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Editorial

End of the Bedaquiline patent – a crucial development for moving forward affordable drugs, diagnostics, and vaccines for infectious diseases in low- and middle-income countries

When Johnson & Johnson (J&J) developed the new tuberculosis (TB) drug bedaquiline (Sirturo) [1], it was one the few new drugs to have been conditionally approved by the United States Food and Drug Administration (FDA) in 2012 for treatment of multi-drug resistant tuberculosis (MDR-TB). It offered renewed hope to patients providing a unique opportunity to radically transform management of MDR-TB to shorter, easier-to-administer, and more patient-tolerable treatment regimens [2]. Evaluation in clinical trials over the ensuing seven years showed that bedaquiline was a game-changer, demonstrating substantial improved treatment outcomes among people with MDR-TB and extensively drug-resistant TB (XDR-TB) [3]. J&J, like all pharmaceutical companies who hold the patent rights on drugs, had the sole authority over setting the high price of bedaquiline. In October 2019 Médecins Sans Frontières (MSF), TB activists and civil society launched a global campaign protesting outside J&J offices in the United States, South Africa, Brazil, Belgium, Ukraine and Spain calling on lowering the price of bedaquiline to no more than US$ 1 per day for patients with MDR-TB, so as to allow rapid scale-up and the ability to treat patients, rendering them non-infectious and reducing further spread within the community [3]. Bedaquiline is now considered an essential drug in an all-oral treatment regimen for MDR-TB [2,4,5]. The rates of MDR-TB have, however, remained extremely high in Asia, Africa and Eastern Europe and deaths due to drug-resistance remain high [5]. Most of the estimated annual 500,000 MDR-TB cases do not have access to oral MDR-TB treatment regimens due to their high cost, lack of affordability, and limited availability.

The recent rejection by India's patent office of J&J's application to extend their patent on bedaquiline beyond July 2023 for an additional 4 years effectively ends the company's eight-year monopoly on a crucial drug for oral treatment of MDR/XDR-TB. (5). The challenge to the patent was originally filed in February 2019 by a Mumbai journalist [6] who contracted TB twice and wanted safer oral options tan injectables to be made available for millions of people who could not afford the drug. The decision by the Indian patent office opens the door for other companies to produce cheaper and more accessible versions of bedaquiline, with some health experts estimating that the costs of treatment could be cut by 80%, from US$46 (€42.6) to US$8 (€7.4) a month per patient [7]. This historic decision by the India patent office clears the way for cheaper versions of bedaquiline to be manufactured and be made available more widely, especially in poor resource high MDR-TB endemic countries. It is also a critical decision that sets an important precedent for increasing access to affordable drugs, diagnostics and vaccines for other epidemic diseases affecting resource-poor countries. In April, 2021, a Brazil judge suspended drug patent extensions, a preliminary decision that could lower costs for drugs critical to treating COVID-19 patients at the expense of pharmaceutical firms [8].

During the COVID-19 pandemic, South Africa and India proposed a broad waiver of the Trade-Related aspects of Intellectual Property (TRIPS) agreement covering COVID-19 vaccines, tests, and treatments to allow enhanced affordable supplies for low- and middle-income countries (LMICs) [9]. The European Union, United Kingdom and Switzerland blocked that proposal, whilst the United States supported an IP waiver for only vaccines [10], although this did not happen. In May 2021 the World Trade Organization (WTO), published a joint declaration on the importance of Intellectual Property Rights (IPRs) to COVID-19 vaccines, stating that "the respect for intellectual property rights is key and will ensure the fastest possible production of urgently needed vaccines" [11].

GAVI, the Vaccines Alliance, as well as its other three core partners, the Coalition for Epidemic Preparedness Innovations, the World Health Organization and UNICEF stated in August 2021 that "seventeen COVID-19 vaccines are already in use, 105 in clinical trials and further 184 vaccine candidates in pre-clinical development. However, given that global demand for these vaccines is several times larger than the total annual global supply for all vaccines, we clearly need to do everything in our power to increase manufacturing capacity and intellectual property is an important part of vaccine development and critical for innovation" [12]. COVAX has been a strong supporter of encouraging manufacturers to share intellectual property and technical know-how with other manufacturers. COVAX has delivered approximately 1.5 billion doses to LMICs far short of demand and this model TB drug access is required.

Infectious diseases which are threats to global public health security cannot be controlled by actions of individual pharmaceuticals or governments, but they need transnational organizations with adequate funding to ensure unified actions across countries. Recently the Global Fund to Fight AIDS, Tuberculosis and Malaria has been successful in providing low-cost treatment for HIV/AIDS, impregnated bed nets for malaria and tuberculosis treatment. The

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decision by the Indian patent office is important and local manufacturing in LMICs will ensure more drugs for the treatment of MDR/XDR-TB at an affordable budget. A previous program ensuring access to drugs and vaccines for LMICs is the World Health Organization (WHO)'s Expanded Programme on Immunizations (EPI) [13], providing cheap vaccines to children in LMICs supported by donors and succeeding in negotiating lower prices through coordinated bulk purchase. This is a model for exploring differential pricing between LMICs and industrialized countries to ensure adequate vaccine supplies to LMICs. This also applies to development and rollout of affordable diagnostics. The outbreak of monkeypox (mpox) and the emergence of other pathogens with epidemic potential [14,15] underline the fact that the lack of reliable and cheap diagnostics in many LMICs impaired proper assessment of disease epidemiology, detection and response capacities [16]. Access to rapid diagnostics, treatments and vaccines is critical in all infectious disease outbreaks with pandemic potential. To accelerate impact, greater collaboration between public and private sectors is required so that capabilities and experiences can be jointly harnessed for an enhanced multiplier effect.

In conclusion, while patent rights should be preserved to encourage development of new drugs, vaccines and diagnostics, implementing mechanisms to ensure adequate supplies worldwide are urgently needed. This includes expansion of manufacturing facilities to LMICs providing employment and professional development opportunities, donation programs funded by industrialized countries, and price reductions through bulk purchase arrangement. The buzz phrase "no one is safe unless everyone is safe" is very true and the COVID-19 pandemic once again underlined that. When new products that could save lives or prevent infections are developed by pharmaceutical companies, it becomes essential that in resource-limited settings they are made affordable through equity-based tiered pricing or having shorter patents for facilitating widespread manufacturing.

Declaration of competing interest

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