

PRODUCT INFORMATION REPORT

RIFAPENTINE-ISONIAZID FDC

OCTOBER 2019





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Executive Summary

Rifapentine (RPT), an antitubercular agent marketed under the brand name of Priftin[®] (by Sanofi Aventis US LLC) in the US, is used in combination with other anti-tuberculosis (anti-TB) drugs for the treatment of active pulmonary tuberculosis (TB) caused by *Mycobacterium tuberculosis* in patients 12 years of age and older. Specifically, the combination of RPT and isoniazid (INH) is indicated for the treatment of latent tuberculosis infection (LTBI) in patients 2 years of age and older at high risk of progression to TB disease.¹ INH was first approved in the US in 1952 (New Drug Application (NDA)# 008678, Sandoz).² Currently, multiple manufacturers provide generic isoniazid tablets in the US market.

In the past decade, several clinical trials have established the effectiveness of the RPT/INH combination regimen in reducing the treatment duration for TB,³⁻⁶although there is no marketed fixed dose combination (FDC) of RPT and INH. An FDC (300 mg RPT and 300 mg INH) has appeared in the WHO list of pre-qualified Finished Pharmaceutical Products (FPPs)⁷ and another FDC (150 mg RPT and 150 mg INH) is in clinical trials in children.⁸ Currently, there are no unexpired patents or exclusivities for RPT-based and INH-based products in US Food and Drug Administration's "Orange Book" database.^{9, 10}

This product information report aims to provide expert scientific analyses of the analytical, formulation, and manufacturing aspects of (Rifapentine / Isoniazid) RPT/INH FDC. Due to the lack of such a combination in the market, conclusions have been drawn based upon the available literature for individual molecules and their possible interactions. Moreover, since a PIR (Product Information Report) already exists for RPT, only the highlights are provided in this document.¹¹ It is expected that this PIR will provide critical information and guidance to manufacturers planning to develop this FDC.

Key Manufacturing Challenges

The table below summarizes the key challenges associated with the manufacturing of RPT/INH FDC:

Challenges	Description of the challenges and solution
Product	INH is known to accelerate the decomposition of RPT and the potential
development	degradation product is isonicotynl hydrazone. Such an interaction will not only
(formulation and analytical)	tend to lower the potency of the two drug substances, but could also affect the oral bioavailability. No direct studies are available in literature that describe the role of this interaction on the bioavailability of RPT. However, such studies are available for rifampin, which is structurally similar to RPT. Hence, the formulation manufacturing process needs to be designed to prevent any interaction of the two drug substances during product manufacturing or storage. The potential interactions <i>in vivo</i> , before absorption into systemic circulation, also warrant consideration.
	Finally, the development and validation of the stability indicating assay method to enable characterization of the RPT, INH, and their impurities can also be challenging. Please refer to the section on Chemical Incompatibility for additional discussion.
Product	Pharmacopeial monographs exist for INH and INH tablets, but not for RPT. The
development (quality specification)	availability of several generic formulations of INH suggest ready accessibility of approved generic sources of INH active pharmaceutical ingredient (API). Multiple DMF approved vendors were identified for INH, but none were identified for RPT. ¹² Thus, API sourcing from qualified vendors could be a challenge.
Bioequivalence (BE) and Biowaiver	Biowaiver monographs have been proposed for immediate release isoniazid tablets. ^{13, 14} However, owing to its potential of interaction with excipients and other APIs, including RPT, a biowaiver is not expected for the RPT/INH FDC. Further, there is no specific guidance on the BE requirements of RPT and there is no approved FDC of RPT/INH. Hence, the manufacturers need to establish the BE of each API with that of concurrently administered separate single ingredient preparations. ¹⁵
	Refer to the section on Bioequivalence and Biowaiver for additional discussion.
Inherent properties	RPT is a red-colored dye and the equipment cleaning and cleaning validation can be a challenge. Hence, the product may require dedicated equipment and rooms, thereby adding to the financial, technical, and operational challenges. Refer the PIR ¹¹ of RPT for additional discussion.

Introduction

RPT is an antitubercular agent marketed under the brand name Priftin[®] by Sanofi in the US. Priftin was approved by the US Food and Drug Administration (FDA) for use in combination with other anti-TB drugs for the treatment of active pulmonary TB caused by *Mycobacterium tuberculosis* in patients 12 years of age and older.^{1, 16} In November 2014, a supplementary new drug application was approved by FDA for the treatment of LTBI caused by *M. tuberculosis* in combination with INH in patients 2 years of age and older at high risk of progression to TB disease.¹⁶ Thereafter, several clinical trials and reports have further established the combination regimens of RPT and INH, popularly known as 3HP (12 weeks of RPT and INH taken together once a week) and 1HP (one month of RPT and INH taken together once a day) as shorter treatment alternatives to the older standard of care.⁴⁻⁶

In the 3HP regimen, adults are administered 900 mg of RPT, 900 mg of INH and a vitamin B6 supplement. Similarly, in the 1HP regimen, adults are administered 600 mg of RPT, 300 mg of INH, and vitamin B6.^{8, 17} As per our current knowledge, RPT/INH FDC is not available in the market. However, a recent report suggested that a water dispersible 3HP FDC tablet (150 mg RPT and 150 mg INH) for children (manufactured by Sanofi) is undergoing a clinical trial.⁸ Additionally, a film coated tablet (300 mg RPT and 300 mg INH) has been listed in the WHO list of pre-qualified Finished Pharmaceutical Products (FPPs).⁷

Active Pharmaceutical Ingredients (APIs)

Description and Pharmacopeia Status

RPT is available as a practically odorless, brick-red to reddish brown crystalline solid or powder. ^{11, 18} RPT has poor aqueous solubility. RPT is not official in USP, the *European Pharmacopeia* (Ph. Eur.), *British Pharmacopeia* (BP), and the International Pharmacopeia. INH is available as colorless or white crystals, or as white, crystalline powder. It is freely soluble in water, sparingly soluble in alcohol, slightly soluble in chloroform, and very slightly soluble in ether. It is odorless and is slowly affected by exposure to air and light.¹⁹ The API is official in USP, *Ph. Eur.*, and the International Pharmacopeia.

We could not locate any DMF holders associated with the RPT API in the FDA database.¹² However, three active DMF approved vendors were identified for INH (Table 1).

DMF#	Туре	Submit date	Holder	Subject (Title)
4772	II	12/7/1982	Yuki Gosei Kogyo Co Ltd	Isoniazid bulk form
16235	II	11/5/2002	Yangzhou Pharmaceutical Co Ltd	Isoniazid
21322	II	2/7/2008	Calyx Chemicals and Pharmaceuticals Ltd	Isoniazid

Table 1. Active DMFs for INH API as of March 31, 2019

Polymorphic Forms

INH is not known to exhibit polymorphism.¹¹ The crystal structure of INH is reported.²⁰ RPT can exist in different solid forms, including solvates, crystalline chloride and bromide salts, and an amorphous bromide salt form.^{11, 18, 21, 22} The crystal structure of methanol solvate of RPT is reported¹⁸, while INH is not known to form stoichiometric hydrates or solvates.¹³

Cross Contamination

As highlighted in the PIR of RPT, the administration is reported to cause discoloration of human excreta and eyes.^{11, 23} Its intense brick-red color makes cleaning difficult. Thus, it is recommended to manufacture products containing RPT using dedicated equipment and rooms. Refer to the PIR¹¹ of RPT for additional discussion.

Chemical Structure and Molecular Formula

	Rifapentine (RPT)	lsoniazid (INH)
Molecular formula	C47H64N4O12	C ₆ H ₇ N ₃ O
Molecular weight	877.031 g/mol	137.139 g/mol
Chemical structure		N H
IUPAC name	(7S,9E,11S,12R,13S,14R,15R,16R,17S,18S,19E,21Z)-26-[(1E)- [(4-Cyclopentylpiperazin-1-yl)imino]methyl]-2,15,17,27,29- pentahydroxy-11-methoxy-3,7,12,14,16,18,22-heptamethyl- 6,23dioxo-8,30-dioxa-24-azatetracyclo[23.3.1.1[5].0[6]] triacont a-1,3,5(28),9,19,21,25(29),26-octaen-13-yl-acetate	Pyridine-4- carbohydrazide

Physical Properties

The physical properties of INH have been compiled in the following section. For the detailed physical properties of RPT, refer to its PIR.¹¹

Solubility

INH is freely soluble in water.¹⁹ One part of INH is soluble in 8 parts of water and in 40 parts of ethanol.²⁴ The solubility of INH, as a function of temperature in different organic solvents,

namely ethanol, methanol, ethyl acetate, and acetone was reported by Heryantu *et al.* and the results are presented in Figure 1.²⁵



Figure 1. Mole fraction solubility (x1) of isoniazid in different solvents.

 $\mathbf{\nabla}$, ethyl acetate; •, ethanol; \triangle , acetone; 0, methanol ²⁵

Other Physicochemical Properties

The logP of INH is 1.1 in octanol/buffer pH 7.4 system.²⁶ The calculated log P using ClogP1 program (version 3.0, Biobyte Corp, Claremont, CA) is 0.64.^{13, 27} Three pK_a values have been reported for INH at 20°C: i) 1.8 (range: 1.4–2.2) for the pyridine nitrogen; ii) 3.5 (range: 3.5–3.9) for the hydrazide nitrogen; and iii) 10.8 (range: 9.8–11.2) for the deprotonation of the hydrazide group to a mesomerism stabilized anion.^{13, 26} The compound melts over the temperature range of 170-174 °C.²⁴

Chemical Incompatibility

RPT and INH are reported to interact and the reaction mechanism is given in Figure 2. The main degradation product of the interaction is expected to be isonicotinyl hydrazone.



Figure 2. Mechanistic scheme for the interaction of RPT with INH in acidic conditions

(Reproduced from Prasad et al 2006²⁸)

The acidic nature of INH further accelerates this decomposition reaction. Thus, RPT drug substance should not be in direct contact with INH.²⁸ In addition to lowering the potency of RPT, this interaction is also expected to lower the oral bioavailability of RPT when such a product is administered orally.²⁸ As a result, creating a barrier that prevents direct interaction in the formulation as well as in vivo, before absorption into systemic circulation is a major formulation challenge for fixed dose combination products containing the two drug substances together. Similar incompatibilities have also been reported for rifampicin and INH.^{29, 30} Further, the toxicological profile of the degradation product, isonicotinyl hydrazone, has not been established.

Characterization by Various Techniques

The characterization of INH has been compiled in the following section. For detailed characterization of RPT, Refer to its PIR.¹¹

X-Ray Diffraction (XRD) Study

The overlay of calculated XRD patterns of INH and RPT methanol solvate (ref codes INICAC01 and MAFLAI, respectively in Cambridge Structure Database) is presented in Figure 3 (CuK α radiation). INH is characterized by peaks at 9.8°, 12.1°, 14.4°, 15.7°, 16.8°, 19.7°, 24.2°, 25.5°, 26.4°, and 27.6° 20. The characteristic peaks of RPT methanol solvate were at 7.8°, 8.9°, 9.7°, 12.4°, 13.6°, and 19.9° 20. The experimental powder XRD patterns for INH and RPT methanol solvate are presented in Figure 4.



Figure 3. Overlay of calculated XRD patterns of isoniazid and rifapentine methanol solvate.





(Figure reproduced and modified from Banik et al.³¹ and Zhou et al.¹⁸)

FTIR Spectrum of INH

The FTIR spectrum of isoniazid is shown in Figure 5. INH shows three medium intensity bands at 3304, 3209, and 3171 cm⁻¹ corresponding to the N–H stretching vibrations. A strong band is observed at 1668 cm⁻¹, due to the C=O (carboxyl) stretching vibration. Peaks at 1635 cm⁻¹ and 845 cm⁻¹ are attributed to the deformation of the NH₂ and NH₂ wagging, respectively. A medium intensity band at 1335 cm⁻¹ is attributed to the C–N stretching vibration. The ring breathing mode is assigned at 996 cm⁻¹.³²

Figure 5. The FT-IR solid phase spectrum of isoniazid.



(Reproduced from Yilmaz et al.³²)

Mass Spectrum

Figure 6 shows the mass spectral pattern of INH and the structures of major fragments are shown in Figure 7. The major peaks and the possible fragment attribution are presented in Table 1. The data was collected under the following experimental conditions: source temperature of 200°C, sample temperature of 140 °C, and reservoir of 75 eV.³³





Figure 7. Chemical structures of the major fragments of isoniazid (reproduced from SDBS database).³³



m/z	Intensity	Possible peak attribution
51	52.1	
78	98.8	-CONHNH3 removed
106	100	-NHNH ₂ removed
137	58.2	Whole molecule

Table 2. Main fragment attribution of isoniazid in mass spectrum

Nuclear Magnetic Resonance Spectrum

The ¹³C-NMR spectrum of INH (0.13 g: 0.8 mL) in DMSO-d₆ (Di Methyl Sulfoxide) is presented in Figure 8. The chemical shifts and their attribution are shown in Figure 9.³³

Figure 8. ¹³C-NMR spectrum (15 MHz) of isoniazid.



The chemical shift is with respect to tetramethylsilane in DMSO.³³





The ¹H-NMR spectrum of INH (0.038 g: 0.5 ml) in DMSO-d₆ is presented in Figure 10. The chemical shifts and their attribution are showed in Figure 11.

Figure 10. Proton NMR spectrum (90 MHz) of isoniazid in DMSO.



The chemical shift is with respect to tetramethylsilane in DMSO.³³





Ultra-violet (UV) and Visible Spectrum

The UV-visible spectrophotometric based method has been used for rapid quantification of INH.³⁴ The absorption spectra of INH in (a) HCl 0.012 M and (b) phosphate buffer solution pH 7.4 are presented in Figure 12. The UV spectrum of INH in dilute HCl (0.01 N) exhibits two maxima at 213 nm and 267 nm.²⁶

Figure 12. Absorption spectra of isoniazid (20 μ g/mL) in (a) HCl 0.012 M and (b) phosphate buffer solution pH 7.4.



(Reproduced from Benetton et al. 1998³⁴)

Analyses by Reverse Phase (RP) High-performance Liquid Chromatography (HPLC) Methods

An HPLC-UV method was developed for the separation of RPT and INH and was utilized to study the of interaction between the two drugs.²⁸ The HPLC method utilized a C₁₈ column (250 mm x 4.6 mm, particle size 5 μ m) and a mobile phase consisting of 65% methanol and 35% 0.02 M phosphate buffer, pH 5.2. The flow rate was 1 mL/min and the detection wavelength was 238 nm. The retention times of RPT and INH were 18.55 min and 3.10 min, respectively. The method was validated for linearity, range, specificity, selectivity, accuracy, and precision (intra-day, inter-day and inter-column).

Additionally, INH is frequently co-administered with other first-line anti-TB drugs, including pyrazinamide, ethambutol, and rifampicin. Among these drugs, rifampicin and RPT are structural analogs belonging to the rifamycin class of anti-TB drugs. Hence, compilation of HPLC methods capable of separating INH and rifampicin may be a good starting point for developing a method for RPT/INH FDC. These methods have been summarized in Table 3. A detailed review of analytical methods for INH and RPT are also available.^{11, 35}

Analytes	Mobile Phase	Column	Drug Product	Reference
lsoniazid, pyrazinamide, and rifampicin	Isocratic: ethanol, water, chloroform and acetonitrile (55:40:4:1, v/v/v/v)	Column C18 YMC-ODS (150 × 4.6 mm; 5.0 µm)	Tablets	36
lsoniazid, pyrazinamide, and rifampicin	Gradient: (A) acetonitrile; (B) 50 mM phosphate buffer pH 3.5 3% A: 97% B (v/v) 5.0 min 50% A: 50% B (v/v) 25 min 3% A: 97% B (v/v) 10 min	Column C18 Lichrospher 100 RP-18 (250 × 4.0 mm; 5 µm)	Tablets	37
lsoniazid, pyridoxine,	Isocratic: acetonitrile and tetrabutylammonium hydroxide 0.0002	Column C18 mBondapak	Tablets	38

Table 3. HPLC-UV methods for isoniazid in combination with rifampicin and other anti-tubercular drugs in drug products

pyrazinamide, and rifampicin	M (42.5:57.5, v/v; pH 3.10 adjusted with H3PO4)	(250 × 4.6 mm; 10 μm)		
lsoniazid, pyridoxine, pyrazinamide, and rifampicin	Gradient: (A) acetonitrile; (B) potassium dihydrogen phosphate buffer 15 mmol/L of pH adjusted to 4.0 with orthophosphoric acid 11% A: 89% B (v/v) 4.5 min 50% A: 50% B (v/v) 15.5 min	Column C18 Phenomenex Luna (250 × 4.6 mm; 5 µm)	Tablets	39
lsoniazid, ethambutol, pyrazinamide, and rifampicin	Gradient: (A) acetonitrile; (B) potassium dihydrogen phosphate buffer (8 mM; pH 6.8) 10% A: 90% B (v/v) 0 min 60% A: 40% B (v/v) 18 min 60% A: 40% B (v/v) 6.0 min	Column C18 Phenomenex Luna (250 × 4.6 mm; 5 µm)	Tablets	40
lsoniazid, ethambutol, pyrazinamide, and rifampicin	Gradient: (A) 20 mM monobasic sodium phosphate buffer with 0.2% triethylamine (pH 7.0) and acetonitrile (96:4, v/v); (B) acetonitrile 100% A: 0% B (v/v) 5 min 48% A: 52% B (v/v) 7 min 100% A: 0% B (v/v) 5 min	Column C18 Purosphere Star RP-18 (250 × 4.6 mm; 5 µm)	Tablets	41

Analyses by Reverse Phase (RP) High-performance Liquid Chromatography (HPLC) Methods

Availability of Pharmacopeial Standards

No pharmacopeial monograph has been reported for the RPT so far. However, INH reference standard monographs exist in USP and *Ph. Eur.*

Impurities with Their Availability

Details of the impurities in RPT were provided in the PIR¹¹ of RPT. The USP monograph of INH lists four impurities (Table 4), each with acceptance criterion of not more than 0.1%.¹⁹

S. No.	Impurity name	Chemical Structure
1	lsoniacin (Isonicotinic acid)	OH
2	Isonicotinamide	NH ₂
3	Picolinohydrazide (2-Isoniazid)	N N N N NH ₂
4	lsonicotinonitrile (4-Cyanopyridine)	CN

Table 4. Chemical structures of specified impurities of Isoniazid

"Impurity reference standards" are commercially available from many suppliers including Sigma Aldrich, TCI Chemicals Pvt. Ltd, and Tokyo Chemical Industry Co., Ltd.

Stability

Stability of RPT and INH in Combination in Solution

Decomposition of RPT and INH was evaluated in acidic pH conditions, using a validated HPLC method. It was established that the maximum decomposition (RPT and INH degraded by ~30% and ~9%, respectively) occurred at pH 2. RPT was found to convert to 3-formylrifmycin in acidic conditions, which reacted further with INH to form isonicotinyl hydrazone. The shape of the pH-rate profile was similar to that observed for combination of rifampin and INH, suggesting similar nature of interaction between the two APIs.²⁸

RPT Alone in Solution

RPT was found to be most stable near neutral pH. Under alkaline conditions (pH of 7.5 to 9.0), RPT oxidized to form rifapentine-quinone. Addition of ascorbic acid reduced this oxidation reaction.¹¹

INH Alone in Solution

INH in solution is reported to be prone to oxidation. The presence of aldehydes and ketones, such as sugars, and metal ions enhance its degradation. Metal chelating agents are reported to prevent its degradation in neutral and alkaline media.²⁶

Assay in Biological Samples

Recently, Lee *et al.* developed an LC-MS based method for quantification of INH and RPT along with their metabolites, acetyl-INH and desacetyl-RPT, in human serum⁴². This method utilized a C18 column, ZORBAX Eclipse Plus ($2.1 \times 100 \text{ mm}^2$; $1.8 \mu\text{m}$). Deuterium isotopes of the analytes were used as internal standards. The mobile phase was composed of ammonium acetate (5 mM; solvent A) and 0.1% formic acid in 90% acetonitrile (solvent B). Separation was achieved by using a linear gradient (solvent B increased from 1% to 95%) for 6 min followed by an isocratic elution (with 95% solvent B) for 6-7 min, at a flow rate of 0.4 mL/min. The mass spectrometric analysis was performed using the positive electrospray ionization mode with the following parameters: dry gas temperature of 350 °C, dry gas flow rate of 11 L/min, nozzle voltage of 0 V, and capillary voltage of 3500 V⁴².

Additionally, several methods have been reported to quantify INH following the administration of a combination of anti-TB drugs (Table 5). Many of techniques enabled simultaneous quantification of multiple analytes. Two of these methods, reported by Panchagnula *et al.*⁴³ and Xu *et al.*,⁴⁴ utilized RPT as the internal standard, suggesting adequate resolution between INH and RPT.

Table 5. HPLC methods for assay determination of isoniazid in combination with rifampicin and other anti-tubercular drugs in biological samples

		Internal				
Method	Analytes	standard(s)	Mobile Phase	Column	Matrices	References
HPLC- UV	lsoniazid, pyrazinamide, and rifampicin	None	Isocratic: ethanol, water, chloroform and acetonitrile (55:40:4:1, v/v/v/v)	Column C18 YMC-ODS (150 × 4.6 mm; 5.0 μm)	Human serum	36
	lsoniazid, acetylisoniazid, pyrazinamide, and rifampicin	Terramycin	Gradient: (A) methanol; (B) acetonitrile; (C) 20 mM 1-heptanesulfonic acid sodium pH 2.5 10% A: 8% B: 82% C (v/v) 6 min 0% A: 65% B: 35% C (v/v) 13 min 10% A: 8% B: 82% C (v/v) 5.5 min	Column C12 Synergi Max- RP (250 × 4.6 mm; 4 µm)	Human plasma	45
	lsoniazid, pyrazinamide, and rifampicin	Guanosine and phenacetine	Isocratic: 50 mM phosphate buffer pH 4.2 and acetonitrile 0.25% (v/v)	Column C18 Purosphere LichroCart RP-18 (125 × 4.6 mm; 5 μm)	Human plasma and cerebrospinal fluid	46
	Rifampicin in presence of isoniazid and pyrazinamide	Rifapentine	Isocratic: methanol, sodium phosphate buffer (pH 5.2; 0.01 M) (65:35, v:v)	Column C18 Nova-Pak (250 × 4 mm; 4 µm)	Human plasma and urine	43

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Method	Analvtes	Internal standard(s)	Mobile Phase	Column	Matrices	References
HPLC- MS/MS	Isoniazid, ethambutol, pyrazinamide, and rifampicin	Rifabutin and 6-amino- nicotinic acid	Gradient: (A) methanol and formic acid 0.3%; (B) water and formic acid 0.3% 60% A: 40% B (v/v) 1.8 min 80% A: 20% B (v/v) 0.2 min 60% A: 40% B (v/v) 2.0 min	Column C18 Hydrosphere (50 × 2.0 mm; 3 µm)	Human serum	47
	lsoniazid, rifampicin, and levofloxacin	Gatifloxacin	Gradient: (A) water and formic acid 0.05%; (B) methanol 93% A: 7% B (v/v) 4.5 min 88% A: 12% B (v/v) 4.5 min 10% A: 90% B (v/v) 4 min 93% A: 7% B (v/v) 3.5 min	Column C4 Hydrosphere (250 × 4.6 mm; 5 μm)	Mouse plasma and tissues	48
	lsoniazid, ethambutol, pyrazinamide, and rifampicin	Rifapentine	Isocratic: acetonitrile and water containing 0.1% formic acid (60:40, v/v)	Column C18 Agilent Zorbax SB (50 × 2.1 mm; 1.8 µm)	Human plasma	44
	Isoniazid, acetylisoniazid, isonicotinic acid, and rifampicin	Deuterium labelled analytes	Gradient: (A) 5 mM ammonium acetate pH 6.7; (B) 90% acetonitrile in water containing 0.1% formic acid 100% A: % B (v/v) 1 min 97% A: 3% B (v/v) 2 min 50% A: 50% B (v/v) 0.1 min 30% A: 70% B (v/v) 1.9 min 5% A: 95% B (v/v) 1 min	Column C18 Agilent Zorbax SB-Aq (50 × 4.6 mm; 5 mm)	Human plasma	49

Bioequivalence (BE) and Biowaiver

Generally, the purpose of an *in vivo* BE study involving an FDC drug product is to compare the rate and extent of absorption of each API in the FDC to the rate and extent of absorption of each API administered concurrently in separate single-ingredient preparations.¹⁵ The US FDA draft guidance on BABE (bioavailability/bioequivalence) studies recommends that the following studies be conducted for an FDC drug product¹⁵:

• A two-treatment, single-dose, fasting study of the combination drug product versus single-ingredient drug products administered concurrently as a single treatment or an approved combination product containing the same active ingredients. This study should use the highest strength of the combination product with matching doses of individual drug products.

Also, it should be noted that BE studies for an FDC product should include the measurement of systemic concentrations of each API. The confidence interval approach should be applied to each measured entity of the FDC and its reference product.¹⁵

INH is freely soluble in water with rapid dissolution. So, *in vivo* dissolution was not expected to be a rate limiting factor for its absorption, as long as the dosage form meets the *in vitro* dissolution requirements. Biowaiver monographs have been proposed for immediate release tablets of INH, containing INH as the sole API.^{13, 14} However, INH can interact with saccharides likes lactose and this can impact its bioavailability.⁵⁰ The potential of INH to interact with other APIs, like rifampicin and RPT is also established.^{28, 30} Hence, a biowaiver request is not expected to be granted for the RPT/INH FDC. There is no specific guidance on the BE requirements of RPT in addition to the absence of its absolute bioavailability specific BCS classification. The market also does not have an approved FDC of RPT/INH available. Hence, the manufacturers need to establish the BE of each API with that of concurrently administered separate single ingredient preparations.¹⁵ WHO released a BE guidance for the design of bioequivalence study of INH/Rifampicin,⁵¹ which can be a good starting point for designing BE studies for RPT/INH FDC.

Conclusion

The combination of RPT and INH is indicated for the treatment of LTBI in patients, 2 years of age and older at high risk of progression to TB disease and has been proven to be more efficacious than INH alone in reducing treatment duration. However, there is no FDC formulation containing both the APIs available in the market. There are reports revealing such formulations in the pipeline. The present product information report attempts to provide background information required to develop an RPT/INH FDC formulation. The chemical incompatibility between the two APIs seems to be a major challenge for developing such an FDC. The formulation development strategy needs to be cautiously chosen to prevent interactions between RPT and INH during manufacturing and storage. Due to the potential interaction affecting the oral bioavailability of RPT/INH, a bio-waiver will likely not be approved for an FDC. Further, because RPT is a red-colored dye, this product may necessitate dedicated manufacturing equipment and areas. Development of analytical method does not seem to be problematic because multiple chromatographic methods are available for assays of drug content formulations containing INH, rifampin (a structural analog of RPT), and other anti-TB drugs.

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