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Between financial capitalism and humanitarian concerns: value, price and profits of hepatitis C antivirals and artemisinin-based combinations therapies for malaria

Maurice Cassier, CNRS, june 2016

When sofosbuvir, an effective direct-acting antiviral for the treatment of hepatitis C virus, was put on the market in 2014, huge controversy broke out on the value of medicines and the profits derived from them. In countries of the global North, parliamentary inquiries had shown possible restrictions on access to treatment, and had highlighted the attendant risk of breakdown of the compromises reached since the 1940s between health insurance schemes, the right to health, and pharmaceutical profits – compromises that Michel Foucault had pointed out in 1974 in a lecture series on the birth of social medicine¹. The US Senate commissioned an inquiry into the price of sofosbuvir, sold at \$85,000 for a 12-week treatment, and in September 2014 the French Ministry of Health pointed to the threat of a compulsory license, at which Gilead agreed to reduce the price from \$56,000 to \$41,000². In countries of the South, the advocates of access to HIV/Aids treatments denounced the new price barriers to medicines for the poorest populations. They immediately filed

¹ « Crise de la médecine ou crise de l'antimédecine ? » ; « La naissance de la médecine sociale » ; « L'Incorporation de l'hôpital dans la technologie moderne », Dits et Ecrits tome III, 1976-1979, Gallimard 1994.

² In France, the *Haute Autorité de Santé* (HAS) drew attention to the risks of breakdown of the Social Security system, fearing “the significant budgetary impact of these products and the risks that the national solidarity system may not cover other treatment consequent to that” (June 2014). In June 2015 the report of national health insurance (*Assurance Maladie*) report pointed out the same fragility: “The arrival of new hepatitis C treatments has set off a shock wave in all health systems. For the first time, the question of access to innovative medicines has arisen, not for developing or emergent countries, but for the wealthiest ones”.

petitions to have the patents cancelled so that generics of the new antiviral could be produced, mainly in India, Egypt and Brazil. Michel Kazatchkine, former director of France's national Aids research agency (*Agence Nationale de Recherche sur le Sida*), and of the Global Fund for Aids, Tuberculosis and Malaria, summed up the situation as follows: "If the prices [of new VHC treatments] were to be once again unaffordable, it would be one more scandal around inequity of access to health care"(Michel Kazatchkine, the United Nations Secretary General's Special Envoy on HIV/AIDS in Eastern Europe and Central Asia)³.

During the same period, in March 2014, Sanofi and the foundation set up by MSF, Drugs and Neglected Disease Initiatives (DNDI), based in Geneva and on several continents, received the Corporate Social Responsibility Excellence award from the Association of Strategic Alliance Professionals (ASAP) for the development and distribution of ASA, an artemisinin-based combination therapy used to treat malaria in endemic areas where there was resistance to former treatments, especially in sub-Saharan Africa. In 2004 Sanofi and DNDI had signed a partnership agreement to industrialize the new fixed-dose combination, the formulation technology of which had been developed at Bordeaux University in France, and had not been patented. The contract stipulated that it was to be distributed in the public sector at a maximum price of \$1 for the adult formula and \$0.5 for the paediatric formula: "Partnership agreement between DNDi and Sanofi to jointly develop ASAQ Winthrop®, a non-patented ASAQ FDC to be sold at cost plus a small margin" (DNDI, 2015). MSF/DNDI and Sanofi have maintained their agreement on the price of ASAQ

³ In April 2014, *Nature* ran an article titled: "Hepatitis C drugs not reaching poor", 17 April 2014, p. 295-296.

since 2004, in a context of declining prices and competition opened by Indian and Chinese generics that came onto the market in 2012.

In the story of ASAQ's invention that MSF published in October 2015, it congratulated Sanofi for its policy and its "Access to medicines" programme that had been instrumental in down-regulating prices of the entire class of ACTs, as it compelled Novartis to reduce the price of its leading drug, Coartem, composed of artemether and lumefantrine. Simultaneously, the DNDI announced in April 2016 that it was set to produce a sofosbuvir generic for hepatitis C, in partnership with an Egyptian manufacturer, at a price of just under \$300. This thwarted the strategy of Gilead, which owned the molecule and had offered its medicine to the Egyptian Health Ministry in 2014, for \$900. In the meantime the Egyptian patent office had cancelled Gilead's patent. The DNDI was alternately either the partner or the opponent of the pharmaceutical multinationals.

In this paper I draw a parallel between these two drugs and these two therapeutic classes, to examine the determination, discussion and regulation of the value and price of drugs and of the pharmaceutical industry's profits. To this end, I draw on the political and legal inquiries, reports and actions taken by governments, parliaments and firms in both the North and the South, as well as patient organizations, NGOs, and public- and private-sector payers, to contain or reduce these prices. I also draw on the survey published in December 2015 by the US Senate⁴, which provided a detailed description of the price-setting process of sofosbuvir, based on documents that Gilead had agreed to provide to the Senators. I was thus able to identify the matrix that links between drug prices and anticipation of share prices on the stock exchange, as well as tables

⁴ The price of sovaldi and its impact on the US Health Care System" Committee on Finance, United States Senate, December 2015, 144 pages.

of hypotheses of prices adjusted in relation to acceptance or refusal by doctors, patients and public- and private-sector payers, especially in the USA and Europe. I furthermore draw on accounting documents and financial analyses of the two firms involved successively in the development of sofosbuvir, Pharmasset and Gilead. Other sources include my own findings in France, during the preparation of legal proceedings instituted by Médecins du Monde in February 2015, to have the sofosbuvir patent cancelled by the European Patent Office. Finally, I use a survey initiated in November 2014 with my colleagues at the Oswaldo Cruz Foundation, Wanise Barroso and Marilena Correa, on the intellectual property battles and on projects for the manufacturing of sofosbuvir generics by Brazilian public- and private-sector laboratories. As regards ASAQ, I provide a synthesis of the surveys that I have led or conducted over the past few years concerning the invention and industrialization of this fixed-dose combination. These surveys were carried out on researchers collaborating with MSF and the DNDI, and researchers at the Sanofi division in charge of malaria and access to medicines, which I visited in February 2016. Finally, available data on the structure of the ASAQ market, provided by donors (Global Fund, WHO), are very precise⁵.

These two singular drugs, sofosbuvir and ASAQ, are prominent in the globalization of pharmaceutical products, but with very different configurations. ASAQ was developed on the initiative of MSF in the early 2000s, in an international consortium FACT (Fixed-Dose Artesunate Combination Therapy) that brought together scientific and pharmaceutical institutions from the North and the South, in France, the UK, Germany, Brazil, Malaysia, Thailand and Burkino Faso. It had been set up following the WHO recommendations published in 2001, prescribing the use of artemisinin-based

⁵ Cf. Malaria Medicines Landscape 2015, UNITAID, 117 pages.

combinationstherapies in endemic regions resistant to former treatments (chloroquine and sulfadoxine-pyrimethamine). Globalization has thus been a strong feature of the innovation, production and distribution of ASAQ. The basic ACT molecules were discovered in China, assembled in France, and tested in West Africa, and the combination is currently produced in Morocco, India, China and soon in Tanzania. ASAQ is distributed primarily in sub-Saharan Africa in the framework of the Global Fund, to treat “tropical” and “neglected” diseases. Sofosbuvir was invented by a private-sector research firm, Pharmasset, a spin-off of Emory University in the south-east of the United States. In 2011 the molecule was appropriated by a second firm specialized in HIV/Aids and hepatitis, Gilead, when it acquired Pharmasset’s shares. The geography of sofosbuvir use is potentially vast and concerns countries in both the North and the South. Some countries are strongly affected by hepatitis C, especially Egypt, where the prevalence rate is 18%. The medicine is applied to what is sometimes called “global diseases” that concern both the North and the South. The production of sofosbuvir, controlled by Gilead, is also found in many countries of the South, primarily for two reasons: first, in september 2014, in a context of mounting controversy over prices and access, Gilead organized a system of voluntary licences for Indian manufacturers, to supply a list of low-income countries that it had itself defined; second, generics producers in Egypt and Morocco embarked on copying sofosbuvir independently when the patent had been refused, as in Egypt, or had simply not been filed, as in Morocco.

The capitalistic and intellectual property (IP) configurations have been very different for the two drugs, which has had structuring effects on their values and prices. The sofosbuvir R&D and industry mobilized venture capital, as well as the new financial markets specialized in new technologies – in this

case the Nasdaq ; then banking capital and Gilead's own capital when it bought the molecule and invested in its industrialization and commercialization. By contrast, R&D on ASAQ was based primarily on funds from the public sector and philanthropic organizations, from The Republic of China, the DNDI, the *Agence Française de Développement*, and European Funds, while industrial capital was invested by Sanofi, with a rate of return close to nil, and by generics manufacturers in India and China. While the former biotechnological and pharmaceutical configuration made intense use of patent rights, both to mobilize capital and to capture innovation rents, the latter deliberately opted for a common goods regime without patents or exclusive licenses.

We will see that the capital and values, and the processes of price determination and regulation by profits, which were excessively high for Gilead and almost nil for Sanofi for this social or humanitarian pharmaceutical segment of the multinational's business, illustrate the polarization of capitalism and contemporary pharmaceutical markets. While multinational firms are the main actors of these economies, they have had to compromise with major public- and private-sector payers, Ministries of Health and law makers, patient associations and humanitarian organizations, which are involved both to challenge the monopoly price of sofosbuvir and to conduct and regulate innovation, especially in the field of neglected tropical diseases. The creation and regulation of drug values and prices sum up these multiple tensions between therapeutic use value and exchange values on product markets, between exclusive and common property, between financial capital and public or philanthropic funds, and between producers, governments and users.

1- Inflation of capital, social State and right to health: multiple conflicts over the value and price of sofosbuvir

While battles over prices and access to antiretrovirals for HIV/Aids focused primarily on developing countries, especially Brazil and sub-Saharan Africa⁶, with the year 2001 showing a peak in these conflicts, controversies over sofosbuvir prices spread in 2014 and 2015 and concerned health systems in both the North and the South. In July 2014, US Senators Wyden and Grassley sent a letter to Gilead CEO seeking information about how the company priced sovaldi :“Given the impact Sovaldi’s cost will have on Medicare, Medicaid and other federal spending, we need a better understanding of how your company arrived at the price for this drug. ... It is unclear how Gilead set the price for Sovaldi. That price appears to be higher than expected given the costs of development and production, and the steep discounts offered in other countries”. This letter requested the disclosure of documents on the determination of the medicine’s prices, including documents concerning the valuation of the R&D firm that had developed the molecule, Pharmasset, and its acquisition by Gilead. The senators had drawn up a detailed chronology of noteworthy actions and events in the process of determining the drug’s value and price⁷.

The report published by the US Senate in December 2015⁸ provides a detailed description of the process of sofosbuvir’s price formation, based on

⁶ Economics of AIDS and Access to HIV/AIDS Care in Developing Countries. Issues and Challenge, Edited by Moatti et al., ANRS, 486 pages.

⁷ The Senate’s letter contains a list of 21 questions, along with requests for documents that refer to precise events in the molecule’s history. For example, Question 4: “Please provide copies of Pharmasset’s revised forecasts (prepared before the American Association for the Study of Liver Diseases conference in November 2011) and all supporting documents, including but not limited to assumptions about the pricing and market for PSI-7977”.

⁸ “The price of sovaldi and its impact on the US Healthcare system”, US Senate, Committee on Finance, 144 pages.

documents that Gilead agreed to disclose. The rapporteurs indicated that they were unable to obtain detailed information on Gilead's costs in getting the drug to the market after buying out Pharmasset, the firm that had done the first scientific and clinical developments (p.3). The report clearly shows the disconnection between the combined R&D costs of these two firms, Gilead and Pharmasset, and the commercial earnings in 2014 and the first three quarters of 2015. Income from Sovaldi (sofosbuvir) amounted to \$26.5 billions in less than two years, while R&D investments from 2009 totalled no more than \$942m (Pharmasset had invested \$62.5m in the medicine's development between 2009 and 2011, and Gilead showed a budget of 880m between 2012 and 2014 for the development of sofosbuvir and three other molecules)⁹. As for the production costs, the senators noted that they were so small that some of Gilead's senior executives were not even aware of them¹⁰. It was therefore not there that the main explanation for the determination of the value of the pharmaceutical capital and the price of this drug lay. Here I will mention three main arguments and three types of instrument that Gilead provided to the senators.

The first was a matrix devised by a financial analyst for Pharmasset in November 2011, two days before the firm was bought out by Gilead. The matrix combines Sovaldi price hypotheses with hypothetical prices of the firm's shares. The share price that the owners of Pharmasset were to agree to was combined with a price of \$36,000 for this drug (the senators noted that Pharmasset's price hypothesis in November 2011, \$36,000 was way below that which was finally set by Gilead in 2013: \$85,000). The price of medicine was associated with the share price set for the buyout of Pharmasset. The actual

⁹ The price of sovaldi, op. cit., p.22 and 23.

¹⁰ "The price of sovaldi and its impact on the US Healthcare system", US Senate, Committee on Finance, 144 pages.

transaction took place on 20 November, at \$137 a share, and an acquisition of \$11.2bn. We can infer that the final price set by Gilead at the end of 2013, \$85,000, corresponds to a very higher value set for the financial capital. In fact, the market capitalization was \$142bn in 2014 while the firm's assets were valued at \$34bn in the balance sheet.

The second tool put forward to determine the price was based on cost/therapeutic benefit evaluations, compared to existing molecules and treatments for the same pathology. The use values of the various drugs or treatments were compared in terms of medical services, and their respective prices compared. Gilead based its price, which consequently structured the market, on claims of a "major innovation" in terms of therapeutic efficacy, with vastly improved healing rates and shorter treatment times than those of available molecules.¹¹ "Company officials surmised that its drug had a 'value premium' because of increased efficacy and tolerability, shorter treatment duration, and its potential to ultimately be part of an all-oral regimen (as it ultimately would be in combination with ledipasvir in Harvoni)". Gilead's price committee referred to the costs of treating hepatitis C with two antiviral molecules launched two years earlier by Merck (telaprevir) and by Vertex (boceprevir), used with ribavirine and interferon (molecules introduced in the late 1990s). This price fixing model depended on the past and on the state of the market, that is, on the prices of preceding or competing molecules. Earlier

¹¹ An article published in the JAMA on 13 August 2014 defended the "value driven" approach, which it contrasted with the "return on investment" approach to justify the high price of Sovaldi: "For instance, according to the average wholesale price from MediSpan, the cost of a 12-week course of sofosbuvir plus pegylated interferon and ribavirin is \$116 910.72. This price is expensive, but the cost of a 24-week course of the first-generation protease inhibitor telaprevir plus pegylated interferon and ribavirin is \$111,606.48, and the 48-week course that many patients need is \$143,827.92", T. Brennan, W. Schrank, "New Expensive Treatments for Hepatitis C infection", JAMA, vol 312, n°6, p 593-594.

prices and those of comparable products are regarded as “black boxes” and no information was provided to explain or regulate them. A letter to the editor of the JAMA noted: “However, overinflated prices of the alternative drugs are likely to make the cost-effectiveness of sofosbuvir appear more favourable” (Letters to the editor, JAMA, November 26, 2014 Volume 312, Number 20, p 2128)¹².

The firm used a third tool: a strategic analysis table, to assess the reactions of the organizations that paid for health care, as well as those of doctors, patients and activists (AIDS Health Foundation or Fair Pricing Coalition), to the various price hypotheses¹³. The payers’ reluctance and the restrictions on access that they were likely to apply were considered to be possible from \$60,000 and highly probable from \$95,000, whereas doctors might delay the treatment for certain groups of patients or oppose the price from \$60,000 and were very likely to do so from \$95,000. Patients’ and activists’ negative reactions and their impact on public opinion were considered to be likely from \$60,000 and very likely from \$80,000¹⁴. Gilead had commissioned consultants to carry out a survey on 90 public- and private-sector payers, in which the clinical data of the new drug were compared to existing treatments. The survey suggested that setting the price between \$80,000 and \$90,000 was ‘acceptable’ and did not limit access: “most payers

¹²Hence the limits of drug price-setting committees’ regulatory action, like that of the *Comité Economique des Produits de Santé* (health products economic council) in France. These committees focus on the therapeutic value of treatment, without opening the black box of the capitalistic value of therapeutic innovations, seen as taboo: “Faut-il changer le modèle financier de la recherche pharmaceutique ?”, (E. Fagon, vice-president of the CEPS, September 2014).

¹³ “Aside from payer access and physician demand, there are a number of softer issues that could affect pricing decisions”, Gilead document reproduced in the Senate report, page 30.

¹⁴ Gilead noted that even at \$50,000, activists would protest: “despite pricing at this level, activists are still likely to voice dissatisfaction with the strategy”, p 47.

are willing to accept at least \$85k for GT-1 before considering additional access restrictions” (page 41). The firm calculated that, despite their budgetary restrictions, payers would prefer a drug that had a noteworthy therapeutic advantage¹⁵. In view of this preference, it saw an opportunity to set a high price and to capture the cost savings that payers would gain a shorter treatment period, which sovaldi allowed: “The new sofosbuvir regimen would only require 12 weeks —a potential savings of more than \$27,000 at whole-sale costs. Instead of passing the potential savings onto payers, the consulting firm suggested an approach in which the savings would be added to sofosbuvir’s topline revenue ... Gilead was aware it was in a position to create clear savings for payers, but chose to pursue a “regimen neutral” price justified by “cost-per-cure” calculations that resulted in greater revenue per treatment than previous DAAs” (p 42). The Senate could but conclude that the firm was clearly oriented towards the maximization of its financial returns: “it was always Gilead's plan to max out revenue, and that accessibility and affordability were pretty much an afterthought”. The Senate Commission documented in detail the access restrictions instituted by payers: “As a result, these public payers, as well as traditional insurance plans, adopted access restrictions to limit the number of patients who could benefit from this new class of HCV therapies” (p 79).

The Senate Committee on Finance concluded its survey with questions on the levers that are available to public health programmes to introduce competition, faced with suppliers of highly innovative drugs that are in a monopoly position. In the case of sovaldi, Gilead was forced to agree to back

¹⁵ A presentation in July 2013 to Gilead’s Pricing Committee nevertheless “predicted that 24% of the payers it had surveyed would institute access restrictions of some sort for genotype 1 patients if Sovaldi were priced at \$75,000, and that 47% would institute restrictions at \$90,000” (page 43).

down slightly, following the introduction of a rival drug, Viekira Pak, a combination of several molecules, commercialized by Abbvie a year later. Yet, despite this beneficial effect of competition, the general level of prices of new antivirals for hepatitis C remained high: “Despite the benefits of competition, many state Medicaid programs remained concerned about the cost of new HCV therapies”. We could explain the ultimately limited impact of competition for treatments that cost tens of thousands of dollars, by the refusal of firms to engage in a price war that would destroy the value of their capital. A Gilead document cited by the Senate on competition between sovaldi and simeprevir, a direct-action antiviral put on the market two years earlier, illustrates this: “An aggressive pricing strategy for [simeprevir] could create some challenges for sofosbuvir in some high control accounts, but a low price strategy would be value-destroying for Janssen” (p 47). The discount agreed by Abbvie for Viekira Pak maintained prices at the level of Gilead’s price on sovaldi in Europe: \$51,373 in France and \$66,000 in Germany. We could posit that if a newcomer came along with an innovative treatment that could replace sovaldi in terms of therapeutic use value, it would be tempted to overshadow Gilead by seeking in turn to capture the value derived from payers. Second, the Senate noted that the average duration of the introduction of generics is 12, 6 years, which meant that for a number of years payers would not be able to benefit from significant price cuts: “Among other things, this report reflects the reality that federal health care programs —notably Medicare and Medicaid— have little to no policy levers at their disposal to significantly impact the price of a single source innovator drug”. In 1960 the report by Senator Kefauver, who was already concerned about the high prices of medicines in the US, suggested limiting the period of patent exclusivity to three years, and thus to enable

competition from generics to develop rapidly¹⁶. This option was rejected at the time by the syndicate of pharmaceutical industries and by President Kennedy, but it remained a source of reflection¹⁷. The threat of suspension of a patent was again used by the US State Secretary for Health in September 2001 during the anthrax crisis.

Faced with the new barriers to low- and medium-income populations' access to the drug that was emerging, a collective of chemists in the UK and the US decided to go to war against sovaldi prices by drawing up hypotheses on the production costs of generic medicines that could cover the needs of these specific markets. These chemists proposed to reproduce the generic drug policy that had been followed since the 2000s to treat the HIV/Aids epidemic, especially since the chemical structures of antivirals to treat hepatitis were similar to those of antiretrovirals. Learning costs would thus be reduced for generics manufacturers. Some of these chemists, for example Joseph Fortunak, had previously assisted chemists in Brazilian laboratories in duplicating certain ARVs, such as tenofovir, also active against hepatitis B, and in validating their production lines¹⁸. This technical-economic work determined the production value of sofosbuvir, without integrating either the value of R&D work – since the aim was to produce generics that duplicated the invention – or the

¹⁶ Report of the judiciary US Senate made by its subcommittee on antitrust and monopoly: study of administered prices in the drug industry, June 27, 1961, 384 pages; and Bill S. 1552 proposed by Senator Kefauver: "REQUIRING A DRUG PATENT HOLDER, THREE YEARS AFTER RECEIVING PATENT, WHO CHARGED MORE THAN 500 PERCENT OF PRODUCTION COSTS, TO LICENSE OTHER MANUFACTURES TO USE THE PATENT" (July 1962).

¹⁷ In the 1970s and 1980s, by virtue of a reform of the patent law (Bill C 102), the Canadian government authorized 400 compulsory licences to reduce the price of medicines. This helped to boost the local generics industry.

¹⁸ In 2006, Joseph Fortunak undertook an evaluation of Brazilian production laboratories, at the request of MSF and patient organizations in Brazil: "ARV production in Brazil: an evaluation", J Fortunak and O Antunes, 21 pages.

innovation rents derived from patents, since the idea here was to cancel or suspend industrial property rights by means of compulsory licences. These production prices, that cover the entire new therapeutic class of direct-action antivirals for hepatitis C and B, were calculated for a production scale of at least 1 million annual treatments, which implied an increase in international funding to acquire the molecules. The production costs that these chemists managed to achieve were extremely low compared to the prices of the proprietary molecules¹⁹: “large-scale manufacture of 2 or 3 drug combinations of HCV DAAs is feasible, with minimum target prices of \$100–\$250 per 12-week treatment course. These low prices could make wide-spread access to HCV treatment in low- and middle-income countries a realistic goal”²⁰. This study on the production prices of antivirals for hepatitis, published shortly after sovaldi was put on the market, served as an argument for all activists in the South and the North who were calling for a drastic reduction of the price of these molecules through changes to intellectual property rights, along with the production of generic medicines.

What was new with the arrival of sovaldi was the extension of the field of legal and political battles in both the South and the North. The aim was to reduce prices and circumvent the barriers of the profitability Gilead’s capital. Disputes around patents spread rapidly in India, Egypt and Brazil. A new development was that, in France, for the first time, Médecins du Monde filed a

¹⁹Theses valuations are relatively close, but lower, to the production costs calculated by Pharmasset and Gilead for sovaldi: “The presentation shows that manufacturing costs for Pharmasset would be de minimis compared to the revenue each course of therapy would generate—ranging from 0.9% for a \$50,000 course to 1.5% for a \$30,000 course”, p 19, US Senate report.

²⁰ “Minimum Costs for Producing Hepatitis C Direct-Acting Antivirals for Use in Large-Scale Treatment Access Programs in Developing Countries”, Andrew Hill, Saye Khoo, Joe Fortunak, Bryony Simmons, and Nathan Ford, CID, 2014, 58, p 928-936.

petition at the European Patent Office (EPO) against the the sovaldi patent. In 2014 I found the same Indian and Brazilian NGOs that I had studied in 2006 when they had won the battle against Gilead's patent on tenofovir in both countries. This time their action was against sovaldi. I was also invited by Mdm in Paris, in January 2015 when the humanitarian organization was about to file its opposition at the EPO. Médecins du Monde was not the only opponent in Europe: no fewer than 9 generics producers also called for the sovaldi patent's cancellation, on the grounds that it presented nothing new, and claimed that they were ready to produce generics.

The action taken against intellectual property, via legal opposition calling for the cancellation of patents by IP offices, or via demands for compulsory licences decided by governments, aimed to circumvent the proprietor's profits and capital and to cancel or drastically reduce innovation rents derived from patents. The idea was to use the private or public (in the case of Brazil) capital of generics manufacturers whose commercial prices were low and close to production prices. These prices included the generics firm's industrial profits, but not the innovator's R&D capital and especially not the over-accumulation of Pharmasset's and Gilead's financial capital that require its remuneration, twice : firstly to pay Pharmasset's investors; secondly to remunerate Gilead's shareholders. The lowest prices announced in India or Egypt in early 2016 were \$300 to \$550 for 12 months of treatment.

Informed by past struggles over IP on HIV/Aids medicines, and having lost a great deal in 2006 in India, and in 2008 in Brazil, two countries in which its tenofovir patent was cancelled, Gilead endeavoured in two ways to save the day: first, by applying a policy of differentiated prices for low-income countries²¹; and second, from September 2014, by offering voluntary licences

²¹ The US Senate Committee on Finance asked Gilead to justify the considerably lower price

to eleven Indian manufacturers²², which also had the advantage of pulling the rug from under the patent opponents' feet (an Indian firm actually withdrew its opposition). This strategy of voluntary licences followed a patent pool system created by UNITAID in 2010 at the insistent request of MSF, to reduce the barrier of access for populations of the South²³. Gilead did nevertheless maintain the direct management of the patent on sofosbuvir and decided on what licences to grant, whereas the patents placed in the patent pool were administered by UNITAID. Gilead authorized its Indian licensees to sell their medicines to a list that it had drawn up, of 91 low- and medium-income countries. The NGOs' reactions to this strategy were divided: some celebrated the use of voluntary licenses, which they had been demanding for years, while criticizing restrictions on intermediate countries (J. Love's Knowledge Ecology International)²⁴; others such as MSF were highly critical when medium-income countries (such as Brazil and Thailand) were excluded from this system since they accounted for half of the world's population affected by hepatitis C. The latter NGOs appealed to Indian producers to refuse these licenses²⁵. The DNDI, the R&D laboratory created by MSF, adopted a strategy of circumventing

that the firm agreed to for Egypt: "In a written response to the senators, Gilead explained that it engaged in separate pricing approaches for developed- and less- developed countries" (page 58).

²² "Gilead is committed to increasing access to its medicines for all people who can benefit from them, regardless of where they live or their ability to pay", CHRONIC HEPATITIS C TREATMENT EXPANSION Generic Manufacturing for Developing Countries, Gilead, February 2015.

²³ The Medicine Patent Pool signed agreements with patent holders and then sub-licensed generic manufacturers. MSF jurist Ellen T'Hoen was to be administrator, along with Jorge Bermudez of the Oswaldo Cruz Foundation.

²⁴ "KEI welcomes the Gilead HCV licenses, as a step to expand access to treatments. Notes challenges that remain", 15 September 2014.

²⁵ "Indian generic companies should reject Gilead's controversial hepatitis C 'Anti-Diversion' programme", MSF, 19 March 2015.

Gilead's system by partnering with an Egyptian producer and a biotechnology firm in the US, Predisio, to offer sofosbuvir in combination with ravidasvir at \$300 (the sovaldi patent had previously been cancelled by the Egyptian patent office)²⁶.

Brazil found itself in an original position as regards the production of sovaldi when one of its pharmaceutical firms was involved in the Pharmasset innovation network at the turn of the 2000s. The founder of this Brazilian chemicals and pharmaceuticals firm even sat on the Pharmasset Board in the late 1990s and had entered a strategic partnership with the US firm. This Brazilian firm, the first to copy AZT in 1993 in Brazil, had all the technological knowledge and industrial capacities to produce sofosbuvir and that entire new therapeutic class in Brazil. At that stage, two Brazilian private-sector firms had produced sofosbuvir samples, but they were blocked by Gilead's patents²⁷. They hoped that the Brazilian patent office would cancel the patent, following an opposition filed in early 2015 by the HIV/Aids patent organization Abia, which in 2008 had brought down Gilead's patent on tenofovir and had paved the way to local production of generics.

The determination of sofosbuvir's value was relative to the capital invested to invent, develop and test it, and in 2011 to appropriate all the assets, tangible and intangible, needed for its production and commercialization from 2014, with a promise of considerable income. The setting of prices, likely to vary from one country to the next, or at least one payer to the next, was linked to the negotiations with public- and private-

²⁶ "Given the estimated costs of producing most DAAs is low, this price may well fall further, making massive scale-up in affected countries feasible, provided patent barriers can be overcome", DNDI, April 2016.

²⁷ Interview with Jaime Rabi, Novembre 2014, Rio de Janeiro.

sector payers²⁸. The differentiated price policy was a strategic arm for Gilead, while the price disparities reflected the resistance of certain countries and manufacturers that refused patents²⁹. Value and exchange values could not be dissociated from the qualities of use value, and here, especially not from the therapeutic advantages of the new medicine compared to preceding or rival treatments. The growth of the sofosbuvir's financial value was set on the announcement of clinical trial results, especially in the last semester of 2011, when the price Pharmasset shares soared on the Nasdaq. The reports of financial analysts on Gilead's value were a complex entanglement of extremely detailed clinical data with commercial and financial data³⁰.

The levels of sofosbuvir prices were directly related to the capital advanced and invested in the invention, production and commercialization of this medicine, by the two firms that had successfully developed it: Pharmasset and Gilead. This capitalistic story was at the same time about the unfolding of the new structure of the post-1980s and 1990s pharmaceutical economy, with the disintegration between, on the one hand R&D firms fed by venture capital and the new financial markets – the Nasdaq –, and on the other hand pharmaceutical firms specialized in buying out therapeutic innovations that had already been developed industrially, that is, at a stage when the risks related to clinical research tend to decline³¹. Pharmasset and Gilead were ideal types of

²⁸ Here we find the calculation instruments used by Gilead, especially the drug price and share value matrix and the table of agreements and of resistances by payers, doctors and patient organizations, in relation to price hypotheses.

²⁹ On the heterogeneity of sofosbuvir prices, see the public inquiry published by MSF in *The Lancet* in November 2015: "Disparity in market prices for Hepatitis C virus direct-acting drugs", Isabelle Andrieux-Myer, Jennifer Cohn, Evaldo S. Affonso de Araújo, Saeed S Hamid, *The Lancet*, vol 3, November 2015 p 676-677.

³⁰ Cf. the Barclays reports that covered the transaction between Pharmasset and Gilead.

³¹ Financial analysts noted that Gilead's internal R&D investments were relatively low for this sector, which could constitute a difficulty to subsequently supply the product pipeline:

this new scientific and capitalistic structure. Pharmasset, founded in 1998 by an academic who was also a venture capitalist, was floated on the Nasdaq in 2007. This medium-sized R&D company (82 employees in 2011) generated revenue through R&D contracts with a few pharmaceutical firms and through financial investments secured by these intangible assets, primarily patents. It was a firm without any products, which showed accumulated losses of \$92m in 2011, and which carried on funding itself on the promise of its intellectual property rights and its clinical trials³². This financial economy of biotech companies has been documented fully by a financial economist, Elli Malki³³. The announcement of favourable clinical trial results for sofosbuvir, carefully distilled by Pharmasset executives, produced an inflation of stock market capitalization between September and November 2011, which was of serious concern to the analysts³⁴. The value of the capital bought by Gilead, using its own capital and bank loans, also needed to be remunerated. Through its detailed inquiry and its conclusions, the US senate Committee on Finance linked the high prices of sofosbuvir to the acquisition of Pharmasset capital and the return on investment that it promised³⁵. But the cycle of capital did not stop there,

“Finding such products internally (particularly given low relative R&D spend) or externally (particularly given high asset prices) is unlikely to be easy” (Jeffries, 2015).

³² Note also that Pharmasset’s scientific and financial team, which had already spawned other pharmaceutical start-ups (Triangle, Idenix), had extensive expertise in small molecule chemistry and in the field of viral diseases (interviews with Jaime Rabi, Rio de Janeiro, April 2003 and November 2014). The particularity of this R&D company was that it funded the first clinical trials on sofosbuvir itself, which contributed significantly to increasing the firm’s value.

³³ Malki, Elli, 1997, “Intellectual property and the valuation of biotechnology companies: GEN-Dex versus Dow Jones”, Working Paper ewp-fin/9709002, Economic Working Paper Archive (EconWP A).

³⁴ “Pharmasset has no drugs on the market, which is the biggest reason why people question the valuation”, Seeking Alpha 28/11/2011.

³⁵ “ ... there is scant evidence that return on these investments played a significant role in

otherwise the price of sovaldi could tend towards its production price, which was tiny, from 2015. The capital inflation has continued since, with the growth of market capitalization and that of Gilead's real capital, evaluated in the firm's balance sheet. From then on prices were driven by the maximization of the net earnings per share ratio and the economic return on capital³⁶. Gilead's price policy was of course also designed to contain conflicts over its patents in both the North and the South, at the European Patent Office, and to consolidate the value captured from the major public- and private-sector payers in the North, provided that a few adjustments and discounts were included. Finally, a controversy published by the JAMA in 2014 pointed out that the capital spent by Pharmasset on developing sofosbuvir (at the most \$350m, according to the author, for Pharmasset's entire molecule portfolio) was completely disproportional to the capital accumulated by Gilead on that medicine: "Moreover, substantial ethical questions are raised when the market then bears a 600-to-1 overall return on investment for this drug", JAMA November 26 volume 312, n° 20³⁷. Marx defined the financial capital of proprietors by its disconnection from the operations of industrial capital³⁸. On the other hand, it

determining the pricing of these drugs. Similarly, the cost of manufacturing Sovaldi, which was nominal, played no part in establishing the price", The price of sovaldi, p 117.

³⁶Gilead's net margin for 2014, presented by Barclays, was 50% higher and kept rising in 2015. The overall rate of return measured by the net profit on the total asset was 40% in 2014. The rate of financial returns on own capital was 76% in 2014, the year that sofosbuvir was put on the market, compared to only 26% in the preceding years.

³⁷ « Even though the return on investment to Gilead may be loosely estimated as 20 to 1 based on the purchase price, this ignores the 30-to-1 return on investment paid to Pharmasset investors » (JAMA, November 26, 2014 Volume 312, Number 20).

³⁸ Marx *The Capital*, volume 3, chapter 27, The role of credit in capitalist production : "Transformation of the actually functioning capitalist into a mere manager, administrator of other people's capital, and of the owner of capital into a mere owner, a mere money-capitalist" (p. 566, Penguin Classic). He then discussed the role of the stock market in the transmission and accumulation of capital. In *Biocapital. The Constitution of Postgenomic Life*

was effectively the industrial production and sale of medicines as commodities that supported the recovery of the capitalistic value advanced and required³⁹.

2) The frugality of capital devoted to medicines for neglected diseases: the arrangement between MSF/DNDI and Sanofi to produce the artesunate and amodiaquine combination

I will now look at the development, appropriation, production and distribution of an artemisinin-based combination, ASAQ, used primarily in malaria endemic regions in Africa to treat the simplest forms of malaria that are resistant to former treatments (chloroquine, sulfadoxine-pyriméthamine). This was a therapeutic innovation put on the market by Sanofi in 2008, when it also obtained a WHO pre-qualification. Unlike sofosbuvir, which had involved considerable capital investments, ASAQ was noteworthy for its low capital inputs. This frugal capitalistic regime is explained by the history and economics of its invention, and especially the types of capital involved, the appropriation regime adopted, the low-income populations targeted, and the governance of this economy by a humanitarian organization: MSF/DNDI⁴⁰. While the

(Duke University Press, 2006), K.S. Rajan pointed out this disconnection between speculative and industrial capital with regard to the biotech sector and the pharmaceutical sector in the US. I discussed this issue in *Actuel Marx* in 2003 : Cassier M., L'expansion du capitalisme dans le domaine du vivant : droits de propriété intellectuelle et marchés de la science, de la matière biologique et de la santé (Capitalism's Expansion into the Realm of the Biosphere), *Actuel Marx* 2003/2, n° 34, p.63-80.

³⁹We need to relativize the break that Birch and Tyfield identified between the commodity based economy and the asset based economy : « Theorizing the Bioeconomy: Biovalue, Biocapital, Bioeconomics or . . . What? », *Science, Technology and Human Values*, 2012, 29 pages.

⁴⁰The low prices of CTAs related not only to their consumption by the lowest-income populations, neglected by innovation, but also, and most importantly, to the property regime and the type of governance of these projects. The relatively high prices of new

sofosbuvir innovation system is based on the new division of work and the technology and ownership transfers between the biotechnology and pharmaceutical sectors⁴¹, located mainly in North America – except for our Brazilian firm that was quickly excluded –, ACT innovation was originally located in the South, in the People’s Republic of China, and then governed by filiation and cooperation between the WHO Tropical Disease Research project (TDR) created in the mid-1970s, and the R&D laboratory created by MSF in 2003, the Drugs and Neglected Diseases Initiative (DNDI). All the basic molecules assembled today in ACTs, whether it be artemisinin itself or its derivatives, and even the most frequently used combination in the world today, arthemether and lumefantrine⁴², are the products of the research programmes of Chinese science and industry⁴³. These basic molecules, including artesunate used in the artesunate and amodiaquine combination, were developed at a time of public property in China and are free of patent rights. When MSF and the DNDI decided in 2002 to develop ASAQ, they were able to use the molecule freely. It was a first source of capital saving.

ASAQ’s R&D programme was set up by MSF in the early 2000s with a

tuberculosis medicines, bedaquiline and delamanid, denounced by MSF, are probably related to a more capitalistic and property-based economic model than that of ACTs: “the report shows that the most frequently used TB-DR treatments today cost between 1,800 and 4,600 dollars per patient... In order to improve the access to new medicines, Janssen and Otsuka, the laboratories that produce them, had to accelerate their registration in those countries that had the most TB patents, and to propose affordable prices to all developing countries and to those most affected by TB.” DR-TB drugs under the microscope, MSF, March 2016.

⁴¹ Iain Cockburn, 2003, « What a brave new industry that has such patents in it ! » *Advances in genetics* 50:385-98.

⁴² This combination was appropriated in 1990 by a patent co-owned by Chinese government institutions and Ciba Geigy. All the inventors cited in this patent were Chinese researchers.

⁴³ Zhang Jianfang Ed : A detailed chronological record of project 523 and the discovery and development of Qinghaosu (artemisinin), translated from the chinese by Muoi and Keith Arnold, 2013, 175 pages.

view to rapidly developing fixed-dose artemisinin-based combinations to control malaria resistant to existing treatments. It was an innovation project run by a humanitarian organization that had experience with resistance to malaria treatments in Africa from the 1990s, and that undertook to introduce artemisinin-based medicines from south-east Asia to East Africa, from 1999, possibly even against the will of States in the region⁴⁴. It was also an innovation that stemmed from the movement for neglected diseases which had been revived by MSF and Pharmaciens Sans Frontières from 1996, and that sought to compensate for the failure of the proprietary model of innovation for dealing with tropical diseases. In 1999 MSF published an article in the JAMA (B Pecoul, P Chirac, P Trouiller, J Pinel, "Access to essential drugs in poor countries: a lost battle?" JAMA, January 27, 1999, vol 281, p 361-367) and launched the DND Working Group that brought together experts from the WHO, who had been working for a long time on tropical diseases, and from the Walter Reed Army Institute of Research and the HARVARD School of Public Health, as well as several experts from scientific or pharmaceutical institutions in developing countries, including the University of Mahidol in Malaysia and the Oswaldo Cruz Foundation in Brazil. The FACT (Fixed-Dose Artesunate Combination Therapy) consortium was organized to develop two combinations in parallel: the artesunate-amodiaquine combination was to be developed around Bordeaux University in France, and the artesunate-mefloquine combination was to be developed at the Fiocruz Farmanguinhos Institute in Rio de Janeiro.

The funds mobilized for the FACT consortium were public subsidies from the European Union, the *Agence Française de Développement* or the Swiss government, or else philanthropic organizations, primarily MSF and the DNDI,

⁴⁴ « Les résistances traitées par une médiation sud-sud », Sunna Balkan and JF Corty, in *Innovations médicales en situations humanitaires*, (ed.) JH Bradol and C Vidal, l'Harmattan, 2009.

which accounted for half of the total and expected no returns on their investments. The amounts concerned remained modest, given that certain work was directly funded by Bordeaux University, at no charge. The development costs of ASAQ borne by the DNDI totalled \$12.5m (clinical trials and industrialization costs borne by Sanofi were not included). The majority of costs carried by the consortium were devoted to development and registration. The distribution of these funds corresponded to a large degree to the coverage of R&D expenditures for malaria, as UNITAID economists evaluated it for the period 2007-2001: 51% of these expenditures were covered by government grants, 32% by philanthropic organizations, and only 17% by industry⁴⁵. The share of industrial R&D tends to increase when the molecules reach the clinical trial and registration phase. These innovation projects, initiated and partially funded by humanitarian organizations, were intended to break down the barrier of ownership and accessibility for low-income populations.

The artesunate-amodiaquine combination technology was developed by a network of academic research laboratories and R&D start-ups in France and, to some extent, in Brazil and Germany⁴⁶. Although it was not patented, at the insistence of MSF/DNDI, the formulation of this fixed-dose combination with two molecules that were difficult to combine in the same pill was based on an inventive technology designed by researchers at the University. Some of these researchers had participated in the MSF working group, at the DNDI. The University provided its technology free of charge, while the pharmaceutical development start-up, Ellipse Pharmaceuticals, supported by a large French engineering group, Bertin, derived some profits from its work, funded by the

⁴⁵ Malaria Medicines Landscape 2015, UNITAID, 117 pages.

⁴⁶ The toxicological studies were carried out at two Brazilian start-ups; the analytical methods were entrusted to Sains University in Malaysia; and the first scale-up was subcontracted to Rottendorf Pharma in Germany.

DNDI research contract. An original feature of the design of this medicine lies in the humanitarian organization's strong involvement in the definition of the therapeutic use value of the medicine, and in that of its value in terms of production costs. The head of the Bordeaux start-up set out the constraints involved: *"Finding a somewhat sophisticated technical solution to separate these products was possible, but we quickly encountered problems of cost price incompatibility with the spirit of a tropical medicine"* (Ellipse)⁴⁷. The DNDI incorporated its knowledge of the conditions of use and circulation of medicines in Africa – for example on informal markets and in central buying offices – to demand specific work on the conditions of conservation of the medicine over time in a tropical environment. In the marketing of ASAQ it was claimed that the medicine could be kept for three years without alternation. Specific work was also requested to develop a paediatric formulation, as children account for the majority of deaths due to malaria. The idea was also to improve the use symbols corresponding to ages, on medicine boxes⁴⁸. The form of the fixed-dose combination corresponds to the WHO guidelines published in 2001⁴⁹.

The R&D was thus essentially taken care of by public-sector laboratories and university spin-offs. In no instances did the latter own the technology; they worked as sub-contractors on specific development tasks that the consortium had entrusted them with. The FACT consortium had also partially funded

⁴⁷ Sandra Mignot: « Le consortium FACT et le traitement du paludisme : Exploration d'un nouveau modèle d'innovation thérapeutique, ou comment l'implication d'institutions du Sud et la coopération ONG /public/privé ont permis de mettre sur le marché deux nouveaux traitements à prix abordable », Paris, Master's thesis, EHESS, 2010, 86 pages.

⁴⁸ "Pionnering ways of working through innovative partnerships: The successful development of a fixed dose combination of artesunate plus amodiaquine antimalarial", DNDI, October 2015, 16 pages.

⁴⁹ "They're responding to the kind of drug profile we've been promoting." Dr. Arata Kochi, chief of World Health Organization's global malaria program, 2007.

clinical trials⁵⁰ and registering the medicine, before Sanofi stepped into take care of its industrialization, to complete the clinical trials and to make the necessary investments for the pre-qualification of its production unit in Morocco. Here the pharmaceutical multinational entered the game only after the development stage had begun, under the DNDI's authority. The agreement signed in 2004 between the DNDI and Sanofi – with temporary exclusivity granted to the firm until the registration of the medicine by the WHO in 2008 – was based on a common good regime for the new medicine. The latter was therefore not patented, even though the Bordeaux academic researchers would have preferred to have some form of control over the invention⁵¹. The agreement specified a regime of “not for profit” prices or “with a minimum profit” to ensure the medicine's accessibility to the public sector” (Partnership agreement between DNDi and Sanofi to jointly develop ASAQ Winthrop[®], a non-patented ASAQ FDC to be sold at cost -plus a small margin” DNDI 2015 p 12). This agreement also provided for the payment of royalties on sales of the ASAQ version that was to be commercialized by Sanofi on private markets under the trade name Coarsucam⁵². These royalties covered 4% of the consortium's funding, particularly surveillance studies on the medicine's side-

⁵⁰The Burkina Faso malaria research centre was to be involved in ASAQ clinical trials.

⁵¹ “On the other hand, this approach may be difficult to replicate in all situations; while it relies heavily on partners absorbing part of the costs and risks, or working at cost, there is clearly no or limited prospects for return for those (typically in this case, the public sector) that allocate resources and take the risks inherent in the early phases of pharmaceutical development”, C Lacaze and al, *Malaria Journal* 2011, “The initial pharmaceutical development of an artesunate/amodiaquine oral formulation for the treatment of malaria: a public-private partnership”, 12 pages.

⁵² “Sanofi will also produce a branded version, called Coarsucam, for the private market, to be sold at three or four times the public price. It will be sold only in Africa, Indonesia and the Philippines, the company said, not in the United States or Europe”, *The New York Times*, March 1, 2007.

effects in several African countries, and were reinvested to improve the medicine's use conditions. Yet the amount of royalties paid to the DNDI, which was already very small, declined with the reduction of ASAQ Coarsucam production for the private-sector market⁵³. Sanofi-produced ASAQ is now intended primarily for the donor market, especially the Global Fund, for low- and medium-income countries.

Once most of the market was covered by the Global fund and the major international donors⁵⁴, the DNDI and Sanofi applied to the WHO for a prequalification of ASAQ. The prequalification norm had been invented in 2001 by the WHO to regulate the market for generic medicines intended for countries of the South⁵⁵. Today, it is still essentially generics producers, especially those in India, that apply for prequalification. It is interesting to see that, with regard to malaria, two multinationals, Novartis and Aventis, both engaged in the production of ACTs, called for this certification (Novartis in 2004 then Sanofi in 2008). According to the Sanofi executives whom I interviewed, the prequalification procedure of ASAQ, the production of which was located at the firm's factory in Morocco, required a major undertaking of codifying production procedures, along with investments in the modernization of equipment, which Sanofi estimated at 45 million Euros. Sanofi plant in Casablanca is the only one to be WHO prequalified in Morocco and one of the

⁵³ Interview with the Sanofi executives in charge of malaria, in February 2016. In 2014 the royalties paid by Sanofi to the DNDI (3% of ASAQ sales in the private sector) totalled 5,762 Euros, as opposed to 15,270 Euros in 2013 (DNDI Annual Report 2014, 84 pages).

⁵⁴ "Sanofi-Aventis, the world's fourth-largest drug company, based in Paris, will sell the pill at cost to international health agencies like the W.H.O., [Unicef](#) and the Global Fund for [AIDS](#), [Tuberculosis](#) and Malaria", The New York Times, March 1, 2007.

⁵⁵ La « préqualification » OMS : origines, déploiement et impacts sur la disponibilité des antirétroviraux dans les pays du Sud, (*The WHO Prequalification. Origins, implementation and impacts on the availability of ARVs in South Country*) C Lantenois and B Coriat, Sciences Sociales et santé, 2014/1 (vol 32)71-99.

few in Africa⁵⁶.ASAQ was thus a commodity certified by the WHO and produced for the donor-funded market for the African continent⁵⁷. For Sanofi, its presence in Morocco was a strategic move. It thus had a WHO-certified industrial site, advantageous production costs compared to those in Europe, and a modernized logistics platform to distribute its medicine in some forty African countries: “In short, the Zenata industrial site is the military wing of the policy of access to medicines of the Sanofi Group, which regularly submits tenders to the WHO” (Sanofi group, Access to medicines Department). The multinational’s marketing thus adopted the local production argument to cover the region’s health needs: “This wish for proximity with patients is illustrated by a few examples: The production of ASAQ Winthrop® in Morocco: malaria medicine produced at the heart of the African continent” (Sanofi group).

Although the DNDI applied a principle of non-exclusive licences to the ASAQ, Sanofi maintained a near monopoly on production until 2013: “In 2012, Sanofi accounted for approximately 98% of ASAQ volumes procured. Between June and November 2012, six more FDC ASAQ became prequalified from two manufacturers (Ipca Laboratories Ltd [hereinafter Ipca] and Guilin), however, these still represent very small portions of the market.” (Malaria Medicines Landscape, p 45). Sanofi’s share started to decline from 2013, to the benefit of a Chinese manufacturer, Guilin (6% of the market) and an Indian one, Ipeca (4%). Our interviewees at Sanofi explained that the Asian generics producers’ share had increased in the previous two years, as Sanofi was unable to remain

⁵⁶ “Making medicines in Africa, The Political Economy of Industrializing for Local Health”, Watu Wamae; Maureen Mackintosh; Paula Tibandebage; Geoffrey Banda, Palgrave Macmillan, 2015.

⁵⁷ Prequalification is also a barrier for producers of artesunate-amodiaquine in Africa, who do not have WHO certification affording them access to donor markets and to the fixed-dose technology combination. Cf. the research that Jessica Pourraz is doing in Ghana for her thesis.

price competitive⁵⁸. Since 2008, the price of ASAQ, set according to the “neither profit nor loss” principle (Sanofi, Access to Medicines programme), wavered around \$1, in a context of steep growth of production volumes. This stability was related to the partnership between the DNDI and Sanofi. The arrival of Asian manufacturers subsequently led to price decreases: “The median unit price of Ipca sales in 2012 was US\$ 0.87, that is, US\$ 0.06 lower than Sanofi US\$ 0,93 for that year. In 2012, a third ASAQ product manufactured by Guilin was prequalified for procurement in the donor market. Partial data indicate that Guilin’s ASAQ product was purchased at a median price of US\$ 0.85 in 2013” (UNITAID, 2015). In the next few years, the generics producers’ share is likely to increase significantly for ASAQ, thus mirroring the ACT market that was initially monopolized by Novartis, arthemeter and lumefantrine, and which is increasingly supplied by Indian and Chinese manufacturers.

In 2015 a manufacturer in Tanzania, Zenufa, started to produce ASAQ, the technology of which had been transferred to it by the DNDI. The latter thus applied its principles of non-exclusive exploitation of a new malaria medicine⁵⁹. The dissemination of the technology stemmed here from a technology transfer agreement between a local firm, Zenufa, and the charity DNDI, assisted by an engineering firm (Bertin Pharma). The technology transfer operation was described by Zenufa as: “One such partnership is the affiliation the company now has with the Drugs for Neglected Diseases Initiative (DNDi), who pass on their technical knowhow in assisting the most stable formulation of the anti-malarial artesunate and amodiaquine, fixed dose combination as a bi-layered

⁵⁸ I recently visited the Sanofi plant in Casablanca in may 2016. The production of Asaq-Whintrop by Sanofi has dramatically been reduced since 2 years.

⁵⁹ “The non-exclusivity agreement with Sanofi allowed for increased access and subsequent technology transfer to Zenufa in Tanzania, which will ensure a second source of the ASAQ Winthrop® product in the future” (DNDI, June 2015).

tablet, by way of a technology transfer agreement” (December 2014). The DNDI thus diversified the offer on the African continent (Sanofi in Morocco and Zenufa in Tanzania) and simultaneously worked towards WHO certification of the new production plant. Zenufa was later able to enter the donor market owing to the prequalification norm that the WHO had granted it. Note that the technology transfer process and WHO normalization took no less than five years. In India and China, the dissemination of the technology took the route not of technological agreement but of copying. At Sanofi those responsible for work on malaria thought that the Indian producers had been able to access their formula directly when it was inadvertently disclosed on the Internet by the WHO after a training session. The formula was thus accessible for several months and Indian chemists would have been able to obtain details on the Casablanca factory’s industrial technology. They were also able to recreate the technology by reverse engineering and to reproduce it freely since the formulation had not been patented. Irrespective of how the information was leaked, the technology and production of ASAQ were disseminated in Africa and Asia, which is exactly what the DNDI wanted.

Sanofi’s involvement in the production of ASAQ, “a no profit no loss model for the public sector” (Sanofi Morocco) covered a segment of Sanofi’s global capital that was “devalorized”, meaning that it was not regulated by the firm’s norms of average profitability. In 2014 the net result displayed by the firm’s accounts was €4.5bn, for a financial return on own capital of 8%, while the dividends paid to shareholders totalled €3.7bn. Sanofi’s ASAQ activity was based in the multinational’s “Access to medicines” department, created in 2001 in an attempt to respond to the struggles for access to treatment (Pretoria court case). R. Sebbag, Sanofi’s vice-president for access to medicines, described the partnership with MSF/DNDI as follows: “This was not a love

wedding, it was a reasonable wedding. But reasonableness is often more important for a long marriage. They've seen we are not nasty people working against poor countries and seeking only profits". "Neither version, at either price, will bring Sanofi much profit, but in terms of symbolism, it means a lot", he was reported to have commented (New York Times, March 1st, 2007).

At the same time, these very modest investments – in view of the funds from the public and philanthropic sector in the ASAQ project – participated in the multinational's more long-term strategy regarding malaria and the African medicines market, especially from the Moroccan factory. Industrial investments needed in the Moroccan factory to bring it up to international standards were granted, as well as logistic equipment to supply the entire continent: "We have invested over 45 million Euros in the modernization of the industrial tool and the production of ASAQ Winthrop®. This production for export to Africa enhances the Moroccan pharmaceutical industry's value", noted Haissam Chraïteh, Sanofi General Manager in Morocco (Sanofi, 2015). As for the technological investments in malaria treatments, Sanofi diversified them, also in partnership with philanthropic organizations – Path, Medecine for Malaria Venture, Bill Gates Foundation –, especially to develop an original technology to produce a semi-synthetic artemisinin that could be used as a substitute for natural artemisinin produced mainly in China and Vietnam⁶⁰. Sanofi and Medecine for Malaria Venture also developed two new therapeutic

⁶⁰The R&D of semi-synthetic artemisinin benefited from the support of \$64m from the Gates Foundation. The semi-synthetic artemisinin factory located in Italy, which started to produce in 2013, was sold by Sanofi in early 2016. This production, justified to regulate the erratic natural artemisinin market, has been faced in recent years by a natural artemisinin price below the floor price set by Sanofi: "For the past two years, the naturally derived chemical has sold for less than \$250 per kilogram — below Sanofi's 'no profit–no loss' margin of around \$350– 400 per kilogram"(Nature News, 23 February 2016). Moreover, Sanofi's ASAQ production was tending to stagnate.

combinations, without using artemisinin derivatives, and these combinations are currently in the clinical phase⁶¹. These R&D investments attest to a long-term strategy on “so-called neglected diseases”, in the framework of humanitarian and public partnerships and thus of co-funding of innovation, for markets are based primarily on international donations.

The price of ASAQ, adjusted to the production price, was regulated by the partnership agreement between Sanofi and the DNDI⁶², as well as by the competition between generics that appeared from 2012, given the invention’s common good status, and by the calls for tenders from international donor markets, primarily the Global Fund. The pharmaceutical use value was calibrated by WHO prescriptions (fixed-dose combinations rather than co-blisters) and by standards also attributed by the WHO (pre-qualification of medicines), while the value of capital for this medicine was reduced by the contribution of public and philanthropic funds, which expected no returns, and by the devaluation of a part – albeit a tiny one – of Sanofi’s capital, on which a return rate of virtually nil was applied.

3) Concluding comments: tensions between financial and humanitarian values, and the plurality of pharmaceutical capitalisms implemented

The two economies that we have examined in the case of sofosbuvir and ASAQ illustrate the strength of current contradictions between the inflation or frugality of the capital input, between the barriers of exclusive property and the commons regime, and between the protection and extension of the right to health and the norms of financial returns on capital that are applied and

⁶¹“Sanofi extends its collaboration with Medicines for Malaria Venture in the fight against one of the world’s most lethal parasitic diseases” July 2015.

⁶²My interviewees at Sanofi insisted on the “contractual” nature of the price.

modulated. We have seen that the inflation of financial capital that supported the development and commercialization of sofosbuvir was increased by the disintegration between biotech R&D companies and the pharmaceutical firms, and by the addition of the financial profits captured by the shareholders of Pharmasset and the financial yields paid to the shareholders of the pharmaceutical company Gilead (in the form both of dividends and of the purchasing of their actions, on a huge scale in 2014 and 2015, drawing on the astronomical net returns on the medicine). The capital cost of therapeutic innovation could but be high, and put tremendous strain on public and private payers in higher income countries. The proprietary firm sought to reduce the gap in access for low- and medium-income countries, or at least some of them, by organizing a pharmaceutical generics market devoted to them. It thus granted voluntary licences to 11 Indian manufacturers who were authorized to produce generics for a list of countries. This division of markets reflects an idea put forward in the early 2000s by an economist, J.O. Lanjouwe, who recommended a system of medicines patented for the North and of generics for the South⁶³. Gilead's particularly acute form of financial capitalism thus integrated humanitarian preoccupations and used devices recommended by MSF at the end of the 2000s, in the form of a patent pool and voluntary licences to cover poor countries. Financial capital was thus fully deployed, having cut its losses in the carefully delimited area of beneficiary countries of humanitarian aid.

It was precisely a humanitarian organization, the DNDI, that governed the ASAQ economy, to make up for the failure of proprietary pharmaceutical capitalism and invent enough therapeutic solutions for neglected diseases, in

⁶³ J.O Lanjouw : "A Patent Policy for Global Diseases. US and International Legal Issues", Harvard Journal of Law and Technology, vol 16, 2002.

order to solve the problem of resistance to former treatments. The DNDI initiated a process of collective invention that was deployed in the North as well as the South, instated a non-exclusive property regime, and organized a distributed industry in Europe, Africa and Asia. The capital mobilized was mixed and the financial yields were cancelled. MSF and the DNDI invented a biopolitics of access based on a minimization of pharmaceutical profitability, while prices and technical norms were governed by the WHO, the DNDI, and international donors. Pharmaceutical capitalism participated in the R&D and especially in industrialization and commercialization, through the play of increasingly open competition between a pharmaceutical multinational, Sanofi Aventis, and Indian, Chinese and African pharmaceutical firms. Our interviewees at Sanofi identified this production with public markets and a policy of access that differ from the firm's proprietary model ⁶⁴. Sanofi found a compromise between a financial and a humanitarian approach, the latter corresponding to a very small portion of its investments. Sanofi and Gilead both adopted ethical discourses on access and reached agreements with humanitarian organizations: with DNDI in Sanofi's case, and with voluntary licences in Gilead's.

The value and price regimes of medicines were the product and the justification of knowledge and innovation proprietary regimes. The accumulation of capital and the price regime were structured by property. If we consider the trajectory of sofosbuvir, the mobilization of venture capitalists and then of Nasdaq shareholders was based on the portfolio of Pharmasset patents. The evaluation of the promise of revenue from medicines was based on the monopolization of markets, at least for countries of the North (those of

⁶⁴“We're not going to judge projects on the same criteria, if it's a potentially lucrative market or a subsidized type of market like malaria, neglected tropical diseases” (Access to Medicines Department, interview 2016).

the South were not even mentioned by Gilead's pricing committee in 2012 and 2013). And the financial analysts made no mistakes: if the patent barrier were to come down, for example in Europe where Médecins du Monde and nine generics manufacturers requested the invalidation of patents for lack of novelty, the scaffolding of value would be threatened: "Gilead relies on patents to protect its investment in drug development. Gilead is facing multiple patent challenges to its hep C business. While we believe Gilead will ultimately prevail and failure to successfully defend its hep C patents could significantly reduce future sales and pressure GILD shares" (Barclays, 2015). On the other hand, the capital accumulation, profitability and price of ASAQ could not be based on patents and exclusive licences: Sanofi's industrial investments in Morocco were soon confronted with the industrial investments of Indian and Chinese laboratories and the DNDI's initiatives in transferring technology to one or another manufacturer. Here, partnership on prices did not allow the disconnection between ASAQ's financial value and its industrial value. Price of ASAQ is continuously reduced to the production cost. As for the proprietary regimes, they could be rearranged or undone by political mobilization on the price front and the accessibility of treatment. The Brazilian firms, ready to produce sofosbuvir for the Health Ministry⁶⁵, relied on the opposition filed at the INPI by the patient organizations. In return, Gilead tried to reach an agreement directly with Bahiafarma, a Brazilian public laboratory in the State of Bahia, to pull the rug from under the feet of independent Brazilian producers if its patent were invalidated by the National Industrial Property Institute. This aroused Brazilian activists' anger. In Egypt, where the sofosbuvir patent was refused, Gilead tried to get round generics manufacturers by negotiating

⁶⁵ Communication by the Oswaldo Cruz Foundation on 11 May 2016: a consortium, BMK, supervised by the CEO of Microbiologica, Jaime Rabi, consisting of three private Brazilian laboratories and the Oswaldo Cruz Foundation, produced the first samples of sofosbuvir.

directly with the Health Ministry. In France, patient organizations asked the Health Ministry to opt for a compulsory licence to authorize competition from generics and to preserve the Social Security. It took ten years of legal and political battles in Lula's Brazil to obtain the only compulsory license ever in the country for a medicine: Merck's efavirenz, now produced by the public and private capital of a national consortium. Here the making of the value of medicines implies political and juridical struggles—notably between the right to health and proprietary rights.