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2014

A Review of the SQ-109 Patent Landscape

A scoping report

JANUARY 2014

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1. INTRODUCTION

The World Health Organization (WHO) estimates that a third of the world's population is latently infected with *Mycobacterium tuberculosis*. In 2012, there were an estimated 8.6 million incident cases of tuberculosis (TB), with 12 million prevalent cases, 940 000 deaths among HIV-negative people, and 320 000 deaths among HIV-positive people.[1] Most cases (58%) were in the WHO South-East Asia and Western Pacific regions, while the WHO African region had 27% of the world's cases. Despite being curable, TB claimed the lives of 1.3 million people in 2012.

TB treatment has become more complex, particularly with the emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis*. There were approximately 450 000 new cases of multidrug-resistant tuberculosis (MDR-TB) worldwide in 2012.[1] MDR-TB is resistant to the two most commonly used TB drugs, isoniazid and rifampicin. It requires extended treatment with second-line drugs that are less effective and have more adverse effects than isoniazid- and rifampicin-based regimens.[2]

Given the emergence of MDR-TB, and the need to shorten treatment duration, new drugs are required. The last of the current anti-TB treatments—rifampicin—was introduced in 1963. Since then, research for new TB treatments had largely come to a halt. However, in recent years the pipeline for potential new TB treatments has started to look more promising than it has for the past 50 years.

One compound that is currently in the pipeline and generating interest is Sequella Inc's investigational compound SQ109. SQ109 has been identified as a possible candidate for enhancing the treatment of TB and for treating MDR-TB.

Given the potential of SQ109, this report explores the patent landscape and considers possible access issues relating to the drug should it become available on the market.

1 Global tuberculosis report 2013. Geneva: World Health Organization; 2013 (http://www.who.int/tb/publications/global_report/en/, accessed 31 December 2013).

2 Diacon.A et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. New England Journal of Medicine. 2009;360:2397-2405.

2. BACKGROUND

SQ109 falls into the class of drugs known as ethylenediamines. The compound was discovered by Sequella Inc in collaboration with the United States National Institutes of Health (NIH).[3] A solid phase method was developed to synthesize more than 63 000 compounds based on the 1,2-ethylenediamine structure of ethambutol.[3, 4] Using a high-throughput screening assay, compounds were identified that affected genes activated during cell membrane repair by the TB bacilli.

SQ109 has the same core structure as ethambutol. The structure of SQ 109 (chemical name: N-[(2E)-3,7-dimethyl-2,6-octadienyl]-N′-tricyclo[3.3.1.13,7]dec-2-yl-1,2-ethanediamine) is shown in Figure 1.

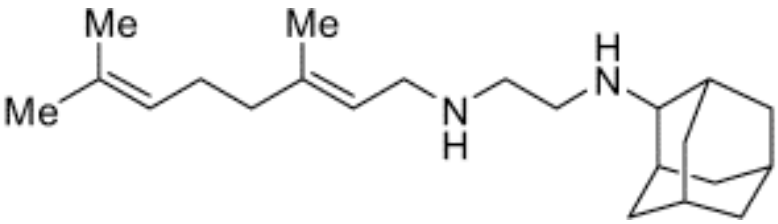

Figure 1. Structure of SQ109

Sequella has publicly stated that it has been seeking partners worldwide for the development and commercialization of the compound.[5] In October 2010, Sequella announced that it had signed an agreement with the Ludwig Maximilian University, Munich, Germany, to coordinate a European Union grant for Phase II clinical trials in adult pulmonary TB in seven sites in Africa. The studies would be funded by a ′12 million grant by the European and Developing Countries Clinical Trials Partnership (EDCTP) and a ′3 million commitment by Sequella.[5]

In 2011, Sequella licensed the rights to commercialize SQ109 for TB in Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan and Ukraine to the Maxwell Biotech Venture Funds subsidiary Infectex.[6] In December 2012, Infectex announced the enrollment of the first patients in its Phase IIb-III clinical trial of SQ109 for MDR-TB. The study will be conducted in Russia. [7]

SQ109 is currently undergoing Phase II clinical trials to determine safety, sputum clearance of mycobacterium and pharmacokinetics of multiple doses of SQ109 alone or with rifampicin in patients with smear-positive pulmonary TB. Subsequent trials will evaluate safety, efficacy and pharmacokinetics of several dose ranges of SQ109 in combination with other antitubercular drugs in patients with drug-susceptible and drug-resistant tuberculosis infection.[8]

SQ109 received fast-track designation from the United States Food and Drug Administration (FDA) on the basis of its potential to fulfill an unmet need in treating pulmonary TB. SQ109 was also awarded orphan drug status by the FDA and by the European Medicines Agency (EMA).

3 SQ109: a broadly active, bactericidal, small molecule antibiotic. (Product description). Rockville, MD: Sequella Inc. (http://www.sequella.com/docs/Sequella_1sheet_SQ109_TB_v3.pdf, accessed 3 January 2014).

4 Kolyva AS, Karakousis PC. Old and new TB drugs: mechanisms of action and resistance. Chapter 9, in: Cardona P-C. Understanding tuberculosis—new approaches to fighting against drug resistance. Rijeka, Croatia: InTech; 2012 (Open Access publication; DOI 10.5772/2477).

5 Sequella receives international support for Phase 2 clinical trials of SQ109, its lead antitubercular drug candidate. (Press release, 10 October 2010). Rockville, MD: Sequella Inc. (http://www.sequella.com/docs/Sequella_EDCTP_LMU_SQ109_Release18Oct2010.pdf, accessed 3 January 2014).

6 Sequella licenses rights to commercialise SQ109 for tuberculosis in Russia to Maxwell Biotech Venture Fund subsidiary. (Press release, 25 April 2011). (http://www.businesswire.com/news/home/20110424005001/en/Sequella-Licenses-Rights-Commercialize-SQ109-Tuberculosis-Russia, accessed 3 January 2014).

7 Maxwell Biotech Venture Fund's portfolio company, Infectex, enrolls first multi-drug resistant tuberculosis (MDR-TB) patients in pivotal clinical trial of SQ109, licensed from Sequella. Press release, 19 December 2012). Rockville, MD: Sequella Inc. (http://www.sequella.com/docs/Sequella_Infectex_Release_19Dec2012.pdf, accessed 3 January 2014).

8 Stop TB Partnership Working Group on New TB Drugs. SQ109 Ethylenediamine. Geneva: Stop TB Partnership (http://www.newtbdrugs.org/project.php?id=144, accessed 3 January 2014).

3. SQ109: THE PATENT LANDSCAPE

The patent landscape in Annex I of this report sets out the key patents and patent applications for SQ109, including their geographical patent coverage, as of May 2013. While every effort has been made to obtain comprehensive and accurate information on the status and geographical scope of the patents covering SQ109, in many countries patent information is not readily available to the public or not updated on a regular basis. In addition, some patent applications may have been published only after the searches were conducted. As such, there may be other relevant patents which have subsequently been published and which are not included in this landscape. Accordingly, the information provided herein is subject to the above disclaimers.

The patent searches identified three relevant patents. For ease of reference these three patents have been identified as Patents 1–3 in Annex I. Patents 1 and 3 were filed in the name of Sequella Inc, while Patent 2 was filed in the name of the NIH.

Patent 1, as filed in the international application, covers a series of compounds including SQ109, methods of use and compositions for the diagnosis and treatment of infectious disease. The information available for Patent 1 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China, India and South Africa, as well as Eurasia (including Russia).

It should be noted that Patent 2 as filed also claims a series of compounds, including SQ109. As such, it will be necessary to check any final granted claims for Patent 1 as they may be amended during prosecution. For example, the equivalent European Patent application for Patent 1 does not maintain a claim for SQ109.

Patent 2, as filed in the international application, covers a series of compounds, including SQ109, methods of use and compositions as an antitubercular drug. SQ109 is specifically disclosed as compound 109 in Patent 2 and in Example III of the international application. The information available for Patent 2 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particularly in Africa. However, key countries where the patent has been granted to date include China and India as well as Eurasia (including Russia). The international application has entered the national phase in South Africa, although further checks would be necessary to confirm the current status.

As noted above, Patent 1 as filed also claims a series of compounds that include SQ109. As such, it will be necessary to check any final granted claims for Patent 2 as they may be amended during prosecution.

Patent 3 covers compositions, including SQ109 in combination with other antibacterial agents such as rifampicin, isoniazid, pyrazinamide, moxifloxacin and ethambutol. The information available for Patent 3 is limited in terms of whether there is patent coverage in all high-burden TB and MDR-TB countries, particular in Africa. However, key countries where the international patent application has entered the national phase are China and India, as well as Eurasia.

4. CONCLUSION

As this analysis shows, the two international patent applications that initially claimed the base compound have been granted in key high burden countries such as China, India, Russia (under the Eurasian patents) and South Africa. As a result, and depending on the final granted claims of the patents, generic companies in these countries that are capable of manufacturing SQ109 would need to obtain a licence from Sequella/NIH.

Determining the patent situation is a useful starting point for understanding the possible access issues, since patents can bar competitors from manufacturing, selling, importing or exporting a product.[9] Moreover, although only a granted patent can actually bar competition, patent applications serve as a deterrent.

Nevertheless, competition and access to medicines are not determined exclusively by patents, but also by, among other things, the patent-holder's licensing strategies and/or access programme. At the time of writing there was little public information on Sequella's policy for access to SQ109 in TB-endemic countries should it obtain marketing approval.

However, it appears that Sequella is looking for partners to develop and commercialize SQ109. For example, in Russia and neighbouring countries, Sequella has licensed the development and commercialization of SQ109 to Infectex. Details of this licence are not known. If the licences are exclusive, they may limit competition and thus affect the price.

9 Companies typically file their patents in a manner that enables them to control access to a drug in key developing-country markets (usually middle income economies); this includes filing in countries where there is a risk of generic competitors being able to produce the drug locally.

ANNEX I: SQ-109 PATENT LANDSCAPE

	Patent 1	Patent 2	Patent 3
	Methods of use and compositions for the diagnosis and treatment of infectious disease ***(This patent covers a series of compounds, including SQ-109)***	**Antitubercular drug: compositions and methods** ***(This patent covers a series of compounds, including SQ-109)***	**Antitubercular drugs: compositions and methods** ***(This patent covers compositions, including SQ 109 in combination with other antibacterial agents, including rifampicin, isoniazid, pyrazinamide, moxifloxacin and ethambutol)***
Applicant	**Sequella Inc**	**National Institutes of Health**	**Sequella Inc**
International Patent Publication No.	**WO 2003/096987**	**WO 2003/096989**	**WO 2007/005896**
Expected expiry (if granted and not subject to patent term extensions)	**18 May 2023**	**18 May 2023**	**2 July 2026**
	PATENT STATUS		
Australia	Granted Patent No. 2003228240 Pub/App No. 2003228240	Granted Patent No. 2003233610 Pub/App No. 2003233610	NA
Canada	Pending Pub No. 2485586 App No. 20032485586	Pending Pub No. 2485592 App No. 20032485592	NA
China	Granted Patent No. 101404986 Pub No. 101404986 App No. 20038014424	Granted Patent No. 1665801 Pub No. 1665801 App No. 20038015457	Pending Pub No. 101636376 App No. 20068031468
Eurasian Patent Organization	Granted Patent No. 016659 Pub/App No. 20040001523	Granted Patent No. 013965 Pub/App No. 20040001523	Pending Pub/App Pub No. 2010000643
European Patent Office	Granted Patent No. 1578353 Pub No. 1578353 App No. 03726938.9	Pending Pub No. 1513825 App No. 03729047.5	Pending Pub No. 1909780 App No. 06786287.0
India	Granted Patent No. 250595 Pub/App No. 1908/KOLNP/2004	Granted Patent No. 239549 Pub/App No. 1698/KOLNP/2004	Pending Pub/App No. 741/KOLNP/2008

	Patent 1	Patent 2	Patent 3
Japan	Granted Patent No. 4563797 Pub No. 2006504633 App No. 20040504986	Granted Patent No. 4667862 Pub No. 2005526129 App No. 20040504988	NA
Singapore	Pending App No. 200406780-7	Pending App No. 200406779-9	Pending App No. 201000918-1
South Africa	Granted Patent No. 2004/9166 Pub/App No. 2004/9166	Pending Pub/App No. 2004/9169	NA
USA	Granted Patent No. 7456222 Pub No. 2006148904 App No. 11/173192	Granted Patent No. 6951961 Pub No. 2003236225 App No. 10/147587	Granted Patent No. 8202910 Pub No. 2009/0192173 App No. 12/255976
	Granted Patent No. 7652039 Pub No. 2004024022 App No. 10/441272	Granted Patent No. 7842729 Pub No. 2006020041 App No. 11/145499	
	Granted Patent No. 8198303 Pub No. 2010273826 App No. 12/693252	Granted Patent No. 8268894 Pub No. 20110118307 App No. 12/944231	
		Abandoned Pub No. 20040019117 App No. 10/4411467	
		Abandoned Pub No. 20040033986 App No. 10/440017	

NA: Data not available or the international application had not yet entered the national phase and was not published at the time the patent searches were conducted (May 2013).

Eurasian patent applications cover the following countries: Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan and Turkmenistan.