



ACCESS TO SOFOSBUVIR, LEDIPASVIR AND VELPATASVIR ANALYSIS & KEY RECOMMENDATIONS ON GILEAD'S VOLUNTARY LICENSE

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BACKGROUND

The international medical humanitarian organisation Médecins Sans Frontières/Doctors Without Borders (MSF) is currently seeking to scale up access to treatment for hepatitis C virus (HCV) in at least nine countries. To do so, MSF requires access to low-cost, quality generic versions of direct acting antivirals (DAAs), free of barriers that could interfere with procurement and patient care. A number of generic producers in India, Egypt, Bangladesh and China are investing in producing the active pharmaceutical ingredients (APIs) or formulations of DAAs.

In November 2013 and February 2014, public interest groups and generics companies filed the first patent oppositions against Gilead Sciences (Gilead)'s patent applications in India. Within months, Gilead signed voluntary license agreements with eleven Indian generics pharmaceutical companies¹ and API manufacturers for the HCV DAAs sofosbuvir, ledipasvir and velpatasvir.² A number of key companies that were developing generic versions and challenging relevant patent applications decided to sign the license. Other companies that have not yet invested in HCV DAAs also signed.

MSF is concerned that existing obligations and restrictions under Gilead's license will undermine access and exclude millions of patients with HCV in low- and middle-income countries.

This analysis highlights MSF's key concerns and recommends modifications to the license that Gilead and the Indian generic companies that have signed the license (licensees) should take into consideration.

KEY CONCERNS

1. The geographic scope of the license excludes millions of people with HCV in middle-income countries

Although the license includes 91 low-income and lower-middle-income countries in its geographic coverage, it excludes 50 middle-income countries (see Table 1). Out of the excluded middle-income countries, 13 are lower middle income (including Ukraine) and 37 are upper middle income (including Iran). MSF is preparing to start HCV treatment in both Iran and Ukraine. There are approximately 49 million people living with HCV in excluded

¹ Aurobindo Pharma Ltd., Biocon Limited, Natco Pharma Ltd., Cadila Healthcare Ltd., Ranbaxy Laboratories Ltd., Sequent Scientific Ltd., Strides Arcolab Ltd., Cipla Ltd., Hetero Labs Ltd., Laurus Labs Pvt. Ltd, Mylan Laboratories Ltd.

² Gilead expanded the license to include velpatasvir in late January 2015. See: <http://www.gilead.com/news/press-releases/2015/1/gilead-expands-hepatitis-c-generic-licensing-agreements-to-include-investigational-pangenotypic-agent>.

middle-income countries, including nearly 2.6 million in Brazil, 1.5 million in Thailand and 30 million in China. Together, people living with HCV in excluded middle-income countries represent 43% of the total population of people living with HCV in all middle-income countries.³

Gilead has introduced a range of restrictions that segment these markets and inhibit licensees from supplying the excluded countries with low-cost versions of DAAs, as discussed below.

Table 1: Middle-Income Countries Excluded from Gilead’s Voluntary License

| Gilead’s license excludes the following middle-income countries: | | | |
|--|--------------------|------------------|------------------|
| Albania | Dominican Republic | Libya | Romania |
| Algeria | Ecuador | Macedonia | Serbia |
| Argentina | El Salvador | Malaysia | St. Lucia |
| Armenia | Georgia | Marshall Islands | Syria |
| Azerbaijan | Grenada | Mexico | Thailand |
| Belarus | Hungary | Micronesia | Tunisia |
| Belize | Iran | Moldova | Turkey |
| Bosnia Herzegovina | Iraq | Montenegro | Ukraine |
| Brazil | Jamaica | Morocco | Venezuela |
| Bulgaria | Jordan | Panama | West Bank & Gaza |
| China | Kazakhstan | Paraguay | Yemen |
| Columbia | Kosovo | Peru | |
| Costa Rica | Lebanon | Philippines | |

2. The patent landscape for Gilead’s DAAs lacks transparency and is indicative of an evergreening strategy

Gilead has published the license for sofosbuvir and ledipasvir that the company signed with seven Indian generics manufacturers in 2014; however the company has not published a new or amended license since expanding the license to include velpatasvir and four additional companies. Furthermore, Gilead does not provide sufficient transparency with respect to patent applications in countries included or excluded from the license. Specifically, Gilead has released incomplete information concerning patents for sofosbuvir and ledipasvir, and no patent information related to velpatasvir since its announcement of expanding the license in January 2015.

The World Health Organization (WHO) issued and is currently updating a study⁴ that highlights the pending applications and granted patents for both sofosbuvir and ledipasvir, as well as other DAAs.⁵ Additionally, UNITAID is completing a study that will include a patent landscape for velpatasvir. However, even these studies may not be able to identify all claims for secondary (derivatives, composition, fixed-dose combinations, process) patents. Though these patents are usually weak in nature, if granted by patent offices in developing countries, they could further block generic competition, extend patent terms and undermine access.

It is not clear how many countries included in the license will have patents in force that would have otherwise blocked access to Gilead’s DAAs in the absence of a license agreement; there

³ Baker B. Gilead’s hepatitis C medicines license- troubling territorial exclusions, illusory exceptions, and tiered pricing policy fracture global access. Health GAP (2014). See: http://www.healthgap.org/hep_c.

⁴ For sofosbuvir, the two primary patents are WO/2005/003147A2 for the base compound and WO/2008/121634A2 for the structural formula and prodrug. For ledipasvir, the two primary patents are WO/2010/132601A1 for base compound and WO/2013/184698A1 for the product and crystalline forms. See: http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/.

⁵ Ibid.

are patent oppositions and significant litigation for the key primary patents for sofosbuvir in multiple countries. Recently, the Indian Patent Controller rejected Gilead's patent application for the sofosbuvir base compound.⁶ Numerous oppositions on sofosbuvir patents have also been filed before the European Patent Office by patient organisations and generics companies.⁷ Depending on the outcome of these oppositions, other litigation and examination of the pending patent applications, generic companies that do not sign a license with Gilead might have more opportunities over the years to sell to more middle-income countries, thus reaching more patients.

One significant outcome is that licensees will not invest in challenging patent applications at the examination stage, even on secondary patent applications that might be easier to oppose in middle-income countries, including India. Indirectly, the license operates as a patent settlement between Gilead and Indian generics companies. In particular, the patent challenges filed by the generic company Natco Pharma (licensee) should be closely watched as the company is now unlikely to pursue these oppositions seriously.

3. Licensees may not terminate or unbundle the license for five years

Generics firms are bound to the license for five years, regardless of changes in circumstances of patents in India and other export markets. By contrast, Gilead's license to the Medicines Patent Pool for the antiretroviral medicine tenofovir disoproxil fumarate (TDF) allowed for companies to immediately terminate a voluntary license, including and especially if a pre-grant opposition was successful.

In January 2015, the Patent Controller in India denied Gilead's patent application for the base compound of sofosbuvir, one substantial barrier to generic competition. This decision will largely enhance the opportunity for generic production of sofosbuvir in India. However companies that have signed the license cannot opt out, in order to benefit from the decision, due to the restrictive termination clause.

After five years, a licensee can unbundle the license so that it could maintain a voluntary license for one or more DAA(s) while severing the license with Gilead for the other DAA(s). This could allow licensees to sell the DAAs for lower prices or to more patients in more countries, depending on the patent landscape for each drug, and depending on the use of pre-grant oppositions or other TRIPS flexibilities by excluded countries. It is unfortunate that unbundling is not immediately available.

4. The definitions of patents under the license are excessively broad

According to the license, the definition of patents includes granted patents, applications and other secondary patents (including granted patents and applications) that are related to the production of the three DAAs and their APIs. The license also includes patents on method of use or method of manufacture under "*product patent*," which is unusual and excessive for a legal definition of a product patent. Furthermore, the situation of "*no patent*" in eligible countries under the license can only be established if there is no "*reasonable possibility of obtaining such a Product Patent within a reasonable period of time*," which includes pending applications, the filing of additional (including future) patent applications or legal actions, including appeals.

⁶ Ibid.

Such definitions have three immediate consequences:

1. It perpetuates the strategy of ‘evergreening’ patents, particularly secondary patents with a strong likelihood of failing the inventiveness test in many jurisdictions.
2. It imposes upon Indian generics manufacturers legal requirements that exceed India’s patent law, according to which enforcement and compulsory licensing is only legally possible after an application is granted.
3. It introduces a self-evolving scope of definition that would include both existing and future patents, including those that have not been filed yet.

In this regard, any future possibility of a secondary patent filing could be interpreted as falling within this scope. The broad definitions of patents carry a number of consequences for ensuring access to generic versions of relevant medicines for the excluded countries as the analysis below illustrates.

5. The license could prevent licensees from selling APIs and finished products to excluded countries

The broad definitions of patents, when applied to the license, create barriers that prevent licensees from selling DAAs to excluded countries. A summary table (Table 2) of the conditions under which licensees may sell DAAs to the excluded countries illustrates that the license either explicitly prevents or creates unnecessary ambiguities with respect to sales of DAAs to the excluded countries:

Table 2: Challenges for the excluded countries to import generic DAAs from Gilead’s Licensees

| Can excluded countries get access to generic sofosbuvir, ledipasvir and velpatasvir from licensee generic companies? ⁸ | | | | |
|---|--|--|--|--|
| Patent(s) status in India | Patent(s) status in importing country | | | |
| | Patent(s) granted | Patent(s) pending | Patent(s) rejected but in process of appeal | No patents (includes final appeal decisions) |
| Patent(s) granted | Yes, if CL is issued in both the importing country and in India* | Yes, if CL for export is issued in India upon request and CL is issued in importing country*** | Yes, if CL for export issued in India upon request and CL is issued in importing country *** | Yes, export allowed under 10.3 (c) (ii)***** |
| Patent(s) pending | Yes, if CL is issued in importing country** | No | No | No |
| Patent(s) rejected but in process of appeal | Yes, if CL is issued in importing country** | No | No | No |
| No patents (includes final appeal decisions) | Yes, if CL is issued in importing country** | No | No | Yes**** |
| Legend | | | | |
| CL | ‘CL’ stands for compulsory license. | | | |
| * | Final patent decisions in India and importing country may take years. | | | |
| ** | Clause Z of Article 10.3(d) needs to be clarified. | | | |
| *** | Product patent is not yet granted in India (and a final decision may not be forthcoming for years). India cannot issue a compulsory license on a pending patent, and most importing countries may not issue a compulsory license on a pending patent (or a patent that has been rejected but is under appeal). | | | |
| **** | Final rejection required in India and importing country, which could take years. | | | |
| ***** | Final rejection required in the importing country (which could take years) and product patent must be granted in India (a final decision on product patent application may take years). | | | |

⁸ Table adapted from UNITAID Hepatitis C Medicines Technology and Market Landscape (2015). See: http://unitaid.org/images/marketdynamics/publications/HCV_Meds_Landscape_Feb2015.pdf.

Under Article 10.3 (c) of the license, Gilead prevents licensees from supplying DAAs to the excluded countries except under extremely restrictive circumstances when there is no product patent (as broadly defined by the license) and no reasonable possibility for Gilead to pursue a patent. Therefore, even if patents are successfully opposed or invalidated, or are unlikely to meet patentability standards, it would be difficult for licensees to determine that there is no “*reasonable possibility*” for Gilead to obtain a patent in an excluded country.

In addition, since Gilead has the option to keep filing secondary patent applications, it is not likely that there will be a scenario in which there is no “*reasonable possibility*” for Gilead to obtain a patent in an excluded country.⁹ With this broad definition of a patent, Gilead can prevent sales in excluded countries merely by evergreening, which includes filing new patent applications on derivatives and combinations, divisional applications or amendments to existing claims, and appeals to rejected patents that can take substantial time even for an efficient court system to address.

Under Article 10.3 (d) of the license, Gilead may offer limited means for the excluded countries to seek access to low-cost generic versions of these medicines. However, ambiguity in the text may prevent full use of the provision. Other potential routes to enable low-cost access are not necessarily possible, even if there are no granted product patents in India or in the excluded countries. In particular:

- Excluded countries that have issued a product patent may be able to unilaterally import generic versions of licensed DAAs from licensees by issuing a compulsory license. However, 10.3 (d) – due to its construction, may also require issuance of a compulsory license in India – in particular due to the ambiguous wording of clause (ii) (Y)(1),(2) and (Z) of Article 10.3 (d). If a compulsory license is required in India, it would preclude use of the provision for the foreseeable future since currently there are no granted product patents in India and compulsory licenses cannot be issued on pending or rejected patent applications.
- If a product patent is granted in India, and India issues a compulsory license, licensees can export to the excluded countries that have no patents or that have issued a compulsory license. However, as mentioned directly above, product patents may not be granted or denied in India for a considerable period of time and a compulsory license can only be issued in India if the product patent is granted. Most, if not all importing countries will be unable to issue a compulsory license on a pending patent (or upon a rejected patent that is under appeal), and final decisions on the patent status (whether to grant or deny) may also take considerable time.
- If there are no applications, patents or pending appeals in either India or the importing country, then a licensee may export DAAs outside of the license. However, due to the broad definition of a patent, such a scenario is not possible in India or an importing

⁹A case in point is the case of PAHO’s tender for procurement of the HIV medicine atazanavir for Venezuela, which was won by the Indian subsidiary of the US generic company Mylan in 2012 and 2014. Using a licensing agreement with Mylan that defines patents as covering pending applications and pending appeals of rejected applications, BMS sued Mylan in Indian and US courts to prevent export to Venezuela (which was not included in the list of licensed territories), despite the fact that there were and are no granted product patents on the compound, pro-drug or salt form in India or Venezuela. BMS has pending patent applications in both jurisdictions and, in addition, process patents granted in India for which generic companies have developed non-infringing processes. After considerable delay due to BMS’s efforts to secure an injunction in Indian courts, Mylan was finally able to export the consignment of medicine (100,000 bottles) in the last quarter of 2014 after securing a hard-won decision from the District Court of Hyderabad, followed by the Appeals Court (High Court of Telangana & Andhra Pradesh), which rejected the injunction application and instructed Mylan to deposit 5% of the invoice price with the court registrar pending completion of the suit. Such litigation has a chilling effect on generic companies that wish to supply in territories not included in the license.

country for many years, especially as it is expected that Gilead is likely to pursue litigation extensively and file evergreening patent claims or divisional applications.

6. Only Indian generics companies are offered licenses for finished products and APIs

Gilead opened negotiations for licenses with only Indian generics producers for both the finished products and the APIs. Gilead has not initiated negotiations for licenses with any generics company based outside of India, such as manufacturers in China and Brazil. Although the Indian industry's role as the 'pharmacy of the developing world' is well-documented, this role is threatened by the fact that more Indian generics companies are either entering into long-term business partnerships for lucrative high-income markets with multinational pharmaceutical companies or are being wholly acquired by them. These generics companies are increasingly unwilling to 'launch at risk'¹⁰ generic versions of treatments or challenge patent applications filed by originator companies in developing countries as a result of these business relationships. At the same time, the Government of India remains under constant pressure to adopt more restrictive levels of intellectual property protection that will undermine the use of TRIPS flexibilities for generic competition.¹¹

Restricting the licensee scope to India is problematic in terms of limiting the potential of generic competition emerging from producers in other developing countries, establishing global economies of scale for generic competition on the finished products, and in securing sufficient sourcing options for APIs and finished formulations in different regions to eventually secure sustainable supplies and affordable prices for HCV treatment in developing countries.

7. The license segments the API market and increases the cost of production and final DAA prices

Gilead has segmented the market for finished products, undermining low-cost generic competition across all developing countries. Similarly, Gilead has segmented the market for APIs worldwide, both through the license and through its own sourcing. APIs constitute a significant percentage of the total cost of production, and the flexibility and ability to source a wide range of low-cost APIs and intermediates plays an important role in ensuring affordable prices for finished products.

Gilead is segmenting the API market through the following strategies:

- Licensees can only source APIs and intermediates from other Indian licensees, or from Gilead's suppliers, upon Gilead's prior approval. Such restrictions, if they create shortages or limit access to producers developing and selling APIs at lower costs, would increase the cost of production and therefore the overall cost of the finished product.
- Gilead has listed intermediate patents under the license and such patents have already been granted in India and China. Companies that are not licensees must develop non-infringing processes and/or challenge the patents to remove this barrier.

¹⁰ A pharmaceutical company may seek to place a generic version of a patented drug on the market even when it anticipates an infringement suit. This is because the company may have a non-infringement defence and/or strong invalidity argument for the patent/s in question that can be used for a counterclaim for revocation.

¹¹ MSF has documented a timeline of U.S. pressure on India regarding India's intellectual property policies. See: http://www.msfaaccess.org/sites/default/files/IP_US-India_Briefing%20Doc_final_2%20pager.pdf

- When an Indian API producer is a licensee, this license also blocks the producer's right to export APIs to other countries or generic producers, except for small developmental quantities required for marketing approval applications before regulatory authorities.
- Finally, Gilead is not working with or allowing the licensees to access a range of API producers in China that would be able to produce key intermediates and APIs at substantially lower prices and could improve the ability of Gilead, licensees and other manufacturers to offer DAAs at lower prices worldwide.

8. Licensees are required to implement an anti-diversion programme which will egregiously restrict access to medicines and undermine patient confidentiality

Gilead's license mandates licensees to introduce a specific anti-diversion plan on a country-by-country basis, including a mechanism of "*sold directly to patients.*" This plan emulates Gilead's own anti-diversion programme in developing countries which have threatened to undermine access and patient confidentiality, exclude significant numbers of vulnerable patients, and place an undue burden on health systems and treatment providers for no legitimate medical reasons, but rather for purely commercial reasons. MSF has also provided a detailed analysis on these measures.¹²

The far-reaching consequences of the programme, especially since Gilead requires licensees to imitate this in their marketing and distribution plans, would set a negative precedent that substantially undermines HCV treatment scale-up in high-burden countries and confidentiality of patients' data, and is likely to exclude the most marginalised communities, including refugees, injecting drug users and patients with unstable living arrangements who will have difficulty meeting the burdensome requirements of the programme.

9. Additional barriers will undermine registration and marketing of optimal, low-cost DAA combinations

Alongside the anti-diversion program, there are additional, non-patent barriers that will limit the effectiveness of the license to enable access to low-cost generic medicines:

- **Timely registration:** The license does not contain any enforceable obligation for Gilead or its licensees to pursue registration of the products in developing countries apart from a loose requirement for licensees to obtain regulatory approvals in the countries in the territory and Gilead's discretion of filing for registration for APIs and finished product "*in the Territory.*" If Gilead chooses not to apply for registration in one country where the originator's registration is a prerequisite for initiating generic registration, options for those countries to utilize local generic supply or import of generic versions would not be possible. Gilead and its licensees must register the licensed DAAs with the national drug regulatory systems of included countries to ensure access for patients in all 91 countries covered by the license. Registration of the generic products in countries outside of the geographic scope of the license similarly depends on the commercial willingness of Gilead and its business partners. However, for countries that are excluded from the license, generic licensees are unlikely to pursue registration, hindering the use of compulsory licensing as well.

¹² A detailed analysis from MSF is available online. See: http://www.msfaccess.org/sites/default/files/HepC_Gilead_anti-diversion_FINAL.pdf

- **Data exclusivity:** Data exclusivity barriers could restrict access to generic versions of DAAs produced by licensees. The license provides for a waiver of Gilead's regulatory data exclusivity only when a licensee seeks regulatory approval in countries included in the license. No specific clause under the license ensures excluded countries can benefit from a waiver of data exclusivity. If an excluded country uses compulsory licensing for importation or production, domestic legal discretion to avoid enforcement of data exclusivity would be critical to ensure that regulatory approval is not delayed, potentially for many years depending on a term of data exclusivity in the country.

CONCLUSION AND RECOMMENDATIONS

Gilead's license includes a number of restrictions, ambiguities and exclusions that undermine access to low-cost generic HCV medicines in developing countries. These legal restrictions will limit scale up for access to DAAs and lead to artificially high prices for patients, treatment providers and governments around the world.

To ensure low-cost access to these key DAAs in all low- and middle-income countries, MSF makes the following recommendations:

1. Gilead and its licensees should publish the actual, executed license agreements signed for all the three DAAs with a sufficient and clear patent landscape affecting countries of concern, and provide it to stakeholders on request.
2. Gilead should expand the scope of the license to include all low- and middle-income countries, or at least to include developing countries with a high burden of HCV, including Iran, Ukraine, Thailand, China and Brazil.
3. Gilead should abandon its anti-diversion programme for its branded product and stop mandating implementation of the anti-diversion programme by its licensees.
4. The broad and excessive definitions of patents should be modified to only include granted patents, and exclude pending patent applications or pending appeals to rejected applications. Method of use or manufacture should be excluded from the product patent definition. Gilead should revise its definitions of patents, and ensure they are aligned with the definition under the World Trade Organization's TRIPS Agreement, regardless of whether a compulsory license can be issued on a pending patent.
5. Article 10.3 (d) of the license should be rewritten to clarify that Clause Z of the license only relates to 10.3 (d)(ii).
6. The termination of the license should be available upon notice provided by the licensees.
7. Gilead should establish a clear obligation and schedule of product registration in developing countries.
8. Gilead should issue a clear waiver of data exclusivity for all low- and middle-income countries where data exclusivity may apply.
9. Gilead should not prevent licensees from selling APIs to any company outside of the license and should allow licensees to source APIs from any appropriate supplier.
10. Gilead should publish a full and comprehensive patent landscape for all three DAAs in all low- and middle-income countries, and refrain from evergreening through the filing of serial patent applications.