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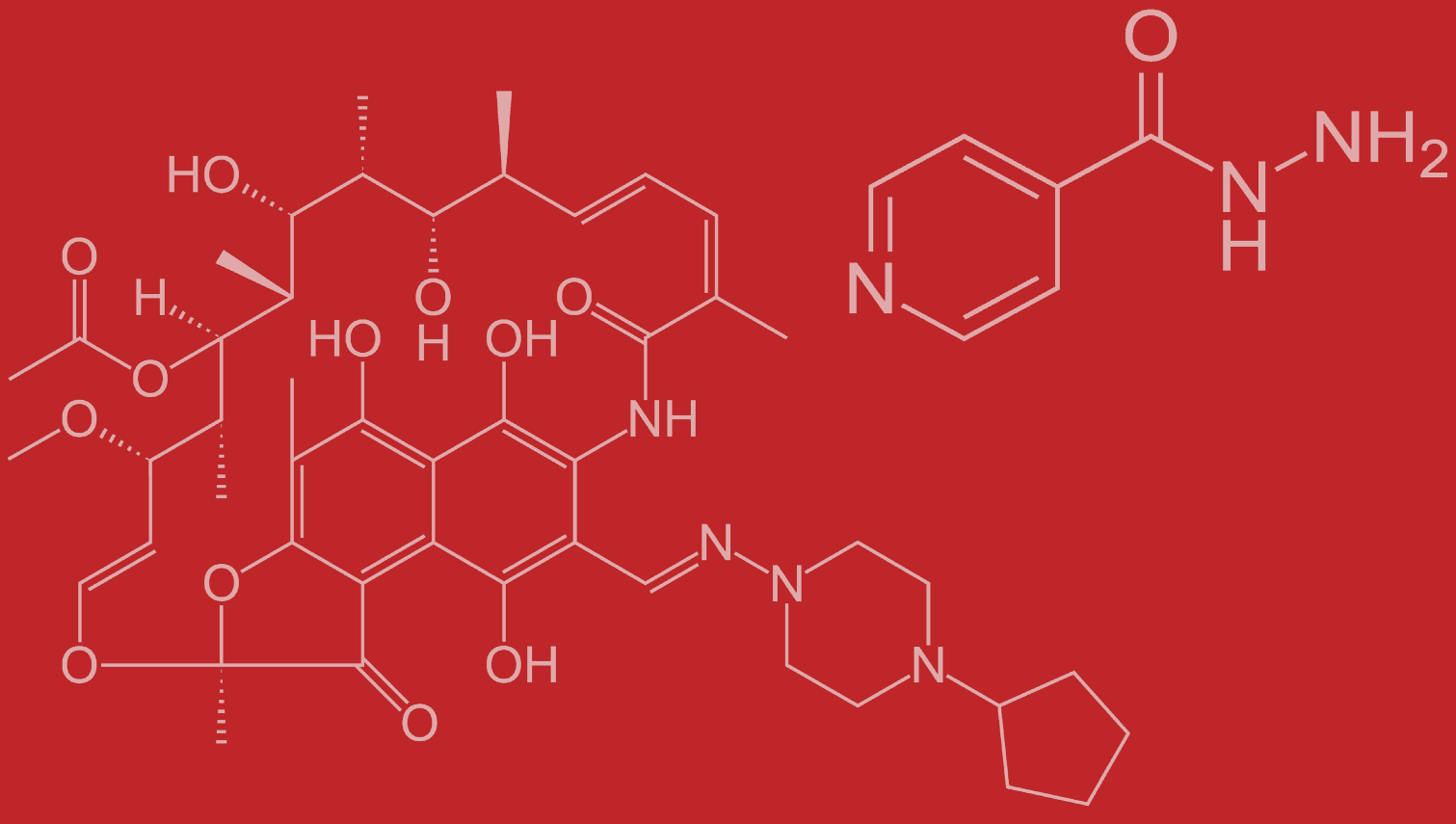
Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape



Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape

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Treatment Action Group

Treatment Action Group (TAG) is an independent, activist and community-based research and policy think tank fighting for better treatment, prevention, a vaccine, and a cure for HIV, tuberculosis, and hepatitis C virus.

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Introduction

This publication provides an access roadmap and patent landscape for two important products used in the prevention of tuberculosis (TB). The products are for combinations of two drugs—**rifapentine** and **isoniazid**—formulated for use in the so-called 3HP regimen. In this regimen, isoniazid (H) and rifapentine (P) are taken together once a week for 12 weeks in order to prevent TB disease.[1] One product is a fixed-dose combination (FDC) tablet of granules containing isoniazid and rifapentine dosed for children. The tablet dissolves in water, making it easier for children to swallow (hereinafter "pediatric FDC"). The second product is a film-coated FDC tablet of isoniazid and rifapentine dosed for older children, adolescents, and adults (hereinafter "adult FDC"). The French pharmaceutical company Sanofi, one of the biggest pharmaceutical corporations in the world, has applied for patents on each product. If granted, these patents could limit the availability, accessibility, and affordability of 3HP for many people at risk of TB.

Information related to the patent status of a medicine may seem very technical for many advocates. However, knowing the status of a patent or of a patent application is a critical first step toward ensuring the equitable availability and accessibility of medicines by, for example, acting to overcome patent-protected monopolies that keep drug prices high by limiting generic competition. This information is not only critical for advocates, but also for purchase agencies as well as generic producers who want to evaluate their "freedom to operate" and to produce, import, and export a certain health product to a given territory. However, patent status information is not always easy to access and analyze, even when it is available. The aim of this *Isoniazid/Rifapentine (3HP) Access Roadmap and Patent Landscape* is to detail the status of patent applications for the adult and pediatric 3HP FDCs in countries around the world. Applications for these two patents are still pending in the majority of the 69 countries/territories where Sanofi filed them.

The information contained in the *Roadmap* is intended to inform the access strategies of TB-affected communities, civil society organizations, national patent examiners, generic producers, and other stakeholders. After reading this document, patent examiners will understand why Sanofi's patent claims do not fulfill patentability criteria. Activists from TB-affected communities and civil society can use this document as a key reference to develop evidence-based arguments to challenge Sanofi's patent applications through either pre- or post-grant oppositions or revocation applications, or through the use other legal tools to bypass potential monopoly control of 3HP. In fact, activists in India and Thailand have already acted on this information by filing pre-grant oppositions against both patents at the Indian Patent Office in Kolkata and at the Thai Department of Intellectual Property in Bangkok.[2,3]

Understanding the patent landscape for 3HP FDCs for adults and children is essential for devising strategies to unlock access to TB preventive therapy (TPT). TPT is one of the most powerful ways to treat TB infection. It protects people who are already infected with the TB bacterium from falling ill with active TB disease, and it shields people who are uninfected but at risk of TB exposure from getting infected in the first place. Among available TPT regimens, 3HP is one of the shortest and safest.[4] A closely related regimen called 1HP consists of rifapentine and isoniazid taken together daily for one month. The rifapentine-based TPT regimens 3HP and 1HP are quickly becoming the preferred choice for many providers, patients, and national TB programs. We need to give more people access to TPT regimens like 3HP and 1HP if we hope to end TB in our communities.

[1] For more information on the pharmaceutical properties of rifapentine and isoniazid, see Appendices 3 and 4.

[2] The patent challenges in India were lodged by the Delhi Network of Positive People and TB survivor and activist Ganesh Acharya of Mumbai, with support from the Third World Network (TWN). For a copy of each opposition, see: https://www.patentoppositions.org/en/drugs/isoniazid-rifapentine-3hp/patent_oppositions/5dccee99d2708f0005f65664 (adult FDC) AND https://www.patentoppositions.org/en/drugs/isoniazid-rifapentine-3hp/patent_oppositions/5dccf4c6d2708f0005f6568e (pediatric FDC).

[3] The patent challenges in Thailand were lodged by the AIDS Access Foundation.

Background on Patents and Terminology

A **patent** is an intellectual property title that grants its holder an exclusivity to operate for a period of at least 20 years. The minimum period of 20 years is one of the standards required of all the World Trade Organization (WTO) members since the adoption of The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) in 1995. Least-developed countries have a transition period until 2033 before they must grant patents on pharmaceutical products.

Although the **TRIPS Agreement** compels member states to grant patents, TRIPS also provides leverage to countries to adapt their national patent/intellectual property laws, and to incorporate pro-health safeguards. One of these **flexibilities** is the possibility for countries to define what is patentable or not. For instance, under some national laws, combinations of two pharmaceutical products are not patentable. In these countries, a simple FDC of two drugs such as isoniazid and rifapentine would not receive a patent. Another flexibility creates the opportunity for third parties to send "observations" (e.g., in the Brazilian patent law) or "oppositions" (e.g., in the Indian Patent Act) before the patent office makes a decision on whether or not to grant a patent. This is often referred to as "**pre-grant opposition**." Under other laws, third parties can submit **post-grant oppositions** after a patent is granted (e.g., in the European Patent Convention). The window in which third parties can submit oppositions varies from country to country.

An additional flexibility under TRIPS is the possibility for governments to issue non-voluntary licenses to a third party (either public or private). This is referred to as a "**compulsory license**" or "compulsory license for governmental use." A compulsory license does not have the effect of revoking a patent, but it does allow the country that issues it to import or locally produce the product without the consent of the patent holder. The conditions of a non-voluntary license—including the rationale behind the decision of authorities to issue this license, as well as the specific terms of the license, including its duration, royalties paid to the patent holder, and volume of product manufactured—are flexible. Under the TRIPS agreement, there is always the possibility for national courts to revoke a patent or to issue a non-voluntary license. The Doha Declaration on the TRIPS Agreement and Public Health (2001) reaffirms the use of non-voluntary licenses and compulsory licenses to protect public health and promote access to medicines for all.[5]

These flexibilities are critical access safeguards, but another vital and often overlooked flexibility is the stringent and thorough examination of patent applications by national patent offices. Even in some countries with strict patentability criteria, it is not uncommon to see patents that obviously fail to fulfill the patentability criteria granted (e.g., in India).[6] Perversely, in other countries, the law explicitly requires that patent examiners not examine the legitimacy of an application and grant a patent if basic administrative requirements are fulfilled (e.g., in Nigeria).

In the tables that follow in Appendix 1, "**granted**" means that a patent was granted, for a minimum period of 20 years starting from the priority date (and/or depending on the national law from the filing date of the application in the given country or the date of filing the Patent Cooperation

[4] For a summary of the efficacy and safety of 3HP and 1HP, see : Frick M. An activist's guide to rifapentine for the treatment of TB infection. New York: Treatment Action Group ; 2019. https://www.treatmentactiongroup.org/publication/an-activists-guide-to-rifapentine-for-the-treatment-of-tb-infection/

[5] Doha Declaration/WTO (2001): "5. Accordingly and in the light of paragraph 4 above, while maintaining our commitments in the TRIPS Agreement, we recognize that these flexibilities include: [...] .(b) Each Member has the right to grant compulsory licenses and the freedom to determine the grounds upon which such licenses are granted. (c) Each Member has the right to determine what constitutes a national emergency or other circumstances of extreme urgency, it being understood that public health crises, including those relating to HIV/AIDS, tuberculosis, malaria and other epidemics, can represent a national emergency or other circumstances of extreme urgency." See: https://www.wto.org/english/res_e/booksp_e/ddec_e.pdf

Treaty application). **"Filed"** means that the patent application was filed and that the patent office has not yet reviewed the application and/or taken a decision on the application or published the decision. "**Not filed**" means that no patent application could be found for a given patent with the relevant patent office. This means that generic producers would have a freedom to operate in these territories. "**Withdrawn**" means that the applicant withdrew the application. Applications might be withdrawn for several reasons, including anticipation that the application would be rejected. "**Rejected**" means that the application was not approved by the patent office. A rejection can follow the decision of the patent officers after their examination or follow from a pre-grant opposition submitted by a third party. "**Opposed**" means that a third party (e.g., a generic producer, a civil society organization, etc.) sent the patent office in a given country arguments questioning the legitimacy of granting the patent with respect to the patentability criteria under the country's national patent law. "**Revoked**" means that the patent office decided to accept the arguments of the opposition for an already granted patent and/or that some administrative requirements were not fulfilled (e.g., a patent holder stopped paying the yearly fees to maintain the patent).

Patent Examinations and Patent Oppositions

Patent examinations and patent opposition are strategies to guard against the abuse of the patent system by pharmaceutical companies. Patents are supposed to reward innovation. The exclusivity title that is granted to the holder of a patent is a reward given in exchange for disclosing information on the invention. The idea is that once a patent is granted, this information will enter the public domain and the invention will benefit society and function as a common good. This is part of the social contract underlying patents—in order to reap the rewards granted by a patent, inventors must facilitate public use of the invention.

A newly marketed medicine can both constitute a major improvement for the people who need it, and at the same time fail to fulfill the basic requirements of patentability, such as demonstrating an inventive step and non-obviousness. For instance, patents on sofosbuvir, the backbone of the new treatments used against hepatitis C virus, were rejected in different countries (e.g., Argentina[7]) for lack of inventiveness and because the invention had already been disclosed/published in other countries. Another example is GlaxoSmithKline's trizivir, a combination tablet of three drugs used to treat HIV (lamivudine, zidovudine, and abacavir sulfate). In response to a pre-grant patent opposition lodged by generic drug manufacturer Cipla in 2006, GlaxoSmithKline announced that it would withdraw its patent application in India "in the public interest." Cipla had argued that the combination of drugs in trizivir did not merit a patent under Section 3(d) of the Indian Patents Act, which disallows patents on combinations of already known substances.[8]

The patent applications filed by Sanofi in 2014 cover two combination formulations of isoniazid and rifapentine for use in the prevention of TB. Sanofi was not the first entity to discover or commercialize either isoniazid or rifapentine; these compounds were discovered decades ago and have since become core components of the most common regimens to prevent and treat TB (see next section). How can Sanofi call combinations of two decades-old and commonly used compounds innovation? If some patent laws and patent examiners are equipped to recognize and reject such spurious claims, other countries will most likely grant these patents, which could give Sanofi a monopoly on these 3HP FDC products, potentially blocking generic competition. Such a monopoly would prevent people with TB—children, adults, or both—from accessing affordable, patient-friendly forms of 3HP.

[6] For example, Dr Feroz Ali analyzed the error rate at the Indian patent office (IPO): "This report identifies pharmaceutical drug patents granted in likely contravention of anti-evergreening provisions under section 3 of the Indian Patents Act, from a cohort of 2293 patents granted between 2009 and 2016. An estimate of the rate at which the Indian Patent Office (IPO) erroneously grants such patents, as well as the rationale for grants were arrived at by analysing the prosecution history of some grants and the claim language of all granted patents. [...] Inconsistencies in practice exist at the IPO, even while dealing with different secondary patents for the same drug. Our earlier study demonstrated several instances where the IPO granted some secondary patents for a drug, while rejecting others. Differing standards may impact the access to medicines for a variety of diseases." Ali F, Rajagopal S, Raman V, John R. Pharmaceutical patent grants in India: how our safeguards against evergreening have failed, and why the system must be reformed. New Delhi: accessibsa; 2018. https://accessibsa.org/media/2018/04/Pharmaceutical-Patent-Grants-in-India.pdf

[7] Make Medicines Affordable. Argentina: Patent rejected on hepatitis C drug, sofosbuvir. December 2017. http://makemedicinesaffordable.org/en/argentina-patent-rejected-on-hepatitis-c-drug-sofosbuvir/

[8] Unnikrishnan CH. GSK withdraws Trizivir patent application in public interest. Livemint. 10 October 2007. https://www.livemint.com/Home-Page/kx90CkvbspY4ApeAOxPFZP/GSK-withdraws-Trizivir-patent-application-8216in-public-i.html

Rifapentine and Isoniazid: History and Patent Status Timeline

Rifapentine: A Global Public Good

Rifapentine is a member of a class of TB drugs called rifamycins, along with the drugs rifampicin and rifabutin. The rifamycins are one of the oldest TB drug classes, first discovered in 1957 in northern Italy and synthesized by Lepetit Labs (Gruppo Lepetit SpA). Scientists at Lepetit Labs discovered the first rifamycin—rifamycin B—while investigating the antibiotic properties of natural metabolites produced by the bacterium *Nocardia mediterranei,* isolated from a soil sample brought to the lab from pine forests near the town of St. Raphael on the French Riviera.[9] Although rifamycin B proved inactive, subsequent modifications of this compound led to the discovery of rifamycin SV and the three rifamycin compounds used in TB treatment today: rifampicin, rifapentine, and rifabutin.[10]

Lepetit Labs first synthesized rifapentine in 1965 (the same year as rifampicin).[11,12,13] The earliest patent on a rifamycin compound dates to a patent filing in the United Kingdom on rifamycin B by Lepetit Labs in 1958. Lepetit Labs went on to obtain patents on "derivatives of rifamycin SV" in the United states in 1967 and on "piperazinylimino rifamycins," including the chemical composition of rifapentine, in 1977. The U.S. Food and Drug Administration (FDA) first approved rifapentine for use in the treatment of active TB disease in 1998. Sanofi updated rifapentine's approved indication with the U.S. FDA to include its use as preventive therapy when used in combination with isoniazid in 2014.[14] This expanded indication resulted from publicly funded research described below.

Nearly four decades elapsed between the initial patent filings on rifapentine and the drug's approval by the U.S. FDA and endorsement by the World Health Organization (WHO) as an essential medicine and key component of the 3HP and 1HP regimens for preventing TB. This journey was long and not always straightforward. Along the way, rifapentine "has had many private owners and mostly public benefactors."[15] This complex corporate parentage unfolded as rifapentine was traded from one company to another through a series of pharmaceutical industry mergers and acquisitions. As summarized in Treatment Action Group's 2018 *Pipeline Report*, "Sanofi inherited rifapentine when it acquired the pharmaceutical company Aventis in 2004. Aventis, in turn, obtained rifapentine in 1999 through the acquisition of Hoechst-Marion Roussell, the corporate child of a merger between Hoechst AG and Marion-Merrell-Dow, which itself came into possession of rifapentine when its forbears Merrell-Dow and Dow Chemical purchased a major stake in Lepetit Labs."[16]

Although owned by a succession of pharmaceutical companies, rifapentine's clinical development relied on public funding. The phase III trial that established the safety and efficacy of 3HP in preventing TB disease was sponsored, funded, and conducted by the Tuberculosis Trials Consortium at the U.S. Centers for Disease Control and Prevention (CDC). The 1HP regimen was developed by the AIDS Clinical Trials Group at the U.S. National Institutes of Health (NIH). Other public funders of rifapentine clinical trials include the U.S. Agency for International Development, the International

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[9] Margalith P, Beretta G. Rifomycin XI taxonomic study on streptomyces mediterranei nov. sp. Mycopathologia et mycologia applicata. 1960;13(4):321–330. doi: 10.1007/BF02089930.
[10] Sensi P. History of the development of rifampin. Rev Infect Dis. 1983;5(S3):S402–6.
[11] Antibiotic rifamycin b and method of production. U.S. patent no. 3150046A. Filed: 04 March 1960. Granted: 22 September 1964. Piero Sensi, Pinhas Margalith. Lepetit SpA. https://patents.google.com/patent/US3150046A/en?oq=US3150046A
[12] Derivatives of rifamycin sv. U.S. patent no. 3342810A. Filed: 09 July 1965. Granted: 19 September 1967. Nicola Maggi, Piero Sensi. Lepetit SpA. https://patents.google.com/patent/US3342810A/en
[13] Piperazinylimino rifamycins. U.S. patent no. 4002752A. Filed: 26 February 1976. Granted: 11 January 1977. Cricchio Renato, Arioli Vittorio. Gruppo Lepetit SpA. https://patents.google.com/patent/US4002752
[14] Sanofi. Sanofi receives FDA approval of Priftin® (rifapentine) tablets for the treatment of latent tuberculosis infection. 2 December 2014. http://www.news.sanofi.us/press-releases?item=136875
[15] Frick M. The TB prevention pipeline: rifapentine-based TB preventive therapy—technically available, but where is it? New York: Treatment Action Group; 2018. https://www.treatmentactiongroup.org/resources/pipeline-report/2018-pipeline-report/
[16] Ibid.

Maternal, Pediatric, Adolescent AIDS Clinical Trials Network at the U.S. NIH, the European and Developing Countries Clinical Trials Partnership, and Unitaid. While Sanofi made contributions to this research agenda—for example, it provided study drug for most of these clinical trials and conducted a small drug-drug interaction study between rifapentine and an HIV medication called efavirenz—public money underwrote the vast majority of this research.[17]

Isoniazid: A Global Public Good

Isoniazid is one of the oldest—and still one of the most important—TB drugs. Like rifapentine, it should be considered a global public good. Isoniazid "opened the modern era of antituberculosis chemotherapy" when introduced into clinical use in 1952 (it was approved by the U.S. FDA the same year).[18] In 1951, scientists at three pharmaceutical companies—Hoffmann-La Roche, Squibb, and Bayer Chemical—synthesized isoniazid at around the same time in what has been called "an astonishing therapeutic coincidence" and "one of the most extraordinary pharmaceutical coincidences of all time."[19,20] With unusual candor, executives at Hoffman-La Roche and Squibb stated that they had no idea which company demonstrated the anti-tuberculosis activity of isoniazid first.[21] The TB field avoided a three-way legal battle over isoniazid patent rights when evidence surfaced that isoniazid was first discovered and synthesized by two doctoral students in Czechoslovakia in 1912 (Hans Meyer and Joseph Malley).[22] Thus, primary patents on isoniazid were precluded on the basis of prior art demonstrating lack of novelty. A company history of isoniazid's discovery published by Roche concedes: "Isoniazid, the active substance that Roche brought to market as Rimifon, was known long before it was found to be effective against tuberculosis....Isoniazid could not have been patented, simply because it was no longer new. Novelty is mandatory for patentability."[23] Additionally, no company could obtain process patents[24] on the synthesis or manufacture of isoniazid because "various manufacturing processes were already known, [so] there was no way of achieving anything like effective [patent] protection even with process patents."[25] Roche did obtain a use patent[26] on isoniazid in the United States, but this did not block the entry of other manufacturers.[27]

The lack of isoniazid patents meant that any interested manufacturer could make and sell the drug. Within a year, eight companies brought an isoniazid product to market, each under a different brand name. The market competition enabled by the lack of monopoly ownership rapidly drove down the price of isoniazid. (Roche reports the price of isoniazid active pharmaceutical ingredient dropped from US$200–300/kg to less than US$18/kg within the space of a year.)[28] Isoniazid was as potent as it was affordable, and the drug soon became the backbone of TB treatment regimens—from the early breakthrough "triple therapy" of isoniazid-streptomycin-PAS to the four-drug, six-month regimen still recommended by the WHO for treating drug-susceptible TB today. In addition, isoniazid became the standard of care for preventing TB when given to people infected by TB but without active disease. Isoniazid preventive therapy (IPT)—in which isoniazid is taken daily for six, nine, 12, or up to 36 months—remains an important TPT regimen, although the rifapentine-based regimens 3HP and 1HP are shorter, easier to complete, and carry a lower risk of liver toxicity.

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[17] Ibid.
[18] Murray J, Schraufnagel D, Hopewell P. Treatment of tuberculosis: a historical perspective. Ann Am Thorac Soc. 2015;12(12):1749–1759. doi: 10.1513/AnnalsATS.201509-632PS.
[19] Ibid.
[20] Murray J. A century of tuberculosis. Am J Respire Cit Care Med. 2004;(169):1181–1186. doi: 10.1164/rccm.200402-140OE.
[21] McDermott W. The story of INH. J Infect Dis. 1969;119(6):678–83. doi: 10.1093/infdis/119.6.678.
[22] Meyer H, Mally J. On hydrazine derivatives of pyridine carbonic acids. Monatshefte Chemie verwandte Teile anderer Wissenschaften. 1912;23: 393-414.
[23] Pauser S. Isoniazid (Rimifon): first specific against tuberculosis. In: Lifesavers for Milions. Eds. S Pauser, Morgeli C, Schaad U. Basel: Roche; 2012. https://www.roche.de/res/literatur/153/Lifesavers-for-millions-original-0e0c6031240f3e63ee17b4db61146b93.pdf
[24] Process patents (sometimes called "method patents") apply to a series of steps for reaching a certain outcome, e.g., manufacturing a drug molecule. Process patents are distinct from other patent types (e.g., composition of matter, machine, and article of manufacture).
[25] Pauser S. Isoniazid (Rimifon).
[26] Use patents protect a specific use of a known molecule, often for a purpose different from that initially intended by the patent owner. For example, the same drug compound may be used to treat different forms of a disease (e.g., TB infection versus drug-susceptible TB versus drug-resistant TB).
[27] Compositions for combatting tuberculosis. U.S. Patent No. 2596069A. Filed: 07 March 1952. Granted: 06 May 1952. Fox Herman Herbert. F Hoffmann La Roche AG. https://patents.google.com/patent/US2596069A/en?oq=2596069
[28] Pauser S. Isoniazid (Rimifon).

Timeline: Isoniazid and Rifapentine History and Patent Status

1912	Isoniazid first discovered and synthesized by two doctoral students in Czechoslovakia.
1951	Isoniazid synthesized by Hoffman-La Roche, Squibb, and Bayer Chemical.
1957	Rifamycins discovered by Lepetit Labs.
1958	First patent on a rifamycin compound (rifamycin B) filed by Lepetit Labs in the U.K.
1965	Patent application filed by Lepetit Labs for "derivatives of rifamycin SV."
1976	Patent application filed by Lepetit Labs on a chemical composition of rifapentine.
1998	Rifapentine approved by the U.S. FDA for treating active TB disease.
2004	Sanofi inherits rifapentine with the acquisition of Aventis.
2011	Results of U.S. CDC-funded study demonstrating safety and efficacy of the combination of rifapentine and isoniazid (3HP regimen) for preventing TB published in the New England Journal of Medicine. U.S. CDC recommends 3HP regimen as preventive therapy in people with TB infection.
2014	Rifapentine approved by U.S. FDA for preventing TB when used with isoniazid. Patent applications filed by Sanofi on rifapentine and isoniazid fixed-dose combinations (FDCs). WHO recommends 3HP as TB preventive therapy.
2019	Sanofi transfers its R&D activities in infectious diseases to Evotec.
2034	Expected expiration date on the two patents filed by Sanofi on the FDCs of rifapentine and isoniazid.

Sanofi's 3HP Patent Claims

The following tables present the claims in the two patent applications as filed by Sanofi. Note that the claims might have been amended country by country.

Table 1. Sanofi's Claims Under the Adult 3HP FDC Patent Application[29]

ANTI-TUBERCULOSIS STABLE PHARMACEUTICAL COMPOSITION IN A FORM OF A COATED TABLET COMPRISING GRANULES OF ISONIAZID AND GRANULES OF RIFAPENTINE AND ITS PROCESS OF PREPARATION Pub. No.: W0/2015/011161 Pub. Date: January 29, 2015 International Application No.: PCT/EP2014/065761 International Filing Date: July 22, 2014	
Claim Content	Patent on Composition, Process, Main Compound, etc.
1. An oral pharmaceutical fixed dose composition for use in the treatment of tuberculosis, said oral pharmaceutical composition comprising: a) granules comprising isoniazid and at least one intragranular excipient, b) granules comprising rifapentine and at least one intragranular excipient, and c) at least one extragranular excipient.	Composition
2. An oral pharmaceutical composition according to claim 1, wherein said oral pharmaceutical composition is chemically stable.	Composition
3. An oral pharmaceutical composition according to claim 1 or 2, wherein said oral pharmaceutical composition is in the form of a coated tablet.	Composition
4. An oral pharmaceutical composition according to any one of the claims 1 to 3, wherein said oral pharmaceutical composition is in the form of a coated bilayer tablet comprising: - a layer comprising isoniazid granules (a) and at least one extra-granular excipient, - a layer comprising rifapentine granules (b) and at least one ex-tragranular excipient, and - a film coating.	Composition
5. An oral pharmaceutical composition according to any one of the claims 1 to 4, wherein the ratio of rifapentine to isoniazid is comprised from 5:1 to 1:0.5, preferably the ratio is 1:1.	Composition
6. A process for the preparation of an oral pharmaceutical composition according to any one of the claims 1 to 5, characterized in that it comprises distinct steps of granulating isoniazid and granulating rifapentine.	Process
7. A process according to claim 6, characterized in that the preparation of the granules is made by wet granulation, preferably in an aqueous solvent.	Process

[29] Information in the table is reproduced from the WIPO Patentscope database: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015011161

8. A process according to claim 6 or 7, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) preparing the rifapentine granules, c) mixing the granules obtained from steps a) and b) with the extragranular excipients, d) compressing the mixture of step c) to obtain tablets, and e) film coating the tablets.	Process
9. A process according to claims 6 to 8, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) mixing the granules obtained from step a) with at least a part of the extragranular excipients, c) preparing the rifapentine granules, d) mixing the granules obtained from step c) with the remaining part of the extragranular excipients, e) compressing the mixture of steps b) and d) to obtain bi-layer tablets, and f) film coating the tablets.	Process

Table 2. Sanofi's Claims Under the Pediatric 3HP FDC Patent Application[30]

ANTI-TUBERCULOSIS STABLE PHARMACEUTICAL COMPOSITION IN A FORM OF A COATED TABLET COMPRISING GRANULES OF ISONIAZID AND GRANULES OF RIFAPENTINE AND ITS PROCESS OF PREPARATION Pub. No.: WO/2015/011162 Pub. Date: January 29, 2015 International Application No.: PCT/EP2014/065762 International Filing Date: July 22, 2014	
Claim Content	Patent on Composition, Process, Main Compound, etc.
1. An oral pharmaceutical fixed dose composition in a form of a dispersible tablet for use in the treatment of tuberculosis, said oral pharmaceutical composition comprising: a) granules comprising isoniazid and at least one intragranular excipient, b) granules comprising rifapentine and at least one intragranular excipient, and c) at least one extragranular excipient.	Composition
2. An oral pharmaceutical composition according to claim 1, wherein said oral pharmaceutical composition is chemically stable.	Composition
3. . An oral pharmaceutical composition according to any one of claim 1 or 2, wherein said oral pharmaceutical composition is in the form of a dispersible bilayer tablet comprising: - a layer comprising isoniazid granules (a) and at least one extragranular excipient, and - a layer comprising rifapentine granules (b) and at least one extragranular excipient.	Composition
4. An oral pharmaceutical composition according to any one of the claims 1 to 3, wherein the ratio of rifapentine to isoniazid is comprised from 3:1 to 1:0.5, preferably the ratio is 1:1.	Composition
5. A process for the preparation of an oral pharmaceutical composition according to any one of the claims 1 to 4, characterized in that it comprises distinct steps of granulating isoniazid and granulating rifapentine.	Process
6. A process according to claim 5, characterized in that the preparation of the granules is made by wet granulation, preferably in an aqueous solvent.	Process
7. A process according to claim 5 or 6, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) preparing the rifapentine granules, c) mixing the granules obtained from steps a) and b) with the extragranular excipients, and d) compressing the mixture of step c) to obtain tablets.	Process

[30] Information in the table reproduced from the WIPO Patentscope database: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015011162

8. A process according to claims 5 to 7, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) mixing the granules obtained from step a) with at least a part of the extragranular excipients, c) preparing the rifapentine granules, d) mixing the granules obtained from step c) with the remaining part of the extragranular excipients, and e) compressing the mixture of steps b) and d) to obtain bi-layer tablets.	Process

Analyses of Sanofi's Patent Claims by Patent Examiners

U.S. Patent and Trademark Office Ruling

The United States Patent and Trademark Office (USPTO) has twice issued negative opinions rejecting Sanofi's application for a patent on the adult 3HP FDC (US20160158157/ WO2015011161).[31] Under United States law, patent applications are made directly to the USPTO, which assesses each application in relation to five criteria that must be met: 1) patentable subject matter, 2) utility, 3) novelty, 4) non-obviousness, and 5) disclosure. In the case of the adult 3HP FDC, the USPTO examiner has twice rejected Sanofi's application on the grounds of obviousness. As basis for its negative decisions, the USPTO cited Title 35 of United States Code section 103 (35 U.S.C. §103); this is the section of the U.S. legal code which forms the basis of rejections on grounds of obviousness. It reads:

> "*A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.*"

Essentially, 35 U.S.C. §103 requires that an invention represent "a nontrivial extension of what was known." An invention might be new and useful, but if it does not represent a significant enough technical advance over prior art, then it does not merit a patent. **Prior art** is constituted by all the information that have been made public in any form in the public domain before a given date that might be relevant for a patent's claim to originality. USPTO examiners have issued a series of five rejections of Sanofi's patent claims on 07-01-2016 (non-final rejection), 01-09-2017 (final rejection), 05-24-2018 (non-final rejection), 10-03-2018 (final rejection), and 04-08-2019 (non-final rejection). In each, they rejected the various claims made in the applications as failing to meet the standard of non-obviousness in light of the teachings of prior art. The USPTO examiners relied on the following sources of prior art in reaching these decisions:

1. Singh et al, U.S. Patent 7195769 B2, published 03/27/2007, "Pharmaceutical compositions of anti-tubercular drugs and process for their preparation."

2. Sen et al, International application published under the PCT WO 02/087547 A1, published 11/07/2002, "An improved process for preparation of four-drug anti-tubercular fixed-dose combination."

3. Badawy et al, U.S. Patent application publication 2005/0059719 A1, published 03/17/2005, "Solid dosage formulation containing a Factor Xa inhibitor and method."

4. Hwang et al, Korean patent number KR2010090138A, published 08/13/2010, "Oral solid preparation for treatment and prevention of tuberculosis."

[31] See WIPO Patentscope database: https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2015011161&tab=PCTBIBLIO

2019 USPTO Rejection of Adult 3HP FDC Patent

The text below reproduces the most recent USPTO decision made on April 8, 2019 to illustrate how one national patent office judged Sanofi's patent application on the adult 3HP FDC as failing to meet the standard of non-obviousness in light of prior art. The full record of actions on this application before the USPTO can be found at the link in the footnote.[32]

"*This is a new ground of rejection.*

Claim 1–19 and 21 is/are rejected under 35 U.S.C. 103 as being unpatentable over Singh et al. (US Patent 7195769 B2, Published 03/27/2007) in view of Hwang et al. (Korean Patent Application Publication 2010090138 A, Published 08/13/2010).

The claims are directed to an oral fixed dose tablet comprising a first layer comprising isoniazid granules comprising isoniazid and an intragranular excipient such as provodone and extragranular excipient, a second layer comprising rifapentine granules comprising rifapentine and an intrgranular excipient such as microcrystalline cellulose and extragranular excipient such as sodium ascorbate; wherein the tablet has a film coating. The claims are further directed to the ratio of rifapentine to isoniazid is from 5:1 to 1:0.5. The claims are further directed to a process of preparing the fixed dose tablet.

Singh et al. teach forming a tablet-in-tablet (bilayer tablet) formulation comprising forming rifapentine granules comprising 150 rifapentine and microcrystalline cellulose (intragranular excipient) by wet granulation, combining the granules with magnesium stearate, disodium edetate, sodium lauryl sulfate, and purified talc (extragranular excipients) and compressed into a tablet, forming isoniazid granules comprising 150mg isoniazid and starch paste (intrgranular excipient) by wet granulation, combining the granules with magnesium stearate, disodium edetate, sodium lauryl sulfate, and purified talc (extragranular excipients) compressing along with rifapentine tablet to form one tablet and providing the tablet with a film coating; the ratio of rifapentine to isoniazid is 1:1 (column 16, lines 17–67 and column 17, lines 1–21). In an alternative tablet-in-tablet formulation embodiment isoniazid is granulated with providone (column 10, lines 1–65). The tablet is fixed dose tablet for treating tuberculosis (column 1, lines 10–17).

Singh et al. lack a teaching wherein the extragranular excipient also includes sodium ascorbate.

Hwang et al. teach a solid oral dosage of rifapentine for the treatment or prevention of tuberculosis comprising an antioxidant being sodium ascorbate (abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time of the instant invention to add providone to the granulate of example 29 of Singh et al. and have a reasonable expectation of success. One would have been motivated to do so since Singh et al. teach this as an alternate embodiment.

It would have been prima facie obvious to one of ordinary skill in the art at the time of the instant invention to add sodium ascorbate to the extragranular component of the bi-layer tablet taught by Singh et al. and have a reasonable expectation of success. One would have been motivated to do so in order to add antioxidant activity to the formulation of Singh et al. comprising rifapentine. Therefore, the instant claims are rendered obvious by the teachings of the prior art."

[32] For the record of materials, opinions, and correspondance on this patent application before the USPTO, see: https://portal.uspto.gov/pair/PublicPair (search patent application no. 14/906876).

Patent Cooperation Treaty International Search Authority Opinion

The International Search Authority (ISA) is part of the Patent Cooperation Treaty (PCT) at the World Intellectual Property Organization (WIPO).[33] The PCT allows for the applicant to file one patent application in a centralized place and to select which countries to send the application to. When a patent application is filed with the PCT, the ISA analyzes the claims with respect to novelty, inventive step, and other patentability criteria. This analysis proceeds from the ISA's search of the prior art (technical literature and published patent documents related to the application) and is published The International Search Authority (ISA) is part of the Patent Cooperation Treaty (PCT) at the World Intellectual Property Organization (WIPO).[33] The PCT allows for the applicant to file one patent application in a centralized place and to select which countries to send the application to. When a patent application is filed with the PCT, the ISA analyzes the claims with respect to novelty, inventive step, and other patentability criteria. This analysis proceeds from the ISA's search of the prior art (technical literature and published patent documents related to the application) and is published in an International Search Report (ISR).

Based on the ISR, the ISA issues a written opinion about whether the application meets the patentability criteria of novelty, inventive step, and industrial application. **The ISR is not intended to replace patent application examinations at the national level.** Many countries have national laws that establish stricter patentability standards than those applied in ISA opinions. Additionally, ISA analyses may be incomplete. Therefore, these opinions should not be taken as judgements based on a "maximalist" or "most stringent" standard; where the ISA judges a claim as fulfilling patentability criteria based on novelty or inventive step, many national patent offices may take the opposite decision. For these reasons, the actual examination and decision regarding the application happen at the country/regional level. Moreover, the ISA opinion on the patent claims is not binding on national/regional patent offices.

Even with these caveats and limitations, ISA opinions provide valuable information about patentability in regards to prior art.

In a written opinion, the ISA analysis for the patent W0/2015/011161 (the adult 3HP FDC) concluded that while all the claims presented by Sanofi fulfill the requirements of industrial application, only several claims fulfil the novelty criteria and none fulfill the inventive step criteria. This opinion highlights numerous grounds by which national patent offices might reject the adult 3HP FDC patent application, particularly with regard to lack of inventive step and failure to demonstrate non-obviousness.

Based on its analyses, the ISA concluded that for patent W0/2015/011162 (the pediatric 3HP FDC) all the claims presented by Sanofi fulfill the requirements on industrial application, none fulfill the inventive step requirements, and only the claims 3 (composition) and claims 5–8 (on the process) meet the novelty aspect. This opinion highlights numerous grounds by which national patent offices might reject the pediatric 3HP FDC patent application, particularly with regard to lack of inventive step and failure to demonstrate non-obviousness. The full text of the ISA reports can be found here (adult 3HP FDC) and here (pediatric 3HP FDC).

Prior Art Cited in Patent Oppositions

The pre-grant patent oppositions filed in India by Ganesh Acharya and DNP+ point to the following prior art as grounds on which the Indian Patent Office should reject Sanofi's applications for patents on the adult and pediatric 3HP FDC formulations. Many of the sources cited by Acharya and DNP+ are also referenced in the negative USPTO judgement on the patentability of the adult 3HP FDC (see above). National patent examiners should consult these sources when determining whether the claims in Sanofi's applications fulfill local patentability criteria.

[33] The patent cooperation treaty (PCT) is a treaty signed in 1970 to allow patent applicants to file international patent applications. The PCT is attached to WIPO (World International Property Organization).

Table 3: Prior Art Cited in 3HP Patent Oppositions Filed in India

Patent No.	Title and Publication Date	Excerpt of Relevant Teachings
CN1217912 (A)	Composite rifapentine preparation and preparing method therefore 06/02/1999	"A compound rifapentine preparation for treating tuberculosis, especially the recurrent pulmonary tuberculosis is made up of rifapentine, other antituberculotics such as isoniazid, and medicinal carrier and features high curative effect."
US7195769 B2	Pharmaceutical compositions of anti-tubercular drugs and process for their preparation 03/27/2017	"A pharmaceutical composition of anti-tubercular drugs for oral use comprising rifampicin and/or isoniziad wherein the bioavailability of rifampicin and/or other drugs is enhanced." Also discloses a tablet-in-tablet formulation of rifapentine and isoniazid in a ratio of 1:1.
ZA9706795B	Pharmaceutical formulation 03/20/1998	"Discloses a dispersible tablet formulation of isoniazid and rifampicin as active ingredients with one or more disintegrating agents for the treatment of TB in children."
CN1408354A	Compound preparation containing rifampicin and isoniazid and its preparing method 04/09/2003	"A compound preparation containing rifampicin isoniazid, characterized in that a chip pharmaceutically therapeutically effective amount of a vector containing rifampicin and medicine, an outer layer to be a therapeutically effective amount of medicine comprising isoniazid and bilayer chip acceptable carrier."
WO2002087547A1	An improved process for preparation of four- drug anti-tubercular fixed dose combination	"An improved process for preparation of a composition comprising fixed dose combination (FDC) of four anti-tubercular drugs viz. rifampicin, isoniazid, pyrazinamide and ethambutol hydrochloride, which improves the dissolution of poorly soluble drug rifampicin and hence improve its bioavailability."
US20120027853A1	Process for preparation of anti-tubercular combination and pharmaceutical composition prepared there from 02/02/2012	"A process for preparing a pharmaceutical composition comprising four antitubercular drugs: rifampin or a pharmaceutically acceptable salt thereof, isoniazid or a pharmaceutically acceptable salt thereof, pyrazinamide or a pharmaceutically acceptable salt thereof and ethambutol or a pharmaceutically acceptable salt thereof, wherein rifampin and isoniazid are in separate layers."
KR2010/0090138	Oral solid preparation for treatment and prevention of tuberculosis 08/13/2010	"A solid pharmaceutical dosage form for treating tuberculosis comprising rifapentine, a binder, stabilizers like sodium ascorbate and a diluent. This document also describes the preparation of rifapentine granules using wet granulation process comprising rifapentine and 26 microcrystalline cellulose (diluent), hydropropyl cellulose (binder) disodium EDTA (stabilizers) (intragranular excipients)."
IN500/BOM/96 (application no.)	An antitubercular pharmaceutical composition 05/10/1997	"Teaches that rifampicin is stable in solid state but it's stability in the presence of moisture and other anti-tubercular agents is questionable.[...]further goes on to teach that that among the tablet formation method, wet granulation is one of the most advantageous method since it produces products with low moisture content and hence increases their stability, thus providing stable anti-tubercular drugs."

Patent Landscape Overview and Analysis

Methodology for the Patent Landscape

Both patent applications WO2015011161 and WO2015011162 were first filed in India. Under the Indian Patent Act, the applicant has to disclose the full list of the countries where the patent applications will be filed ("form 3"). Under the PCT, the applicant has 30 months from the priority date to send the application for a given patent to all the countries where they want to file. The "form 3" was therefore the starting point of our search as it enabled us to see the countries where the two patent applications had been filed. Communication with the Medicines Patent Pool (MPP) helped us to consolidate some of this information. We also consulted the databases PatentScope from WIPO and EspaceNet from the European Patent Office/EPO, as well as other regional and national databases, when accessible.

Patent databases consulted:	
Patentscope (WIPO)	Espacenet (EPO)
Orangebook (U.S. FDA)	HealthCanada
Medspal (MPP)	INPI (Brazil)

Summary of Major Findings

The patent landscape shows that Sanofi used the same strategy for the two patents, one covering the adult form (film-coated tablet) and one covering the pediatric form (dispersible tablet). Applications for the two patents were filed in 69 countries, counting all the EPO members individually. In December 2019, Sanofi withdrew both patent applications before the EPO. [34,35] The timing of these withdrawals closely follows the lodging of patent oppositions in India and Thailand. Sanofi also withdrew both applications before the Indonesia patent authority in November 2019. The applications remain pending in all other countries where they were filed, except the United States and China (where the pediatric 3HP FDC patent was granted) and Australia, Russia, and South Africa (where both the adult and pediatric 3HP FDC patents were granted). The adult FDC patent was rejected in the United States and China (though the decision in the United States is under appeal).

Out of the 30 high-TB-burden countries recognized by WHO, Sanofi has filed patents in ten: Brazil, China, India, Indonesia, Nigeria, the Philippines, Russia, South Africa, Thailand, and Vietnam. In these ten countries, over 6 million people fell sick with TB in 2018 (out of 10 million worldwide). Sanofi did not file for patents in the following TB-high-burden countries: Congo, DPR Korea, Kenya, Namibia, Pakistan, Papua New Guinea, and Zimbabwe. All the other countries with a high TB burden are least developed countries (LDCs)—Angola, Bangladesh, Cambodia, Central African Republic, DR Congo, Ethiopia, Lesotho, Liberia, Mozambique, Myanmar, Sierra Leone, Tanzania, and Zambia—and have an extension until 2033 to implement the TRIPS agreement and grant patents on pharmaceuticals. Sanofi did not file any applications in LDCs.

The patent landscape suggests that **Sanofi followed a strategy of filing the patent applications in countries with the highest number of people affected by TB**, and among these countries, in those with the highest economic status among middle-income countries. Many of these countries have significant local pharmaceutical manufacturing capacity (e.g., Brazil, China, India, Nigeria, Thailand). It is no surprise that, in addition to these places, Sanofi filed in all high-income countries

[34] European Patent Office. Acknowledgement of withdrawal of the European patent application. Ref. S224 EP SANOFI. Application No./ Patent No.: 14741646.5–1109/3024443. 15 January 2020. (on file)

[35] European Patent Office. Acknowledgement of withdrawal of the European patent application. Ref. S225 EP SANOFI. Application No./ Patent No.: 14741647.3–1109/3024444. 17 January 2020. (on file)

as well as in most other middle-income countries with local production capacity such as Algeria, Colombia, and Egypt. However, it is important to note that some other countries with local production capacity were left out of Sanofi's strategy, such as Bangladesh and Pakistan, where these two patents were not filed.

Summary of the Patent Status for the Adult 3HP FDC as of January 2020

Granted	Withdrawn	Rejected	Awaiting or under examination
Australia, Russia, South Africa	European Patent Office (EPO), Indonesia	China	Algeria, Brazil, Canada, Chile, Colombia, Ecuador, Egypt, Hong Kong, India (opposition filed), Israel, Japan, Malaysia, Mexico, New Zealand, Nigeria, Panama, Peru, Philippines, Saudi Arabia, Singapore, South Korea, Taiwan, Thailand (opposition filed), United States, Vietnam

Summary of the Patent Status for the Pediatric 3HP FDC as of January 2020

Granted	Withdrawn	Rejected	Awaiting or under examination
Australia, China, Russia, South Africa, United States	European Patent Office (EPO), Indonesia		Algeria, Brazil, Canada, Chile, Colombia, Ecuador, Egypt, Hong Kong, India (opposition filed), Israel, Japan, Malaysia, Mexico, New Zealand, Nigeria, Panama, Peru, Philippines, Saudi Arabia, Singapore, South Korea, Taiwan, Thailand (opposition filed), Vietnam

Table 4: TB Burden in Countries where Sanofi Applied for Patents

	Country	World Bank classification[36]	High TB-Burden country?[37]	TB Incidence (2018)[38]
1	India	LMIC	Y	2,700,000
2	China	UMIC	Y	866,000
3	Indonesia	LMIC	Y	845,000
4	Philippines	LMIC	Y	591,000
5	Nigeria	LMIC	Y	429,000
6	South Africa	UMIC	Y	301,000
7	Vietnam	LMIC	Y	174,000
8	Thailand	UMIC	Y	106,000
9	Brazil	UMIC	Y	95,000
10	Russian Federation	UMIC	Y	79,000
11	EPO (member states)	HIC	N	74,000
12	Peru	UMIC	N	39,000
13	South Korea	HIC	N	34,000
14	Malaysia	UMIC	N	29,000
15	Mexico	UMIC	N	29,000
16	Algeria	UMIC	N	29,000
17	Japan	HIC	N	18,000
18	Colombia	UMIC	N	16,000
19	Egypt	LMIC	N	12,000
20	United States	HIC	N	9,800
21	Ecuador	UMIC	N	7,400
22	Hong Kong (SAR)	HIC	N	4,900
23	Saudi Arabia	HIC	N	3,400
24	Chile	HIC	N	3,400
25	Singapore	HIC	N	2,700
26	Panama	HIC	N	2,200
27	Canada	HIC	N	2,100
28	Australia	HIC	N	1,700
29	New Zealand	HIC	N	350
30	Israel	HIC	N	340
Note: Applications for the two patents were filed in a total of 69 countries, counting all the EPO member states.				
Key HIC = high-income country LMIC = lower middle-income country UMIC = upper middle-income country				

[36] Available from the World Bank: https://data.worldbank.org/country/
[37] Available from the WHO Global TB Report: https://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020summary.pdf?ua=1
[38] Available from the WHO Global TB Report: https://www.who.int/tb/country/data/profiles/en/

In Focus: Cambodia, Morocco and Tunisia

Cambodia, Morocco, and Tunisia have all signed bilateral agreements with the EPO.[39] These agreements—which will start to be enforced in 2015 in Morocco,[40] 2017 in Tunisia,[41] and in 2018 in Cambodia[42] —automatically consider as filed or granted any patent filed or granted at the EPO if the country appears as a designated state in the EPO application. Thus, although Tunisia has stricter criteria in regard to patentability and excludes from patentability drug combinations, patents on combinations granted at the EPO are automatically granted in Tunisia. It is unclear whether the 3HP patents will be considered filed through the EPO at the Tunisian, Moroccan, and Cambodia patent offices, or if the fact that the application was anterior to the enforcement of the agreements will prevent this. This is a particularly relevant concern for Morocco and Tunisia, which each boast growing generic production capacity (see, for example, the recent production of hepatitis C medicines by Tahr Pharma in Tunisia and Galenica and Pharma5 in Morocco).

In Focus: Nigeria and South Africa[43]

In Sub-Saharan Africa, Sanofi did not apply for patents in ARIPO[44] and OAPI[45] regions. However, Sanofi did apply for patents in Nigeria and South Africa. In Nigeria, the patent office does not examine patentability criteria before granting patents. In addition, combinations can be patented under Nigerian law.[46] This means that the two 3HP patents will most likely be granted there.

The situation is similar in South Africa, where both patent applications were granted in October 2019. South African patent law largely reflects the principles of the TRIPS Agreement and the Doha Declaration. However, South Africa continues to face challenges in implementing certain TRIPS Agreement provisions. As a result, its laws and policies have not been effective in protecting the public against patent monopolies and ensuring equitable access to essential medicines at affordable prices.

The spirit of promoting equity in health care services was clearly and boldly articulated under Article 27 of the Constitution of the Republic of South Africa Act 108 of 1996.[47] Article 27(2) read with Article 27(3) state that:

> "(2) The state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights.
> (3) No one may be refused emergency medical treatment."
> Article 25(1) and 25(4)(b) of the South African constitution provide for the protection of property but do not expressly mention intellectual property (though Article 25(4)(b) qualifies that "property is not limited to land").

The legislative framework regulating the patent system in South Africa is the Patents Act no. 57 of 1978,[48] read alongside the implementing patent regulations.[49] There have since been

[39] See the report: Krikorian G, Londeix P. Access to medicines and intellectual property in Tunisia: law and practices. ITP-MENA; 2018. (on file with authors)
[40] Validation of European patents in Morocco (MA) with effect from 1 March 2015, see: https://www.epo.org/law-practice/legal-texts/official-journal/2016/etc/se4/p552.html
[41] Validation of European patents in Tunisia (TN) with effect from 1 December 2017, see: https://www.epo.org/law-practice/legal-texts/official-journal/2017/10/a85.html
[42] Validation of European patents in Cambodia (KH) with effect from 1 March 2018, see: https://www.epo.org/law-practice/legal-texts/official-journal/information-epo/archive/20180209.html
[43] The analysis of South African patent law was written by Lynette Mabote.
[44] ARIPO stands for the African Regional Intellectual Property Organization. Established in 1976, it has the ability to handle patent applications for its 19 member states under the Harare Protocol.
[45] OAPI stands for the Organisation Africaine de la Propriété Intellectuelle. Established in 1977, it has the ability to handle patent applications for its 17 member states.
[46] South African Patents and Design Act, Chapter 344, (2) (b).
[47] The Constitution of the Republic of South Africa Act 108 of 1996, see: https://www.gov.za/documents/constitution-republic-south-africa-1996
[48] Act 57 of 1978, which came into operation on 1 January 1979. See: https://www.gov.za/sites/default/files/gcis_document/201504/act-57-1978.pdf
[49] Patents Act 57 of 1978, Patents Regulations 1978, as published in Government Notice R2470 in Government Gazette 6247 of 15 December 1978 (with its various amendments noted). See: http://www.cipc.co.za/files/4814/2615/1436/Patent_Regulations.pdf

various amendments to the Act and the implementing regulations.[50] With respect to patents on medicinal or pharmaceutical products, the Medicines and Related Substances Control Amendment Act applies.[51] This Act was amended in 2008 and more recently in 2015.[52]

In terms of patent search and examination, South Africa currently does not conduct substantive patent examinations and employs a deposit system. This is regulated by Section 34 of the Patents Act, read together with the Patents Regulations, 1978 (Patents Regulations). These limit the examination duties and scope of the Companies Intellectual Property Commission (CIPC) to the formalities of the application. Section 34 of the Patents Act provides that: *"The registrar shall examine in the prescribed manner every application for a patent and every complete specification accompanying such application or lodged at the patent office in pursuance of such application and if it complies with the requirements of this Act, he shall accept it."*

In terms of patent oppositions, the Patents Act makes provisions for interested third parties to lodge oppositions, but only under the following four types of proceedings:

- An application for the restoration of the patent (section 54 of the Patents Act);
- An application for "the correction of any clerical error or error in translation in any patent, application for a patent or document lodged in pursuance of such an application, or in the register" (section 50 of the Patents Act);
- An application for the amendment of a patent specification (section 51 of the Patents Act);
- An application for a compulsory license (section 56 of the Patents Act).

As the Patents Act currently reads, no provision is made for any form of third party opposition to the grant of a patent, whether pre- or post-grant.

The Intellectual Property Policy of the Republic of South Africa, Phase 1 (2018) (IP Policy) was announced in September 2018. This policy has deeply contemplated the feasibility and establishment of a substantive patent examination system in the country in the coming years.

In Focus: Brazil and Egypt

In Brazil, the applications on these two patents are still pending, awaiting the opinion of the Brazilian Health Regulatory Agency (ANVISA) to be sent to the National Institute of Industrial Property (INPI), which will afterwards take a final decision on whether the applications fulfill the requirements of the Brazilian patent law. While this process remains open, third parties may submit "observations" to INPI, a form of pre-grant patent opposition.

In Egypt, the patent applications are still under review, but the Egyptian patent law does not allow patents on drug combinations. In addition, the Egyptian patent office is known to be one of the most rigorous in terms of reviewing applications and strictly analyses the novelty and the inventive steps criteria. The Sanofi patent applications should therefore be rejected in Egypt.

[50] The Patents Amendment Act 20 of 2005, was the last amendment to the Patents Act from 14 December 2007. Its objective was to amend the Patents Act (1978) by inserting 'certain definitions; and to require an applicant for a patent to furnish information relating to any role played by an indigenous biological resource, a genetic resource or traditional knowledge or use in an invention; and to provide for matters connected therewith'. It is noteworthy to mention that South Africa is a signatory to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (1970). See: https://www.gov.za/sites/default/files/gcis_document/201409/a20-050.pdf

[51] Act 90 of 1997.

[52] Medicines and Related Substances Amendment Act, (No. 14 of 2015).

Table 5: TRIPS Flexibilities in Countries where Sanofi Applied for Patents

Key
✓ = flexibility exists under national law
Blanks = flexibility does not exist under national law, or unknown
HIC = high-income country
LMIC = lower middle-income country
MIC = middle-income country

Country	World Bank classification[53]	TB high-burden country?[54] Y/N	Third party observation and protest?	Pre-grant opposition	Re-examination	Post-grant opposition	Administrative revocation or Invalidation
1. Algeria*	UMIC	N	-	-	-	-	-
2. Australia	HIC	N	✓	✓	✓		
3. Brazil	UMIC	Y	✓			✓	✓
4. Canada	HIC	N	✓		✓		
5. Chile	HIC	N					✓
6. China	UMIC	Y	✓				✓
7. Colombia	UMIC	N		✓			
8. Ecuador	UMIC	N		✓			✓
9. Egypt	LMIC	N		✓			✓
10. EAPO	MIC	N/A	✓			✓	
11. EPO	HIC	N/A	✓			✓	Different from one member state to the next
12. Hong Kong (SAR)	HIC	N	✓				
13. India	LMIC	Y		✓		✓	✓
14. Indonesia	LMIC	Y		✓		✓	✓
15. Israel	HIC	N					
16. Japan	HIC	N	✓			✓	✓
17. Malaysia	UMIC	N					✓
18. Mexico	UMIC	N	✓				✓
19. New Zealand	HIC	N					
20. Nigeria	LMIC	Y					✓
21. Panama	HIC	N					
22. Peru	UMIC	N		✓			
23. Philippines	LMIC	Y	✓				✓
24. Russian Federation	UMIC	Y	✓				✓
25. Saudi Arabia	HIC	N					✓
26. Singapore	HIC	N	✓		✓		

27. South Africa	UMIC	Y					
28. South Korea	HIC	N	✓		✓	✓	✓
29. Thailand	UMIC	Y	✓				✓
30. United States	HIC	N	✓		✓	✓	
31. Vietnam	LMIC	Y	✓	✓	✓		
A description of the provisions under each law was found from various sources, primarily from WIPO. Regarding Nigeria, we consulted an analysis of the law made by ITPC-West Africa. For Egypt, we referred to a comparative study prepared and published by ITPC-MENA.[55] *Algeria is not a WTO member.							

Among the countries where Sanofi filed applications, third party observations are allowed in approximately half of the countries/territories. Third party observations mean that a third party can send formal comments to the patent office regarding the application; patent officers can take these comments into consideration when examining the application. The content of the observation can provide a strict analysis of the law, a pharmacological analysis, and/or comments on the importance of the medicine with regard to the public health situation of the country. Among these countries, at least two allow the Ministry of Health or the regulatory agency to send observations to the patent office. This is the case in Egypt with the Ministry of Health and in Brazil where the medicines agency ANVISA has one year to submit its comment to the patent office (INPI) before the office takes a decision. (Previously, ANVISA's opinion was binding and was known as ANVISA's prior consent, but this is no longer the case.)

Among the countries where Sanofi filed applications, a minority allow formal pre-grant oppositions or reexamination. The window for third parties to file oppositions varies country by country. At least half of them allow an administrative revocation or a compulsory license. For instance, in Europe, even if the patents are filed and granted at the EPO level, the conditions to issue a compulsory license are defined under the national laws, with some differences from one country to the next.

[53] Available from the World Bank: https://data.worldbank.org/country/

[54] Available from WHO Global TB Report: https://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020summary.pdf?ua=1

[55] See the study published by « Access Ibsa » https://accessibsa.org/data/ (2018)

Conclusion

Isoniazid and rifapentine were first synthesized decades ago and are common goods in the public domain. Patents are supposed to reward innovation and be granted after a thorough and rigorous analysis of criteria including industrial application, novelty, and inventive step. In 2014, Sanofi filed patent applications on two fixed-dose combinations of isoniazid and rifapentine—neither of which it discovered or developed—for the adult and pediatric formulations of the 3HP regimen used to prevent TB. If granted, the patents will run until at least 2034, potentially providing Sanofi with a monopoly and preventing generic competitors from entering these markets. In some countries, legal safeguards exist in national patent law to prevent the granting of patents on combinations of medicines, or on molecules that do not represent true innovation in the sense of inventiveness or non-obviousness. Although FDCs are more convenient than standalone tablets, and therefore represent an improvement for the quality of life of adults and children exposed to TB, do these products deserve another 20 years of monopoly protection? Does a firm which did not develop either isoniazid or rifapentine deserve exclusive ownership over their combinations, especially considering the wealth of published prior art on the topic? (Moreover, Sanofi has halted most of its R&D activities on infectious diseases, including TB, and therefore cannot claim that it will reinvest its revenues from 3HP sales into further innovation on TB.) These are the questions that national patent examiners will need to answer when evaluating Sanofi's patent applications.

Recommendations

Sanofi's claims under these two applications clearly illustrate the abuses allowed under the patent system. Stopping these abuses will require action by a number of actors. We encourage and call on:

- When and where patents have not been granted – yet: **Patent offices** to strictly apply the patentability criteria under their national laws, in particular in regard to the lack of inventive step and of novelty that these combinations present. Countries that do not allow for patents on combinations of medicines should reject each application outright.

- When and where patents have not been granted – yet: **Generic producers and civil society organizations** to send a written analysis or pre-grant oppositions to their patent offices so that patent officers may become aware of the lack of inventive step and of novelty that these combinations present and to convey the public health importance of accessing 3HP to prevent TB.

- When and where patents have been already granted: **Civil society organizations and generic producers** to file post-grant oppositions.

- When and where patents have been already granted: **Sanofi** to let the patents lapse and publicly commit to refraining from any action to enforce their patent rights.

- When and where patents have been already granted: **Governments and courts** to invalidate these patents or to issue a compulsory license for governmental use. In addition, generic producers may also consider making applications for a compulsory license for commercial use.

- In all countries where patents have been filed: **Civil society organizations** to denounce Sanofi's patent filings, which could potentially block access to a live-saving preventive therapy, in particular in many low-and-middle income countries highly affected by TB.

- In all countries where patents have been filed: **Sanofi** to withdraw patent applications on 3HP combinations.

Table 6: Patent Landscape (last updated 20/01/2020)

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
1. Albania	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
2. Algeria	Filed	DZ-PCT/ EP2014/065761	22/07/2034	Filed	DZ-PCT/ EP2014/065762	22/07/2034
3. Australia	**Granted (7/11/2019)**	2014295098	22/07/2034	**Granted (7/11/2019)**	2014295099	22/07/2034
4. Austria (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
5. Belgium (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
6. Brazil	Filed	BR 11 2016 001531 2 A2	22/07/2034	Filed	BR 11 2016 001559 2 A2	22/07/2034
7. Bulgaria (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
8. Canada	Filed	CA2918827	22/07/2034	Filed	CA2918528	
9. Chile	Filed	CL2016000182	22/01/2034	Filed	CL2016000183	22/01/2034
10. China	**Rejected**	CN201480041953	22/07/2034	Granted	CN201480041954	22/07/2034

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
11. Colombia	Filed	CO16046126	22/07/2034	Filed	CO-PCT/ EP2014/065762	22/07/2034
12. Croatia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
13. Cyprus (EP0)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
14. Czech Republic (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
15. Denmark	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
16. Ecuador	Filed	EC20165208	22/07/2034	Filed	EC-PCT/ EP2014/065762	22/07/2034
17. Egypt	Filed	EG20160113	22/07/2034	Filed	EG20160114	22/07/2034
18. Estonia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
19. European Patent Office (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
20. Finland (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
21. France (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
22. Germany (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
23. Greece (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
24. Hong Kong	Filed	HK1218862	22/03/2034	Filed	HK1218861	22/03/2034
25. Hungary (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
26. India	Filed *Opposed	IN201637002757	22/03/2034	Filed *Opposed	IN201637002758	22/03/2034
27. Indonesia	**Withdrawn (17/11/2019)**	IDP00201601205	22/03/2034	**Withdrawn (17/11/2019)**	IDP00201601207	22/03/2034
28. Ireland (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
29. Iceland (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
30. Israel	Filed	243368	22/07/2034	Filed	243369	22/07/2034
31. Italy (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
32. Japan	Filed	JP2016528509	22/07/2034	Filed	JP2016528510	22/07/2034
33. Latvia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034
34. Liechtenstein (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034
35. Lithuania (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
36. Luxembourg (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034
37. Macedonia (North) (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
38. Malaysia	Filed *Opposed	MYPI2015704801	22/07/2034	Filed *Opposed	MYPI2015704792	22/07/2034
39. Malta (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	
40. Mexico	Filed	MX/a/2016/ 001154	22/07/2034	Filed	MX/a/2016/001155	22/07/2034
41. Monaco (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
42. Netherlands (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
43. New Zealand	Filed	NZ716060	22/07/2034	Filed	NZ716062	22/07/2034
44. Nigeria	Filed	NG/ PT/C/2016/1719	22/07/2034	Filed	NG/ PT/C/2016/1720	22/07/2034
45. Norway (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
46. Panama	Filed	PA90998-01	22/07/2034	Filed	PA90997-01	22/07/2034

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
47. Peru	Filed	PE2016000096	22/07/2034	Filed	PE2016000090	22/07/2034
48. Philippines	Filed *Opposed	PH12016500120	22/07/2034	Filed *Opposed	PH12016500119	22/07/2034
49. Poland (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
50. Portugal (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
51. Romania (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
52. Russian Federation (EAPO)	Granted (15/03/2019, source: patentscope)	RU2016106384	22/07/2034	Granted (source: medspal)	RU2016106328A RU2694056C2	22/07/2034
53. San Marino (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
54. Saudi Arabia	Filed	SA516370446	22/07/2034	Filed	SA516370441	22/07/2034
55. Serbia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
56. Singapore	Filed	SG11201510730U	22/07/2034	Filed	SG11201510732V / SG10201803996W	N/A
57. Slovakia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
58. Slovenia (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034

	isoniazid/rifapentine coated tablet compositions (adult 3HP FDC)			isoniazid/rifapentine dispersible tablet compositions (pediatric 3HP FDC)		
WIPO Corresponding No:	PCT/EP2014/065761 - WO2015/011161 - Priority : INDIA 3341/CHE/2013 - Date : 26/07/2013			PCT/EP2014/065762 - WO2015/011162 - Priority : INDIA 3342/CHE/2013 - Date : 26/07/2013		
Country	*Status*	*Country number*	*Expected expiration date if granted*	*Status*	*Country number*	*Expected expiration date if granted*
59. South Africa	**Granted**	ZA201600109	22/07/2034	**Granted**	ZA201600110 (B)	22/07/2034
60. South Korea	Filed	1020167004316	22/07/2034	Filed	Not available	N/A
61. Spain (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	
62. Sweden (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
63. Switzerland (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
64. Taiwan	Filed	TW201605442 TWI651084	22/07/2034	Filed	TW201601723 TWI630911	N/A
65. Thailand	Filed	TH1601000414	22/07/2034	Filed	TH1601000296	22/07/2034
66. Turkey (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
67. United Kingdom (EPO)	**Withdrawn (11/12/2019)**	EP14741646 Publication no.: EP3024443	22/07/2034	**Withdrawn (11/12/2019)**	EP14741647 Publication no.: EP3024444	22/07/2034
68. United States	Filed	US20160158157A1	22/07/2034	**Granted (14/11/2017)**	US9814680B2	07/11/2034
69. Vietnam	Filed	VN1201600462	22/07/2034	Filed	VN1201600461	22/07/2034

Appendix 2: Judgement of the ISA on Sanofi's Patent Claims

Sanofi's Claims Under the Adult 3HP FDC Patent Application and ISA Opinion

ANTI-TUBERCULOSIS STABLE PHARMACEUTICAL COMPOSITION IN A FORM OF A COATED TABLET COMPRISING GRANULES OF ISONIAZID AND GRANULES OF RIFAPENTINE AND ITS PROCESS OF PREPARATION Pub. No.: WO/2015/011161 Pub. Date: January 29, 2015 International Application No.: PCT/EP2014/065761 International Filing Date: July 22, 2014		**Opinion of the ISA (PCT)**	
Claim Content	Patent on composition, process, main compound, etc.	Novelty	Inventive Step
1. An oral pharmaceutical fixed dose composition for use in the treatment of tuberculosis, said oral pharmaceutical composition comprising: a) granules comprising isoniazid and at least one intragranular excipient, b) granules comprising rifapentine and at least one intragranular excipient, and c) at least one extragranular excipient.	Composition	No	No (all claims)
2. An oral pharmaceutical composition according to claim 1, wherein said oral pharmaceutical composition is chemically stable.	Composition	No	
3. An oral pharmaceutical composition according to claim 1 or 2, wherein said oral pharmaceutical composition is in the form of a coated tablet.	Composition	No	
4. An oral pharmaceutical composition according to any one of the claims 1 to 3, wherein said oral pharmaceutical composition is in the form of a coated bilayer tablet comprising: - a layer comprising isoniazid granules (a) and at least one extragranular excipient, - a layer comprising rifapentine granules (b) and at least one extragranular excipient, and - a film coating.	Composition	Yes	
5. An oral pharmaceutical composition according to any one of the claims 1 to 4, wherein the ratio of rifapentine to isoniazid is comprised from 5:1 to 1:0.5, preferably the ratio is 1:1.	Composition	No	
6. A process for the preparation of an oral pharmaceutical composition according to any one of the claims 1 to 5, characterized in that it comprises distinct steps of granulating isoniazid and granulating rifapentine.	Process	Yes	
7. A process according to claim 6, characterized in that the preparation of the granules is made by wet granulation, preferably in an aqueous solvent.	Process	Yes	

8. A process according to claim 6 or 7, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) preparing the rifapentine granules, c) mixing the granules obtained from steps a) and b) with the extragranular excipients, d) compressing the mixture of step c) to obtain tablets, and e) film coating the tablets.	Process	Yes	
9. A process according to claims 6 to 8, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) mixing the granules obtained from step a) with at least a part of the extragranular excipients, c) preparing the rifapentine granules, d) mixing the granules obtained from step c) with the remaining part of the extragranular excipients, e) compressing the mixture of steps b) and d) to obtain bi-layer tablets, and f) film coating the tablets.	Process	Yes	

ANTI-TUBERCULOSIS STABLE PHARMACEUTICAL COMPOSITION IN A FORM OF A DISPERSIBLE TABLET COMPRISING GRANULES OF ISONIAZID AND GRANULES OF RIFAPENTINE AND ITS PROCESS OF PREPARATION Pub. No.: WO/2015/011162 Pub. Date: January 29, 2015 International Application No.: PCT/EP2014/065762 International Filing Date: July 22, 2014		**Opinion of the ISA (PCT)**	
Claim Content	Patent on composition, process, main compound, etc.	Novelty	Inventive step
1. An oral pharmaceutical fixed dose composition in a form of a dispersible tablet for use in the treatment of tuberculosis, said oral pharmaceutical composition comprising: a) granules comprising isoniazid and at least one intragranular excipient, b) granules comprising rifapentine and at least one intragranular excipient, and c) at least one extragranular excipient.	Composition	No	No (all claims)
2. An oral pharmaceutical composition according to claim 1, wherein said oral pharmaceutical composition is chemically stable.	Composition	No	
3. An oral pharmaceutical composition according to any one of claim 1 or 2, wherein said oral pharmaceutical composition is in the form of a dispersible bilayer tablet comprising: - a layer comprising isoniazid granules (a) and at least one extragranular excipient, and - a layer comprising rifapentine granules (b) and at least one extragranular excipient.	Composition	Yes	
4. An oral pharmaceutical composition according to any one of the claims 1 to 3, wherein the ratio of rifapentine to isoniazid is comprised from 3:1 to 1:0.5, preferably the ratio is 1:1.	Composition	No	
5. A process for the preparation of an oral pharmaceutical composition according to any one of the claims 1 to 4, characterized in that it comprises distinct steps of granulating isoniazid and granulating rifapentine.	Process	Yes	
6. A process according to claim 5, characterized in that the preparation of the granules is made by wet granulation, preferably in an aqueous solvent.	Process	Yes	
7. A process according to claim 5 or 6, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) preparing the rifapentine granules, c) mixing the granules obtained from steps a) and b) with the extragranular excipients, and d) compressing the mixture of step c) to obtain tablets.	Process	Yes	

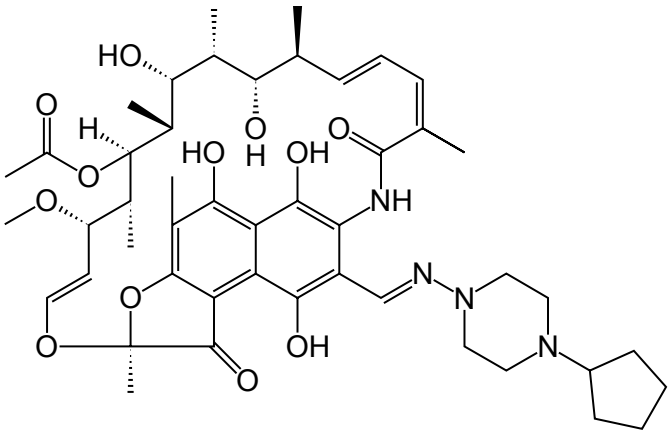
8. A process according to claims 5 to 7, characterized in that it comprises the steps of: a) preparing the isoniazid granules, b) mixing the granules obtained from step a) with at least a part of the extragranular excipients, c) preparing the rifapentine granules, d) mixing the granules obtained from step c) with the remaining part of the extragranular excipients, and e) compressing the mixture of steps b) and d) to obtain bi-layer tablets.	Process	Yes	

Appendix 3: What Is Rifapentine?

Rifapentine is an antibiotic used to treat infection with *Mycobacterium tuberculosis* (MTB), the causative agent of TB disease. Treatment of TB infection is referred to as TB preventive therapy (TPT) and is one of the most powerful ways to prevent TB. In 2014, the U.S. FDA approved rifapentine for the treatment of TB infection when used in combination with isoniazid as part of the so-called 3HP regimen. This approval expanded rifapentine's indication; the drug was first approved by the U.S. FDA in 1998 for treatment of active, drug-susceptible TB.[59] Today, rifapentine is most commonly used in combination with isoniazid as part of the TPT regimens 3HP and 1HP. The 3HP regimen consists of rifapentine and isoniazid taken together once weekly for 12 weeks. The 1HP regimen requires taking rifapentine and isoniazid together once a day for one month.[60]

Rifapentine belongs to a class of drugs called rifamycins. Other approved drugs in this class include rifampicin and rifabutin. These drugs share a similar chemical structure and method of action. Rifapentine inhibits DNA-dependent RNA polymerase, which leads to the suppression of RNA synthesis and cell death. DNA-dependent RNA polymerase (commonly called "RNA polymerase" or RNAP) is an enzyme that synthesizes RNA from DNA in a process called transcription. RNA polymerase is essential for life because the expression of genes through transcription and translation enables cells to adapt to changing environments, perform specialized functions, and maintain metabolic processes necessary for survival.[61] Rifapentine acts against MTB by inhibiting this process.

Rifapentine is processed by the body through the liver and is a potent inducer of cytochrome P450 enzymes. Because cytochrome P450 enzymes underlie the metabolism of many drugs for other conditions, rifapentine can enhance the clearance and reduce the bioavailability of other medications (e.g., certain antiretorivals to treat HIV and most direct-acting antiretroviral drugs used to treat hepatitis C virus).[62] Compared to rifampicin, rifapentine is more potent, has a longer half-life, and is more highly protein bound (meaning that rifapentine penetrates less easily into tissue than rifampicin.)[63,64]



Rifapentine | 3-(((4-Cyclopentyl-1-piperazinyl)imino)methyl)rifamycin (Cyclopentylrifampicin)

[59] Sanofi. Sanofi receives FDA approval of Priftin® (rifapentine) tablets for the treatment of latent tuberculosis infection [Press Release]. 2014 December 2. http://www.news.sanofi.us/press-releases?item=136875

[60] Frick M. An activist's guide to rifapentine.

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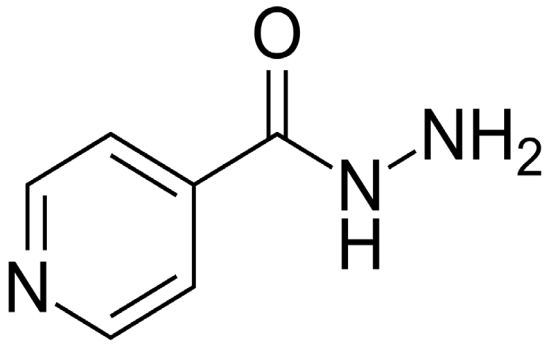
Appendix 4: What Is Isoniazid?

Isoniazid is an antibiotic used to treat both TB infection and active TB disease. Together with rifampicin, isoniazid comprises the backbone of the first-line, four-drug regimen used to treat drug-susceptible TB disease. In addition, isoniazid has several applications as TB preventive therapy. When paired with rifapentine, isoniazid forms the 3HP regimen (taken once weekly for 12 weeks) and the 1HP regimen (taken once a day for one month). Isoniazid can also be administered daily on its own for six, nine, 12 or up to 36 months in what is known as isoniazid preventive therapy (IPT).[65] The U.S. FDA approved isoniazid for the treatment of TB in 1952.[66]

Isoniazid has both bactericidal and bacteriostatic properties.[67] (Bacteriostatic agents stop bacteria from reproducing, while bactericidal drugs act by killing bacteria.) Isoniazid is a prodrug, meaning that it remains inactive until metabolized into a compound with pharmacologic activity. Isoniazid is activated by a mycobacterial enzyme found in MTB called KatG.[68] Once activated, isoniazid inhibits the synthesis of mycolic acids, long chains of fatty acids that are an essential component of the MTB cell wall. Recent research has also suggested that free radicals such as nitric oxide formed from isoniazid during KatG-mediated oxidation can depress the metabolic activity of MTB. The combined effect of these mechanisms of action result in "the exceptional and highly selective potency of INH against MTB."[69]

Isoniazid is processed by the liver and can obtain therapeutic concentrations in the blood, cerebrospinal fluid, and within the granulomas (lesions) formed by MTB bacteria in the lungs. Resistance to isoniazid emerges due to mutations in one of two genes: katG and inhA. Although drug-resistant TB (DR-TB) is by definition resistant to isoniazid, the drug is sometimes used in DR-TB treatment since resistance arising from inhA mutations can be overcome with high-dose isoniazid.[70]



Isoniazid | 4-pyridinecarbohydrazide

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