Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Isoniazid

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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 isoniazid as the only active pharmaceutical ingredient (API) are reviewed. Isoniazid's solubility and permeability characteristics according to the Biopharmaceutics Classification System (BCS), as well as its therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported BE/bioavailability (BA) problems were taken into consideration. Isoniazid is "highly soluble" but data on its oral absorption and permeability are inconclusive, suggesting this API to be on the borderline of BCS Class I and III. For a number of excipients, an interaction with the permeability is extreme unlikely, but lactose and other deoxidizing saccharides can form condensation products with isoniazid, which may be less permeable than the free API. A biowaiver is recommended for IR solid oral drug products containing isoniazid as the sole API, provided that the test product meets the WHO requirements for "very rapidly dissolving" and contains only the excipients commonly used in isoniazid products, as listed in this article. Lactose and/or other deoxidizing saccharides containing formulations should be subjected to an *in vivo* BE study. J Pharm Sci 96:522–531, 2007

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

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INTRODUCTION

A biowaiver monograph of isoniazid based on literature data, together with some additional, new 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 dosage forms containing isoniazid ("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 isoniazid 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 a 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 an incorrect biowaiver decision in terms of public health and individual patient risks. On the basis of these considerations, a recommendation is made as to whether a biowaiver is advisable or not. This systematic approach to recommend or advise against a biowaivers decision is referred to the recently published WHO Guideline,[2] stating that these monographs provide detailed information which should be taken into account whenever available in the biowaiver consideration.

Biowaiver monographs have already been published on acetaminophen (=paracetamol),[3] amitriptyline,[4] atenolol,[1] chloroquine,[5] cimetidine,[6] ibuprofen,[7] propranolol,[1] ranitidine,[8] and verapamil.[1] The details and progress of the project of writing these biowaiver monographs are available at www.fip.org/bcs.

GENERAL CHARACTERISTICS

Name

Isoniazid (INN)[9,10]
Isonicotinic acid hydrazide
4-Pyridinecarboxylic acid hydrazide
The structure of isoniazid is shown in Figure 1.

Therapeutic Indications

Isoniazid is one of the key APIs used in the combination treatment of tuberculosis recommended by the World Health Organization (WHO). 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.[11] Isoniazid is also recommended for prophylaxis of tuberculosis, especially in the elderly and other populations at high risk, and in the combination treatment of leprosy.[12,13]

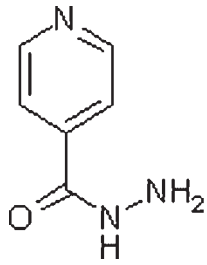

Figure 1. Structure of isoniazid.

Therapeutic Index and Toxicity

The WHO recommends a dosage range from 4 to 6 mg/kg, with the maximum daily dose not to exceed 300 mg.[11] The 300 mg maximum daily dose is also used as preventive therapy for populations at high risk. At this dose the antibiotic is generally well tolerated. The WHO recommends that patients who are at risk of developing peripheral neuropathy (often undernourished persons), should receive a supplement dose of 10 mg of pyridoxine per day.

The most commonly occurring adverse effect in the treatment with isoniazid is hepatotoxicity. Serious toxic symptoms have been reported to occur at doses of 2–3 g or higher in adults. Doses of 10–15 g may be fatal without appropriate treatment.[13–15]

CHEMICAL PROPERTIES

Polymorphs, Hydrates

Isoniazid is not known to exhibit polymorphism or to form defined hydrates. Its synthesis results in crystals, which have been reported to be orthorhombic.[16]

Solubility

Commonly used reference books and pharmacopoeias indicate that isoniazid is soluble to the

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

	37°C		40°C	D/S Ratio[a](mL)	
Medium, pH	Maejima[48]	New Experimental Data	Florey's[16]	200 mg Tablet[b]	300 mg Tablet[c]
Water	196			1.0	1.5
Water		159[d]		1.3	1.9
Water			260	0.77	1.2
1.2	211			0.95	1.4
1.2		174[d]		1.1	1.7
4.5		161[d]		1.2	1.9
6.8	188			1.1	1.6
6.8		153[d]		1.3	2.0

[a]Critical limit is 250 mL.[2,45–47]
[b]Highest strength on the DE and NL market.
[c]Highest strength on the FI, DK, and SE market and on WHO Essential Medicines List.[22]
[d]The formation of colored degradation products was observed after 6 h.

extent of 125 mg/mL of water at room temperature.[10,17,18] The solubility of isoniazid at 37°C was determined in buffers pH 1.2, 4.5, and 6.8, using the standard USP shake-flask method over 4 h.[†] The pH of the buffers was monitored and readjusted when necessary to the initial pH values.[19] The standard USP photometric quantification assay was used.[20] A summary of the solubility literature data, as well as the obtained experimental solubility data, is presented in Table 1.

Partition Coefficient (logP)

A logP of 1.1 was reported in octanol/buffer pH 7.4, without reporting the temperature and buffer composition.[16,17] Calculations by Kasim et al.,[21] using fragmentation methods based on atomic contributions to lipophilicity and by using the ClogP® program (version 3.0, Biobyte Corp, Claremont, CA, http://www.biobyte.com) gave values of 0.64 for logP and −0.67 for ClogP®, respectively.

pKa

Depending on methods used to measure the dissociation constant, different pKa values have been obtained. At 20°C, pKa values of 1.8 (range: 1.4–2.2) for the pyridine nitrogen, 3.5 (range: 3.5–3.9) for the hydrazide nitrogen, and of 10.8 (range: 9.8–11.2) for the deprotonation of the hydrazide group to a mesomerism stabilized anion have been reported.[16,17]

Dosage Form Strengths

Isoniazid only containing tablets are listed on the WHO Essential Medicines List as ranging from strengths of 100 to 300 mg.[22] Single API dosage forms with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), The Netherlands (NL), and Sweden (SE) contain 300 mg (DK, FI); 50, 100, 200 mg (DE); 200 mg (NL); and 300 mg (SE) isoniazid, respectively.

PHARMACOKINETIC PROPERTIES

Permeability and Absorption

No studies investigating the *in situ* or *ex vivo* intestinal permeability or Caco-2 cell permeability of isoniazid could be identified in the literature. Kasim et al.[21] grouped APIs into "highly permeability" and "low permeability" according to their ClogP® and logP values based on correlations of experimentally determined human intestinal permeabilities of selected compounds with ClogP® and logP values. APIs with a ClogP® and logP greater than the corresponding values of the reference substance metoprolol, with values

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

for ClogP® and logP of 1.35 and 1.72, respectively, were classified as "highly permeable." Isoniazid, with values for ClogP® and logP of −0.67 and 0.64, respectively, was therefore classified "poorly permeable."[21]

Mariappan et al. and Kakemi et al. showed in a study in rats that the drug is poorly permeable in the stomach and that its main absorption site is located in the intestine. Lower permeability in the stomach can be explained on the basis of isoniazid protonation in the acidic medium due to its weak base properties.[23,24]

Isoniazid is reported to be readily absorbed from the gut after oral application.[13] In a study carried out as early as 1952, the urinary recovery within 24 h after oral administration of a 3 mg/kg dose to adult patients with advanced or moderately advanced tuberculosis ranged from 48% to 70%, although it was not clear that these values reflected total urinary recovery.[25] In 1979, Kleber et al.[26] reported an absolute BA of 91% ± 10% in tuberculosis patients, several of whom had undergone resection operations of the stomach. The plasma assays in that study were based on a complexation reaction followed by UV analysis. At about the same time, Polk et al. demonstrated that even after various surgical procedures, including jejunoileal bypass, the oral absorption, and C_{max} of this antituberculosis drug was not altered.[27,28] All studies reviewed employed doses in the dosage range from 3 to 10 mg/kg per day; in this range dose-dependent absorption was not observed.

T_{max} values determined by different authors ranged from about 1 to 2 h after oral application, values consistent with a moderate to fast rate of absorption and suggestive of good permeability.

Männisto et al.[29] explored the influence of various test meals on the absorption of isoniazid in healthy volunteers. All types of meals reduced the absorbed amount and the maximum concentration of the drug in the blood but the decrease was most marked after the ingestion of a high carbohydrate meal. It was hypothesized from these results that the carbohydrates interact with isoniazid.[30] Rao et al.[31] subsequently investigated condensation reactions of isoniazid in different sugar containing solutions over 30 days at room temperature (26°C). The free isoniazid in solution was determined using extraction followed by photometric detection. *In vitro*, the condensation reaction was most pronounced in a commercially purchased blackcurrant syrup, in a solution of 5% of glucose and in a mixture of 60% sucrose, 5% fructose and 5% glucose. A subsequent urinary recovery study over 24 h compared the absorption of isoniazid from the blackcurrant syrup to a freshly prepared mixture of isoniazid with milk. The study revealed reduced absorption from the syrup preparation with a urinary recovery of about 47%, compared to 82% after the milk mixture, when administered in each case on an empty stomach. On the basis of these results, it was hypothesized that a considerable percentage of isoniazid was converted to hydrazones as a consequence of condensation reactions and thus less available for absorption.[31]

This finding is in line with the work of Kakemi et al.,[23] who investigated the absorption of the condensation product of isoniazid with glucose, glucose isonicotinylhydrazone, in humans and of various sugar-isoniazid-hydrazones in rats. Glucose-, lactose-, glucuronolactone-, and sodium-pyruvate ketone isonicotinoylhydrazones were slowly and poorly absorbed from the rat intestine. In humans, urinary excretion was studied after ingestion of pure isoniazid or mixtures of 460 mg glucose isonicotinylhydrazone with different amounts of glucose in 200 mL of water. It was found that, compared to the solution of the pure API, the cumulative amount of isoniazid excreted was reduced when glucose isonicotinylhydrazone was administered. Further, with increasing amounts of glucose added to the mixture, a greater reduction in the urinary recovery of isoniazid was observed.

Chavan et al.[32] assessed the relative BA of a sorbitol-based isoniazid liquid dosage form, Isokin liquid®, against a reference solution of pure isoniazid powder in water. After administration of 300 mg of isoniazid to 10 healthy volunteers, no significant differences were observed either in the blood levels or in the urinary excretion between the two preparations. This finding indicates that sorbitol, a nonreducing sugar substitute, does not form significant amounts of condensation products with isoniazid.

Hurwitz et al.[33] observed a significant decrease in the plasma concentrations after 1 h, C_{max} and the area under the plasma concentration curve (AUC) after pretreatment with aluminium hydroxide containing antacids before oral administration of isoniazid to 11 patients with tuberculosis. The effect also occurred, albeit less pronounced, after application of a magnesium/aluminium combination antacid (magaldrate). On this basis it was recommended that antacids should be given at least 1 h prior to the administration of isoniazid.[33]

Distribution

Isoniazid exhibits an apparent volume of distribution of 43 L after oral application, consistent with penetration of various organs.[34] High concentrations can be detected in the cerebrospinal fluid, lung, and skin.[35] Boxenbaum et al.[36] described isoniazid as being not significantly bound to plasma proteins. Previous studies had reported plasma protein binding values ranging from 0% to 74%. The large range of values can be explained by the use of assays that likely varied in their ability to detect decomposition products and/or metabolites of isoniazid.[36]

Metabolism and Elimination

The main metabolic pathway of isoniazid is acetylation by *N*-acetyltransferase, which is located in both the liver and the small intestine.[14] The enzyme activity exhibits genetic variation and there is a bimodal distribution of persons who acetylate rapidly (about 40%) or slowly (about 60%) resulting in different half lives: 45–110 min for rapid and 2–4.5 h for slow metabolizers.[37,38] Other metabolites are generated by hydrolysis, glycine conjugation, hydrazone formation, and *N*-methylation. None of the metabolites are active, apart from monoacetylhydrazine, which has tuberculostatic activity and is considered to be hepatotoxic. Urinary excretion is the primary elimination route; over 80% of the oral dose appears in the urine within 24 h after application, mostly as metabolites. Less than 10% of the oral dose is excreted in the feces.[13,16,35]

DOSAGE FORM PERFORMANCE

Bioavailability and Bioequivalence Studies

Gelber et al.[39] investigated the relative BA of three brand name and three generic formulations commercially available in the USA. The composition of the formulations was not specified. All formulations released more than 98% of the labelled amount within 30 min at 37°C in USP Simulated Gastric Fluid sine pepsin (SGF_{sp}) using the paddle apparatus at 75 rpm. The commensurate *in vivo* BE study was carried out with six healthy volunteers in a crossover design.[39] A dose of 10 mg/kg per day with a sampling period of 8 h was used. With this study design all tested products were deemed to be bioequivalent. Because a rapid intravenous (i.v.) infusion was also administered to the volunteers in a separate study arm, it was possible to calculate the absolute BA of the isoniazid formulations. However, the AUC after oral application was found to be greater than the AUC after i.v. dosing.

Sved et al.[40] demonstrated the BE of three Canadian isoniazid formulations *in vivo*. Detailed compositions of the tested formulations were not given in the article. The blood concentrations of free isoniazid in the plasma were followed up over 24 h in nine healthy volunteers, all slow acetylators. A dose of 400 mg per day corresponding to a dose of about 5.7 mg per kg and per day was used. Although one of the formulations studied contained small amounts of lactose, it was shown to be bioequivalent to the two other formulations. The same formulations were also subjected to *in vitro* dissolution testing in water; all released more than 90% within 30 min.

Several *in vivo* and *in vitro* BE studies have compared isoniazid fixed dose combination formulations to formulations containing isoniazid as the only API at the same dose level. The BE of the products under investigation was demonstrated in all cases.[41,42]

Excipients

Table 2 shows the excipients present in isoniazid IR solid oral drug products with an MA in DE, DK, FI, NL, and SE. It can be expected that the drug products having a MA in these countries successfully passed an *in vivo* BE study. In DE, the exemption from demonstration of BE *in vivo* that existed for some APIs in the 1980s and 1990s was not applied to isoniazid.[43] Also, the minimum and maximum amount of the listed excipients present per dosage unit in solid oral drug products with a MA in the USA, taken from the FDA Inactive Ingredient Data Base,[44] is indicated.

Dissolution

The current USP specifies for Isoniazid Tablets not less than $Q \geq 80\%$ within 45 min in 900 mL 0.01 N HCl at 37°C in the basket apparatus at 100 rpm.[20] In the Gelber study[39] and in the Sved study,[40] all formulations successfully passed an *in vivo* BE study and also complied with the *in vitro* dissolution criteria, see above, although the tests were not fully identical to the current USP specification.

The dissolution behaviour of pure isoniazid powder was experimentally assessed according to the WHO requirements for BE.[45] Within 10 min almost 100% of the drug substance was dissolved in USP SGF_{sp} pH 1.2, in USP SIF_{sp} pH 6.8, and in a

Table 2. Excipients[#] Present in Isoniazid IR Solid Oral Drug Products with a Marketing Authorization (MA) in Germany (DE), Denmark (DK), Finland (FI), The Netherlands (NL), and Sweden (SE) 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 (mg) Present in Solid Oral Dosage Forms with a MA in the USA
Cellulose	DE(1), FI(2), SE (3)	4.6–1385[a]
Copovidone	DE(1)	86–500
Crospovidone	DE(1)	4.4–792[a]
Glycerol	NL(4)	0.14–198[a]
Hypromellose	DE(1)	0.8–80
Lactose[b]	DK(5), NL(4,6)	23–1020[a]
Macrogol	DE(1), DK(5)	0.12–500[a]
Magnesium stearate	DE(1), DK(5), FI(2), NL(4,6)	0.9–401[a]
Maize starch	FI(2), NL(6)	9.9–1135[a]
Potato starch	DK(5), NL(4)	2.1–80
Povidone	DK(5), NL(4)	0.17–75
Silica	DE(1), FI(2), NL(4,6), SE (3)	0.65–99
Stearic acid	SE (3)	0.9–72[a]
Talc	DE(1), DK(5), SE(3)	0.1–220[a]

[a]The upper range value reported is unusual high for solid oral dosage forms and the authors doubt on its correctness.

[b]Because of the potential interaction between lactose and isoniazid, drug products containing lactose are not recommended for a biowaiver.

1. Isozid® 50 mg/–100 mg/–200 mg.
2. Tubilysin® 300 mg tabletti.
3. Tibinide 300 mg tabletter.
4. Isoniazide 200 PCH, tabletten 200 mg.
5. Isoniazid "OBA," tabletter 300 mg.
6. Isoniazide ratiopharm 200 mg, tabletten.

Sources of data: DE: www.rote-liste.de (assessed 24-04-2006); DK: www.dkma.dk (assessed 24-04-2006), FI: www.nam.fi (assessed 24-04-2006); NL: www.cbg-meb.nl. (assessed 21-04-2006), SE: www. lakemedelsverket.se (assessed 24-04-2006). USA: http://www.fda.gov/cder/iig/iigfaqWEB.htm# purpose (IIGQInte.txt version date 02-02-2006).

[#]Excipients present in printing ink only are not included.

Drug products containing more than one API are excluded.

phosphate buffer pH 4.5.[‡] These results were confirmed using a slightly modified methodology and commercial raw material from the South African market (Dekker T, 2006, unpublished results).

DISCUSSION

Solubility

The solubility values taken from the literature were not assessed under the conditions specified for the BCS.[2,45–47] Studies were done at room temperature instead of 37°C, water was used as the medium; the pH was not confirmed to remain constant during the solubility determination and the instability of isoniazid in an aqueous environment was not taken into account.[16] For example, Maejima et al.[48] carried out their solubility determination of isoniazid over 20 h, even though it has been separately reported that facile hydrolysis of the hydrazone group leads to decomposition within this time frame. To obtain more reliable data, new solubility determinations were carried out. Within the time frame used, no appreciable instability was observed and the minimum solubility of isoniazid found was 153 mg/mL, at pH 6.8, see Table 1. Higher solubilities were observed at acidic pH, probably due to the weak basic nature of the API. All determinations, calculated for the highest available tablet strengths on the German market and on the WHO EML, resulted in D/S values of 2 mL or lower, 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

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

250 mL.[2,45–47] Thus, isoniazid can be classified as "highly soluble."

Permeability

Available data for urinary excretion and absolute BA are consistent with high permeability, especially when the first pass metabolism of isoniazid is taken into account. However, most these data cannot be considered as completely reliable. In some cases older, less reliable methodologies were used, such as urinary excretion[25] and assay techniques based on color reactions.[26] In another case, after dose-normalization, in the same individuals higher AUCs were observed following oral administration than following intravenous administration, reflecting a flaw in the study design and/or analysis.[39]

One observation that might be consistent with less than optimal permeability is the reduction in absorption after postprandial administration.[30] However, in the case of isoniazid, the decrease in BA postprandially is at least partially attributable to specific decomposition/binding reactions with meal components.[29,31]

No studies investigating the intestinal permeability in humans or *in vitro* permeability studies (for example, with Caco-2 cells) could be found in the literature. The assignment of isoniazid by Kasim et al.[21] to BCS Class III, and hence not meeting the criterion "highly permeable" is questionable. Their classification is based on correlations of partition coefficients with permeability and such correlations have only limited predictablity. For instance, the correlation of logP with permeability resulted in 8 false negatives from 25 predictions and the correlation of ClogP® with permeability resulted in 8 false negatives and 1 false positive from 28 predictions. Moreover, their correlations are based on calculated partition coefficients, not on experimentally measured partition coefficients. Wu et al.[49] used the disposition characteristics of the drug for BCS classification. Being intensively metabolized, isoniazid was assigned to BCS Class I, that is, "highly permeable." Lindenberg et al.[50] classified isoniazid as a BCS Class III drug, using literature BA data. The WHO Guideline classified the permeability of isoniazid as "borderline 3/1."[2]

BCS Classification

Isoniazid meets the criteria for a "highly soluble" API, according to the present Guidelines.[2,45–47] Data on its oral absorption and permeability are inconclusive but suggest this API to be on the borderline of BCS Class I and Class III, also depending on the criterion for "highly permeable." The FDA and the EMEA Guidances[46,47] set a limit for the fraction of dose absorbed of not less than 90%, whereas the WHO sets a limit of not less than 85% of the fraction of dose absorbed.[2,45]

Surrogate Techniques for *In Vivo* BE Testing

Isoniazid is "highly soluble," see above. Further, "very rapid dissolution" appears to be a property of the pure drug. So, dissolution *in vivo* is unlikely to pose a limitation in the absorption process, as long as the dosage form meets the *in vitro* dissolution requirements. The FDA and EMEA guidances require drug products to be "rapidly dissolving," but allow biowaiving only for BCS Class I.[46,47] The WHO Guidance also allows BCS Class III APIs to be considered for biowaiving, with the provision that the drug product is "very rapidly dissolving."[2,45] As isoniazid is on the borderline of BCS Class I and III, see above, requiring the test product to comply with the requirements for "very rapidly dissolving" is a conservative approach. However, changes in the permeability of isoniazid due to excipient interactions, for example the formation of condensation products of the API with lactose and/or other deoxidizing saccharides, cannot be detected by *in vitro* dissolution testing. Therefore, the biowaiver approval is not suitable for the BE prediction of isoniazid formulations containing excipients known or suspected to form condensation products with the API.

Risk for Bioinequivalence Caused by Excipients and/or Manufacturing

Isoniazid can interact with saccharides such as lactose, with consequences for the BA.[23,31] The extent of this reaction seems to depend on the amount of excipients present in the formulation: in the Sved study,[40] two of the three isoniazid formulations tested contained lactose in amounts of less than 4% and no significant differences were found in the BA of the three products. Moreover, Isoniazide 200 PCH tabletten 200 mg®, which has a MA in NL, contains lactose, see Table 2. To be on the conservative side, we conclude that the presence of lactose and other deoxidizing saccharides in the test formulation is associated with some risk of bio*in*equivalence.

The interaction between isoniazid and magnesium oxide was only established *in vitro*, not *in vivo*.[51] Moreover, no products with MAs combine isoniazid with antacids, see Table 2. Other excipients seem unlikely to cause BE problems, as isoniazid has been shown to be one of the less problematic APIs in the formulation of multi-API antituberculosis drug products.[52,53]

In conclusion, by excluding lactose and/or other deoxidizing saccharides and furthermore restricting biowaiving to formulations containing only excipients also present in drug products having a MA in a number of countries, as shown in Table 2, a reduction of the permeability of isoniazid due to an excipient interaction can be excluded with a high degree of probability.

Patient Risks Associated with Bioinequivalence

Isoniazid is, together with rifampicin, pyrazinamide, and ethambutol, one of the first line compounds in the routine treatment of tuberculosis recommended by WHO and the International Union against Tuberculosis and Lung Disease.[11] Generally, isoniazid has neither a low therapeutic index nor its application can be designated as "critical use" even in the treatment of tuberculosis or leprosy. On the other hand, a long-term combination treatment, as recommended by the WHO represents a laborious and expensive therapy. Sub-therapeutic blood levels due to bad quality and reduced BA could lead to treatment failure or may elongate treatment, elevate the risk of emergence of resistant strains and necessitate the use of second line drugs. This is of particular concern because the rate of primary and acquired resistance is higher for isoniazid than for other antituberculosis drugs.[14]

CONCLUSIONS

The biowaiver procedure for IR solid oral single API isoniazid drug products is unlikely to result in an incorrect product approval decision for products containing only excipients present in drug products having an MA in DE, DK, FI, NL, and/or SE, as shown in Table 2, except for products containing lactose and/or other deoxidizing saccharide excipients. In addition, the requirements of the FDA, EMEA and WHO for "very rapidly dissolving" must be met, by the comparator as well as the multisource product, that is $\geq$85% dissolution of the labeled amount of API within 15 min in pH 1.2, 4.5 and 6.8, using the paddle apparatus at 75 rpm or the basket apparatus at 100 rpm.[2,45,47,48] When all these conditions are fulfilled, the risk of a false approval decision is extremely small, and the associated public health and individual patient risks are acceptable.

This conclusion is in line within the recommendation given by the WHO for biowaiving of isoniazid,[2] but is more explicit with respect to the excipients that are acceptable for a positive biowaiver decision and, by excluding lactose and other deoxidizing saccharide excipients, also somewhat more restrictive.

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