamide (10 mg/mL) with Ora-Sweet[®] or Ora-Plus[®] (1:1) with and without cherry syrup over 60 days at 25°C.^{75–77}

In the Peloquin study 30 mL of an aluminum–magnesium antacid (Mylanda[®]) was administered orally 9 h prior to, at the time of dosing, at bedtime and after meals.⁷³ The pharmacokinetics of pyrazinamide were not significantly influenced by the pre-, co-, or postdose administration of the

antacid. In an early study (1957) Caccia⁶⁵ showed that activated charcoal totally adsorbs pyrazinamide in diluted urine *in vitro*.

DOSAGE FORM PERFORMANCE

Bioavailability and Bioequivalence Studies

No absolute oral BA of pyrazinamide formulations could be identified in the literature. However, the generic product *Pyrazinamide “Lederle,”* marketed in DE, was approved on the basis of a BE study in 8 volunteers.³⁷ 500 mg Pyrazinamide “Lederle” and 500 mg of the reference product were administered in a crossover design. At a 0.05 significance level, AUC and C_{\max} of the tested pyrazinamide formulations were found not to be significantly different ($p > 0.05$).

Several *in vivo* and *in vitro* BE studies have compared pyrazinamide fixed dose combination formulations to formulations containing pyrazinamide as the only API at the same dose level. The BE of the product under investigation was confirmed in each case.^{37,76,78–80}

Excipients

Table 2 shows the excipients present in IR solid oral drug products containing pyrazinamide as sole API, with an MA in DE, DK, FI, FR, and NL. It can be inferred that the drug products having an MA in these countries successfully passed an *in vivo* BE study. In the third column of this table, the minimum and maximum amount of the listed excipients present per dosage unit in solid oral drug products with an MA in the USA is indicated.

Dissolution

The current USP specifies for pyrazinamide tablets not less than ($Q \geq$) 75% dissolved within 45 min in 900 mL of water at 37°C in the paddle apparatus at 50 rpm.⁸¹ Comparative *in vitro* dissolution studies of pyrazinamide drug products could not be identified in the literature.

The dissolution behavior of 400 mg pyrazinamide raw powder and two drug products having a MA in DE: Pyrafat[®] and Pyrazinamide “Lederle,” both containing 400 mg of pyrazinamide, were experimentally¹ assessed according to the WHO

¹Experiments performed at the Institute of Pharmaceutical Technology, J.W. Goethe University, Frankfurt am Main, Germany.

Table 2. Excipients* Present in Pyrazinamide IR Solid Oral Drug Products** with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), France (FR), The Netherlands (NL), and the Minimal and Maximal Amount of That Excipient Present Pro dosage Unit in Solid Oral Drug Products with an MA in the USA

Excipient	Drug Products Containing That Excipient with an MA Granted by the Named Country	Range Present in Solid Oral Dosage Forms with an MA in the USA (mg)
Basic butylated methacrylate copolymer	DE(1)	
Calcium stearate	DE(2)	0.7–43 ^a
Castor oil hydrogenated	FI(3)	0.93–37.6 ^a
Cellulose	DE(1,2,4)	4.6–1385 ^a
Copovidone	DE(4)	357–854
Croscarmellose sodium	DE(1,4)	2–180
Crospovidone	DE(1,4)	4.4–792 ^a
Ethanol	DK(5)	
Gelatin	DE(2) DK(6) FI(3)	1–756 ^a
Glycerol	DK(5) FI(3)	0.14–198 ^b
Hypromellose	DE(4)	0.8–86
Lactose	DE(2,4) FI(3)	23–1020 ^a
Macrogol	DE(1,4)	0.12–500 ^a
Magnesium stearate	DE(1,4,7) DK(5,6) FI(3) NL(8)	0.15–401 ^a
Povidone	DE(1) DK(5) FR (9) NL(8)	0.17–75
Silica	DE(4) DK(5) FI(3) NL(8)	0.65–99
Sodium starch glycolate	DE(2) FI(3) NL(8)	2–876 ^a
Starch	DE(2,7) DK(5,6) FI(3) FR (9) NL(8)	0.44–1135 ^a
Stearic acid	DE(1) FR (9)	0.9–72 ^a
Stearic palmitic acid	DE(7)	
Talc	DE(1,2) DK(5,6) FI(3) FR (9) NL(8)	0.26–220 ^a

1, PZAHefa Filmtabletten (Mono); 2, Pyrazinamid 500 mg JENAPHARM[®] Tabletten (Mono); 3, Tisamid 500 mg tabletti; 4, Pyrafat[®] 500 mg Filmtabletten (Mono); 5, Pyrazinamid SAD, tableter 500 mg; 6, Pyrazinamid “Medic”, tableter 500 mg; 7, “Pyrazinamid, Lederle” Tabletten (Mono); 8, Pyrazinamide CF 500 mg, tableten; 9, PIRILENE 500 mg cp séc.

*Colourants are not included.

**Drug products containing more than one API are excluded.

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

^bThe authors doubt the correctness of these data. Such amounts are normally present in a soft gelatin capsules, but not in capsules, as indicated by FDA Inactive Ingredients Database.

requirements for BE.^{2,82} Within 10 min, almost 95% of the powder and at least 88% of the labeled amount of API of the two tablet formulations were dissolved in USP SGF_{sp} pH 1.2, in USP SIF_{sp} pH 6.8 and in a phosphate buffer pH 4.5. These results were confirmed using a slightly modified methodology with commercially available raw materials from the South African market from three different sources. (Dekker T.G. 2006. personal communication).

DISCUSSION

Solubility

The solubility values found in the literature were not assessed under the conditions specified for the BCS classification of drugs.^{2,82–84} For example,

studies were done at room temperature instead of 37°C, water was used as the medium and/or the pH was not confirmed to remain constant during the solubility determination. To obtain more reliable data, new solubility determinations were carried out. The solubility of pyrazinamide at 37°C was virtually constant (at about 22 mg/mL) over the pH range studied, as illustrated in Table 1. All determinations, calculated for the highest available tablet strengths on the German market and on the WHO Essential Medicines List, resulted in D/S ratios of 20 mL or lower, far below the critical limit of 250 mL, see Table 1.

According to the current BCS guidelines, an API is *highly soluble* if the volume required to dissolve the highest dosage strength is less than or equal to 250 mL.^{2,82–84} Thus, pyrazinamide can be clearly classified as *highly soluble*. As differences in solubility of the polymorphic forms have not

been reported and pharmacopoeias do not stipulate any specific polymorph, it is not expected that for any specific polymorph that conclusion would be different.

Permeability

The only available information regarding pyrazinamide's permeability were taken from urinary recovery studies. Urinary recoveries of 40% of the oral dose after 48 h, using a questionable detection method based on extraction and subsequent color reactions,³² and of 73% after 72 h, using a HPLC analytical method with fluorimetric detection for quantification, were reported.⁶³ But, since pyrazinamide as parent drug is actively reabsorbed by the kidneys, it can be assumed that the parent molecule has a longer plasma half-life.^{65,70} Therefore the collection period of 72 h might be not sufficiently long enough to measure the complete urinary recovery. As a result, no firm conclusion can be drawn about the permeability classification of pyrazinamide.

BCS Classification

According to the present Guidances pyrazinamide meets the criteria for *highly soluble*.^{2,82-84} Data on its permeability are inconclusive but suggest this API to be BCS Class III with moderate permeability properties. Kasim et al.⁵³ and Lindenberg et al.⁸⁵ provisionally classified pyrazinamide as a BCS Class III drug, using log P/ClogP[®] and literature BA data, respectively. Because of the lack of definitive literature data for the fraction absorbed orally, the WHO Guideline classified the permeability of pyrazinamide as "borderline III/I."^{2,82}

Currently, the FDA and the EMEA do not accept biowaivers for BCS Class III APIs.^{83,84} The recent WHO guidance extended the possibility of a biowaiver approval to Class III APIs under certain conditions. As a Class III compound, pyrazinamide is therefore a potential candidate for biowaiving according to the WHO guidance.

Surrogate Techniques for *In Vivo* BE Testing

Pyrazinamide is *highly soluble*, with the pure powder as well as the pyrazinamide drug products with an MA in DE showing *very rapid dissolution*. Furthermore, *bioinequivalence* of pyrazinamide

formulations has not been reported either *in vivo* or *in vitro* in the literature and appears unlikely to occur for this very soluble API. Hence, the stricter dissolution methodology for biowaiving of BCS Class III drugs according the WHO guidance, that is, *very rapid dissolution* of the test and the comparator over the pH range of 1.2–6.8,^{2,82} should be capable of detecting a *bioinequivalent* test product. A caveat to these arguments is that *in vitro* dissolution tests are not able to detect excipient effects on permeability and/or GI transit time that may cause *bioinequivalence*.

Risks with Respect to Excipient and Manufacturing Variations

Studies describing BA problems, interactions of pyrazinamide with excipients or *bioinequivalence* of pyrazinamide products could not be found in the open literature. All *in vivo* BE studies of pyrazinamide in fixed dose combinations versus formulations containing pyrazinamide as the only API confirmed the BE of the products under investigation.^{76,78-80}

Since there are no reports of *bioinequivalent* drug products in the open literature, and BE of drug products differing in composition with respect to the excipients can be assumed by virtue of their MA in a number of countries, the risk of *bioinequivalence* of pyrazinamide IR dosage forms appears to be low. The risk of *bioinequivalence* caused by an excipient interaction can be further reduced by using in the test product only excipients present in drug products having a MA in an ICH or associated country, as listed as a guide in Table 2.²

Patient Risks Associated with *Bioinequivalence*

When an API has a narrow therapeutic index (NTI), this precludes the possibility of a biowaiver. The FDA guidance⁸⁴ excludes APIs having a NTI for biowaivers, defining NTI APIs as those subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. The EMEA guidance⁸³ provides a general statement indicating that when plasma concentrations are critical, this needs to be taken into consideration; the WHO guidance² states that pharmaceutical products containing an API with

²CFR name: narrow therapeutic ratio.

NTI always should be tested *in vivo*, because the risk to the patient resulting from a possible incorrect BE decision using the biowaiver procedure is considered too high with these kinds of APIs. According to the Code of Federal Regulations (CFR), an API has a NTI² when there is less than a twofold difference between the *minimum* toxic concentrations and *minimum* effective concentrations in the blood, and/or safe and effective use of the drug products requires careful dosage titration and patient monitoring.⁸⁶ With respect to the first criterion: the minimum toxic concentration of pyrazinamide can be taken as 59 $\mu\text{g/mL}$, see above. Assuming that the peak serum concentrations of 33 and 39 $\mu\text{g/mL}$ reported above, for doses of 1.5 g and 27 mg/kg, respectively, are well above the minimum effective concentrations, pyrazinamide is borderline or below the first CFR criterion for NTI. However, according to the CFR's second criterion it would be considered NTI.

Due to the borderline NTI characteristics of pyrazinamide, it is worth looking at the particular risks associated with pyrazinamide drug products more in detail. The first consideration is the consequence of an inadvertently low AUC and/or low C_{max} . The peak concentration is not important for the bactericidal effect. AUC is important, but the wide range of recommended doses and serum concentrations indicate that pyrazinamide's dose-response curve is not steep. So under-dosing poses comparatively little risk for the patient. The second consideration is the consequence of inadvertently high AUC and/or C_{max} . Patients under pyrazinamide treatment are monitored primarily because of the risk of hepatic toxicity. Serious, dose-dependent hepatic ADRs theoretically could occur as a consequence of a higher AUC and/or C_{max} . The therapeutic dose (20–30 mg/kg/day) and the dose at which the risk of hepatic ADR increases, ≥ 43 mg/kg/day, differ by a factor of around two. Based on the evidence presented, it is highly unlikely that a test product would show twice the AUC and/or C_{max} of a pharmaceutically equivalent comparator when both are *very rapidly dissolving* and the test drug product is formulated exclusively with excipients that have been used in pyrazinamide formulations which have passed an *in vivo* BE study. When, in addition, patients treated with the test product are also regularly monitored for hepatic toxicity, the additional risk associated with the very small risk of an inadvertently incorrect BE decision can be deemed acceptable. Most SmPCs for pyrazinamide pro-

ducts contain such a warning and have instructions for regular hepatic monitoring.^{37,43,46}

CONCLUSION

A biowaiver can be recommended for IR solid oral dosage when the test product (a) contains only excipients present in pyrazinamide IR solid oral drug products approved in ICH or associated countries, for example those presented in this article in Table 2, and (b) only in amounts in normal use in IR solid oral dosage forms, (c) the test product complies with the criteria for *very rapidly dissolving*^{2,82} and (d) the SmPC of the test product indicates the necessity to test liver function prior to initiating pyrazinamide therapy, to continue regular monitoring during therapy, and provides an adequate description of the symptoms of impending acute liver failure. If not all of these conditions can be fulfilled, BE should be established on the basis of an *in vivo* pharmacokinetic BE study.

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