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Secondary patents threaten access to new TB medicines

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Introduction

On 29 September, Johnson and Johnson (J&J) announced its intent not to enforce the patents it owns and controls for the tuberculosis (TB) medicine bedaquiline in 134 low- and middle-income countries.[1] J&J said this move is to allow generic manufacturers to produce and supply good-quality, medically acceptable bedaquiline in the 134 countries. (The list of countries is not publicly available.) The company made this announcement following pressure from various quarters.[2] Since the original patent on bedaquiline has expired, the announcement is in relation to the secondary patents. (Presently there are seven patents for bedaquiline.) However, secondary patents (also known as 'evergreening' patents) continue to threaten access to many other new TB medicines.

New TB medicines have enabled all-oral regimens for TB treatment. This has improved the success of drug-resistant TB (DR-TB) treatment. Prior to the introduction of these new medicines, the treatment for DR-TB used injectables which caused serious side-effects including irreversible hearing loss.[3]

Despite the introduction of new medicines, scaling up of the treatment is lagging, due to several reasons including treatment being complex, onerous, expensive and in some countries beyond the reach of many patients who need it. For instance, in 2021, only 161,746 people requiring treatment of multi-drug-resistant / rifampicin-resistant (MDR/RR) TB received it, indicating that there are serious barriers in accessing these new medicines.[4]

Access to new TB medicines thus still remains at sub-optimal level due to high prices and restrictive licensing arrangements between pharmaceutical companies and other drug developers. Patents are one of the important reasons for the high prices and restrictive licences.

Globally about 10.6 million people fell ill with TB in 2021, equivalent to 134 cases per 100,000 population.[5] Of all TB cases, 6.7% were among people living with HIV.[6] Eight countries accounted for more than two-thirds of the global TB cases: India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%).[7] The burden of drug-resistant TB also increased by 3% between 2020 and 2021, with 450,000 cases of rifampicin-resistant TB reported in 2021.[8] An estimated 191,000 deaths occurred due to MDR/RR-TB in 2021.

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Despite the increase in the research and development (R&D) pipeline and marketing approval of new TB medicines, access to these new medicines has been a problem in countries with high TB burden. Multiple secondary patents on the new TB drugs bedaquiline and delamanid have delayed the introduction of cost-effective generic versions and thus compromised affordable access. In 2014, the World Health Assembly adopted the World Health Organization (WHO)'s End TB Strategy, which counts among its aims an 80% decrease in TB incidence by 2030, in accordance with United Nations Sustainable Development Goal 3, which includes ending the global TB epidemic.[9] However, without access to newer medicines, attaining this goal is a tall order.

Secondary/evergreening patents refer to new patents on a known medicine or molecule.[10] Pharmaceutical companies often file multiple patents on other than the active ingredients, such as on different dosage forms, formulations, method of treatment etc. Secondary patents also emerge from changes to formulations or new use of the medicine for another disease discovered during clinical trials. Companies also file patent applications on combinations of new and repurposed medicines. Secondary patents are a common strategy used by pharmaceutical companies to ward off competitors by delaying the entry of generic versions of the drugs.

This briefing paper highlights the presence of secondary patents on new TB medicines beyond bedaquiline and discusses their potential impact on access to TB treatment.

Secondary patents on new TB medicines: a patent landscape

For the first time in decades, there are multiple new drugs in the pipeline that are being investigated for TB treatment. Additionally, many existing medicines are being repurposed or optimised for TB to provide treatment in shorter durations for drug-susceptible TB (DS-TB) and safer, shorter treatment for MDR-TB.

To assess the extent of secondary patents, the Third World Network (TWN) commissioned a review of patents and patent applications on these new and pipeline TB drugs. The patent landscape was completed in April 2021.[11]

The objective of the landscape was to generate a better understanding of the patents on a particular medicine to initiate discussion at the international level and to gauge the extent of monopoly, both geographically and in terms of duration, on the medicine.

The landscape was developed based on a chemical structure search for each individual medicine on free and commercial databases and websites.[12] It mapped out the granted patents or patent applications on 17 medicines in 13 countries (see Table 1).[13] The landscape revealed that many medicines have more than one patent or patent application pending on them.[14]

Table 1: List of new and pipeline investigational TB medicines

Names of medicines	
1. SPR 720 2. TBI-223 3. TBI-166 pyrifazimine 4. BTZ-043 5. Macozinone (PBTZ-169) 6. GSK-3036656 (070) 7. TBA-7371 8. Contezolid acefosamil (MRX-4) 9. OPC-167832	10. Telacebec (Q203) 11. Delpazolid (LCB01-0371) 12. Sutezolid (PNUI00480) 13. SQ-109 14. Pretomanid 15. Bedaquiline 16. Delamanid 17. Bedaquiline + pretomanid + linezolid combination (BPaL) 18. Sudapyridine[15]

Some of these (bedaquiline and delamanid) have obtained conditional approval and others are undergoing phase II clinical trials.

The patent landscape revealed that, of the 17 medicines, 10 have secondary patent applications pending on them, including bedaquiline, delamanid, GSK-656, contezolid and SPR 720 (see Table 2). Secondary patents have been filed for medicines that are still in clinical development; for instance, SPR 720 has six patent applications including for compound, salt form, process, crystalline form and method of treatment. Many countries with high TB burden have granted multiple secondary patents on these medicines. Secondary patents on the active pharmaceutical ingredient (API) may extend the monopoly and block the entry of generics.

Table 2: TB medicines with pending secondary patent applications

Name of medicine and patent applicant	No. of PCT patent applications filed	Scope of coverage of the patents/patent applications
SPR 720 Spero Therapeutics, Inc (initially Vertex)	6	Markush[16] (initial or base patent), compound, salt form, process, crystalline form and method of treatment
SQ-109 Department of Health and Human Services, National Institute of Health	2	Compositions and methods
TBI-166 pyrifazimine Global Alliance for TB Drug Development, Inst of Materia Medica	2 (one filed only in China)	Compound and API process claims
Macozinone (PBTZ-169) Ecole Polytechnique Federale de Lausanne	2	Markush structure, compound and API process
GSK-3036656 (070) Anacor Pharmaceuticals Ltd	4	Markush structure and compound claims
Contezolid acefosamil MicuRx Pharmaceuticals, Inc	7 (3 applications only filed in China)	Contezolid compound, crystal form, micronized formulation, particle size of drug, API process, contezolid acefosamil, contezolid acefosamil crystal form
Delpazolid Legochem Biosciences, Inc	2	Markush structure and process claims
Delamanid Otsuka Pharmaceutical Co. Ltd	8	Compound, formulation, API/ intermediate process, combination
Sutezolid Upjohn Company (later Pfizer)	2	Markush structure and composition and use
Bedaquiline	7	Compound, salt form, dispersible tablet, process, combination

Meanwhile, TB Alliance, a non-profit organisation, has filed a patent application for a combination regimen consisting of bedaquiline + pretomanid + linezolid (BPaL).[17,18] In 2022, WHO recommended the use of BPaL and BPaLM (bedaquiline + pretomanid + linezolid + moxifloxacin), two new all-oral regimens both of 6-month duration, for MDR/RR-TB and pre-extensively drug-resistant (pre-XDR) TB.[19]

A 2022 study reports that national governments could save up to US$740 million annually by switching to BPaL and BPaLM regimens, and aid in the treatment of 400,000 TB patients.[20] It estimates that the cost of implementing this therapy is potentially 40-90% less expensive than current regimens.[21] Thus countries with high burden of TB especially DR-TB need to weigh their options and national budgets before granting multiple patents to existing and old drugs.

In addition, many studies and reports reveal that some of the pipeline and new TB drugs have been developed with a lot of public funding.[22] Pharmaceutical companies receive philanthropic/public funding/contributions at different stages of drug development. Of the 17 medicines that were analysed in TWN's patent landscape, nine new and pipeline TB drugs have received public or philanthropic funding/contributions (see Table 3). However, such funding/contributions do not lead to a different approach in the patenting behaviour.

Table 3: List of medicines that received some kind of public or philanthropic funding for their development

Name of TB medicines receiving public funding or philanthropic contributions
Bedaquiline
SPR 720
TBI-166 pyrifazimine
BTZ-043
Macozinone (PBTZ-169)
TBA-7371
Telacebec (Q203)
Sutezolid
SQ-109

Bedaquiline

The case of bedaquiline is illustrative in this regard. After decades without a new treatment, bedaquiline was approved by the United States Food and Drug Administration (USFDA) in 2012, and it became the first new treatment and a core component of treatment for MDR-TB.[23] This medicine was developed with a lot of public contributions in the form of clinical trials, tax credits, tax deductions, administration of donation programme and PRV[24] (priority review voucher) revenues.[25] It is estimated that the total public investments were US$455-747 million, compared with estimated originator investments of US$90-240 million.[26]

However, when bedaquiline received conditional approval for the treatment of DR-TB, Janssen Pharmaceuticals, the J&J-owned pharmaceutical company holding the patent for the medicine, priced a six-month treatment course at US$3,000 for middle- and upper-middle-income countries and US$900 in least-developed and resource-limited countries. The company had also filed multiple patent applications, many of which have been granted in several countries with high burden of the disease. These patents/patent applications cover the bedaquiline compound, its use to treat MDR-TB or its combinations with other antimycobacterial agents, process, fumarate salt of bedaquiline, long-acting formulations of bedaquiline and dispersible tablet.

The patent on the salt form of bedaquiline will expire only in 2027, and the one on the dispersible tablet will go on until 2037.[27] As mentioned above, there is also a patent application pending on the BPaL combination.

(In India, there were two pre-grant oppositions filed to the patent application for the fumarate salt of bedaquiline. The first was by the Maharashtra Network of Positive People, a network of people living with HIV/AIDS, in 2013; and the second by two TB survivors, Nandita Venkatesan and Phumeza Tisile, in 2019. The Indian Patent Office concluded the process on 23 March 2023 and rejected the patent application. Since the original patent was expiring in July 2023, the decision paved the way for the entry of generic bedaquiline in India.[28])

Such patents are a serious barrier to the development of regimens combining new and repurposed TB drugs. For a long period J&J did not agree to engage in bilateral or Medicines Patent Pool–led voluntary licence negotiations, and was reluctant to reduce the price of bedaquiline. Then, in 2016 Janssen offered bedaquiline to the Stop TB Partnership's Global Drug Facility (GDF) for US$150 per patient per month.[29] In July 2020 J&J announced that it would reduce the price of bedaquiline to US$1.50 per day.[30]

However, a study based on the estimated costs of active pharmaceutical ingredients, excipients, formulation, packaging, and a reasonable profit margin (based on a 'cost-plus' model) revealed that the actual price of bedaquiline should be between US$8.80-16.40 per patient per month ($0.25 per day).[31] So the price of bedaquiline set by Janssen was a highly inflated price compared with its actual cost, and creates a barrier to accessing the medicine.

In 2009 TB Alliance entered into a licensing agreement with J&J for bedaquiline to treat DS-TB and this was subsequently sub-licensed to the Indian generic manufacturers Viatris and MacLeod's.[32] However, restrictive terms of the licence may act as a barrier to the entry of the generic versions into the market.

The medical humanitarian organisation Medecins Sans Frontieres (MSF) notes that there are certain terms and conditions in the licence which disallow the generic manufacturers from selling bedaquiline for DR-TB.[33] Hence, whether these companies will be able to provide bedaquiline for DR-TB is not clear. The licensing agreements are not available in the public domain and therefore it is difficult to obtain more details pertaining to the availability of the medicine.

In July 2023 J&J granted the GDF a licence that enabled it to tender, procure and supply generic versions of bedaquiline for the majority of low- and middle-income countries, including countries where patents remained in effect.[34] This move was made just before the original patent expired in India and many other countries on 18 July 2023. Thus the power to conclude such a licence emanated from J&J's secondary patent portfolio. It is important to note that J&J's 29 September announcement is only on the non-enforcement of patents in low- and middle-income countries and not the withdrawal of secondary patents. Thus J&J's secondary patents are still valid and the company still holds the power to enforce them.

To achieve the target set in Sustainable Development Goal 3, countries need to consider the impact secondary patents on new and pipeline TB drugs can have on access to these drugs.

Conclusion

Over the last few years, there have been considerable improvements in TB treatment with the introduction of new medicines, and medicines in the pipeline are replenished by many new candidates. WHO has recommended more effective and patient-friendly treatments and regimens for adults and children with DS-TB/DR-TB. This is an opportunity for governments to scale up treatment, eradicate TB and save lives.

Countries with TB burden therefore need to address high prices for TB medicines, the practice of evergreening patents through multiple secondary patents, and restrictive, non-transparent licensing arrangements by pharmaceutical companies.

It is important to use the flexibilities in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) administered by the World Trade Organization, and put in place more stringent patentability criteria to curb secondary patents. For example, as mentioned above, India has recently used pre-grant opposition and higher inventive-step criteria to reject a patent application on the fumarate salt of bedaquiline.[35]

In the case of patent applications relating to combinations of rifapentine and isoniazid (used for TB preventive treatment), pre-grant opposition in India and third-party observations in Indonesia, the Philippines and Thailand as well as international patient advocacy led to withdrawal of the applications by the pharmaceutical firm Sanofi worldwide in December 2019.[36]

Other steps that governments could adopt include rigorous scrutiny of patent applications using competition law to address the access issues arising out of non-transparent voluntary licences, and price regulation. These measures will facilitate the scaling up of TB treatment and the local production of TB medicines, thereby encouraging the use of safe and effective treatment regimens.

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Endnotes

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10 Note that there is no primary/secondary patent distinction in patent law. However, this distinction is commonly used to distinguish between different claim types in the pharmaceutical field.
11 The TB patent landscape was commissioned by TWN in 2020 and the work was conducted by Sandeep K. Rathod and Chetali Rao.
12 The landscape focused on patents coming from the innovator and not the later/generic companies (in most instances). It covered later patents from the same innovator if they are important from a process or formulation perspective.
13 African Regional Intellectual Property Office (ARIPO), African Intellectual Property Organization (OAPI), Bangladesh, China, Egypt, India, Indonesia, Kenya, Malaysia, the Philippines, South Africa, Thailand and Vietnam.
14 Tuberculosis Medicine Patent Landscape Commissioned by the Third World Network, https://twn.my/title2/briefing_papers/twn/TB%20medicine%20patent%20landscape.xlsx
15 Only Patent Cooperation Treaty search completed. This is not included in the list of 17 medicines discussed in this briefing.
16 A Markush structure is a general representation of the structure of a molecule sharing common properties, used in patents to protect whole classes/range of compounds with common properties. It covers the API and many other compounds which may be disclosed either specifically or generically. Sometimes pharmaceutical companies provide only a generic disclosure of the API in their Markush claims. In such cases the companies file separate patent applications specifically claiming the API.
17 TB Alliance has no plans for direct commercialisation but may license it to some companies for development and marketing.
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25 Public contributions through funding of clinical trials were estimated at US$109-252 million, tax credits at US$22-36 million, tax deductions at US$8-27 million, administration of a donation programme at US$5 million, and PRV revenues at US$300-400 million. Gotham D, et al. (2020). Public investments in the clinical development of bedaquiline. *PLoS One* 15.9: e0239118. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0239118
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