

***Gilead's Proposed Hepatitis C Medicines License – How Badly Will it Miss the Target?*¹**

September 12, 2014

Gilead has been busy building positive publicity for its proposed license on two new direct-acting oral antivirals used to treat infections with the hepatitis C virus (HCV), sofosbuvir (Sovaldi®) and ledipasvir, that will allow Indian generic manufacturers to produce and sell individual versions and a combination of the two medicines in a subset of low- and middle-income countries (LMICs). News stories have been uncritically positive so far about the still-secret license,² and Gilead is quite coy with respect to key details. Health reporters and hep C activists should raise pointed questions about the scope and impact of the proposed license during Gilead's press conference, now scheduled for 3:00 p.m. September 15, 2014 in India.

Gilead's proposed license, and its limitations, is important because Gilead has applied for patents on Sovaldi® and ledipasvir in many countries, although a number of countries in the probable licensed territory are without patents. As a patent holder, Gilead generally has rights to exclude competitors and charge monopoly prices on these life-saving medicines. The anticipated license will set precise terms on which companies can make generic equivalents and where and under what circumstances those generics can be sold. In other words, Gilead sits in the driver's seat and has enormous power to decide who does and doesn't get more affordable access to generics of assured quality.

Early disclosures of select license terms by Gilead³ shows that the planned license falls far short of universal access in LMICs. When armed with actual details, critics should demand that Gilead modify the license to hit the target in the bulls eye: all people living with HCV in LMICs gain access to its life-saving medicines which in turn will have a major impact on the future eradication of this deadly and debilitating liver disease.

How many countries will be included and excluded from the license and why will the majority of HCV-infected people be left uncovered?

Gilead initially announced a proposed license that would cover just 60 countries,⁴ essentially low-income countries from sub-Saharan Africa and poorer countries from South and Southeast

¹ Professor Brook K. Baker, Senior Policy Analyst Health GAP, Northeastern U. School of Law, b.baker@neu.edu (671-373-3217). Extensive comments from Karyn Kaplan, Azzi Momenghalibaf, Rohit Malpani, Els Torrelee, Priti Padhakrishnan, Tahir Amin, and Elliott Abers. There was broad support for issuing a paper on concerns about the possible license even in advance of its announcement from the broad global Hep C coalition.

² See, e.g., <http://www.bloomberg.com/news/print/2014-09-04/gilead-close-to-sending-84-000-drug-to-poor-countries.html>; <http://blogs.marketwatch.com/health-exchange/2014/08/08/gilead-offers-to-sell-hepatitis-c-drug-in-india-at-99-off-u-s-prices/tab/print/>; <http://www.reuters.com/assets/print?aid=USBREA371DI20140408>; <http://www.bizjournals.com/sanfrancisco/blog/biotech/2014/09/gilead-sovaldi-hepatitis-c.html?s=print>; <http://online.wsj.com/articles/gilead-near-deals-to-allow-lower-cost-hepatitis-c-drug-in-developing-countries-1410211486?tesla=y&mg=reno64-wsj&url=http://online.wsj.com/article/SB10001424052970204892304580142290328007612.html>;

<http://timesofindia.indiatimes.com/india/New-Hepatitis-C-drug-99-cheaper-in-India/articleshow/39719323.cms>.

³ Gilead, *Expanding Access to Hepatitis C Treatment* (Feb. 2014).

⁴ Afghanistan, Bangladesh, Benin, Burkina Faso, Burundi, Cameroon, Cambodia, Central African Republic, Chad, Comoros, Democratic Republic of Congo, Djibouti, Eritrea, Ethiopia, Fiji, Ghana, Guinea, Guinea-Bissau, Haiti, India, Ivory Coast, Kiribati, Kenya, Laos, Liberia, Madagascar, Malawi, Maldives, Mali, Mauritania, Mongolia, Mozambique, Myanmar, Nauru, Nepal, Niger, Nigeria, North Korea, Pakistan, Pacific Islands (Palau), Papua New Guinea, Rwanda,

Asia and islands – many of which have no or little HCV prevalence data or demand. Although more affordable generic access would be a boon to any country where a patent otherwise blocks generic sales, that proposed geographic scope was roundly criticized because it excluded key HCV patient populations in large middle-income countries in North Africa, Eastern Europe, Latin America, and Asia. (India was the largest population country included with approximately 18.2 million people living with HCV.)

Recent announcements indicate that Gilead has increased its territorial coverage to 80-90 countries, with specific press mention of Egypt, Indonesia, South Africa, and Vietnam, which have significant HCV burdens (e.g., Egypt 11.8 million; Indonesia 9.4 million; South Africa .9 million, and Vietnam, .8 million); but most of the other countries are likely to be smaller, but will include more from Latin America and Asia. (Note: the probable inclusion of Egypt may be illusory because a patent on Sovaldi® has not been granted in Egypt and local producers in Egypt have developed generic versions already, e.g., Pharco.) Undoubtedly excluded is China, the country with the largest HCV burden of 29.8 million infected. Brazil and Ukraine with 2.6 million and 1.9 million infected respectively are also reportedly excluded because they, like China, are considered to be “commercial” markets. Other large-burden countries likely to be excluded include Turkey (1.5 million), Thailand (1.5 million), Mexico (1.1 million), Romania (1 million), Argentina (.7 million), Morocco (.6 million) Malaysia (.4 million), Colombia (.4 million), and many others.

The demographics and epidemiology of HCV show that there should be licensed coverage in all middle-income countries because that is where the major burden of disease exists and that is where more affordable access will have the most impact: at present, 73% of people living with Hep C live in middle-income countries – only 12% live in low-income countries and 15% live in high-income countries. Translating this to numbers, 135 million of the world’s 185 million people infected with Hep C live in middle-income countries, and a significant portion of these – preliminary estimate 38% - are likely to be excluded from direct coverage in the Gilead license.

Will Gilead allow licensees to supply countries where a patent is not in force (no patented filed or yet granted, successful patent oppositions or grant of compulsory licenses?)

Historically, many voluntary licenses have not allowed licensees to become suppliers for countries where patents are not in force, e.g., where no patent has been filed or granted, patent oppositions and patent invalidations have been successful, or compulsory/government-use licenses have been granted. Patent oppositions have already been filed on Gilead’s sofosbuvir in India, a key producer and high prevalence country. High burden countries that are excluded from the Gilead license would have incentives to use TRIPS-compliant flexibilities⁵ such as issuing compulsory or government use licenses on sofosbuvir and ledipasvir. However, if Gilead succeeds in locking up most of the capable Indian generic producers into a license with narrowly defined geographic scope and a prohibition on serving uncovered markets, other unlicensed countries using such TRIPS-flexibilities might not be able to locate a qualified generic supplier, though China probably has a big enough market and sufficiently qualified generics to become a

Samoa, Sao Tome and Principe, Senegal, Sierra Leone, Solomon Islands, Somalia, South Sudan, Sudan, The Gambia, Togo, Tonga, Tuvalu, Uganda, United Republic of Tanzania, Vanuatu, Zambia and Zimbabwe.

⁵ The WTO Agreement on Trade-Related Intellectual Property Rights (TRIPS) allows countries to bypass patents by allowing generic producers to make and sell a medicines if certain procedures are followed and adequate royalties/remuneration is paid.

plausible source of supply. Nonetheless, a contractual provision prohibiting a Gilead licensee becoming a compulsory licensee could have significantly negative market impacts. Similarly, a prohibition on selling in markets where patent oppositions or invalidations have been successful or where Gilead or the prior owner of sofosbuvir, Pharmasset, had not filed for or been granted a patent would be equally problematic.⁶

Alternatively, if Gilead's license does not prevent licensees from becoming compulsory licensees or from selling in countries where no patent has been filed or granted or where governing patents been successfully opposed or revoked, then the population impact of the Gilead license could be broader than its territorial specifications. To determine this broader impact, it will be necessary to conduct detailed determinations of patent filings and status in excluded countries – a task that would be much easier if Gilead were to disclose its global patent landscape on sofosbuvir and ledipasvir.

Gilead's intentions for excluded countries – is tiered pricing and intra-country sector segmentation and price differentiation good enough?

Gilead has announced tiered pricing plans – where the company offers lower prices in different markets – for its branded HCV medicines in LMICs, and differential pricing between the public/voluntary sector and the private sector in specific countries. Using common drug company metrics, it plans to offer different price bands for the public sector and select NGOs in low-income countries, lower-middle-income countries, and upper-middle-income countries. It is uncertain at this point whether the public/NGO sector tiered pricing will be uniform within each tier or whether Gilead plans to negotiate country-by-country, particularly in the upper-middle-income country tier.

Gilead has already announced imminent deals with Egypt and India that promise a probable price of \$900 for a standard 12-week course of treatment with Sovaldi®. However, this price is only applicable for the public sector and non-governmental organizations engaged in demonstration projects. Meanwhile, Gilead has indicated that it will charge substantially higher prices in the private sector. Since only a handful of LMICs are able to introduce comprehensive public sector treatment programs, especially in the absence of donor funding, most patients will have to access Solvadi® out-of-pocket and solely through the private sector at much higher prices. The total price paid for treatment would even be higher because Sovaldi® must be combined with other medicines to achieve maximum effect.

By means of its tiered pricing strategy, Gilead is trying to maximize its profits in countries excluded from the license by fully controlling sales to both public, NGO and private sectors. In this way, Gilead aims to fragment the generic and brand name markets, leaving its licensees unable to achieve maximum economies of scale and excluding them from some of their most lucrative potential markets. Meanwhile, Gilead will make significant profits on large-volume sales in excluded territories given the huge differential between the projected cost of producing a 12 week supply of sofosbuvir (Sovaldi®) (estimated at \$100, range \$68-136⁷) and projected

⁶ In contrast, licenses on AIDS medicines negotiated by the Medicines Patent Pool uniformly allow licensees to produce and sell in countries where a compulsory license has been issued, and some of the licenses allow sales into countries where opposition or invalidations for drugs have been successful.

⁷ Andrew Hill et al., *Minimum costs for producing Hepatitis C Direct Acting Antivirals, for use in large-scale treatment access programs in developing countries*, 58:7 Clin. Infect. Dis. 928-936 (2014), available at

prices for public/NGO sector sales and even higher price for private sector sales. Spread over millions of LMIC sales per year, Gilead's LMIC profits will add nicely to the excess profits it already reaps in rich country markets where it earned \$5.8 billion in the first six months based on its upper-income country price in the US and Western Europe of \$600 to \$1000 a pill.

How significantly will Gilead's license lower prices – not as much as it could?

Gilead is on record saying that its licensees will not be bound to the tiered prices but rather can sell at lower, more competitive prices at their own discretion. As stated above, the cost of production for a 3-month course of sofosbuvir (Sovaldi®) is relatively modest, estimated between \$68-\$136, and the stated royalties are said to be in the single digits. Production costs will get to the lower end of the range, the more efficiently and competitively active pharmaceutical ingredient (API) and final formulation are produced. Unfortunately, the anticipated Gilead license will not likely result in the lowest possible prices because the size of the generic market is being limited to a minority of people living with HCV. Generic manufacturers will not necessarily be producing at the most efficient economies-of-scale and there will be fewer successful generic competitors⁸ because the smaller market will be less attractive to generic producers. Generic entrants might be particularly reluctant to serve all smaller volume, poorer countries because of the costs of registering their products and establishing distribution systems.

Regardless of the number of licensees, price reductions will not necessarily occur immediately and volume might initially be small. As discussed briefly above, licensees have to register their medicines in licensed territories and arrange marketing and distribution systems and both of these can take a lot of time. In addition, there are no donors at present that are helping countries or patients by subsidizing the costs of HCV treatment. Accordingly, actual treatment access might initially be low, especially in poorer and high prevalence countries because of fiscal limits in health sector budgets.

Will Gilead allow co-formulation with non-Gilead HCV medicines?

The HCV medicines market is dynamic with additional direct-acting antiviral (DAA) (oral) medicines coming to market or in the development pipeline from Gilead, AbbVie, Bristol-Myers Squibb, Merck, and Johnson & Johnson. History has shown that brand name pharmaceutical companies rarely compete on price so these four companies will not likely be undercutting each other for market share. However, an equally important question is whether they will cross-license their DAAs with each other if there are therapeutic advantages to doing so. For example, it is possible that particular combinations will shorten treatment.⁹ (Gilead's medicines, Sovaldi® and ledipasvir, have already shown preliminary effectiveness in as little as eight weeks.¹⁰)

<http://cid.oxfordjournals.org/content/58/7/928.full.pdf+html>.

⁸ Gilead is purportedly negotiating with at least the following companies: Hetero Drugs Ltd., Mylan Inc., Cipla, Ranbaxy, Strides Acrolab.

⁹ See HIV i-BASE/Treatment Action Group, *Hepatitis C Pipeline: BONANZA! The Gold Rush is Underway* in 2014 PIPELINE REPORT (July 2014).

¹⁰ Eric Lawitz et al., *Sofosbuvir and ledipasvir fixed-does combination with and without ribavirin in treatment-naïve and previously treated patients with genotype 1 hepatitis C virus infection (LONGSTAR): an open-label, randomized, phase 2 trial*, 383 *Lancet* 5-5-523 (2014). Paradoxically, the planned license may not cover Gilead's investigational new DAA GS5816, which could provide pan-genotypic coverage.

Similarly, it is possible that combinations of different DAAs could have improved efficacy against different HCV genotypes or at different stages of liver disease. Gilead's past refusal to continue collaboration with BMS on sofosbuvir/daclatasvir that showed 100% cure rates was problematic with respect to product development of rational fixed-dose DAAs. Hopefully, Gilead's license will allow recommended combinations with non-Gilead DAAs.

Will Gilead provide significant support to expedite and broaden country registration?

Gilead's Executive Vice President Gregg Alton is reported to have said that Gilead is working diligently on the registration problem.¹¹ Medicines cannot come to other country markets just because they have been registered in the US or in Europe. Countries have their own regulatory processes that are time-consuming, burdensome, and potentially costly. Registration of generic equivalents is significantly easier and more accelerated if the originator product has already submitted its registration dossier and been approved. So, a fair question to Gilead is about its plans to register its HCV medicines broadly and quickly in the licensed countries. In addition, registration is expedited if the originator affirmatively helps its generic licensees in the rough terrain of in-country registration. It is crucial, therefore, for treatment advocates to obtain information from Gilead what specific plans Gilead has and when their DAAs when products can actually be expected to be registered and available in licensed territories. Until now, Gilead has been reluctant to publicize or share specific country registration information with advocates.

Will Gilead's license lead to universal access and help lead to the eradication of HCV?

Perhaps the most important question is whether Gilead's license – and its tiered pricing policy – will ensure affordable access to these lifesaving drugs for the many patients affected worldwide and thereby contribute to the eradication of the disease. Hepatitis C virus is an infectious disease just like HIV. Globally an estimated 185 million people have been infected¹² and there are 3-4 million new infections and 350,000+ deaths annually. Unlike HIV, HCV can now be cured. When a person is cured of Hep C, he or she is no longer infectious, meaning the more people cured with affordable treatments, the quicker we'll be able to curb the pandemic.

Countries (and donors) are more likely to invest in universal access to a HCV cure if the medicines are available at their most affordable cost. With a low-enough price, even patients who are not actively progressing with HCV-related liver disease will be treated to eliminate the virus and therefore eliminate the risk of onward transmission. (This is the strategy used in rich countries to cure latent tuberculosis.)

Gilead's license is not likely to be well designed to end the HCV pandemic. The license will predictably fail to reach the majority of people living with HCV. Gilead's market fragmentation approach will lead to higher than necessary prices and ultimately to less than universal access. That means that this license will, in all probability, miss both the target of worldwide equitable access to treatment and the ultimate goal of eventual HCV eradication. Many additional efforts will be needed to achieve eradication, including improved diagnostics and linkages to care and

¹¹ *Gilead Close to Sending \$84,000 Drug to Poor Countries*, Bloomberg (Sept. 5, 2014) available at <http://www.bloomberg.com/news/print/2014-09-04/gilead-close-to-sending-84-000-drug-to-poor-countries.html>.

¹² Hanafiah K Mohd et al., *Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence* 57:4 *Hepatology* 1333-42 (2013).

improved therapies.¹³ Also important will be efforts to address the needs of most affected populations, most especially people who inject drugs who require massive scale-up of harm reduction programming, removal of structural barriers to treatment, and measures that address stigma and discrimination and advance a human rights based approach. None of these other efforts will come to fruition, however, unless Gilead and other DAA producers make their therapies universally available and affordable.

¹³ Wei, L. and Lok, ASF. Impact of New Hepatitis C Treatments in Different Regions of the World. *Gastroenterology*. Published Online: March 21, 2014 DOI: <http://dx.doi.org/10.1053/j.gastro.2014.03.008>. Available at: [http://www.gastrojournal.org/article/S0016-5085\(14\)00357-6/fulltext](http://www.gastrojournal.org/article/S0016-5085(14)00357-6/fulltext).

Barriers That Need to Be Overcome to Achieve HCV Eradication

Detect persons who are infected

Identification of high-risk/high-prevalence groups

Availability of sensitive, specific, and affordable tests for screening and for confirmation of infection

Screening programs that are practical and tailored to individual countries or settings

Public awareness of risk groups, sequelae, and treatment options

Link infected persons to care

Access to care for all infected persons

Availability of trained health care providers and resources to manage infected persons

Eradicate HCV with safe and effective drugs

Development of drugs that are potent, safe, and have pangenotype activity

Development of treatment regimens that are simple and effective against all HCV genotypes and all stages of liver disease

Availability of safe and efficacious drugs at affordable price