

THE GROUNDS FOR OPPOSING PATENT APPLICATIONS FOR VELPATASVIR

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BACKGROUND

Hepatitis C continues to remain a significant public health issue in low and middle-income countries, which account for roughly 72% of the 71 million people infected worldwide. Although a pan-genotype oral regimen of the key drugs, velpatasvir and sofosbuvir, has successfully treated all six major genotypes of the hepatitis C virus (HCV), exorbitant drug prices in many countries have rendered treatment inaccessible to the most vulnerable, leaving people at risk for liver cancer or liver failure.

In 2016, Gilead Sciences launched sofosbuvir/velpatasvir in the United States at over \$74,000 for a 12-week regimen. Access to affordable sources of this combination of these direct acting antivirals (DAAs) crucial medicines is critical in the fight against hepatitis C.

PATENT SITUATION IN INDIA

In an effort to make these life-saving drugs accessible to all, civil society organizations from across the world have worked tirelessly to remove patent barriers. The struggle to democratize medicine availability and overcome patent barriers for sofosbuvir and velpatasvir is at a decisive stage in India, which is the largest manufacturer of generic, affordable drugs to the developing world.

Gilead Sciences has applied for multiple patents on sofosbuvir and velpatasvir in India: not only limiting itself to basic patents but also staking claims on a number of secondary patents for routine improvements and derivatives. It is crucial to recognize that a majority of pharmaceutical patent applications are secondary claims for marginal improvements of existing drugs. Such 'evergreening' tactics allow the company to extend their control over the market, in turn delaying the introduction of affordable generic drugs and patient access to treatment in a number of countries.

The Initiative for Medicines, Access & Knowledge (I-MAK) together with the Delhi Network of Positive People (DNP+) have earlier through pre-grant oppositions challenged the basic patent claims on sofosbuvir in 2013; the issue remains under dispute before the High Court of Delhi and the Intellectual Property Appellate Board in India. Notably, patent barriers to sofosbuvir have already been successfully addressed in Egypt, Argentina, Brazil and Malaysia and are under challenge in China, Russia, Ukraine and 38 countries in Europe (signatories to the European Patent Convention).

In February 2017, I-MAK and DNP+ have also challenged the basic patent claim on velpatasvir, asserting that the drug is an obvious structural change to an earlier hepatitis C drug, ledipasvir, and thus, cannot be patented.¹ A decision is now awaited.

Additionally, DNP+ have filed two new pre-grant oppositions on Gilead's secondary patent applications, which, if granted, would significantly aid the multinational pharmaceutical giant to extend its control over the sofosbuvir/velpatasvir market in high- and middle-income countries. The oppositions are based on India's patent law that allows third parties, including civil society organizations, to file 'pre-grant' oppositions to challenge patent applications until the patent is rejected or granted by the Indian Patent Office. In this particular case, the secondary patent claims are for the tablet formulation of the fixed-dose combination of sofosbuvir/velpatasvir and the polymorph form of velpatasvir.

¹ MSF India, "Flawed Patents on Hepatitis C Drugs latest to be Challenged in Global Push for Access", February 2017. Available at: <https://www.msfindia.in/flawed-patents-hepatitis-c-drugs-latest-be-challenged-global-push-access>

A recent study on the Indian patent office has highlighted that a significant portion—over 70% of the patents analysed from 2009–2016—are for marginal improvements, many of which have been granted despite the anti-evergreening provisions in the Indian Patents Act, which restricts the patentability of a host of secondary patents.²

This lack of rigorous assessment of the patentability requirements in pharmaceuticals is a worrying development. Patent oppositions to Gilead’s sofosbuvir/velpatasvir combination and velpatasvir polymorph are vital since they allow civil society to prevent these unmerited patent applications from being granted and subsequently, encourage open competition for generic drugs once the basic compound patents have expired in countries excluded from Gilead’s license agreements.

WHY CHALLENGE PATENT CLAIMS IF LICENSING DEALS WITH INDIAN COMPANIES ARE IN PLACE?

Licensing deals struck between Gilead and Indian generic companies, especially for the pan-genotypic sofosbuvir/velpatasvir combination, enable access to lower-cost generics from India to least-developed countries and an increasing number of middle-income countries.

However, since South America, Russia and eastern European countries are not included in most of these agreements, their governments continue to face many barriers in the importation of raw materials (active pharmaceutical ingredients, or APIs) and finished formulations of generic DAA medicines. Chinese generic companies are also excluded from these licenses and cannot market affordable generic DAA medicines domestically.

Consequently, Gilead has been able to retain its monopolies rendering affordable generic versions largely unavailable and keeping hepatitis C treatment prohibitively high in upper middle- and high-income countries, which include a number of high-burden countries.

For example, Gilead charges an estimated €35,000 in Germany,³ €29,721 in France,⁴ and approximately USD 4,500 in Latin America as negotiated by Pan American Health Organisation Organisation for the recommended 12 weeks of treatment. In contrast, the generic formulation of the sofosbuvir/velpatasvir combination is priced at approximately \$286 USD per 12 weeks in India.

In the coming decade, as the primary patents⁵ on the two drugs start expiring in different jurisdictions,⁶ particularly in high and upper middle-income countries that are not covered by licensing agreements, a number of Indian manufacturers may choose to terminate their geographically restricted voluntary licenses early and supply those new markets. However, the secondary patent claims being put forth by Gilead, if granted in India, will prove to be a crucial barrier to supplying affordable drugs to a number of these countries.⁷

IN-DEPTH FOCUS ON PATENT OPPOSITIONS TO VELPATASVIR

² Dr. Feroze Ali et al., “Pharmaceutical Patent Grants in India”, April 2018. Available at: <https://www.accessibsa.org/media/2018/04/Pharmaceutical-Patent-Grants-in-India.pdf>

³ APM Health Europe, “MSD and Gilead Slash Prices of Zepatier and Epclusa for HCV in Germany”, February 2018. Available at: <https://www.apmhealthurope.com/freestory/10/58074/msd-and-gilead-slash-prices-of-zepatier-and-epclusa-for-hcv-in-germany>

⁴ Vidal France, “EPCLUSA 400 mg/100 mg cp pellic”, March 2018. Available at: <https://www.vidal.fr/Medicament/epclusa-172378-prescription-delivrance-prise-en-charge.htm>

⁵ Primary patents usually cover new pharmaceutical compounds that are referred to as new molecular/chemical entities (NMEs/NCEs). The majority of patent claims for pharmaceuticals are marginal improvements over previously-known drugs.

⁶ See example of termination of voluntary license on the HIV drug, tenofovir, by an Indian manufacturer, which coincided with the expiry of the primary patent on the drug in the European Union and the United States. Available at: <https://medicinespatentpool.org/uploads/2011/07/Laurus-MPP-Gilead-TDF-Cobi-EVG-Termination-070717.pdf>

⁷ MSF Access Campaign Press release, “MSF Joins Europe-wide Action Challenging Patent on Key Hepatitis C Drug”, March 2017. Available at: <https://www.msfaaccess.org/resources/press-releases/2761>

1. Opposition to the patent application for velpatasvir polymorph

The patent opposition, filed at the Indian Patent Office by DNP+, targets Indian patent application 201627039572 (Indian national filing of WO2015/191431) filed by Gilead Pharmasset.⁸ This application titled “Solid Forms of an Antiviral Compound” covers multiple polymorphs and salt forms (i.e., different physical structures of the same drug) of the velpatasvir molecule. If granted, the patent would expire in June 2034. The opposition is based on these primary grounds: lack of novelty, lack of inventive step, lack of enhanced therapeutic efficacy, and non-furnishing of information of corresponding foreign applications.

- **Inventive step:** Patents should not be granted on salt forms/polymorph forms that are obvious to try based on well-known techniques. In addition to the earlier Gilead patent applications that reveal the velpatasvir free-base compound, additional patents and literature have demonstrated that obtaining these alternate salt forms/polymorph forms is obvious to a person skilled in the art.⁹ Thus, the patent application is for old science.
- **Efficacy:** India’s Patents Act stipulates that new forms of known substances have to demonstrate that they enhance the therapeutic efficacy of the product in order to deserve a patent. This provision, known as Section 3(d), was designed to clampdown on evergreening. Gilead’s present patent application covers multiple alternative forms of velpatasvir salt forms/polymorph forms, while velpatasvir base compound already existed or predates them and hence these salt forms/polymorph forms are classified as “new forms of known substances”. Gilead has not provided evidence in its application that demonstrates that any of these new forms have enhanced therapeutic efficacy over the disclosed form of velpatasvir, as stipulated by the Supreme Court decision in Novartis AG vs Union of India, 2013.¹⁰ In April 2013, the legal validity of Section 3(d) was upheld by the Supreme Court of India following a landmark six-year legal battle against Novartis.
- **Non-compliance with Section 8:** This provision of India’s Patents Act places a “duty of disclosure” on the applicant to provide information on details and status of applications pursued in other countries. Non-compliance with Section 8’s requirements is a ground for refusing an application. Gilead has not submitted all the relevant information on the above application to the Indian Patent Office.

For the reasons outlined above, the patent application should be rejected as it does not meet the standards required for a patent to be granted under India’s law.

To read the opposition in detail, see https://www.patentoppositions.org/en/drugs/sofosbuvir-slash-velpatasvir/patent_oppositions/5b41b057d2708f0005fd8af9

2. Opposition to the patent application on velpatasvir/sofosbuvir combination

The patent opposition filed before the Indian Patent Office challenges Gilead Pharmasset’s patent application 201627008488 (WO/2015/030853) titled “Combination Formulation of Two Antiviral Compounds.” If granted, the patent would expire in January 2034. **In China**, MSF has also filed

⁸ Gilead acquired Pharmasset Inc. for \$11.2 billion in 2011. Founded by scientists from Emory University in the United States, Pharmasset was a pharmaceutical company whose primary focus was the development of oral therapies for the treatment of HCV, one of which was sofosbuvir, considered to be the backbone of the cure. The company also received a series of NIH grants that were utilized in the development of antiviral drugs for HCV, including sofosbuvir. (See: <https://www.keionline.org/27205> and <https://www.bmj.com/content/354/bmj.i3718/tr-3>).

⁹ The applications noted above in combination with reference literature like “Pharmaceutical Salts” by Berge et al., and “Salt Selection for Basic Drugs” by Gould PL would make it obvious for a person skilled in this art to make alternative salt forms or polymorph forms of velpatasvir.

¹⁰ Novartis AG v Union of India, Supreme Court of India, AIR 2013 SC 1311.

third-party observations opposing the grant of this patent on the velpatasvir/sofosbuvir combination composition.¹¹This opposition is based on the following grounds:

- **Novelty:** The combination of two drugs is not new. Gilead Pharmasset's earlier patent application already disclosed and claimed a combination of velpatasvir + sofosbuvir.¹²
- **Inventive step:** The patent application is for old science; patents should not be granted to compositions that are based on well-known manufacturing techniques and excipients that are obvious to try and have been used for decades in manufacturing pharmaceutical compositions.
- **Efficacy:** India's Patents Act stipulates that new forms of known substances have to demonstrate that they enhance the therapeutic efficacy of the product in order to deserve a patent. Alternatively, combinations of known substances also qualify as derivatives under Section 3(d) of the Patents Act. Gilead has failed to show any evidence that the combination claimed has an enhanced therapeutic efficacy.
- **Synergistic effect:** India's Patents Act stipulates that admixture with excipients resulting only in the aggregation of the properties are not patentable under Section 3(e) unless the patent applicant can provide *evidence of synergistic effect*. Gilead's present application does not disclose any data on a synergistic effect resulting from the admixture of known compounds, i.e., velpatasvir and Sofosbuvir.

Non-compliance with Section 8: This provision of the Patents Act places on the applicant a "duty of disclosure" to provide information on details and status of applications pursued in other countries. Non-compliance with Section 8's requirements is a ground for refusing an application. Gilead has not submitted all the relevant information on the above application to the Indian Patent Office.

- For the reasons outlined above, the patent application should be rejected as it does not meet the standards required for a patent to be granted under India's law.

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WHAT HAPPENS NEXT?

In India, a pre-grant opposition can be filed at any time and by any person under Section 25 (1) of the Patents Act until the granting of the patent. The pre-grant opposition is then taken up for hearing and a detailed order passed by the Controller of Patents. We strongly believe that the Indian Patent Office should reject the applications based on the pre-grant oppositions and the application of anti-evergreening provisions in the Patents Act.

¹¹ Patent Oppositions Database, "Médecins Sans Frontières (MSF) Opposition, Sofosbuvir/Velpatasvir, (Cn 201480047195.3)". Available at: https://www.patentoppositions.org/en/drugs/sofosbuvir-slash-velpatasvir/patent_oppositions/5a37e551fb1640684a000000

¹² WO2013075029 - at claim # 34, specifically claims a composition combining velpatasvir + sofosbuvir.