MSF Briefing Document
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Strategies to Secure Access to Generic Hepatitis C Medicines

Overcoming patent and regulatory barriers to secure access to generic hepatitis C medicines

Médecins Sans Frontières/Doctors Without Borders (MSF) is in the process of starting to treat people who are living with hepatitis C virus (HCV) in at least nine countries, and therefore is in need of affordable access to direct-acting antiviral (DAA) treatments, including those marketed by Gilead Sciences (Gilead) and Bristol-Myers Squibb (BMS). Gilead has signed voluntary license agreements with 11 Indian generic medicine manufacturers to market generic versions of Gilead's DAAs in some low- and middle-income countries, while BMS will soon sign voluntary license agreements with a few generics manufacturers. However, Gilead's voluntary licenses restrict access to affordable generic versions of these DAAs for millions of people with HCV in 50 middle-income countries (MICs).[1] It is expected that BMS's licenses will have similar restrictions.

There are legal means that countries excluded from voluntary licenses can consider using to get access to affordable generic versions of DAAs. Countries must also overcome regulatory barriers that may keep both branded and generic versions of DAAs from entering the market. This document offers guidance to policy makers to enable access to these medicines to scale up HCV treatment.

Background

Snapshot of hepatitis C medicines

Gilead has obtained or is seeking patents on three DAAs: sofosbuvir, ledipasvir and velpatasvir, from patent offices in multiple countries. BMS has obtained or is seeking patents for one DAA, daclatasvir, in multiple countries. These DAAs can significantly improve treatment over previously available treatment options for HCV.

Sofosbuvir: Sofosbuvir is the only NS5B inhibitor approved for use so far. Available data indicates it has pan-genotypic activity, a good safety profile, low risk for drug-drug interactions and a high barrier to resistance. It has been studied in all genotypes in combinations with either ribavirin or other DAAs, demonstrating good efficacy. Access to sofosbuvir will be critical as it is currently a backbone drug to create powerful, pan-genotypic regimens with other DAAs. Sofosbuvir is already registered as a single compound by the US Food and Drug Administration (US FDA), the European Medicines Agency (EMA) and seven other National Medicines Regulatory Agencies (NMRAs) worldwide.[2]

Sofosbuvir-daclatasvir: Daclatasvir was the first NS5A inhibitor to be registered, and is indicated for use in combination with other potent DAAs, such as sofosbuvir. The combination of sofosbuvir and daclatasvir is an interesting and robust combination that fills all requirements for use in resource-limited settings; it has a well-tolerated, high-efficacy, pan-genotypic profile. It can be used for people with advanced liver

1 A full MSF analysis of Gilead's voluntary license agreement is available at: http://www.msfaccess.org/sites/default/files/MSF_assets/HepC/Docs/HEPC_Analysis_of_Gilead_Hepatitis__License_March_20_2015.pdf.

2 Gilead. Sovaldi registration in the developing world. See: http://www.gilead.com/~/media/Files/pdfs/other/Sovaldi%20Registration%205%205%2015.pdf.

disease, and shows very good results in HIV co-infected people on antiretroviral therapy. Daclatasvir is already registered as a single compound by the EMA and the Japanese Ministry of Health, Labor and Welfare (MHLW).

Sofosbuvir-ledipasvir: The fixed-dose combination (FDC) of sofosbuvir-ledipasvir represents a powerful and effective all-oral treatment for HCV, particularly for people with HCV genotypes 1 and 4. This combination may also be used for genotypes 3, 5 and 6, although the efficacy for genotype 3 may be lower than other sofosbuvir-NS5A inhibitor combinations (e.g. sofosbuvir and daclatasvir), and there were few patients studied with genotypes 5 or 6. This FDC has also been studied in patients with HIV co-infection and advanced liver disease, and maintains a good efficacy and safety profile for these patients. This combination is US FDA approved.

Sofosbuvir-velpatasvir: This FDC combines sofosbuvir with another NS5A inhibitor, velpatasvir. While this drug is still in phase 3 clinical trials, it is expected that it will provide more powerful pan-genotypic coverage than sofosbuvir-ledipasvir, and has demonstrated excellent efficacy in phase 2 studies, including for genotype 3.

In April 2015, the World Health Organization Model List of Essential Medicines was updated by Expert Committee to include several new DAAs, including sofosbuvir, daclatasvir, simeprevir, dasabuvir and ledipasvir (in combination with sofosbuvir).[3]

Generic competition can dramatically reduce the prices of new DAAs

Existing prices offered by Gilead for its products (sofosbuvir or combinations) range from approximately US $900 to $95,000 per 12-week treatment course and are not reflective of the actual manufacturing costs of the DAAs. Prices for BMS's version of daclatasvir are not known for most countries but are expected to be unaffordable, even though the drug is very inexpensive to manufacture. A study authored by Hill et al. in 2013[4] indicates that the actual costs of manufacturing these DAAs is relatively low, at an estimated $101 per 12-week treatment course for sofosbuvir and as little as $20 for a 12-week course of daclatasvir. When there is open generic competition, marketed prices for these drugs will be far lower.

Gilead is not the only company currently selling sofosbuvir. In fact, generic competition from multiple manufacturers is already indicating a downward trend for the prices of sofosbuvir, which should enable low-cost access to quality-assured generic versions of the drug. Sofosbuvir is now available from a generic company in India at approximately $189 per 28-day-supply bottle, or $567 for a full 12-week treatment course. Several countries, such as India, Pakistan and Egypt, can access low-cost, generic versions of sofosbuvir, but the number of countries able to do so is limited and these versions are not yet quality assured. This is in part due to the fact that supply and marketing of generic versions by manufacturers depends upon successfully overcoming patent barriers, demonstrating equivalence to the originator compound (e.g. through bioequivalence studies) and obtaining regulatory approval in a timely manner in each developing country. Additional suppliers for several DAAs are on the verge of entering the market. For other countries, negotiating and overcoming these barriers will be critical to assuring scale-up with low-cost quality-assured treatments.

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3 WHO. 19th WHO Model List of Essential Medicines (2015). See: http://www.who.int/medicines/publications/essentialmedicines/EML2015_8-May-15.pdf.

4 Hill A, et al. What is the minimum cost per person to cure HCV? 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Kuala Lumpur, Malaysia (2013). See: http://pag.ias2013.org/EPosterHandler.axd?aid=3142.

Voluntary licenses from Gilead: 50 middle-income countries excluded

Although Gilead's voluntary license includes 91 low- and middle-income countries in its geographic coverage, it at the same time 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 the excluded middle-income countries, including nearly 2.6 million people in Brazil, 1.5 million people in Thailand and 30 million people 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.[5]

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 and Herzegovina	Iraq	Montenegro	Ukraine
Brazil	Jamaica	Morocco	Venezuela
Bulgaria	Jordan	Panama	West Bank and Gaza
China	Kazakhstan	Paraguay	Yemen
Colombia	Kosovo	Peru	
Costa Rica	Lebanon	Philippines	

Enabling access to low-cost generic sofosbuvir in excluded countries

In addition to sofosbuvir, it is expected that other DAAs will eventually be available as generics. Even if countries are excluded from voluntary licenses or face patent barriers, this does not necessarily preclude them from pursuing access to low-cost generics if adequate legal measures and strategies can be put in place. This document will in particular discuss measures to ensure access to low-cost, generic sofosbuvir, though such strategies might be relevant for other DAAs as well.

Understanding the patent landscape for sofosbuvir is a prerequisite

One of the first steps for a country to develop a practical supply strategy is to have a clear understanding of the patent landscape and legal status of the key patents related to sofosbuvir (and other DAAs) in the country. This is often a significant challenge for the Ministry of Health, which may not be in close contact with the country's patent office. For sofosbuvir and other priority DAAs that will soon come on to the market, the World Health Organization (WHO) has published research that evaluates the patent status in select developing countries.[6] According to the report's findings, patents on sofosbuvir are not yet granted in many developing countries, including countries that have been excluded from Gilead's voluntary license.

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5 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.

6 WHO-sponsored reports of new DAAs can be downloaded from: http://www.who.int/phi/implementation/ip_trade/ip_patent_landscapes/en/.

Without competition-blocking patents on the drug in these countries, there are opportunities to access low-cost generic versions of sofosbuvir and potentially other key DAAs.

Strict patent examination can prevent granting of weak or invalid DAA patents

The technical features of the Gilead patent applications on sofosbuvir have been proven to be weak. According to a technical analysis of a WHO-sponsored report, the base compound patent application of sofosbuvir, which can serve as a blocking patent for generic production, has been presented in the form of a 'Markush claim'. A 'Markush' type of patent application involves a specific drafting technique on patent documents, which includes only a general chemical structure identified at an early stage of drug discovery. This can consequently lead to monopoly protection of a large group (up to millions) of relevant compounds, without adequate disclosure of each compound in the patent document when filed, and without providing a specific technical nature of the core contribution of the invention.[7] Such types of claims are detrimental to public health and should not be allowed.[8]

In January 2015, India's Patent Controller rejected Gilead's patent application on the base compound of sofosbuvir.[9] According to the Patent Controller's decision, "there are a number of earlier compound structures that are very close to what Gilead is trying to get a patent for." In addition, the prodrug patent application on sofosbuvir has been rejected in Egypt for failing to fulfil the legal criteria of Egypt's patent law.[10] In Europe, there have been ten third-party observations before the European Patent Office challenging the patent application on the base compound of sofosbuvir.[11] Entities that have filed those observations include generics companies based in Europe and elsewhere, and non-profit organizations.

Gilead and BMS are filing applications for multiple patents for each DAA, including for derivatives (prodrugs) and FDCs. This industry 'evergreening' strategy could allow Gilead and BMS to extend monopoly protection beyond one 20-year patent. Countries should adopt strict patent examination practices and screen out patent applications that do not meet the criteria set in national patent law to ensure that unwarranted patents are not granted. In the case of sofosbuvir, the technical analyses from patent rejections in other countries and analyses from public health institutions can serve as useful references.

Use of compulsory licenses should be considered where necessary

When HIV programmes for antiretroviral treatment began in 2003, a number of countries relied on compulsory licensing to import or manufacture affordable generic versions of first-line HIV medicines. Compulsory license issuance remains a backbone flexibility enshrined under international law that can be used to promote public health and increase access to essential HCV medicines. Countries, in line with national intellectual property (IP) laws, can issue compulsory licenses on existing patents or applications to facilitate the production and importation of low-cost, quality-assured generic sofosbuvir.

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7 WHO. Patent Situation of Key Products for Treatment of Hepatitis C (2014). See: http://www.who.int/phi/implementation/ip_trade/daclatasvir_report_2014_09-02.pdf.

8 Correa C. Guideline for the examination of pharmaceutical patents: developing a public health perspective (2007). See: http://www.ictsd.org/sites/default/files/research/2008/06/correa_patentability20guidelines.pdf.

9 India Patent Controller. Decision in the matter of application no. 6087/DELNP/2005 (2014). See: http://www.ip-watch.org/weblog/wp-content/uploads/2015/01/India-6087DNP2005-sofusbuvir-Jan-2015.pdf. Report on the case is available at: http://www.ip-watch.org/2015/01/14/key-hepatitis-c-patent-rejected-in-india-for-lack-of-novelty-inventive-step/.

10 Mada Masr. Egypt will not patent new hepatitis C drug (2014). See: http://www.madamasr.com/opinion/egypt-will-not-patent-new-hepatitis-c-drug.

11 IP Watch. Brief: At EPO, patent oppositions to high-priced Gilead hepatitis C drug pile up (2015). See: http://www.ip-watch.org/2015/02/27/at-epo-patent-oppositions-to-high-priced-gilead-hepatitis-c-drug-pile-up/.

Gilead's voluntary license has adopted a broad definition of patents under its remit, which includes both granted patents and pending and evolving applications. This approach has invited criticism and questions on whether a country can issue a compulsory license for a pending patent application. In this regard, it is important to refer to Article 5A(4) of the Paris Convention for the Protection of Industrial Property, which is fully compatible and commensurate with the World Trade Organization Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). Accordingly, countries can issue compulsory licenses upon request on the grounds of non-working or insufficient working of a patent in a country four years after the date of filing of a patent application or three years after the grant of a patent.[12] Many countries have incorporated such a provision in their national patent laws, which might allow granting a compulsory license on a patent application if insufficient work of a patent could be established.

For countries that have been excluded from Gilead's voluntary license, a compulsory license can be issued to enable local production, which is especially relevant for countries that have capacity to produce both raw material and finished products of the medicines, such as China. Compulsory licenses can also be issued to allow countries to import low-cost raw materials in order to support domestic generic production of the finished products to scale. In addition, compulsory licenses can be used to enable countries to import low-cost quality-assured sofosbuvir from generic suppliers from other countries.

Excluded countries can procure generic DAAs through numerous channels when patents are not in force

When the primary patents of sofosbuvir are not in force in a country that has been excluded from Gilead's voluntary license – i.e. if the country has not granted or has rejected Gilead's patent applications, or used other legal measures such as compulsory licensing to overcome patent barriers – this country can consider supply of generic sofosbuvir through the following sources of recently approved HCV drugs that have emerged over the last year:

Generic suppliers outside of India

In countries where Gilead's primary patents have been rejected, not yet granted or not filed, generic production is possible and has already become reality; generics manufacturers in Egypt, Morocco, Bangladesh and Brazil have introduced or are in the process of formulating generic versions of sofosbuvir.[13] Procurement from those sources is possible for countries that have been excluded from Gilead's voluntary license.

Generic suppliers in India who are outside of the voluntary license

It is important to note that there are generics companies in India that have plans to commercialise sofosbuvir and have not signed a voluntary license with Gilead. In addition, there are no product patents granted in India on sofosbuvir to date. Therefore, these generics producers are free to market their drug in countries that have no competition-blocking patents, regardless of whether or not these countries are covered under the geographic scope of Gilead's voluntary license.

Generic suppliers in India who have signed the voluntary license

According to the voluntary license agreement, if a country outside of the geographic scope uses a compulsory license, or there is no patent owned by Gilead in that country, the Indian generics companies who have signed the license (licensees) might be able to export generic versions of sofosbuvir to the

12 Article 5A (4), Paris Convention for Protection of Industrial Property. See: http://www.wipo.int/treaties/en/text.jsp?file_id=288514#P123_15283.

13 See Annex for a list of companies that are currently or planning to manufacture sofosbuvir.

country. However, there are restrictions that could preclude Indian generics licensees from exporting to excluded countries – depending both on the patent status of relevant DAAs in India and on the patent status of these drugs in the destination country. The following table (Table 2) provides an overview of the restrictions and opportunities for Gilead's generics licensees to export drugs to countries excluded under the voluntary license.

Table 2: Restrictions and Opportunities for Licensees to Export DAAs to Excluded Countries

Can excluded countries get access to generic sofosbuvir, ledipasvir and velpatasvir from licensee generic companies?[14]				
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 is 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" 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 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).

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

Addressing registration and regulatory challenges

Not being able to access effective, well-tolerated treatment can be devastating for people with chronic, life-threatening HCV infection and for their health care providers. Seriously ill patients can try to obtain the new DAAs through a compassionate use/named-patient basis in developing countries where they are not yet registered. Compassionate use programmes are governed by legislation in individual countries to make medicines available on a named-patient basis or to cohorts of patients. Early access through this route could save more lives. NMRAs and Ministries of Health should facilitate access for such patients and demand Gilead and BMS not ignore requests from patients and physicians.

In countries like India, where a registration dossier for a generic version of a new medicine can be filed without prior registration of the originator product, the failure of the originator companies (Gilead and BMS) to file dossiers for their DAAs will not impede registration of generic sofosbuvir. In the absence of the originator applying for approval, the Indian NMRA – the Central Drugs Standard Control Organization of India – relies on the originator product's registration elsewhere (i.e. EMA, US FDA and other stringent regulatory bodies) to determine whether to register a therapeutically-equivalent follow-on generic. The generic producer has to submit evidence of bioequivalence and WHO good manufacturing practices. In the case of sofosbuvir, the Central Drugs Standard Control Organization of India also waived the requirement of a local trial, taking into consideration unmet medical need for the drug in the country.

Based on Gilead's website,[15] beyond the USA and Europe, sofosbuvir (Sovaldi®) has already been granted marketing authorisation in Brazil, Chile, Egypt, India, Mongolia, Pakistan and Venezuela. Gilead has already filed registration dossiers in Argentina, Bolivia, Colombia, Dominican Republic, Indonesia, Kenya, Mexico, Nigeria, Philippines, South Africa, Tanzania, Thailand and Uganda.

The WHO Prequalification Programme (WHO PQP) has issued a guidance document regarding the design of a bioequivalence study to compare generic versions of sofosbuvir to Gilead's originator product.[16] This is an important standard regulatory requirement in order to ensure comparable efficacy and safety profiles between generic and originator compounds. Generic producers are being encouraged to apply for prequalification since it will allow their medicine to be procured with donor or national funds by a wider range of countries that rely on WHO PQP. WHO prequalified medicines can also be registered through a fast-track procedure thanks to the Collaborative Registration Procedure set up by the WHO PQP.

Import waivers or compassionate use regulations should be considered to access quality-assured generic versions of sofosbuvir, even when not yet registered in a given country. This could be seen as an interim mechanism to ensure access to sofosbuvir or other DAAs in the medium term.

Funding to pay for DAAs in treatment programs

Securing widespread access to these DAAs requires not only ensuring regulatory review and enabling generic competition, but also a commitment by countries to scale-up treatment programs. More studies are showing that treatment of HCV, particularly for people with HIV co-infection, is cost effective.[17] In order to ensure public markets and achieve the lowest prices, governments must step up to create HCV treatment and care programs and fund the purchase of DAAs.

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[15] Gilead. Sovaldi registration in the developing world. *See:* http://www.gilead.com/~/media/Files/pdfs/other/Sovaldi%20Registration%205%205%2015.pdf.

[16] WHO. Notes on the design of a bioequivalence study: sofosbuvir. Guidance Document 25 March 2015. *See:* http://apps.who.int/prequal/info_applicants/BE/2015/Sofosbuvir_BE25March2015.pdf.

17 Zahnd C, Salazar L, Dufour J, et al. Impact of deferring HCV treatment on liver-related events in HIV+ patients (2015). See: http://www.croiconference.org/sessions/impact-deferring-hcv-treatment-liver-related-events-hiv-patients.

These programs and funding commitments can also be stimulated and encouraged with international treatment program funding support from actors such as UNITAID and the Global Fund to Fight AIDS, Tuberculosis and Malaria (the 'Global Fund') for eligible countries. At its last board meeting, the Global Fund approved a decision to allow Global Fund countries to apply for funding for HCV treatment for HIV-HCV co-infected patients.[18] This funding can be used to catalyse larger national programs. It can also serve as an incentive for producers to provide public market prices and ensure access in countries supporting HCV treatment programs.

Conclusion

With the recent and expected approvals of several DAAs, people living with HCV and governments around the world have high expectations that these medicines can provide effective, non-toxic and relatively simplified treatments. These medicines are inexpensive to manufacture, and in some combinations potentially work across all genotypes of the disease.

Yet patent and regulatory barriers in a range of developing countries, especially middle-income countries, present a formidable challenge to securing access to affordable treatment in the public and private sectors. However, governments do not have to wait for the situation to change. Through measures taken at the domestic level, or through collective engagement at the international level, low-cost generic medicines – which cost a fraction of the high prices charged by Gilead – could be provided.

The Annex to this document provides a brief survey of all generics manufacturers that are marketing or planning to sell at least sofosbuvir where permitted.

18 Global Fund. GF/B33/DP08 Policy on Co-infections and Co-morbidities (2015). See: http://www.theglobalfund.org/Knowledge/Decisions/GF/B33/DP08/.

Annex: Preliminary list of generics manufacturers with interest in sofosbuvir production

Each country should take responsibility for quality assessment of generic versions from these manufacturers according to local regulatory procedures.

Preliminary List of Generics Manufacturers with Interest in Sofosbuvir Production		
Company	**Country**	**Gilead Licensee?**
Hetero Labs	India	Yes
Natco Pharma	India	Yes
Incepta	Bangladesh	No
Microbiologica-Blanver	Brazil	No
Pharco Pharma	Egypt	No
Marcyrl	Egypt	No
Aurobindo Pharma	India	Yes
Biocon Limited	India	Yes
Zydus Cadila	India	Yes
Ranbaxy Labs	India	Yes
Sequent Sc	India	Yes
Strides Arcolab	India	Yes
Cipla Ltd.	India	Yes
Laurus Labs	India	Yes
Mylan Labs	India	Yes
Abbott	India	No
Dr Reddy's	India	No
Pharma 5	Morocco	No