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Chapter 5 : A consortium in times of crisis: producing Brazilian sofosbuvir? (2014-2017)

Maurice Cassier & Marilena Correa

Introduction

In early 2014 the pharmaceutical firm Gilead put a radical new therapeutic innovation for hepatitis C, sofosbuvir, on the US market at US\$84,000 for one 12-week treatment. This price was based not on the molecule's innovation and production costs, but on the maximum price that public and private organizations would agree to pay¹. In September of that year, the multinational announced a policy of voluntary licences for seven generics producers in India who could sell their products, but only to a list of 91 low-income countries. This system excluded Brazil, both as a producer and as a user, even though there was a high prevalence of hepatitis C in that country. During a parliamentary hearing in April 2014, Eloan Pinheiro, head of the federal pharmaceutical laboratory Farmanguinhos from 1992 to 2002, who had spurred the production of national generics to supply the government's policy of universal access to antiretrovirals for Aids, alerted the members of parliament as to this new barrier to access to treatment for many patients with viral hepatitis². In parallel, the Oswaldo Cruz Foundation and a private-sector pharmaceutical laboratory approached the company Microbiologica and its founder, Jaime Rabi, when they heard about its past cooperation with the firm Pharmasset in the early 2000s, during the initial development stages of sofosbuvir. They wanted to know whether Rabi, who had been the first Brazilian to copy AZT at the beginning of the 1990s, could envisage the production of a national sofosbuvir to supply the Health Ministry. The director of innovation at the Oswaldo Cruz Foundation had in mind reproducing the model of the consortium that had produced efavirenz locally from 2007, under compulsory licence. The consultant Karin Bruening, who had worked alongside Eloan Pinheiro at Farmanguinhos, initiated a partnership between Microbiologica and Blanver, a private firm that had entered the ARV domain in 2010, after Gilead's patent on tenofovir had been cancelled in 2008. Civil society organizations, the HIV/Aids patient organization ABIA, and the Working Group on Intellectual Property, the GTPI³, that had led the battle against Gilead over tenofovir in the mid-2000s, mobilized again to demand cancellation of the patent on sofosbuvir, in the absence of a compulsory licence. They petitioned the government with "demands that the Brazilian government immediately begin efforts to enable the production of sofosbuvir by the public sector"⁴. Finally, in May 2016, the Oswaldo Cruz Foundation announced an agreement with the private consortium BMK (Blanver-Microbiologica-Karine Bruening) to develop and produce a generic sofosbuvir. In the meantime, since 2014, Brazil had gradually entered a phase of profound industrial, financial and political crisis.

In this chapter we examine six aspects of the setting up of this consortium during a period of crisis: 1/ the industrial property situation; 2/ the formation of the industrial

¹ "The price of Sovaldi and its impact on the US Health Care System" Committee on Finance, United States Senate, December 2015, 144 pages.

² CÂMARA DOS DEPUTADOS, COMISSÃO DE SEGURIDADE SOCIAL E FAMÍLIA, junho de 2014, p 78.

³ GTPI/Rebrip: "Working Group on Intellectual Property of the Brazilian Network for the Integration of Peoples": cf. Chapter 8.

⁴ Statement of Brazilian CSO (GTPI) on Gilead VL on sofosbuvir, September 22, 2014.

consortium; 3/ the unusual technological situation, which was not comparable with the practice of reverse engineering that Brazilian manufacturers had adopted until then to produce generics; 4/ the creation of new knowledge and new technologies during the development of production; 5/ the crisis of the Brazilian social state and its impact on the consortium devoted to sofosbuvir; 6/ the sudden appearance of the DNDI in the field of hepatitis C, and its relations with the BMK consortium⁵.

1) The uncertainties of the intellectual property situation: opposition still pending

To control the global market for sofosbuvir, Gilead cast its nets wide: a list of 15 patents on substances and processes, filed with the INPI, was recorded at the Brazilian Health Ministry⁶. The firm also set up a system of voluntary licences for a limited number of producers in India who could supply certain low-income countries, selected by Gilead. The founder of Microbiologica pointed out the highly strategic nature of these voluntary licences which allowed Gilead to control Indian producers: “Gilead has a very intelligent market viewpoint to give voluntary licenses to Indian companies because the Indians are the strongest in the world to produce the API” (interview 2016). He immediately stressed the difficulty for Brazil: “Gilead provides a voluntary licence to India and doesn’t provide one to Brazil: India doesn’t treat its patients and Brazil does treat its patients”. Hence, the strong reaction by patient organizations, which denounced this exclusion of Brazil when the price proposed by Gilead in 2014 was \$7,000 per treatment: “Brazil is excluded from a license authorizing the production of generic medicine for hepatitis C” (GTPI, September 2014).

To open the space of local production of sofosbuvir, three legal oppositions were filed at the INPI, calling for cancellation of the patent: the first by the civil society group GTPI, in May 2015; the second by the firm Blanver, a member of the BMK consortium, in December 2015; and finally the third by the state-owned Farmanguinhos laboratory, in February 2017. Civil society groups, primarily the HIV/Aids patient organizations, and the Oswaldo Cruz Foundation, waged their first battles of legal opposition to medicine patents in 2005, when they challenged Gilead’s patent on tenofovir. The firm Blanver used the opposition process as a strategic tool to authorize the production and sale of the consortium’s generic medicine, and to recoup its R&D investments. In a hurry to produce, Blanver even put forward the idea of resorting to a compulsory licence. Like other oppositions filed in the world against Gilead’s patent, its opponents challenged above all the novelty and inventiveness of the invention, which they claimed had been disclosed by several earlier publications and patents, in a highly competitive research field⁷. It is interesting to look at the circulation of arguments between opponents across the world, especially between the Indian opponents, led by I-MAK, an NGO of jurists, and Egyptian and Brazilian opponents. This circulation started at the end of the 2000s when Indian and Brazilian experts and activists met in Rio de Janeiro to attend a seminar on learning to write up opposition procedures.

⁵ We studied the formation of this consortium from 2014, through on-going interaction with the main protagonists: Jaime Rabi from Microbiologica, the consultant Karin Bruening, the company Blanver, the head of innovation at the Oswaldo Cruz Foundation, Jorge Costa, the patent expert Wanise Barroso, who had prepared the opposition document to Gilead’s patent for Fiocruz, and Eloan Pinheiro, the DNDI’s consultant who had worked for several years with viral hepatitis patient organizations.

⁶ Application for priority examination of the sofosbuvir patent, Ministry of Health, 20 April 2016.

⁷ This was the case of the opposition filed in India by I-MAK and in Europe by Médecins du Monde.

Note that the patient organizations engaged in opposition to the sofosbuvir patent were rallied around HIV/Aids, and not viral hepatitis. They already had extensive experience in the intellectual property battlefield. Yet some of these organizations did move closer together, notably the viral hepatitis patients and the neglected diseases movement, under the leadership of Eloan Pinheiro, who organized talks on the topic of patents and access to treatment⁸. Things came together at the 10th HIV/Aids conference in July 2015, when the chairman of the Brazilian movement to combat viral hepatitis (MBHV) spoke out against the barriers to access to new molecules, whereas Gilead had recorded \$23bn of sales for sofosbuvir alone⁹. Yet, while the leader of the hepatitis group in the economically important city of Santos, in São Paulo State, had considered the possibility to engage in legal proceedings¹⁰, the organization finally decided not to join the struggle against the patent at the INPI.

The opponents of the Gilead patent were supported by the Oswaldo Cruz Foundation and the Ministry of Health, in April 2016, when the minister asked the INPI to carry out a priority examination of patents on sofosbuvir with regard to the insufficient number of persons treated until then, and the retail prices of the proprietary medicine that were incompatible with the state of public finances and Brazil's "financial crisis". Jorge Bermudez from Fiocruz justified the demand for a priority examination by the bottlenecks and slow pace of medicine patent examination at the INPI, which was equivalent to an extension of the commercial privilege of sofosbuvir¹¹. In March 2017 the examiners at the sanitary security agency ANVISA issued a negative opinion on the Gilead patent. The National Health Council¹² likewise put out recommendations that month, supporting national production as a solution, along with opposition by civil society, local producers and the federal laboratory.

The firms in the BMK consortium, which had already produced the first batches of sofosbuvir, were in a situation of intense legal insecurity: 1) the INPI had still not made a decision, which meant that Gilead maintained the monopoly¹³; 2) they feared that in case of cancellation of the patent, Gilead would go to court: "they will go to a second instance: it is really dangerous for those who produce sofosbuvir in Brazil because you still have a possibility in the future a judge decides in favour of Gilead S" (J. Rabi, 2016); 3) a compulsory license as a solution, as in 2007 for efavirenz, was highly uncertain in the context of the country's weakening position: while Lula's Brazil had been able to deal with a tug of war with Merck, Temer's Brazil most likely had neither the power nor the political will to tackle Gilead; 4) BMK was also concerned about the government possibly entering directly into negotiations with Gilead, as the company might then reduce its prices and ruin the

⁸ Conhecendo a Lei de Patentes e a posição do Brasil no atual cenário da incorporação de medicamentos', march 2, 2015.

⁹ Sociedade civil realiza ato público em defesa do tratamento da Hepatite C em João Pessoa, juillet 2015, ABIA.

¹⁰ « Dificil acesso à cura das hepatites é debatido no Encontro Regional de Inovações na Prevenção, em Santos » avril 2016.

¹¹ Letter dated 8 April 2016, Fiocruz.

¹² The National Health Council was founded in 1990. It participates in the discussion and government of the public health policies in Brazil, in interaction with the Ministry of Health. Composed of representatives of movements of users (50%), health care professionals (25%) and representatives of the Ministry of Health (25%), it represents an institution of the sanitary democracy of Brazil.

¹³ Everything is not blocked in this field. A few months earlier, in January 2017, the INPI in Brazil invalidated Gilead's patent on Truvada, thus making generics production legal.

consortium's production (Gilead's buyout of the company Pharmasset that had developed sofosbuvir had long since been recouped), or establishing a product development partnership (PDP) that would circumvent it¹⁴. This seemed probable in light of the fact that for a while Gilead had been close to signing an agreement with the public laboratory Bahiafarma, in order to short-circuit the consortium. BMK was moreover envious of the situation of its Argentine counterparts, who benefited from highly favourable jurisprudence that allowed them to start producing a medicine for which the patent had not yet been delivered, without risking a fine¹⁵. Presently, three national manufacturers supply the Argentine Ministry of Health with generics, in parallel to purchases of Gilead's sofosbuvir.

2) Constitution of the industrial consortium

The creation of the private consortium BMK benefited from an impetus from several sources in 2014. The director of innovation at the Oswaldo Cruz Foundation, who had worked with Jaime Rabi in the 1980s, contacted him to see how willing he would be to produce sofosbuvir in Brazil, in cooperation with the Farmanguinhos laboratory: "we had in mind the management model of the efavirenz consortium: we thought that we'd reproduce that model". He also wanted to ensure that no secret agreement had been made around the sale of Pharmasset, in which Jaime Rabi had shares, and that might have prevented it from producing sofosbuvir. In parallel, the pharmaceutical consultant Karin Bruening, a chemical engineer at the head of Farmanguinhos' formulation team in the early 2000s, and who worked for the private firm Blanver, thought of approaching Microbiologica when she learned that Rabi had cooperated with Pharmasset. Her project consisted in combining Microbiologica's R&D resources and Blanver's industrial growth projects. The BMK consortium mobilized several generations of firms: Microbiologica, an academic spin-off founded in 1982 and specialized in nucleoside chemicals; Blanver, specialized in the production of excipients and a new entrant on the playing field of antiretrovirals in the framework of PDP growth, under the impetus of the Ministry of Health, since 2010; and the consulting firm K. Bruening, which was helping Blanver to broaden its range of products in the HIV and hepatitis field. These experts' trajectories fostered cooperation between public and private laboratories.

The BMK consortium has thus brought together two industrial firms with very different and therefore highly complementary profiles. The first, Microbiologica, is a science-based company that creates synthesis technologies in the field of nucleosides (it owns a patent on which it has granted a license to Novartis¹⁶). It is a spin-off of the chemistry department at the federal university of Rio, and was part of North-American innovation networks, alongside two leading companies in the field of antivirals, Idenix, bought out by Merck, and Pharmasset, bought out by Gilead. During its cooperation with Pharmasset and Idenix, Microbiologica even had a research team in the EU. The second company, Blanver, is a family concern initially specialized in excipients, which has industrial growth projects in chemicals and pharmaceuticals. It is highly internationalized on the excipients market. Yet its

¹⁴ We will see further on that Gilead followed this strategy with regard to the list of PDP projects published by the Ministry of Health on 10 August 2017.

¹⁵ "Sofosbuvir is registered by the originator company in Argentina but is not under patent as the applications are under review. This has allowed a local company to produce generic sofosbuvir. In Argentina, the price per patient-month for sofosbuvir from the local generic producer is US\$ 501 (versus US\$ 2086 for sofosbuvir from the originator company)", WHO, Global Report on Access to Hepatitis C Treatment: Focus on overcoming barriers, October 2016.

¹⁶ Methods of manufacture of 2'-deoxy-beta-L-nucleosides, US Patent Application No: 2004/0266996.

entry into pharmaceuticals was relatively recent and its R&D team is still fairly small, albeit growing. These two companies' cooperation within the consortium can facilitate two dynamics: the sofosbuvir consortium's support for a process of nationalization of Microbiologica's R&D, which is now used more to enhance Brazil's industrial strength and to supply the Ministry of Health; and Blanver's acquisition of valuable knowledge and know-how in highly sophisticated pharmaceutical technologies.

The agreement signed in May 2016 between the BMK and the Oswaldo Cruz Foundation was designed to further the development of sofosbuvir and its registration at ANVISA, the national sanitary security agency. The division of work in the development of the medicine involved the various partners' expertise: Microbiologica was charged with developing the synthesis of the active principle (it masters the 14 steps in the synthesis of this molecule) and producing it on an industrial and semi-industrial scale. The first industrial batches were produced in 2016 and tested for stability. Microbiologica also provided the analytical data. Karin Bruening and Blanver were responsible for developing the formulation technology and running the stability tests. In this agreement, the Oswaldo Cruz Foundation was responsible for the bioequivalence studies, which would be carried out by its laboratory, the CEFAR. Although it was planned that the federal laboratory would receive the formulation technology to produce the final medicine in the future, it did not participate in the actual development. At the first meetings in 2014, to which it was invited, Farmanguinhos declined the offer to participate in the R&D work. This is a profound difference compared to the efavirenz consortium set up in 2007, in which the federal laboratory had coordinated the development work and supervised the production (cf. Chapter 2). It had even initiated the reverse engineering of efavirenz – as a result of which Merck sued it. Here, the State as an industrial entrepreneur appears less active than in 2007, even though it is involved in a large number of PDP¹⁷.

3)The originality of the technological situation: a Brazilian firm historically linked to Pharmasset

The profound originality of this project stems from the fact that the leading Brazilian firm in the consortium, Microbiologica, was an “insider” of the sofosbuvir innovation network. This particular situation was described by Jaime Rabi when we interviewed him in April 2003. He pointed out that, faced with competition from Indian producers on ARV copying, he had decided in 1998 to stop investing in reverse engineering and to join innovation networks: “we stopped doing investment in reverse engineering ... and we took another decision, that was to get involved in innovative work ...we started a strategic alliance in the United States. We put together a discovering company”. In 1998 Jaime Rabi was a Board member at Pharmasset. In 2000 a Pharmasset communiqué announcing an alliance with Samschully, a firm producing nucleosides, noted Pharmasset's partnership with Microbiologica and cited Jaime Rabi, who spoke on behalf of Pharmasset: “Dr. Jaime A. Rabi, CEO of Microbiológica Química E Farmacêutica, Ltda., a nucleoside manufacturer in Brazil and an early strategic partner of Pharmasset, said ‘today, more than ever, the product

¹⁷ The federal laboratory nevertheless reappeared as an industrial partner in March 2017 when ANVISA issued a negative opinion for the granting of Gilead's patent. A declaration by the Oswaldo Cruz Foundation highlighted it: “Anvisa e Farmanguinhos são contra a patente do sofosbuvir”, 28 March 2017. In February 2017, FM also filed an opposition to Gilead's patent, with the INPI. In August 2017, FM was involved in three PDP with the BMK consortium, to produce hepatitis C antivirals.

innovation provided by Pharmasset is the driving force that moves the pharmaceutical industry. We welcome the new strategic partnership between Pharmasset and Samchully, a world-class producer of nucleosides. We expect that the integration of our core competencies will provide the necessary expertise and velocity to help Pharmasset become a world leader in antiviral and anticancer therapy development." Jaime Rabi was thus anticipating future therapeutic innovations.

More precisely, in its cooperation with Pharmasset, Microbiologica played a decisive role in the organization of work, developing the production processes of new molecules invented by Pharmasset. Microbiologica was responsible for the process innovations: "So, our participation in this strategic alliance is because of our expertise in nucleic acid process chemistry" (interview 2003). Microbiologica participated in the first R&D phases of sofosbuvir, before the research was repatriated to the US in 2003-2004. Even though Jaime Rabi's patent does not correspond precisely to the sofosbuvir synthesis, it is cited in Gilead's patents on sofosbuvir, filed in 2012; for instance the patent US8889159 B2 titled: "Compositions and methods for treating Hepatitis C virus". Rabi nevertheless insisted on the wide gap between process and product innovation. To participate in the invention of new therapeutic substances, Brazil had to reinforce its scientific organization, especially the multi-disciplinarity of its discovery teams and its investments in basic research.

In this context, it is clear that the development of the sofosbuvir synthesis process was neither too complex nor too long for Microbiologica, even if some adjustments were needed to produce the same polymorph as Gilead's. Microbiologica actually produced sofosbuvir very quickly, and samples were even used by the Oswaldo Cruz Foundation for their biological research.

Considering this technological advance and former relations with Pharmasset, in 2014 Jaime Rabi would have liked to have a voluntary licence with Gilead. This would have facilitated new technological learning and possibly technology returns for Gilead, as we will see later in this chapter. Until then, Gilead's strategy regarding intermediate countries like Brazil had nevertheless excluded this possibility. While the US company granted voluntary licences to India, to avoid any challenges to its own property rights in that country, it excluded Brazil from the field of beneficiaries of these licences and of the generic products produced under them¹⁸.

In 2016, another US firm contacted Microbiologica, to produce two new nucleosides. This confirmed its technological reputation, based on its past cooperation with Pharmasset: "right now, there is another company in the US that is talking with me about the possibility of producing two nucleosides for new applications: why they came to talk to me? Because they learn about the Pharmasset history" (interview, 2016).

4) When the BMK consortium created new knowledge on sofosbuvir and new technologies

The project to develop and produce sofosbuvir in Brazil did not only lead to the creation of a new industrial organization and to the first batches of products, ready for

¹⁸ There has nevertheless been a change in Gilead's stance regarding intermediate countries: at the end of August 2017 it added four intermediate countries to the list of those that benefit from generic sofosbuvir: Malaysia, Thailand, Ukraine and Belarus. And it has just negotiated a partnership with a private-sector firm and a Brazilian government laboratory (Ministry of Health, 13 August 2017).

commercialization. The BMK consortium, associated with Fiocruz, generated new knowledge and new technologies in two areas: the discovery of new sofosbuvir polymorphs, and the discovery of a new therapeutic use for sofosbuvir, which could moreover be used to treat the new epidemic that hit Brazil with the Zika virus.

The development of the sofosbuvir synthesis and the production of the first industrial batches led to the discovery of two new polymorphs of the molecule. Jaime Rabi characterized as follows this process of innovation through use of the technology: “the number one issue is that you exercise the technology; if you don’t exercise the technology, you don’t learn the details of it” (2016). Because these discoveries were made in an industrial context, they remained secret. It turned out that it was industrially more productive to synthesize one of the polymorphs characterized by Microbiologica. Yet, without an industrial agreement with Gilead, this discovery could not be used as long as the polymorph discovered by Microbiologica could not be certified as equivalent to Gilead’s product and thus qualified as a generic. Jaime Rabi lamented the fact that there was no agreement with Gilead to generate mutual benefits: “the leader company cannot take advantage of this discovery, and indirectly the people; multinationals don’t see the possibility that local producers will be able to develop science and technology better”.

The second discovery concerned the use of sofosbuvir to combat the Zika virus. It was the consultant Karin Bruening who first thought of testing sofosbuvir on this virus¹⁹. The research was carried out in several biology laboratories at Fiocruz and at the Farmanguinhos research laboratory. The first draft of the international publication is dated July 2016 and two articles were published in *Nature* in 2017. The BMK consortium was cited in both articles as the donor of the sofosbuvir samples: “The antiviral drug sofosbuvir (β -D-2'-deoxy-2'- α -fluoro-2'- β -C-methyluridine) was donated by the BMK Consortium: Blanver Farmoquímica Ltda; Microbiológica Química e Farmacêutica Ltda” (Carolina Q. Sacramento and al, 2017) and Karin Bruening signed the publications. The discovery of this new therapeutic use contributed towards “Brazilianizing” the molecule a little more, insofar as it was henceforth included in the struggle against the epidemic that has strongly affected Brazil since 2015. It has mobilized both the country’s scientific resources and its new industrial resources that were used to produce the tested samples. In this context, sofosbuvir is becoming an essential medicine for treating both hepatitis C and a tropical disease. This discovery provides an additional argument in the fight for access to treatment and for initiatives to nationalize production of the molecule.

5) Crisis of the social State and maintenance of the health industry complex policy

The BMK consortium was set up in a context of break down due to the industrial, financial and political crisis, which spread from 2014 onwards. Compared to the efavirenz consortium set up in 2007 (cf. Chapter 2) and the sofosbuvir consortium in 2016, the Health Ministry has been less committed in the industrial property field and in the establishment and governance of the consortium. Yet the recent publication of a list of 83 Product Development Partnerships, proposed in 2017²⁰, thirteen of which are dedicated to the local production of new hepatitis C antivirals, shows the resistance of the policy of local production of medicines considered to be essential for public health.

¹⁹ Gilead’s patents cite the Zika virus as one on a list of potential targets, but without any further demonstration of this therapeutic application.

²⁰Informações sobre as novas propostas de Parcerias para o Desenvolvimento Produtivo para o ano de 2017, Brasília, 10 de agosto de 2017.

We have seen that the creation of the industrial consortium in 2007 to produce Merck's efavirenz locally was based on strong State intervention to nationalize the invention by way of a compulsory licence decree, and then to create the consortium and coordinate both the development of the technology and the details of its production. While the Oswaldo Cruz Foundation endeavoured to repeat this process in 2014 for sofosbuvir, the Health Ministry's action was more limited and uncertain. First, the director of innovation at the Foundation noted that the Farmanguinhos federal laboratory had withdrawn from all technology development work during the first meetings with the private companies in 2014. Second, the first opponents to Gilead's patent were the private firm Blanver and the non-governmental organization GTPI, in early 2015, whereas it was not until February 2017, two years later, that the federal laboratory filed an opposition with the INPI. Although the Health Ministry was not inactive (it intervened in April 2016 to demand that the INPI carry out a priority examination of the patents on antivirals for hepatitis C), it was no longer the spearhead in the struggles for access and the demands for compulsory licences, as it had been in the 2000s under the authority of José Serra in 2001 or under Lula's presidency from 2002²¹. Instead, calls for a compulsory licence on Gilead's patent came mainly from civil society organizations or private companies such as Blanver, in December 2016. The members of the private consortium BMK were waiting for tangible signs of the Health Ministry's political will to support the project. They waited for long months for the Health Ministry to provide them with 25 vials of Gilead's sofosbuvir to serve as reference samples in the bioequivalence study carried out by the Oswaldo Cruz Foundation. The 25 vials eventually arrived in early 2017 and the bioequivalence results are expected in December 2017, a full year later than the date set in the agreement between the consortium and the Oswaldo Cruz Foundation. We can see these delays as signs of political instability and staff changes, as well as more profound tensions between the wish to collaborate with the multinationals and the wish to defend local production and oppose patent barriers: "if the government has no interest or had made some agreement with Gilead at this point; because there are two different ideologies in the government» (interview, December 2016); "I think that Gilead Sciences has already negotiated lower prices for the Ministry of Health". The crisis was thus a time of revival of ambivalences and conflicts between a political wish for autonomous development, and special agreements with the multinationals, evidenced in the country's contemporary history (Furtado, 1973, Evans, 1974).

At the same time, despite these hesitations and delays, the local production of sofosbuvir and of this new class of medicines seems to be becoming more real at the end of 2017. The 10 August publication, by the Health Ministry, of 83 Product Development Partnership proposals attests to the continuity of the Health Industrial Complex programme to produce so-called strategic medicines for Brazil (Flynn, 2015, Viana and al. 2016)). No fewer than 13 proposals concern the local production of antivirals for hepatitis C: 4 for the production of Bristol Myers Squibb's daclatasvir; 4 for the production of Janssen's simeprevir; and 5 for Gilead's sofosbuvir.

These PDP cover two types of economic device. The first type consists of partnerships between a public laboratory and national private laboratories. For instance, the firm Cristalia proposed three PDP to produce sofosbuvir, with three different public laboratories. The

²¹ In September 2011, Brazil's president, Dilma Roussef, reaffirmed at the UN the advantages of using the "flexibilities" of the TRIPS agreements in the public health field, and especially compulsory licences: "Brazil guards the compromises regarding intellectual property but we are convinced that the flexibilities foreseen in the TRIPS of the WTO, in Doha's Declaration about TRIPS and Public Health and in the global strategy for public health are indispensable for policies that guarantee the right to health".

private consortium BMK likewise proposed three PDP, in collaboration with the Farmanguinhos federal laboratory, to produce sofosbuvir, daclatasvir, and simeprevir. These PDP correspond to cooperation between Brazilian public and private laboratories.

The second type of device corresponds to a very different kind of alliance between a public laboratory, the LAFEPE, a Brazilian private firm, Nortec, and the multinational Gilead, which owns the patent on sofosbuvir.

In the case of the PDP set up between the BMK and Farmanguinhos, producing locally implies removing the obstacle of Gilead's patent, either through its refusal by the INPI, or by a compulsory licence decision, which is unlikely at present, or else by a voluntary licence granted by Gilead, which is what Jaime Rabi would prefer. In the case of the PDP between Lafepe, Nortec and Gilead, the intellectual property situation has been resolved by a voluntary licence agreement.

It turns out that the competition from the BMK consortium eventually compelled Gilead to negotiate a voluntary licence agreement for local production in Brazil. The members of the consortium had anticipated this solution, which is why they moved closer to Fiocruz: "we think the patent situation is moving on, so we are afraid that if we do not sign a PDP someone will come up with the idea and will steal our position; and say I want to do the PDP; Gilead can also do the PDP" (BMK, December 2016). They were concerned about the emergence of competition from the other public and private laboratories involved in the PDP policy since 2010. This competition has now proved to be real. The BMK consortium hopes that the agreement it negotiated with the Oswaldo Cruz Foundation in May 2016 puts it in a favourable position to be chosen by the government, and it is counting on its technological and industrial advance. As we have seen, it has already produced sofosbuvir on an industrial scale, has provided samples as research material, and the bioequivalence results should enable it to register its product as a generic at Anvisa. One uncertainty remains, however: the INPI has still not given its answer on the three oppositions to the sofosbuvir patent. Yet the establishment of a PDP requires that the situation regarding property rights be sorted out. The question of price can also be thorny, as Gilead has entirely recouped its investments and can therefore offer a relatively low price.

This new list of PDP published in August 2017 shows that the policy of local production is being pursued. It confirms the emergence of a pool of public and private Brazilian laboratories that have acquired sufficient technological and industrial capabilities to develop and produce pharmaceutical technologies as sophisticated as sofosbuvir. And this time one of the players in the invention of this technology, Microbiologica, is a laboratory from the South that is a member of networks in the North.

6) The DNDI's irruption in the hepatitis C field and in that of the BMK consortium

As noted above, the arrival of sofosbuvir on the market revived conflict for access to treatment on a global scale²². MSF was prompted to become involved, in order to explore solutions with regard to intellectual property and the production of generics. In a document dated May 2015, the NGO added the BMK consortium in Brazil to the list of generics manufacturers wanting to produce sofosbuvir²³. MSF's wall-less laboratory, the DNDI, also

²² Hepatitis C drugs re-energize global fight over patents, *Nature* 543, 17–18 (02 March 2017)

²³ Preliminary list of generics manufacturers with an interest in sofosbuvir production, MSF, May 2015. MSF also published an article in *The Lancet* on the prices and competition of

decided to intervene in the field of hepatitis C and to supply new antivirals²⁴. It undertook clinical trials in Malaysia and in Latin America to test the efficacy of the molecules on the most prevalent genotypes in these regions. The DNDI also negotiated an agreement with an Egyptian producer, Pharco, for a sofosbuvir-based combination priced at US\$336. It furthermore obtained a non-exclusive licence from a laboratory in the US, Presidio, to register, produce and distribute in low- and moderate-income countries a new antiviral, ravidasvir, that can be combined with sofosbuvir. In 2016 the DNDI visited the BMK consortium companies to propose a licence that would enable them to produce the sofosbuvir-ravidasvir combination. The link between the DNDI and the BMK consortium was facilitated by the DNDI's strong foothold in Brazil (a regional office with a staff of 16, located in Rio), and the fact that Eloan Pinheiro, the former director of Farmanguinhos, had been instrumental in the creation of the DNDI in 1999, and is now a consultant for it²⁵. The implementation of this type of agreement between the DNDI and the BMK would facilitate the exportation of this combination, as well as its certification by the WHO with the prequalification procedure to which the DNDI gives precedence. This would be new for Brazil, which until now has intended its generics mainly for the domestic market. The crisis may also spawn original solutions.

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²⁴ An alternative research and development strategy to deliver affordable treatments for Hepatitis C patients, DNDI, April 2016.

²⁵ The DNDI had already collaborated with Farmanguinhos in the 2000s to develop an artemisinin-based combination for malaria: "Needs driven versus market driven pharmaceutical innovation: the consortium for the development of a new medicine against malaria in Brazil", K Kameda, *Developing World Bioethics*, 2014.

