



INTELLECTUAL PROPERTY
WORKING GROUP



**THE PATENTS DIRECTOR
NATIONAL INDUSTRIAL PROPERTY INSTITUTE – INPI
(Brazilian Patents and Trademarks Office – BrPTO)**

Proceeding: PI 0719693-8 PCT Filing N°: EP 2007/063186-WO 2008/068231

Filing Date: December 3, 2007

PCPIP Priority: EP 061254439 (December 5, 2006)

Title: FUMARATE SALT OF (ALPHA S, BETA R)-6-BROMO-ALPHA-[2-(DIMETHYLAMINO) ETHYL]-2-METHOXY-ALPHA-1-NAPHTHALENYL-BETA-PHENYL-3-QUINOLINEETHANOL

Registrant: Janssen Pharmaceutica N.V. (BE)

The **BRAZILIAN INTERDISCIPLINARY AIDS ASSOCIATION (ABIA – ASSOCIAÇÃO BRASILEIRA INTERDISCIPLINAR DE AIDS)**, a non-profit civil association registered with the Treasury Ministry on the National Corporate Tax-Payers' Roll under CNPJ/MF N° 29.263.068/0001-45, with head offices at Avenida Presidente Vargas 446, 13th floor, Centro, Rio de Janeiro, Rio de Janeiro State, through its representative as set forth in its By-Laws (Exhibits 3 and 4), in the person of its counsel (Exhibit 5);

The **SOLIDARITY IS LIFE GROUP (GRUPO SOLIDARIEDADE É VIDA)**, a non-profit corporate entity established under private law registered with the Treasury Ministry on the National Corporate Tax-Payers' Roll under CNPJ/MF N° sob N° 69.401.677/0001-38, with head offices at Rua São Gabriel, 200, Bairro Fé em Deus, São Luiz, Maranhão State, Zip Code 65035-000, through its legal representative, as set forth in its By-Laws (Exhibits 6 and 7), in the person of its counsel (Exhibit 8);

The **SÃO PAULO STATE AIDS NGOS FORUM (FOAESP – FÓRUM DAS ONGS AIDS DO ESTADO DE SÃO PAULO)**, a non-profit corporate entity established under private law registered with the Treasury Ministry on the National Corporate Tax-Payers' Roll under CNPJ/MF N° 02.736.953/0001-48, with head offices at Avenida São João 324, 7th floor, Office 701, Centro, São Paulo-SP, through its legal representative as set forth in its By-Laws (Exhibits 9 and 10), in the person of its counsel (Exhibit 11);

The **ALLIED UNIVERSITIES FOR ACCESS TO ESSENTIAL MEDICATIONS (UAEM/BRASIL – UNIVERSIDADES ALIADAS PARA O ACESSO A MEDICAMENTOS ESSENCIAIS)**, a non-profit corporate entity established under private law registered with the Treasury Ministry on the National Corporate Tax-Payers' Roll under CNPJ/MF N° 18.806.411/0001-34, with head offices at Rua do Ouvidor 63, Office 709, Centro, Rio de Janeiro, Rio de Janeiro State, through its legal representative as set forth in its By-Laws (Exhibits 12 and 13), in the person of its counsel (Exhibit 14);



hereby respectfully appears before Your Honor, grounded on Article 31 of the Industrial Property Act – LPI (Law N° 9,279/1996), to present this

SUBMISSION OF INPUT FOR THE TECHNICAL EXAMINATION

of **Patent Application PI 0719693-8**, urging the DISMISSAL of the Application under analysis, as it fails to comply with the patentability requirements and conditions established for **Novelty and an Inventive Step (Articles 8, 11, 13, 25 and 42 of the LPI)**.

SUMMARY OF THE ARGUMENTS

As addressed in this Submission of Input, Patent Application **PI 0719693-8** does not comply with the legal requirements and conditions needed for the grant thereof, as it lacks Novelty and an Inventive Step, in addition to the absence of clarity.

This Submission of Input organized into the following structure:

I. LEGITIMACY OF THE PROPOSING ORGANIZATIONS AND TIMELINESS

I.a Legitimacy of the proposing organizations

I.b Timeliness of this Submission of Input

II. PRELIMINARY INFORMATION ON THE MATTER ADDRESSED BY THE PATENT APPLICATION AND ITS IMPORTANCE FOR HEALTH

II.a Bedaquiline

II.b Development of bedaquiline

II.c Bedaquiline patent status in Brazil

III. MATTER ADDRESSED BY THE PATENT APPLICATION

IV. STATE OF THE ART AND PRIOR FILINGS

V. ANALYSIS OF THE CLAIMS

V.a Claims 1 to 3 (Compound - fumarate salt)

V.b Claims 6 to 15 (Composition)

V.c Claims 16, 17 and 21 (Process)

V.d Claims 4, 5, 18, 19 and 20 (Use)

VI. THE PETITION



I. LEGITIMACY OF THE PROPOSING ORGANIZATIONS AND TIMELINESS

I.a Legitimacy of the Proposing Organizations

As set forth in detail below, the matter addressed by this Patent Application is of the utmost importance for the life and health of people living with drug-resistant tuberculosis associated with cases of multi-resistant *Mycobacterium tuberculosis* and few therapeutic options.¹

Consequently, the legitimacy of the organizations presenting this Submission of Input for the examination is ascertained through their backgrounds and respected track records of defending human rights, particularly the right to health, access to treatment and good quality pharmaceutical assistance, in addition to active advocacy in the field of implementing public policies in the Intellectual Property field, with a view to ensuring the primacy of the public interest.

The Brazilian Interdisciplinary AIDS Association (ABIA) it is a non-profit, philanthropic civil association. Set up on March 12, 1987, it is one of the oldest NGOs set up to fight the HIV epidemic in Brazil and ensure the rights of people living with HIV. One of its founders was sociologist Herbert de Souza (*Betinho*), who was a figure of acknowledged importance in public life in Brazil. This Association still ranks high among entities addressing this issue in Brazil, with widespread recognition among its peers at the domestic and international levels. Its staff and supporters include researchers, practitioners and activists endowed with acknowledged expertise on this issue, who are rated as reference in their specific fields in Brazil. Further information: www.abiaids.org.br.

This Association coordinates the Intellectual Property Working Group (GTPI) of the Brazilian Network for the Integration of Peoples (REBRIP). In turn, this network gathers together Brazilian civil society organizations that oversee and monitor the trade agreements in which the Brazilian government is engaged, in order to assess and minimize potential impacts on the daily lives of the population, as well as public policies designed to ensure the effective implementation of human rights in Brazil. Further information on this Network is available at www.rebrip.org.br.

One of the most significant aspects falling under the aegis of discussions of trade and human rights refers to intellectual property, which is why this Network set up a working group in order to address complaints from civil society on this matter. Set up in 2003, the Intellectual Property Working Group brings together a diversity of civil society entities, striving to discuss, oversee and influence the issue of intellectual property and above all

¹ <https://pubmed.com.br/bedaquilina-anvisa-aprova-novo-medicamento-contratuberculose/>.



**INTELLECTUAL PROPERTY
WORKING GROUP**



mitigate the impact of negative effects on the current patent system controlling access to essential medication for the Brazilian population. Further information on the GTPI/REBRIP is available at www.deolhonaspateentes.org.

For the past twenty years, the Solidarity is Life Group NGO has been working with children, adolescents, young people and adults living and cohabiting with HIV in Maranhão State, focused on promoting their care and citizenship.

Running two support homes in Maranhão State capital, São Luis, this NGO is the only institution providing care and support for people living with HIV in this State. The purpose of this Group is to provide people living with HIV with a better quality of life, together with information on their rights and duties, while fostering the exercise of their citizenship. Further information: <https://www.facebook.com/Grupo-solidariedade-%C3%A9-vida-713276028748877/>.

The São Paulo State AIDS NGOs Forum (FOAESP) is a collegiate entity that brings together organization working in the fields of AIDS, human rights and public health in this State. Operating since 1996 and formally established in October 1997, it today consists of more than one hundred organizations acting at the State, regional and national levels, focusing mainly on social control of public policies; protecting Brazil's Unified National Health System (SUS); extending action designed to prevent HIV and other co-infections; and guaranteeing the rights of people living with HIV and AIDS. This Forum has firmed up its status as an important voice in discussions with HIV/AIDS public policy administrators, particularly the State Healthcare Bureau; it is a reference for its specialization and in-depth activism, particularly setting up Theme Commissions and Working Groups. For further information: <http://www.forumaidssp.org.br>.

The Allied Universities for Access to Essential Medications (UAEM/BRASIL) is a university student group believing that universities have the opportunity and the responsibility to improve global access to public health assets. Set up in August 2010, its mission is to promote access to medications and innovation in healthcare technologies; establish intellectual property policies for easier access to knowledge in the healthcare field; empower students and develop leaders for influencing health-related policies pursuing the public interest. Further information: <https://pt-br.facebook.com/pg/uaembr/about/>.

The Industrial Property Act – LPI, (Law N° 9,279, promulgated on May 26, 1996, establishes that stakeholders may submit information providing input for Patent Application examinations.

Article 31. With the Patent Application published, parties with an interest therein may submit documents and information through to the end of the examination, providing input for the examination.



Sole Paragraph. The examination shall not begin earlier than 60² (sixty) days after the publication of the Application.

The proposing organizations are endowed with ample interest and legitimacy for appearing as parties with an interest in Patent Application **PI 0719693-8**,

Promulgated on January 29, 1999, Law N° 9,784 regulates administrative proceedings under the aegis of the Federal Civil Service, legitimizing the appearance of third party stakeholders, expressly establishing the legal standing of organizations to appear in defense of collective and diffuse rights or interests. This applies to the Proposing Organizations, which have a broad field of action in terms of access to medications, specifically striving to ensure access for persons living with HIV and co-infections – such as multi-resistant tuberculosis – to adequate treatment resources. This is why the Petitioners are endowed with a solid interest in Patent Application **PI 0719693-8** under analysis.

I.b Timeliness of this Submission of Input

The above-mentioned Article 31 of the LPI allows third party stakeholders to present documents and information providing input for the Technical Examination of a Patent Application, during the period between the publication of such Application and the end of the examination.³ In turn, Article 32 of Normative Instruction N° PR 30/2013, establishes that, for the purposes of article 31 of the LPI, the end of the examination shall be deemed to be the date of the conclusive Technical Expert Opinion on patentability, or the thirtieth day prior to the publication of approval, rejection or definitive shelving.⁴

However, the examination has not ended in this case. The INPI website states that Patent Application **PI 0719693-8** was forwarded to Brazil's Public Health Regulator (ANVISA) on March 20, 2018. On December 11, 2019, this application was granted with no feedback from ANVISA, as the medication had not yet been included in Brazil's Unified National Health System (SUS), it was not involved in a Production Development Partnership, and no fast-track examination had been requested by the Ministry of Health.

² BRAZIL. Law N° 9,279, dated May 14, 1996. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at:

http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

³ BRAZIL. Law N° 9,279, dated May 14, 1996. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at:

http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

⁴ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Normative Instruction N° 30, dated December 4, 2013**. Establishment of general procedural standards for clearly presenting and complying with the provisions in the Industrial Property Act – Law N° 9,279, dated May 14, 1996, with regard to the Specifications in Patent Applications. [S. I.]. Available at: http://www.inpi.gov.br/menu-servicos/patente/in_030_in_17_2013_exame_tecnico_versao_final_03_12_2013-1-_1_0.pdf. Accessed on: April 23, 2020.



Consequently, this Petition for Submission of Input is presented within the stipulated deadline, as the case records do not contain a conclusive Technical Expert Opinion.

II. PRELIMINARY INFORMATION ON THE MATTER ADDRESSED BY THE PATENT AND ITS IMPORTANCE FOR HEALTH

According to the World Health Organization (WHO), tuberculosis is a major public health challenge worldwide, particularly in the poorer emerging countries. However, the situation becomes even more complex when taking multi-resistant types of this disease into consideration. A survey conducted in around a hundred countries⁵ between 2009 and 2013 showed that multi-resistant forms tripled during this period.

Although the established medication scheme used to treat tuberculosis in most countries focuses on curing most new cases, resistance to anti-tuberculous drugs is worsening the problems caused by this disease. Particularly serious is joint resistance to the two main treatment drugs: rifampicin and isoniazid, which characterize multidrug-resistant tuberculosis (TB MDR). There are countless factors contributing to the appearance of the multi-resistant form, including: improper use of the prescribed schemes; difficulties in organizing tuberculosis care; lack of treatment standardization and regulation; and little training for teams, with limited attention paid to treatment progress.⁶

The past few years have been characterized by the return of massive social inequalities in Brazil. These inequalities are reflected in steadily-rising poverty, with these conditions noted through longer line-ups of applicants for the *Bolsa Família* income distribution program,⁷ and the dismantling of public services providing healthcare to the Brazilian population. In Rio de Janeiro alone – the second-largest city in Brazil – significant budget was slashed by [BRL] 700 million in 2019, through the Budget Act.⁸

This had negative repercussions on monitoring endemic urban diseases like tuberculosis, whose treatment requires intervention by healthcare practitioners in order to ensure that treatment is not discontinued. According to the new WHO ranking (2016 – 2020), Brazil

⁵ World Health Organization. Global Tuberculosis Report 2014. Geneva: WHO, 2014. Available at: http://apps.who.int/iris/bitstream/handle/10665/137094/9789241564809_eng.pdf?sequence=1&isAllowed=y. Dalcolmo, M. et al. Tuberculose multirresistente no Brasil: histórico e medidas de controle. *Rev Saúde Pública*; 41(Supl. 1): 34-42, 2007.

⁶ Caminero, J. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis.*, 14(4): 382-90, 2010.

⁷ Available at: <https://g1.globo.com/jornal-nacional/noticia/2020/01/27/fila-para-obter-o-bolsa-familia-jachega-a-quase-500-mil-pessoas.ghtml>

⁸ Available at: <https://www.abrasco.org.br/site/outras-noticias/notas-oficiais-abrasco/crivella-and-crise-que-esmaga-saude-do-rio-de-janeiro/38022/>

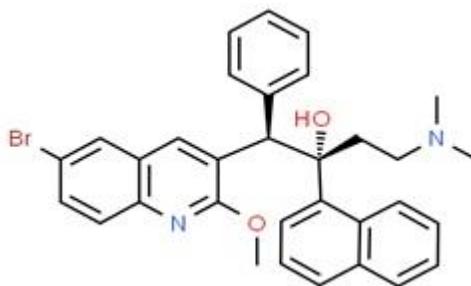
stands twentieth on the list of thirty fast-track countries for TB and ranks 19th in the list of thirty countries tagged as top priority for TB-HIV co-infection.⁹

The decline of tuberculosis control programs has raised massive challenges in the infectious disease field: a significant upsurge in resistance to existing tuberculosis treatment drugs and the appearance of multi-resistant forms.¹⁰ Epidemiological data for 2018 record 548 new cases of TB MDR, of which 309 were in State capitals, which might suggest that identified cases are occurring in upstate areas.¹¹

Taking different scenarios into account, the assessment in the epidemiological bulletin disclosed weak points for controlling the disease. A higher coefficient for tuberculosis outbreaks during the past two years in some sub-scenarios may reflect broader access to diagnostic tools. However, this may also be related to changes in the social and economic contexts in Brazil. Furthermore, a higher percentage of population segments vulnerable to tuberculosis found among these newly-diagnosed cases is an aspect requiring special attention. The epidemiological data raised even more uncertainties when looking at TB MDR cases, as they indicate that Brazil is one of the emerging countries with the largest number of new cases of this disease.¹²

II.a Bedaquiline

Bedaquiline is a diarylquinoline antimycobacterial recommended as part of the combined therapy for treating adults with drug-resistant tuberculosis.¹³ The chemical name of the bedaquiline fumarate compound is: (1*R*,2*S*) – 1-(6-bromo-2-methoxy-3-quinolinyl)-4-(dimethylamino)-2-(1-naphthalenyl)-1-phenyl-butan-2-ol. Its structure is shown in Figure 1.



⁹ World Health Organization. Global tuberculosis report 2019. WHO, 2019.

¹⁰ Dalcolmo, M. et al. Tuberculose multirresistente no Brasil: histórico e medidas de controle. Rev Saúde Pública; v. 41, Supl. 1, p. 34-42, 2007.

¹¹ Boletim Epidemiológico: Brasil livre da tuberculose: evolução dos cenários epidemiológicos e operacionais da doença. Secretaria de Vigilância em Saúde, Ministério da Saúde. v. 50, n. 9, 2019.

¹² Falzon, D.; Mirzayev, F.; Wares, F.; Baena, I.G.; Zignol, M.; Linh, N. Multidrug-resistant tuberculosis around the world: what progress has been made? Eur Respir J., v. 45, n. 1, p. 150-60, 2015.

¹³ Silva, DR; Dalcolmo, M.; Tiberi, S.; Arbex, MA.; Munoz-Torraco M.; Duarte, R.; D'Ambrosio, L. Visca, D.; Rendon, A. Gaga, M. Zumla, A.; Migliori, GB. Novos fármacos e fármacos repropostos para o tratamento da tuberculose multirresistente e extensivamente resistente. J. Bras. Pneumol., v. 44, n. 2, p. 153 – 160, 2018.



Figure 1: Bedaquiline structure¹⁴

Bedaquiline is the first medication with a new mechanism of action approved by the Food and Drug Administration (FDA) in the USA, in 2012 for treating tuberculosis. Since 1971, no new treatment alternatives had been presented. This is particularly vital for children with tuberculosis resistant to commonly-used medications; patients with medication intolerance; and people living with HIV co-infected with antibiotic-resistant tuberculosis.

Acknowledging the pressing need for fewer failures in tuberculosis treatment, the FDA issued approval for bedaquiline on the basis of limited data from Phase II clinical studies. In 2013, the WHO included bedaquiline as a supplementary agent in the TB MDR treatment guidelines.¹⁵

In July 2018, the TB MDR department in South Africa reported higher cure rates and a significant drop in mortality among patients treated with bedaquiline, consequently recommending that access to this medication be provided for all patients diagnosed with any type of medication-resistant tuberculosis.¹⁶

In August 2018, the WHO announced an update in its rifampicin-resistant tuberculosis treatment guidelines, including bedaquiline as the main drug in standard TB MDR treatment regimens, stressing that “immediate steps should be taken to ensure that TB MDR patients receive treatment aligned with the latest evidence on efficacy and safety.”¹⁷

It is estimated that half a million people develop TB MDR each year. This resistance is caused by the absence of treatment, or incomplete or inadequate treatment of poor quality, emerging as a public health crisis, particularly in the developing countries.¹⁸

It is estimated that some 35,000 people all over the world were taking bedaquiline through to October 2019, with drug-resistant tuberculosis treatment needed by some 160,000 people.¹⁹ This means that national tuberculosis programs should immediately extend access to treatment regimens that include bedaquiline. However, the patent barrier (grant or expected grant) continues to block the entry of alternative suppliers.

¹⁴ Structure taken from PubChem. Available at: <https://pubchem.ncbi.nlm.nih.gov/>.

¹⁵ World Health Organization. Global Tuberculosis Report, 2018.

¹⁶ Department of Health, Republic of South Africa. New bedaquiline data show reduction in TB mortality cases. Media Statement. 2018. Available at: http://www.tbonline.info/media/uploads/documents/new_bedaquiline_data_shows_reduction_in_tb_mortality_cases.pdf.

¹⁷ World Health Organization. Rapid Communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB), 2018. Available at: https://www.who.int/tb/publications/2018/rapid_communications_MDR/en/.

¹⁸ Barroso, EC; Mota, RMS; Santos, RO; Sousa, ALO; Barroso, JB; Rodrigues, JLN. Fatores de risco para tuberculose multirresistente adquirida. J. Pneumologia, v. 29, n. 2, p. 89-97, 2003.

¹⁹ DR-TB STAT. Country Updates. Available at: <http://drtb-stat.org/country-updates/>.



II.b Development of bedaquiline

One of the justifications for granting monopoly rights to new medications is the incentive for the patent holder to invest more in researching and developing new medications. However, patents allow pharmaceutical companies to charge exorbitant rates, unchallenged by competition. Nevertheless, it is important to stress that pharmaceutical companies benefit substantially from public funding for research into medications. Furthermore, the researchers working in large corporations who discover molecules often receive negligible amounts for their inventions, due to the legal and economic clout of these companies.

The history of the development bedaquiline reflects collective efforts. Several of the Phase I and II trials conducted before the medication was approved were sponsored by public and philanthropic organizations such as the National Institutes of Health in the USA,²⁰ the National Institute of Allergies and Infectious Diseases²¹ and the TB Alliance.²² Furthermore, the FDA fast-tracked approval for bedaquiline, based on Phase II trial data, due to the pressing need for new TB MDR treatments, prompted by the low success rates of the treatment used previously.

In turn, Johnson & Johnson did not invest directly in Phase III trials as part of its initial bedaquiline development program. Several research institutes invested in additional studies, operational research and pharmacovigilance, in order to document the safety, efficacy and ideal use of bedaquiline for TB MDR treatment, such as the International Union Against Tuberculosis and Lung Disease (IUATLD)²³ and Doctors Without Borders (MSF).²⁴

Johnson & Johnson has already received significant payback for bedaquiline. Designated an orphan medication by the FDA, the pharmaceutical company was awarded a 50% tax credit on identified development and clinical research expenditures. It also

²⁰ National Institute of Allergy and Infectious Diseases. A Phase I Open-Label Trial to Investigate the Pharmacokinetic Interaction Between Rifabutin Or Rifampin And A Single Dose Of TMC207 In Healthy Subjects, 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT01341184>.

²¹ Global Alliance for TB Drug Development. A Phase II Trial to Evaluate the Early Bactericidal Activity, Safety and Tolerability of the Following: TMC207 Alone, TMC207 Plus Pyrazinamide, TMC207 Plus PA-824, PA-824 Plus Pyrazinamide and PA-824 Plus Pyrazinamide and Moxifloxacin, in Adult Patients With Newly Diagnosed, Smear-Positive Pulmonary Tuberculosis, 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT01215851>.

²² Global Alliance for TB Drug Development. A Phase II Dose Ranging Trial to Evaluate the Extended Early Bactericidal Activity, Safety, Tolerability, and Pharmacokinetics of TMC207 in Adult Patients With Newly Diagnosed, Uncomplicated, Smear-Positive, Pulmonary Tuberculosis, 2017. Available at: <https://clinicaltrials.gov/ct2/show/NCT01215110>.

²³ IUATLD, Inc. The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB (STREAM), 2018. Available at: <https://clinicaltrials.gov/ct2/show/NCT02409290>.

²⁴ MSF. Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB): A Clinical Trial, 2018. Available at: <https://clinicaltrials.gov/ct2/show/NCT02754765>.



received a fast-track review in the tropical diseases area, with this privilege deployed by the company in order to fast track the review and authorization of sale for another medication, used for psoriasis: guselkumabe. Sold for around USD 60,000 per patient a year in the USA, it is estimated that this medication will earn some USD 3.4 billion in sales through to 2024.²⁵

Public contributions to the development of bedaquiline must ensure that this medication is accessible to all patients in need through tuberculosis programs all over the world, and more particularly in countries that are more severely affected by this disease. Consequently, the Johnson & Johnson pharmaceutical company – or its pharmaceutical branch, Janssen – should not extend their monopoly on bedaquiline through evergreening strategies, as this is a secondary patent application.

Most patent applications in the pharmaceutical area are registered as secondary claims, meaning with minor modifications to products that have already been patented. The pharmaceutical companies use this tactic of filing countless secondary patents in order to hamper an analysis by state entities, extending analyses periods and blocking the entry of competitors through juridical uncertainty. Upholding monopolies and keeping prices high, this assures exorbitant profits for these companies and their shareholders.

The filing of this secondary patent application by Johnson & Johnson disregards public contributions to the development of this medication. In Brazil, a primary patent has been granted (with Letters Patents issued in 2018), with the company intending to extend this monopoly through this patent application addressing the same active ingredient, in the form of fumarate salt.

All over the world, civil society organizations have been working tirelessly to make life-saving medications accessible to everyone. In September 2018, Doctors without Borders sent an open letter to Johnson & Johnson, requesting this pharmaceutical company to take steps ensuring that countries could acquire affordable and sustainable supplies of bedaquiline for treating TB MDR.²⁶ The struggle to access TB MDR medications is at a decisive stage, in order to prevent the Johnson & Johnson pharmaceutical company from extending its monopoly through granting a secondary patent application for bedaquiline, which is the main drug for treating TB MDR.

The price of six months of treatment with bedaquiline is USD 400 (about BRL 1,980) for countries eligible to purchase this medication through the Global Drug Facility. This is an organization run by the STOP TB Partnership, which supplies tuberculosis medications to low and medium income countries. Some people must take the medication for up to twenty

²⁵ Evaluate Pharma. World Preview 2018: Outlook to 2024. Available at: <http://info.evaluategroup.com/rs/607-YGS-364/images/WP2018.pdf>.



months, stepping up the price of the bedaquiline to USD 1,200 (about BRL 5,040). However, researchers at Liverpool University have calculated that this medication could be produced and sold for USD 0.25 (about BRL 1.50) a day, if at least 108,000 treatments were to be sold each year.²⁷

Although bedaquiline was approved by Brazil's Public Health Regulator (ANVISA) in February 2019, there are as yet no reports on its inclusion in the Unified National Health System (SUS), despite its importance in the Brazilian context. Moreover, no data has been found on government purchases or prices set by the Medications Market Regulation Chamber (CMED) which is the entity regulating the medications market in Brazil, setting a ceiling price for medications before they are made available for sale.

II.c Bedaquiline Patent Status in Brazil

A public database survey²⁸ identified eight Brazilian patent applications for bedaquiline (Table 1) submitted to the INPI. One of them is the main application (with Letters Patents issued) while the others are secondary, claiming formulation, use, processes and combinations. A Johnson & Johnson subsidiary, Janssen did not merely seek a primary patent for the compound, but also submitted several patent applications for bedaquiline, attempting to claim minor improvements in formulations that are used every day in any pharmaceutical setting.

If all these patents had been granted, bedaquiline would be under a patent monopoly until at least 2036.²⁹ This would hamper access to this medication for the population at large for a further eight years, based only on the year of filing, as shown in Figure 2.

²⁶ MSF. Open Letter to J&J: Calling for affordable access to critical TB drug bedaquiline, 2018. Available at: <https://msfaccess.org/open-letter-jj-calling-affordable-access-critical-tb-drug-bedaquiline>.

²⁷ Available at: <https://www.msf.org.br/noticias/msf-protesta-em-frente-bolsa-de-valores-de-nova-iorque-contrapreco-de-medicamento-para>.

²⁸ Searches were conducted in the: Orange Book, Canada Health, WIPO Patentscope, Espacenet, Patent Opposition Database, Medspal.

²⁹ This forecast does not consider the application of the Sole Paragraph of Article 40 of the LPI, which states that the monopoly may be extended, should the analysis period of the Patent Application Extend for More Than 10 Years.



Figure 2: Timeline for Bedaquiline Patent Applications: granted and pending

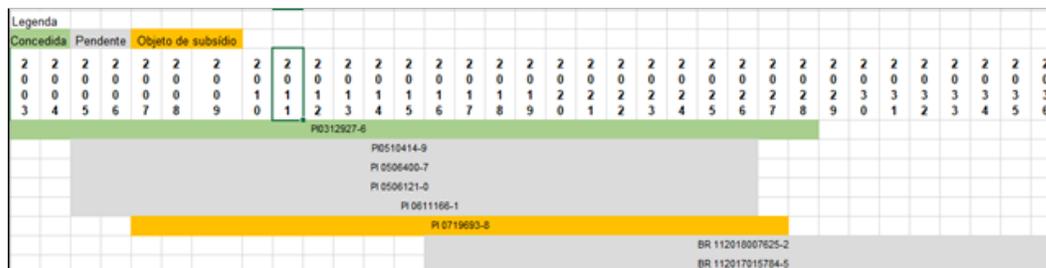


Table 1: Patent applications related to bedaquiline

PATENT APPLICATION	TITLE	REGISTRANT	PATENT STATUS
PI 0312927-6 WO 2004011436 US 7498343	Quinoline derivative compound, composition, their use as mycobacterial inhibitors, and the preparation process for such derivatives	Janssen Pharmaceutica N.V. (BE)	Filed: July 18, 2003 Granted (Valid for 10 years as from July 10, 2018)
PI 0510414-9 WO 2005117875	Use of substitute quinoline derivatives for the treatment of drug-resistant mycobacterial diseases	Janssen Pharmaceutica N.V. (BE)	Filed: May 24, 2005 Pending
PI 0506400-7 WO 2006067048	Treatment of latent tuberculosis	Janssen Pharmaceutica N.V. (BE)	Filed: December 8, 2005 Pending
PI 0506121-0 WO 2006131519	Use of quinolone derivative compound with antibacterial agents, combination, pharmaceutical composition and product	Janssen Pharmaceutica N.V. (BE)	Filed: December 8, 2005 Pending
PI 0611166-1 WO 2006125769	Process for isolating (alpha s, beta r)-6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol, use of 4-oxide of (11br)-4- dinaphtho[2,1-d:1',2'-f][1,3,2] dioxaphosphepin as a resolution agent and a salt	Janssen Pharmaceutica N.V. (BE)	Filed: February 22, 2006 Pending
PI 0719693-8 WO 2008068231	Fumarate salt of (alpha s, beta r)-6-bromo-alpha-[2-(dimethylamino) ethyl]-2-methoxy-alpha-1-naphthalenyl-beta-phenyl-3-quinolineethanol	Janssen Pharmaceutica N.V. (BE)	Filed: December 3, 2007 Pending
BR112018007625-2 WO 2017066053	Combined antibacterial composition and short-term antibacterial regimen	Janssen Pharmaceutica N.V. (BE)	Filed: October 5, 2016 Pending
BR112017015784-5 WO 2016120258	Dispersible compositions	Janssen Pharmaceutica N.V. (BE)	Filed: January 26, 2016 Pending



III. MATTER ADDRESSED BY THE PATENT APPLICATION

Filed in Brazil on December 3, 2007, the **PI 0719693-8** patent application derives from European Application EP 061254439, whose **Priority Filing Date is December 5, 2006**. This Application was submitted under the Patent Cooperation Treaty (PCT) on March 10, 2007 and was published by the World Intellectual Property Organization under N° WO 2008/068231 on June 12, 2008.

Patent Application **PI 0719693-8** has 21 Claims, which address the compound (bedaquiline fumarate), pharmaceutical compositions, salt preparation process, composition and uses. The classification of the Claims is shown on Table 2.

Table 2: Claims Table for Patent Application **PI 0719693-8**

TYPE OF PROTECTION	CLAIMS	DETAILS
Compound (salt)	1 to 3	Fumarate salt of bedaquiline
Use a	4, 5, 18, 19 and 20	Attributions for use
Pharmaceutical composition	6 to 15	Composition
Process	16, 17 and 21	Salt preparation process and composition

IV. STATE OF THE ART AND PRIOR FILINGS

According to Article 11, §1, of the LPI, “the state of the art consists of everything made available to the public prior to the patent application filing date, through written or verbal description, for use or any other means whatsoever in Brazil or elsewhere in the world, except for the provisions set forth in Articles 12, 16 and 17”.³⁰

This definition is reaffirmed by the provisions set forth in Paragraph 3.1, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016, whereby:

the state of the art is consists of everything made available to the public prior to the patent application filing date, through written or verbal description, for use or any other means whatsoever in Brazil or elsewhere in the world, except

³⁰ BRAZIL. Law N° 9,279, dated May 14, 1996. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.



for the provisions set forth in Articles 12 (grace period), 16 (PCPIP Priority) and 17 (Domestic Priority) of the LPI.³¹

Moreover, pursuant to the wording of Paragraph 3.2 of these Guidelines, on what constitutes the state of the art, “there are no geographical language constraints or means through which the relevant information was made available to the public, just as there are no time limit stipulated by the documents or other forms of information.”³² And, pursuant to Paragraph 3.3:

The data to be used in the searches for prior filings must be based on the relevant date, meaning the filing date or the priority filing date, if any. It must also be recalled that different claims or different alternatives claimed under a claim may have different relevant dates. The patentability requirements must be analyzed for each claim or part of a claim, when presenting several alternatives. The state of the art for a claim or part of a claim may include matters that might not be open to citation against another claim or part of a claim, because the latter has a relevant prior date. Evidently, if all the documents constituting the state of the art were available to the public prior to the date of the earliest priority document, the examiner should not be concerned about the association of the priority dates for each matter claimed.³³

Thus, compliant with the provisions set forth in Article 11, §1, of the LPI,³⁴ and the specific matters addressed in Chapter III, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016,³⁵ the following documents are presented as prior filings for the Claims set forth in Patent Application **PI 0719693-8**:

D1: WO 2004011436 (PI 0312927-6) – Compounds derived from quinoline, composition, their use mycobacterial inhibitors, and the preparation process for such derivatives

Priority Filing Date: July 25, 2002.

D2: WO 2005117875 (PI 0510414-9) – Use of substituted quinoline derivatives for the treatment of drug-resistant mycobacterial diseases

³¹ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

³² NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

³³ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: 23 abr. 2020.

³⁴ **Law N° 9,279, dated May 14, 1996.** Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

³⁵ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.



Priority Filing Date: May 28, 2004.

Prior filing D1 refers to the Patent Application submitted by Janssen Pharmaceutica WO 2004011436 (corresponding Brazilian patent: PI 0312927-6), which was granted on July 10, 2018. This Application discloses a free base bedaquiline compound and its salts.

Additionally, compositions and processes are claimed, that are related to bedaquiline and vehicles such as wetting agents, as well as the stereo-isomeric forms of the compound in question, as useful agents for treating diseases caused by mycobacteria, particularly tuberculosis.

Among the salts claimed in the D1 Specification, the fumaric acid composition is listed, resulting in fumarate salt, mentioning that salts formed from synthesized derivatives are endowed with adequate hygroscopicity and bioavailability.

Prior filing D2 refers to the second Patent Application submitted by Janssen Pharmaceutica for bedaquiline in Brazil (corresponding Brazilian patent: PI 0510414-9), whose status is pending. This Patent Application claims the use of bedaquiline for the treatment of mycobacterial diseases. The Specification for this Patent Application also lists fumaric acid for addition and the formation of fumarate salt.

V. ANALYSIS OF THE CLAIMS

V.a Claims 1 to 3 (Compound - fumarate salt)

Claims 1 to 3 of Patent Application **PI 0719693-8** claim bedaquiline fumarate with the usual official nomenclature and structural formula, respectively. The content of these Claims, namely, **fumarate salt of bedaquiline, had already been disclosed previously in D1 and D2,** through Patent Applications WO 2004011436 (PI 0312927-6) and WO 2005117875 (PI 0510414-9).

Figure 3 consists of an excerpt from PI 0312927-6 (Brazilian patent corresponding to D1), with this same wording present in PI 0510414-9 (Brazilian patent corresponding to D2). Consequently, these Claims **do not present Novelty**, not warranting patent protection.

Pharmaceutically acceptable acid addition salts are defined in order to encompass therapeutically active, non-toxic forms of acid addition salts that can be formed by the Formula (Ia) and (Ib) compounds. Such acid addition salts may be obtained through treating the base form of the compounds, in accordance with Formula (Ia) and (Ib) with appropriate acids, for example inorganic acids, for example hydric acid, in particular hydrochloric acid, bromhydric acid, sulfuric acid, nitric acid and phosphoric acid; organic acids, for example acetic acid, hydroxy acetic acid, propanoic acid; lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, fumaric acid, malic acid, tartaric acid, citric acid, methane sulfonic acid,



methane sulfonic acid, benzene sulfonic acid, P-toluene sulfonic acid, cyclonic acid, salicylic acid, p-amino salicylic acid and pamoic acid.

Figure 3: Excerpt from the Specification of D1 that discloses
bedaquiline in the formulation with fumaric acid
(PI 0312927-6 - RPI 1801, p. 10 and 11).

Along these lines, Paragraph 2.1 of the Patent Application Examination Guidelines for the Chemical Area, established by Resolution/INPI/PR N° 208/2017, when specifically addressing the **requirement of Novelty** for matters involving chemical compounds, establishes that

The Technical Examination checking compliance with the patentability requirements for patent applications claiming chemical compounds follows the same procedures as applicable to products in general, set forth in detail in Block II of the Patent Application Examination Guidelines [...]³⁶

Thus, according to the stages for assessing Novelty addressed in Paragraph 4.3, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016, the above-mentioned Claims failed to present the absolute Novelty required by the governing law, whereby they do not warrant protection under the patent system.

According to these Guidelines:

4.3 In order to assess Novelty, the examiner works through the following stages: (i) identify the elements mentioned in the Claim; (ii) decide whether a document under analysis forms part of the state of the art – Chapter III of these Guidelines; (iii) decide and indicate whether all the elements in the Claim were explicitly or inherently combined in the document, for a person versed in the art, in a manner that anticipates the Claim.³⁷

This means that, as they are not deemed to be novel, Claims 1 to 3 of Patent Application **PI 0719693-8** fail to comply with the patentability requirements set forth in Article 8, of the LPI, second whereby “an invention is patentable that complies with the requirements of **Novelty**, an Inventive Step and Industrial Applicability” (emphasis added).³⁸

Finally, according to Article 11 of the LPI, the invention may be deemed novel only when it is not encompassed by the state of the art, which consists of everything made accessible to the public prior to the filing date of the patent application, through written or

³⁶ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 208, dated December 27, 2017.**

Establishes the Patent Application Examination Guidelines for the Chemical Area. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on April 23, 2020.

³⁷ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on April 23, 2020.



verbal description, through use or any other means in Brazil or elsewhere in the world, except for the provisions set forth in Articles 12, 16 and 17”.³⁹

In addition to the bedaquiline formulation already being disclosed previously as a fumarate salt, these Claims **do not present an Inventive Step**, as the claim composition is obvious to a person versed in the art, grounded on the existing knowledge of all known techniques. The use of the formulation as the salt of a known compound is widespread – in this case, bedaquiline – is obvious and may not be deemed inventive. Some examples are: formoterol fumarate, rupatadine fumarate, tenofovir fumarate and bencyclane fumarate.

Under the biopharmaceutical classification system, bedaquiline is a Class 2 compound with low solubility and high permeability, similar to rifampicin. It differs from other medications such as isoniazid, ofloxacin and ethambutol hydrochloride, which are Class III, with high solubility and low permeability.⁴⁰ However, this classification does not prevent the compound from having adequate bioavailability for the treatment, as is the case with rifampicin.

. For a specialist in this field, it is known that formulation as a salt increases the solubility of a compound, compared to its freebase. Different types of salts may be formed from a single drug, although some may excessively increase the fusion point of the molecule, reducing its absorption. Along these lines, fumaric acid salts are the appropriate choice, as they produce salts with lower fusion points, meaning that they are normally endowed with greater solubility. With regard to stability, compounds transformed into salts normally have larger crystal networks, enhancing their stability.⁴¹

The Technical Examination checking for compliance with the **requirement of Inventive Step** in patent applications claiming chemical compounds, similar to the requirement of Novelty, with regard to Paragraph 2.1, of the Patent Application Examination Guidelines in the Chemistry field, established by Resolution/INPI/PR N° 208/2017, must comply with the same procedures applicable to products in general.⁴²

Consequently, in order to decide whether the claimed invention is obvious, compared to the state of the art, Paragraph 5.9, Block II, of the Patent Application

³⁸ BRAZIL. **Law N° 9,279, dated May 14, 1996**. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on April 23, 2020.

³⁹ BRAZIL. **Law N° 9,279, dated May 14, 1996**. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020

⁴⁰ Budha, N.; Lee, R.; Meibohm, B. Biopharmaceutics, Pharmacokinetics and Pharmacodynamics of Antituberculosis Drugs. *Current Medicinal Chemistry*, 15(8), 809-825, 2008.

⁴¹ Gould, PL. Salt selection for basic drugs. *International Journal of Pharmaceutics*, 33(1-3), 201-217, 1986.

⁴² NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 208, dated December 27, 2017**. Establishes the Patent Application Examination Guidelines for the Chemical Area. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020



Examination Guidelines, established by Resolution N° 169/2016, presents three stages to be followed:

- (i) define the closest state of the art; (ii) define the distinctive characteristics of the invention and / or the technical problem actually solved by the invention, and (iii) decide whether in view of the technical problem under consideration and based on the closest state of the art, whether or not the invention is obvious to a person versed in the art.⁴³

On this point, it must be explained that, according to Paragraph 5.10, of these same Guidelines,

the closest state of the art consists of a document of a combination of two documents, exceptionally three, related to the invention addressed in each Independent Claim, which must form the grounds for assessing the presence of an Inventive Step. The closest state of the art may be: (i) one or more existing documents in the same technical field as that of the claimed invention, in which the technical problem to be resolved, the technical effects or the intended use are the closest to the claimed invention; or that describe the largest number of technical characteristics of the claimed invention; or (ii) one or more existing documents that, although being in a technical field other than the field of the claimed invention (see item 5.4 of this Chapter), are able to perform the function of the invention, describing the largest number of technical characteristics of the invention. For further details, see the subsection entitled “Invention by technical field analogy”.⁴⁴

Along these lines, the **D1 and D2 prior filings constitute the closest state of the art** for querying the lack of an Inventive Step in this Patent Application. And based on these documents, as fully demonstrated above, there is no further doubt about the obviousness of these inventions, for a person versed in the art.

This means that, although failing to comply with the requirement of Novelty, Claims 1 to 3, of Patent Application **PI 0719693-8**, also fail to meet the requirement of an Inventive Step, which is also stipulated in Article 8, of the LPI, whereby “an invention is patentable that complies with the requirements of Novelty, **Inventive Step** and Industrial Applicability” (emphasis added).⁴⁵

Indeed, as set forth in Paragraph 5.1, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016, Novelty is a vital requirement in order

⁴³ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016**. Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

⁴⁴ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016**. Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

⁴⁵ BRAZIL. **Law N° 9,279, dated May 14, 1996**. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.



to assess the existence of the Inventive Step whereby Claims 1 to 3 of Patent Application under analysis may not be deemed to comply with this other legal requirement.⁴⁶

Furthermore, Article 13 of the LPI states that “an invention is endowed with an Inventive Step whenever it does not derive in an evident or obvious manner from the state of the art for a person versed in the art”.⁴⁷ And, on a supplementary basis, according to Paragraph 5.1, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016:

5.3 Should a person versed in the art be able to attain the invention solely through logical analysis, inference or without undue experimentation based on the state of the art, the invention is obvious and thus does not present any unexpected technical solution. **Should this be the case, the Application is not patentable, due to the absence of an Inventive Step** (emphasis added).⁴⁸

Indeed, based on the procedures followed so far, it may be categorically affirmed that Claims 1 to 3 of Patent Application **PI 0719693-8** **do not comply with the legal requirements of Novelty and an Inventive Step**. This is why they may not be endowed with an exclusive right.

V.b Claims 6 to 15 (Composition)

Claims 6 to 15 **do not present an Inventive Step**, being a mere mixture of components. The various composition claims do not present an Inventive Step for resolving a problem at the state of the art, nor do they present any unexpected or synergetic effect resulting from the combination of known compounds

In this Patent Application, **there is no information about a composition that would resolve some problem at the state of the art, for example, a problem of stability or bioavailability of a previously known formulation.**

This Patent Application mentions various possibilities for ingredients, not identifying a vehicle or combination of ingredients that might have some unexpected technical effect. It merely lists ingredients and different concentrations that may be used in the formulation, such as wetting agents, diluents, polymers, disintegrants, glidants and lubricants.

⁴⁶ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016**. Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

⁴⁷ BRAZIL. **Law N° 9,279, dated May 14, 1996**. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

⁴⁸ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016**. Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.



The Patent Application addressed by this Submission of Input acknowledges obviousness in the identification and use of specified wetting agents in the development of a formulation, not presenting any notable aspect or innovation among the described techniques, as set forth in the excerpts presented in Figures 4, 5 and 6.

This compound may be formulated in various pharmaceutical compositions for administration purposes. As appropriate compositions, mention may be made of all the compositions usually employed for the systematic administration of drugs. In order to prepare the pharmaceutical compositions addressed by this invention, an efficacious quantity of this salt as the active ingredient is blended into an intimate mixture with a pharmaceutically acceptable vehicle, with this vehicle able to take various forms, depending on the manner of preparation desired for the administration thereof.

Figure 4: Excerpt on the lack of an Inventive Step (Specification of PI 0719693-8, p. 5)

The Application also attempts to associate a wetting agent, seeking to establish a comparative advantage for the invention, but there are no more specific characterizations of the wetting agent, nor any unexpected technical effect:

The wetting agent addressed by this invention may be an anionic, cationic, zwitterionic or non-ionic wetting agent, with the latter preferred. The wetting agent addressed by this invention may also be a blend of two or more wetting agents.

Figure 5: Excerpt on the lack of an Inventive Step (Specification of PI 0719693-8, p. 9)

In another excerpt, the following segment may be highlighted, in which the actual wording of the Specification stressed that **there is no Inventive Step**, as it highlights the state of the art:

Preferably, these compositions shall contain a hydrophilic wetting agent, necessarily noting that the HLB value of a wetting agent is only a gross guide to indicate the hydrophilicity/hydrophobicity of a wetting agent. The HLB value of a specific wetting agent may vary, depending on the method used to determine the HLB value; this may vary, depending on its commercial source; it is subject to variability, batch by batch. A person versed in the state of the art can quickly identify hydrophilic wetting agents that are appropriate for use in the pharmaceutical compositions addressed by this invention.

Figure 6: Excerpt on the lack of an Inventive Step (Specification of PI 0719693-8, p. 8)

The same strategy of not presenting any comparative advantage in the formulation that allows the discovery of an unexpected technical effect was used by the registrant to describe a formulation in a patent application for rilpivarin, which was rejected by the Indian Patents Office⁴⁹ as shown in Figure 7.

⁴⁹ Office of the Controller General of Patents, Designs and Trade Marks. Decision of the Controller refusing patent (Indian Patent Application Number 1594/DELNP/2007). Available from: <http://ipindiaservices.gov.in/decision/1594-DELNP-2007-2593/section15case1594delnp2007.pdf>

Rilpivirine Application	Bedaquiline Salt Application
<p>[Page no. 9, Para no. 077]</p> <p>“Solid pharmaceutical compositions according to the present invention may comprise by weight based on the total weight of the composition:</p> <p>(a) from 5 to 50% of a compound of formula (I), (I-a) or (I-b);</p> <p>(b) from 0.01 to 5% of a wetting agent;</p> <p>(c) from 40 to 92% of a diluent;</p> <p>(d) from 0.1 to 5% of a glidant.”</p>	<p>[Claim no. 3]</p> <p>“3. A pharmaceutical composition according to any one of claims 6 to 10 comprising by weight based on the total weight of the composition:</p> <p>(a) from 5 to 50% of active ingredient;</p> <p>(b) from 0.01 to 5% of a wetting agent;</p> <p>(c) from 40 to 92% of a diluent;</p> <p>(d) from 0.1 to 5% of a glidant.”</p>

Figure 7: Similarity between the Claims in the Patent Applications for rilpivarin and bedaquiline, both submitted by Johnson & Johnson.

This Patent Application **PI 0719693-8** tries to address a fumarate salt of bedaquiline formulation associated with a wetting agent, in an attempt to configure an unexpected technical effect. In its Application, no evidence was provided demonstrating an unexpected technical effect of the purported novel formulation of bedaquiline over its previously known form, as set forth in Patent Applications WO 2004011436 (D1) and WO 2005117875 (D2).

Along these lines, when considering that the preparation of pharmaceutical compositions generally requires the use of techniques and compounds that are commonly known by a person versed in the art, normally lacking an Inventive Step,⁵⁰ and in this specific case as well, there are no doubts about the obviousness of Claims 6 to 15 in this Patent Application.

This is why, as occurred with the above mentioned Claims, **Claims 6 to 15 of Patent Application PI 0719693-8 may not be accepted, as they do not present an Inventive Step and thus clearly fail to comply with the minimum requirements for patentability set forth in Article 8, of the LPI.**⁵¹

V.c Claims 16, 17 and 21 (Process)

⁵⁰ CORREA, Carlos M. **Guidelines for the examination of patent applications relating to pharmaceuticals**. Geneva: United Nations Development Programme, 2016. 44 p. Available at: https://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP_patents_final_web_2.pdf. Accessed on: April 23, 2020.

⁵¹ BRAZIL. **Law N° 9,279, dated May 14, 1996**. Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.



As explained in the previous items, the Claims addressing the salt preparation process and the composition (Claims 16, 17 and 21) **do not present an Inventive Step.**

In Patent Applications WO 20040114326 (D1) and WO 2005117875 (D2), information is anticipated on manufacturing processes and formulation similar to those claimed in the Patent Application addressed by this Submission of Input. Mention is made of diluents, lubricants, stabilizing agents, emulsifying agents, preservatives, surfactants and disintegration agents, among other ingredients in the formulation and their possible concentrations in the formula.

Another excerpt from the Specification indicates that this is a process that does not present an Inventive Step, because it involves knowledge known to a person versed in the art:

A person versed in the art will recognize the most appropriate equipment to be used in the processes described above.

The general route described above for preparing the tablets addressed by this invention may be modified by a person versed in the art, for example through the addition of certain ingredients at other stages, different to those indicated above.

Figure 8: Excerpt on the lack of an Inventive Step (Specification of PI 0719693-8, p. 19)

Indeed, as may be noted, **Claims 16, 17 and 21 also lack an Inventive Step, thus failing to comply with the requirements set forth in Article 8, of the LPI, and thus do not warrant patent protection from the Brazilian State.**⁵²

V.d Claims 4, 5, 18, 19 and 20 (Use)

With regard to the usage claims, it is known that Paragraph 3.73, Block I, of the Patent Application Examination Guidelines, established by Resolution N° 124/2013, states that, for the purposes of the Technical Examination, a “usage” claim must be considered as equivalent to a “process” claim.⁵³

Moreover, it is known that Paragraph 5.40, Block II, of the Patent Application Examination Guidelines, established by Resolution N° 169/2016, states that “an invention

⁵² BRAZIL. b Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

⁵³ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 124, dated December 4, 2013.** Establishes the Patent Application Examination Guidelines – Content of Patent Application. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.



for the novel use of a known product refers to an invention that uses a known product for a novel purpose”.⁵⁴

Along the same lines, it is also known that Chapter 9 of the Patent Application Examination Guidelines for the Chemical Area, established by Resolution/INPI/PR N° 208/2017, supplementing the above mentioned provisions, rules on the “specific characteristics of a Technical Examination of inventions consisting of novel uses for known products, especially novel medical uses”.⁵⁵

However, notwithstanding the existence of these Guidelines, under the aegis of this Submission of Input, attention is drawn to the undeniable contradiction between these provisions and the governing law. After all, under the aegis of the Brazilian juridical arrangements, there is **no doubt about the impossibility of granting usage patents, limiting the scope of patent protection only to products and processes.**

This position is grounded on the provisions set forth in Article 42, of the LPI whereby, the “patent confers on its holder the right to prevent a third party unlicensed thereby, from producing, using, displaying for sale, selling or importing for such purposes: I – **the product** addressed by a patent; II – **a process or product** obtained directly through a patented process” (emphasis added).⁵⁶

This means that, as real *exceptions* to the public domain, free enterprise (Article 1, IV, and Article 170, Head Paragraph, of the Brazilian Constitution)⁵⁷ and free competition (Article 170, IV, of the Brazilian Constitution).⁵⁸ the legal provisions addressing Intellectual Property must be construed in a restrictive manner.⁵⁹ In this specific case, if the LPI makes no specific mention of the possibility of patenting usage claims, **any infra-legal expansion of this scope is not compliant with the Law, and may thus not be accepted.**

Indeed, this directive becomes even weightier as it addressed the patentability of inventions related to medications, with this circumstance playing a crucial role in the public

⁵⁴ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 169, dated July 15, 2016.** Establishes the Patent Application Examination Guidelines – Block II – Patentability. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

⁵⁵ NATIONAL INDUSTRIAL PROPERTY INSTITUTE. **Resolution N° 208, dated December 27, 2017.** Establishes the Patent Application Examination Guidelines for the Chemical Area. [S. I.]. Available at: <http://www.inpi.gov.br/menu-servicos/patente/legislacao-patente-1>. Accessed on: April 23, 2020.

⁵⁶ BRAZIL. **Law N° 9,279, dated May 14, 1996.** Regulates rights and obligations related to Industrial Property. Brasília, DF: President's Office, May 15, 1996. Available at: http://www.planalto.gov.br/ccivil_03/Leis/L9.279.htm. Accessed on: April 23, 2020.

⁵⁷ BRAZIL. **Constitution (1988).** Brasília, DF, Available at: http://www.planalto.gov.br/ccivil_03/constituicao/constituicao.htm. Accessed on: April 23, 2020.

⁵⁸ BRAZIL. **Constitution (1988).** Brasília, DF, Available at: http://www.planalto.gov.br/ccivil_03/constituicao/constituicao.htm. Accessed on: April 23, 2020.

⁵⁹ BARBOSA, Denis Borges. **Tratado da Propriedade Intelectual.** 2. ed. Rio de Janeiro: Lumen Juris, 2019, p.302



domain through embodying the fundamental rights to health (Article 6 and Article 196 of the Brazilian Constitution).⁶⁰ **For the reasons set forth above, Claims 4, 5, 18, 19 and 20 may thus not be accepted, and should initially be dismissed.**

Nevertheless, as shown below, even if substantially considering the content of each one of these Claims, there is no lack of motive for their full rejection by this semi-autonomous government entity.

Claims 4 and 5 address:

4. Compound in accordance with any of Claims 1 to 3, for use as a medication.
5. Compound in accordance with any of Claims 1 to 3 for use as a medication for treating or preventing a mycobacterial infection

Figure 9: Claims 4 and 5

These Claims may not be protected due to a **lack of clarity, thus failing to comply with Article 25 of the LPI**, because the composition is characterized through its usage rather than its technical characteristics, as set forth in the Patent Application Examination Guidelines - Aspects related to the Examination of Patent Applications for the Chemical Area (examples 2 and 3)

Claims 18 and 19 address:

18. Use of a composition according to any of Claims 1 to 3 for the fabrication of a medication for the treatment or prevention of a mycobacterial infection.
19. Use of a composition according to Claim 18 for the fabrication of a medication for the treatment of a mycobacterial infection.

Figure 10: Claims 18 and 19

According to the Patent Examination Guidelines for the Chemical area, this type of Claim may be granted. However, we believe that **the Industrial Property Act (Article 42) does not include usage among the aspects open to patent protection, whereby the Claim may not be granted.**

Claim 20 addresses:

20. Use of a compound according to Claim 18 or 19, for the preparation of a medication for the treatment of a mycobacterial infection wherein the medication must be administered to a patient who has been fed.

⁶⁰. BRAZIL. **Constitution (1988)**. Brasília, DF, Available at: http://www.planalto.gov.br/ccivil_03/constituicao/constituicao.htm. Accessed on: April 23, 2020.



Figure 11: Claim 20

This Claim may not be protected due to **lack of clarity, thus failing to comply with Article 25 of the LPI**, as the additional characteristics of the Claim refers to the manner of administration, which is part of the treatment regimen rather than use, pursuant to the Patent Application Examination Guidelines – Aspects related to the Examination of Patent Applications for the Chemical Area (Example 8).

Once again, in addition to a lack of clarity, the absence of an Inventive Step is stressed, as it may be noted in the Specification that:

The exact dosage and the frequency of administration depends on the specific condition that is being treated, the severity of the condition that is being treated, the age, weight, gender extension of the disorder and the general physical condition of the specific patient, as well as any other medication that the person may be taking, as is well known to a person versed in the art.

Figure 12: Excerpt on the lack of an Inventive Step (Specification of PI 0719693-8, p. 6)

Consequently, **this Patent Application_PI 0719693-8 and its Claims must be rejected in full, as they fail to comply with the patentability criteria**, are obvious to a person versed in the art, and lack Novelty.

VI. THE PETITION

Pursuant to the matters set forth above, the organizations signing this Submission of Input request that:

1. this Petition be accepted and included in the procedural scope of the Patent Application under analysis, as it complies with the admissibility criteria (timeliness and legitimacy) established by Brazilian Law.
2. the application for Patent of Invention **PI 0719693-8** should be rejected in full, as all the Claims presented fail to comply with the patentability requirements established in the LPI.

In which terms,

Approval is requested.

Rio de Janeiro, April 28, 2020.



INTELLECTUAL PROPERTY
WORKING GROUP

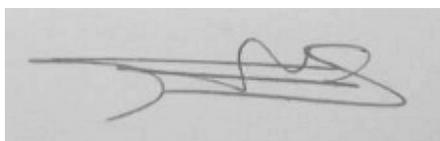


Carolinne Scopel

Carolinne Thays Scopel
CRF/RJ N° 20.318



Roberta Dorneles Ferreira da Costa Silva
CRF/RJ N° 21.051



Tiago Fernandes da Silva
CRF/RJ N° 17.868



Marcela Fogaça Vieira
OAB/SP N° 252.930

Alan Rossi



LIST OF DOCUMENTS AND EXHIBITS:

EXHIBIT 1: WO 2004011436 (PI 0312927-6) – Compounds derived from quinoline, composition, their use mycobacterial inhibitors, and the preparation process for such derivatives.

Priority Filing Date: July 25, 2002 **(D1)**.

EXHIBIT 2: WO 2005117875 (PI 0510414-9) – Use of substituted quinoline derivatives for the treatment of drug-resistant mycobacterial diseases.

Priority Filing Date: May 28, 2004 **(D2)**

EXHIBIT 3: By-Laws – ABIA

EXHIBIT 4: Minutes of the Meeting Electing the Board – ABIA

EXHIBIT 5: Power of Attorney – ABIA

EXHIBIT 6: By-Laws – Grupo Solidariedade é Vida

EXHIBIT 7: Minutes of the Meeting Electing the Board – Grupo Solidariedade é Vida

EXHIBIT 8: Power of Attorney – Grupo Solidariedade é Vida

EXHIBIT 9: By-Laws – FOAESP

EXHIBIT 10: Minutes of the Meeting Electing the Board – FOAESP

EXHIBIT 11: Power of Attorney – FOAESP

EXHIBIT 12: By-Laws – UAEM

EXHIBIT 13: Minutes of the Meeting Electing the Board – UAEM

EXHIBIT 14: Power of Attorney – UAEM