Universitat Autònoma de Barcelona

MARKET ANALYSIS OF NEW-GENERATION MEDICINES FOR HEPATITIS C

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INTRODUCTION

Nowadays we live in the society of information. Lots of different news appears every day in the media, but only a few of them stay for a certain period before becoming obsolete or so exploited that society loses interest in them. Since the second semester of 2014 in Spain, there is a topic that appears very often due to the controversy that surrounds it. I'm talking about hepatitis C and the new-generation medicines to treat it.

But, what is going on? For most of the population, who have never had any contact with this disease, news can be confusing and lead to misunderstandings. This report intends to reflect the current situation of the market of medicines for hepatitis C and analyze the facts that have occurred under an economic point of view.

This issue came into the front page due to the activist actions of the patients of hepatitis C, who have been carrying demonstrations and strikes in many cities of Spain. Why? The old medicines are not good enough, and the new (good) ones are not being supplied (at least, not for everyone). While hepatitis C attacks the liver of the infected, the new medicines have become a headache for the Government.

What are the drivers of consumers' behavior? How can we explain their attitude towards the new situation? How should the Governments face this problem? What can they do? Why is the industry acting the way they are doing?

From now on, all these questions will be presented and analyzed, with the intention of explaining and making clear to everyone all the news that are presented in the media.

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1- HEPATITIS C

Hepatitis C virus (HCV) was discovered in 1989 and is nowadays one of the main agents that cause chronic liver disease and, therefore, one of the most common causes of cirrhosis, cancer and liver transplantation. The virus is transmitted by blood, and the most common causes of infection are unsafe injections, improper sterilization of medical equipment in some health care settings and use of blood and blood products without analyzing (asscat).

Hepatitis C is an asymptomatic infection, and between 10-30% of people who get it, manages to fight it successfully in a 6 months period without the need of a treatment. However, in the rest of the people the virus becomes chronic (OMS).

To present this problem, let me provide some data and statistics:

There are between 130 and 150 million people infected with hepatitis C worldwide, which is about 3% of total population, with 3-4 million new infections per year.

Almost half a million of people die every year from liver disease related to hepatitis C (12 people every day in Spain) (El País).

Egypt is the county in the world with the highest rate of hepatitis c cases, with 15-20% of its population infected. However, those rates are quite above more developed countries'. In the US, Japan and Australia the rate is between 1-2%, while in Europe it is in the 0,5-2% (asscat).

Finally, and this is an important point, it's necessary to be aware that there are six distinct genotypes of hepatitis C (different genetic structure of the virus), each of them divided into several subtypes. Genotype 1 (1a and 1b) is the most common type of hepatitis C in Europe, the US and Japan, and the most difficult to treat as we will see later on (hepatititscentral). This correlation between the most common type and the wealthiest countries and the need of more effective treatments has made possible the interest of big pharmaceuticals for research and development of new treatments.

It is very complicated (actually, impossible) to know exactly how many patients in total there are in every country. Firstly because many of them do not carry official reports about the illness, and secondly because there are many people infected who have not been diagnosed yet due to the asymptomatic characteristic of the virus. In 2011, Cornberg et al. conducted the report: *"A systematic review of hepatitis C virus epidemiology in Europe, Canada and Israel"* where they gathered *"country-specific data on risk factors, prevalence, number of diagnosed individuals and genotype distribution of the hepatitis C virus (HCV) infection in selected European countries, Canada and Israel."*

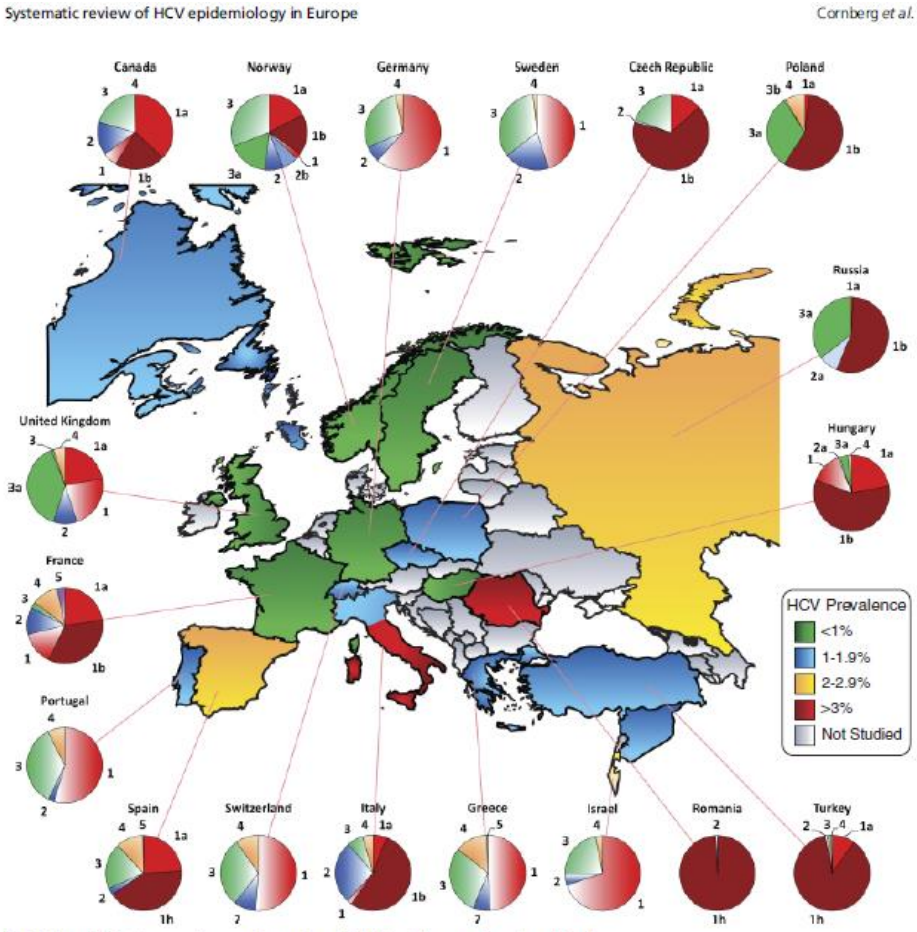


Fig. 1. Hepatitis C virus prevalence and genotype distribution in Europe, Canada and Israel.

COUNTRY	Most common genotype	PREVALENCE IN ADULT POPULATION
USA	1	1%
GERMANY	1	0,40%
CANADA	1	1,01%
UK	1, 3	0,60%
FRANCE	1	0,84%
SPAIN	1	2,64%
ITALY	1	5,20%
ISRAEL	1	1,96%
NORWAY	1, 3	0,70%
ROMANIA	1	3,50%
SWEDEN	1, 3	0,59%
SWITZERLAND	1	1,50%
TURKEY	1	1,00%

Combining Cornberg et al. data with World Health Organization (WHO) calculations, we have that as many as 2 to 4 million persons may be chronically infected in the United States, 5 to 10 million in Europe, and about 12 million in India, and most of them do not know that they are infected. (World Health Organization, 2002)

2- TRADITIONAL TREATMENTS FOR HEPATITIS C

The goal of hepatitis C virus (HCV) treatment is to cure the virus, which can be done by using a combination of drugs. The length of treatment, which can range from 12 to 48 weeks, depends on the person's HCV genotype, whether the person is eligible to take interferon and whether he or she is waiting for a liver transplant.

- **Double therapy**: consists on the combination of
    - Pegylated Interferon Alfa: Interferon is a protein made by the immune system, it signals the immune system to recognize and respond to microorganisms, including viral and bacterial infections.
    - Ribavirin: combining ribavirin with pegylated interferon boosts cure rates and reduces the risk of relapse.

These two drugs do not attack directly the virus but reinforce the immune system in order to increase effectiveness.

An HCV patient is considered to be cured when he or she gets a "sustained virological response" to the treatment (the virus is not detected in the system 24 weeks after finishing the treatment). In genotypes 2 and 3, this is achieved in the 70-80% of the patients after a 24-weeks treatment. In genotypes 1 and 4, response is below 50% after a 48-weeks treatment (asscat and hepmag.com).

- **Triple therapy:** this has been designed for genotype 1 patients, and consists on the addition of a third drug such as Telaprevir or Boceprevir. They are "protease inhibitors", and their function is blocking a protein that plays a critical role in HCV replication.
  The implementation of this therapy has increased cure rates up to 70% (genotype 1 patients).

Even though the cure rates have increased with the addition of the triple therapy, this therapy is not considered good enough due to the many discomforts it generates. Boceprevir requires the intake of four pills every eight hours, two pills in the case of Telaprevir, taking into account the long duration of the treatment (24-48 weeks).
But the most difficult aspect is the side effects. An empirical study carried on by Michael W. Fried ("*Side Effects of Therapy of Hepatitis C and Their Management*") studies the combination of both standard interferon and peginterferon with ribavirin. Research shows the already acknowledged abnormalities like fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms, among many others. It also sets the premature withdrawal from therapy between 10-14% (when treatment is abandoned, it cannot be restarted).

We can see, therefore, that there is still room for improvement in the treatment for hepatitis C genotype 1 so far.

3- FIRST SERIES OF NEW-GENERATION MEDICINES

Once a company develops a drug, it undergoes around three and a half years of laboratory testing, before an application is made to the U.S. Food and Drug Administration (FDA) to begin testing the drug in humans. Only one in 1000 of the compounds that enter laboratory testing will ever make it to human testing. If the FDA gives the green light, the "investigative" drug will then enter three phases of clinical trials. After final approval, the drug becomes available for physicians to prescribe. (Drugs.com, 2015. "*Drug Approval Process Information"*)

The following drugs are the ones that were introduced in first place:

3.1- Olysio ®, an inflection point.

On 22nd of November 2013, the U.S. Food and Drug Administration approved Olysio (simeprevir), a new therapy to treat chronic hepatitis C virus infection. FDA press announcement stated the following:

"The safety and effectiveness of Olysio were evaluated in five clinical studies […] designed to measure whether […] a participant's infection had been cured.

Results showed 80 percent of treatment-naive participants given Olysio plus peginterferon-alfa and ribavirin achieved sustained virologic response, compared to 50 percent of participants receiving peginterferon-alfa and ribavirin alone […]. With treatment-experienced participants whose infection returned (prior relapsers), 79 percent receiving Olysio plus peginterferon-alfa and ribavirin achieved sustained virologic response compared to 37 percent of participants receiving peginterferon-alfa and ribavirin alone.

[…] Adding Olysio improved response rates in each of these subgroups compared to peginterferon-alfa and ribavirin alone." (FDA news release. Nov. 22, 2013)

Simeprevir is a protease inhibitor as well as Telaprevir or Boceprevir, however *"Simeprevir has provided an excellent alternative to the older first-generation NS3/4A protease inhibitors (boceprevir and telaprevir) for the treatment of patients with genotype 1 HCV.*

Simeprevir is convenient (once-daily dosing), well-tolerated, and has less extensive drug-drug interactions than the first-generation protease inhibitors." (hepatitis.uw.edu)

Simeprevir was then an important step forward for hepatitis C genotype 1 patients: higher cure rate, more convenient and fewer side effects. Nevertheless, the co-administration with interferon (main source of side effects and premature withdrawals) was still there to be solved.

In commercial terms, we are talking about a new product in the market that substituted and overcame incumbents. However, its success or failure cannot be analyzed without looking at Sovaldi, approved two weeks later.

3.2- Sovaldi ®, the jewel in the crown

"*Sovaldi is the first drug that has demonstrated safety and efficacy to treat certain types of HCV infection without the need for co-administration of interferon.*

"Today's approval represents a significant shift in the treatment paradigm for some patients with chronic hepatitis C," said Edward Cox, M.D., director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research.

[…]

Results from all clinical trials showed a treatment regimen containing Sovaldi was effective in treating multiple types of the hepatitis C virus. Additionally, Sovaldi demonstrated efficacy in participants who could not tolerate or take an interferon-based treatment regimen and in participants with liver cancer awaiting liver transplantation, addressing unmet medical needs in these populations." (FDA news release. Dec. 6, 2013)

Sofosbuvir (generic name for brand-name Sovaldi) is a nucleotide analog inhibitor that blocks the NS5B protein, which plays a role in the replication of HCV and is involved in creating copies of the viral RNA genome.

GENOTYPE	DURATION	TREATMENT	CURE RATE
1 OR 4	12 WEEKS	SOVALDI + ribavirin + peginterferon alfa	89% / 96%
2	12 WEEKS	SOVALDI + ribavirin	93%
3	24 WEEKS	SOVALDI + ribavirin	84%

Source: (sovaldi.com)

With just a quick glance we can easily see Sovaldi's potential: no need of interferon in genotypes 2 and 3 plus higher cure rates and shorter duration treatment plus higher cure rates for genotypes 1 and 4, although interferon is still necessary.

Let's summarize the information about all available treatments so far:

Genotype	Treatment	Cure Rate	Interferon?	Duration (weeks)
1	Double th	< 50%	Yes	48
	Triple th	< 70%	Yes	24-48
	Olysio	80%	Yes	24-48
	Sovaldi	89%	Yes	12
2	Double th	70-80%	Yes	24
	Sovaldi	93%	No	12
3	Double th	70-80%	Yes	24
	Sovaldi	84%	No	24
4	Double th	< 50%	Yes	48
	Sovaldi	96%	Yes	12

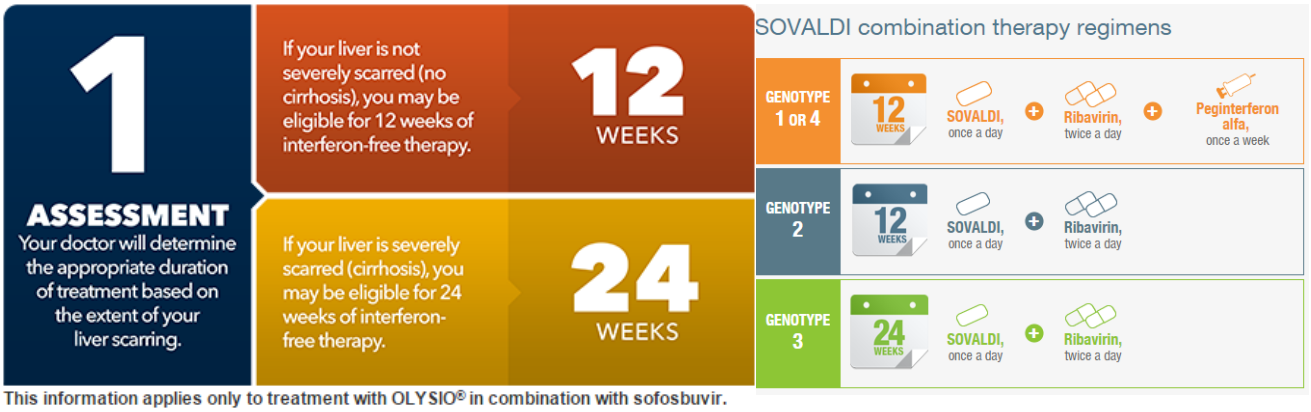
3.3- Combination Sofosbuvir-Simeprevir, towards excellence

Gilead's Sovaldi was the "*one giant leap for mankind*" in hepatitis C, but market never gives a rest. For genotype 1, interferon is still necessary and cure rate improvable (remember genotype 1 is the most common one in developed countries). However, there was no need to wait any longer for a new amazing drug; solution was in the market already.

On 11th November, 2014 FDA approved sofosbuvir and simeprevir (Sovaldi – Olysio) in combination in an interferon-free treatment (ribavirin was necessary in some cases). Trials found an effectiveness of around 95%. Although approval came in late 2014, the combination was being prescribed off-label in advance, a common practice (20%) in the US. Since when? That's hard to say with exactitude, but in April Janssen (Olysio's pharmaceutical owner) announced the start of two Phase 3 trials (investor.jnj.com). If we take a look at sales of both drugs, we can extract some conclusions (the data was obtained from both pharmaceuticals' annual reports):

	Sales (Millions USD)		Growth	
	Olysio	Sovaldi	Olysio	Sovaldi
Q4 2013	23	139		
Q1 2014	354	2274	1439%	1536%
Q2 2014	831	3481	135%	53%
Q3 2014	796	2816	-4%	-19%
Q4 2014	321	1732	-60%	-38%

Outstanding growth of Olysio in the second quarter with respect to the first one in comparison to Sovaldi's suggests that off-label prescription reached its peak in second quarter and benefited Olysio by linking its sales to blockbuster Sovaldi. Also, a study carried out by the American Association for the Study of Liver Diseases about the cost of sofosbuvir+simeprevir treatment published in July 2014 recognizes that *"SOF/SMV is currently used off-label"*. A critical aspect for Olysio after approval is that the combination of simeprevir plus peginterferon plus ribavirin for genotype 1 is no longer a recommended or alternative regimen. Actually, if we go to both Olysio and Sovaldi official webpages where "how to take" each drug is explained, the difference is subtle but revealing.

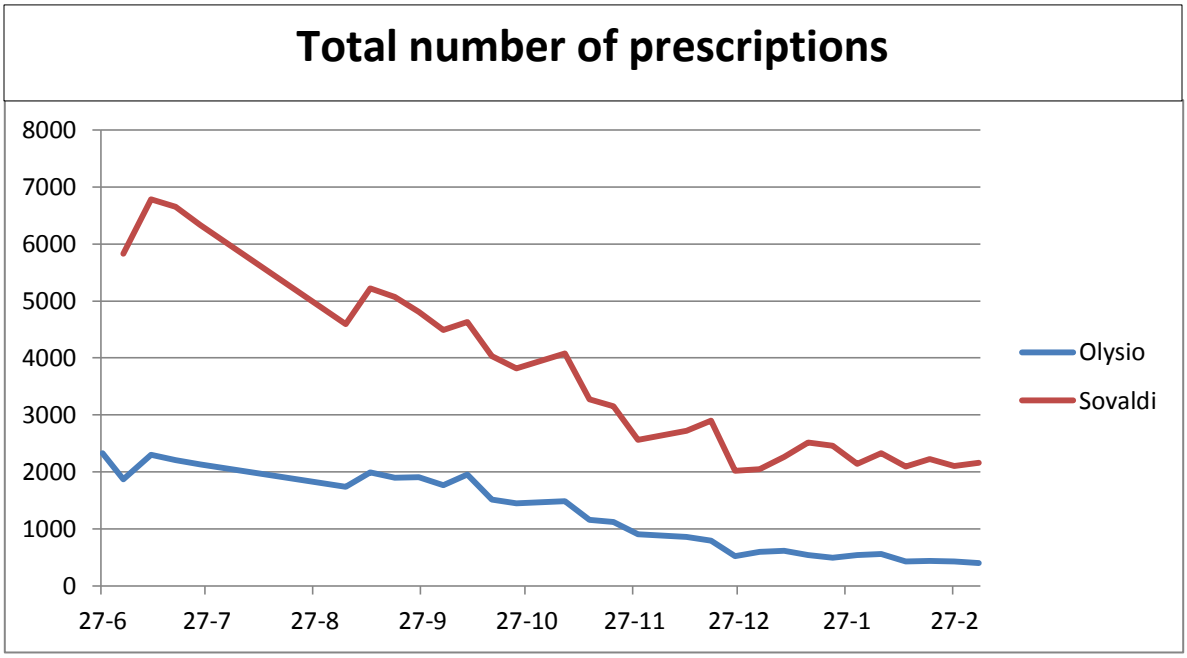


(olysio.com / sovaldi.com)

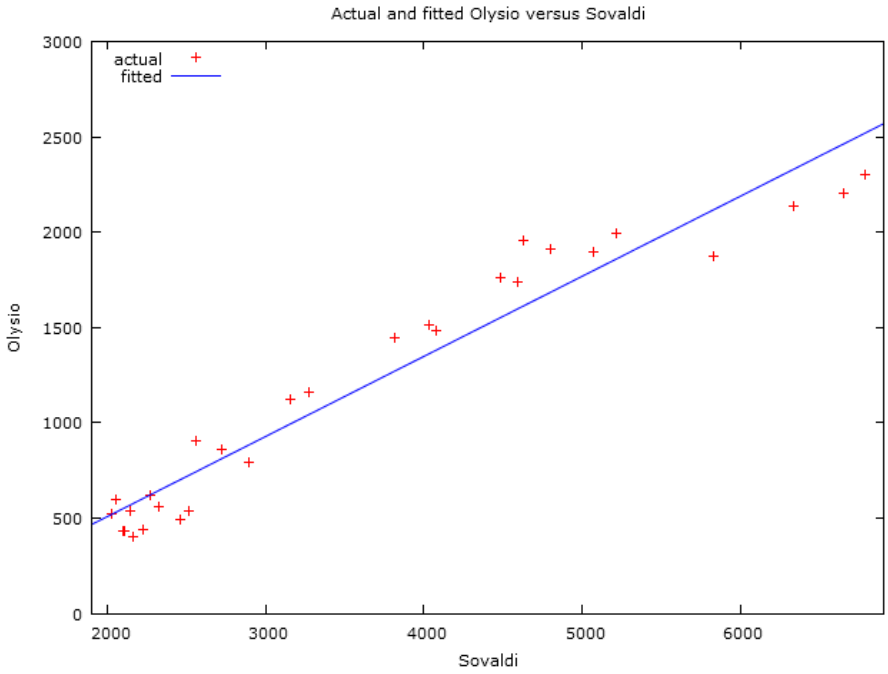
Olysio webpage: "*This information applies only in combination with sofosbuvir*", while there is no trace of the word "simeprevir" at Sovaldi's.

This situation leaves Olysio in a position of weakness. It depends practically in its totality of its complement Sovaldi. This was good in the short term as we have seen, because it helped to boost its revenues to margins they didn't expect. However, in the long run, this is too dangerous due to its non-mutual excessively high degree of complementarity.

If we take a look at the data about sales of each drug, this fact becomes evident:



If we conduct a simple regression analysis to see how the sales of both drugs relate to each other where Olysio's number of prescriptions is the dependent variable and Sovaldi's the independent one, we get an OLS (Ordinary Least Squares model) represented in the following figure:



In our model we got an $R^2 = 0.936658$, which is very high and confirms what was said before, the existence of a strong dependence of Olysio on Sovaldi.[1]

[1] "R^2 is the ratio of the explained variation compared to the total variation; thus, it is interpreted as the fraction of the sample variation in y that is explained by x. If the data points all lie on the same line, OLS provides a perfect fit to the data ($R^2 = 1$)." (Wooldridge)

4- MARKET ANALYSIS

Once explained the situation, it is time now to identify the different players and try to analyze and explain each one's objectives.

We have three different players here: the patients, the payers, and the industry. The patients are the people who suffer the disease, the payer is usually the Government (the case of Spain), and the industry so far in this case is represented by Gilead Sciences, the owner of both blockbuster Sovaldi and Harvoni.

These three parts are the ones in charge of reaching an agreement. However, it is complicated that the final agreement will satisfy all of them, as their objectives are very different from one another and there are many constraints.

The appearance of Sovaldi has been a headache for all the Governments and patients of wealthiest countries of the world. Aware of the breakthrough quality of its product, Gilead Sciences has set a range of very high prices for the standards of local wealth.

COUNTRY	SOVALDI PRICE ($)
USA	84000
GERMANY	67000
ITALY	63000
CANADA	55000
UK	57000
SPAIN	47339
FRANCE	44618

(Forbes)

These are the prices for standard 12-week treatment. On the other side, we find that Gilead allowed seven pharmaceuticals in India to produce sofosbuvir in a generic way at a selling price of 700$. This will be exclusively for 90 low-income countries.

In Spain, this situation has caused a lot of controversy. Government and pharmaceutical have been negotiating for months delaying the final agreement, and social pressure was one of the main reasons of the resignation of former Minister of Health Ana Mato.

What drives each part's actions to act the way they do?

4.1- The Patients

This group is the origin of the problem, as they find themselves in the necessity of getting the treatment. What was supposed to be good news for them as it is the appearance of such a revolutionary product like Sovaldi has turned into a tireless struggle. The "Plataforma de Afectados por la Hepatitis C" (PAHC) has carried out lots of demonstrations including a confinements in several hospitals. How to explain that a situation that should be better seems worse than before?

We could explain this situation by using the concept of utility, and representing the patients' utility in both cases:

When we talk about consumer's choice in traditional microeconomics problems and try to represent it, we base the analysis in two elements: the individual's preferences (represented by the utility function) and the individual's budget constraint. In this case, we cannot talk about budget as patients don't have to pay for the treatment. Therefore, patients face a situation where they'll seek to maximize their utility. For a patient, the utility of a medicine is given by its quality in terms of ability to cure, and could be expressed mathematically like this:

$$U(q_i) = q_i - \beta(q_{max} - q_i)$$

where q_i represents the quality of the medicine taken by the patient, q_{max} the maximum quality available in the market and β is a subjective factor which reflects the perception of the patient about how good the treatment he receives is taking into account the available treatments. This way, if a patient receives the best medicine available, we have that

$$q_i = q_{max}\ and, therefore\ U(q_i) = q_{max} = U_{max}$$

This patient is obtaining the highest possible utility under his circumstances.

What happens if the patient does not receive one of the new generation medicines? The situation would be the following:

$$q_i < q_{max}\ and, therefore\ U(q_i) < U_{max}$$

And what's more, it is not just that the patient gets a utility lower than the maximum, it is also lower than the quality of the medicine itself due to the effect of the term $\beta(q_{max} - q_i)$. This is due to the feeling of unfairness that is experienced by him/her when the best medicine is not received.

Before Sovaldi, at t-1, the traditional treatment (that we will denominate "old" from now on) q^{old} was the best available combination of drugs and hence $q^{old} = q^{t-1}_{max}$ offer a certain utility to the patients:

$$U(old) = q^{Old}$$

$$q^{Old} > 0$$

Therefore, patients receiving the treatment obtained a utility of q^{old}, which is the q^{t-1}_{max} , we have above, while the ones who don't receive it get a utility equal to zero.

After Sovaldi, at period t, $q^{t}_{max} = q^{Sov}$ and we have two different situations: the group of people still getting the old treatments even though new medicines are available, and the ones receiving Sovaldi.

$$U(old, \{old, Sov\}) = x'$$

$$q^{Old} > x' > 0$$

$$U(Sov, \{old, Sov\}) = q^{Sov}$$

$$q^{Sov} > q^{Old} > x' > 0$$

Now we have a different situation: Sovaldi gives us the new highest utility $q^{t}_{max} = q^{Sov}$. What happens to patients receiving old treatments? Before Sovaldi, they got a utility equal to q^{old}, but now they do not receive this utility but a lower one. Why? Due to the factor $\beta(q^{t}_{max} - q_i)$. The feeling of inequality caused by the difference in qualities reduces the utility perceived by them. This makes them feel discriminated (in greater or lesser extent depending on the individual) and with the perception that they are worse off even though, technically (or medically) speaking, they are in the same situation as before.

This factor β will vary from one individual to another, and depend on several factors such as personality against discriminations, disease status, wealth… But it cannot be ignored. The feeling of fairness may depend on the available treatments at hand.

This simple explanation can help to explain the observed reaction of the patients, their demonstrations and strong efforts pressuring the Government to get Sovaldi and why the topic has become so popular occupying lots of hours on TV.

How to measure quality?

When we talk about "quality" it may seem we are talking about a subjective or abstract concept, but nothing further.

During the approach of the topic and the evolution of the market of new medicines, several easily-quantifiable factors have been emphasized to demonstrate the power of these new treatments.

Main and most evident one is the cure rate. The higher the better. But there are more: we have also talked about the importance of quitting interferon, as this was a big source of side effects. It is also important to reduce the duration of the treatment in order to reduce the drop rate.

$$q_i = \alpha \cdot Cure + \beta \cdot FewerSideEff + \gamma \cdot Duration^{-1} + \delta \cdot other$$

$$\alpha + \beta + \gamma + \delta = 1$$

The addition of all of them has to be equal to one because this is a quality index, and each factor is assigned a different fraction depending on their relative importance to the quality of the medicine. The term "other" refers to some other effects that may affect the patient during the treatment and that depend on him/her, for example, ease of administration.

The value of factors will depend on the patients, but if it is the Government who decides on this, they will need to use an average. For example, a regular person will assign a higher level to alpha as this person values the cure rate, but an intolerant patient may obtain a higher value from a lower-side-effects drug and duration of the treatment. However, in this comparison between Sovaldi and old medicines, the evaluation is easy as Sovaldi

overcomes incumbents in every single factor. That means that no matter what weight you assign to each factor, the quality will always be higher with Sovaldi. This comparison will make more sense when more competitors enter the market.

Once analyzed what the patients want, what will the Government (the payer) do? The patients will only accept Sovaldi as we have just seen; it is now turn for the Government to negotiate.

4.2- The payers

When it comes to talk about payers, it is obvious that the main element in the discussion is money. How much? To pay or not to pay, that's the question. If the payer is the Government, as it happens in most of the countries, some other factors such as social pressure, ideology or the proximity of the next elections can grow money trees or look away.

However, as serious as this issue is, there are two perspectives to be taken into account, which are the short and long term.

The short term perspective

Roughly speaking, calculating the impact of the high prices we have seen before is very easy if you have the data (which, unfortunately, is not public knowledge). If we assume that all patients were being treated with the triple therapy (Interferon + ribavirin + Simeprevir [Olysio®]) and from now on the ideal situation is treating them with the double therapy Simeprevir[Olysio®] + Sofosbuvir[Sovaldi®] it is as easy as calculating the difference between Interferon + Ribavirin and Sovaldi and then multiply it by the total number of patients in order to see its total impact and check whether you can afford that level of expenditure.

Taking the data from US (obtained at hepatitis.uw.edu): "*a typical 12-week treatment course of simeprevir when used with a total of 24-weeks of peginterferon plus ribavirin will cost approximately $85,000. A 12-week course of simeprevir plus sofosbuvir costs approximately $150,000*"

That makes a difference of $65,000 per patient. Multiplied by the 140 thousand patients that are currently being treated in US (and supposes just a 9% of total population infected) (Gilead Sciences annual report, 2014), we have an increase of $9,100,000,000. More than 9 billion dollars extra.

"The new issue of the Annals of Internal Medicine, the journal published by the American College of Physicians, says the new costs of hepatitis C treatments are "reaching an average of $27 billion a year, which is equivalent to 10 percent of U.S. prescription spending," researchers at M.D. Anderson Cancer Center wrote in the March 17 issue" (forbes.com)

Of course US represent the furthest point, and exact figures have to be adapted to each country, but what does not change is that there is not a feasible way to afford this problem in the short term.

In Spain, the Ministry of Health approved the 1st of November a plan of € 125 million funding for Sovaldi, which according to calculations of the PAHC would help to treat around 5000 patients among a total of 300,000. The 25th of February of 2015, president of Spain Mariano Rajoy promised in the "Debate on the State of the Nation" that "*We will be the first country to give a global solution to this problem because now it is possible"* (laSexta). He did not specify how exactly is going to manage it.

The long term perspective

Sovaldi is impressive and that makes it very expensive, but, is it worth it? What do Governments think when they are asked to pay such a high amount of money for a medicine?

Once overcome the initial "short-term shock", there are many factors to be considered by Governments in order to set a price they consider fair to negotiate with the pharmaceutical. The main problem with HCV is that nowadays it is one of the main agents that cause chronic liver disease and, therefore, one of the most common causes of cirrhosis, cancer and liver transplantation as said in the beginning of this paper. In Spain, Hepatitis c is the

responsible of the 45% of liver transplantations, being its cost around € 130,000 per transplantation.

Quality of life and life itself are also crucial factors to be taken into account. How much life is? Can it possibly have a price? Article 3 of The Universal Declaration of Human Rights states that "Everyone has the right to life, liberty and security of person". However, since health care resources are inevitably limited, Governments are required to use methods that may seem heartless.

The quality-adjusted life-year (QALY) is a measure of disease burden, including both the quality and the quantity of life lived. It is used in assessing the value for money of a medical intervention. The idea is simple: it consists on multiplying the extra life years after the intervention by the quality of those years. A perfect health would receive a value equal to 1, while a year of life lived in a state of less than this perfect health is worth less than 1.

Many reports have been carried on based on this tool, and almost all of them agree that Sovaldi (and, by extension, all the new generation medicines) is worth it, that means, treating all patients is cost effective. Taking one of them as example: "*the UK's National Institute for Health and Care Excellence (NICE) just approved the drug as being cost-effective, and recommended it for subgroups of patients*"(Forbes). Briefly, the article says that "*the private (long-run cost savings) and social (huge gain in QALYs and very low cost per QALY) benefits absolutely justify the price. This is where NICE's decision to recommend Sovaldi becomes instructive."*

So Governments find themselves in front of an uncomfortable situation: Sovaldi is cost-effective but they can't afford it. Both pharmaceutical and payers will need to work together to develop payment models that split some of the risks of these drugs, and one example of it is the "value-based contract".

4.3- The Industry

Gilead Sciences is the last player in this game to be analyzed. It is unquestionable that they find in a position of power, but for how long? How will the market evolve? To answer all

these questions first we need to introduce what happened while Gilead was commercializing and negotiating Sovaldi around the world.

5- SECOND SERIES OF NEW-GENERATION MEDICINES

2014 was the year when Sovaldi broke into our lives, however, this was just a starting point. The optimal treatment consisted on the combination of two different pills (Olysio and Sovaldi) from two different pharmaceuticals. There was still a big room for improvement for both incumbents and potential entrants.

5.1- Harvoni®

Why settle with half of the monopoly if we can have it all for ourselves? Something like that is probably what came to Gilead Sciences' managers' heads. And so they did.

On October 10th, 2014 FDA approved Harvoni, the first combination pill approved to treat chronic HCV genotype 1 infection. Just one pill: a combination of sofosbuvir (Sovaldi) and ledipasvir, an NS5A Inhibitor which could substitute simeprevir's functions.

"In the first trial, comprised of treatment-naive participants, 94 percent of those who received Harvoni for eight weeks and 96 percent of those who received Harvoni for 12 weeks achieved SVR.

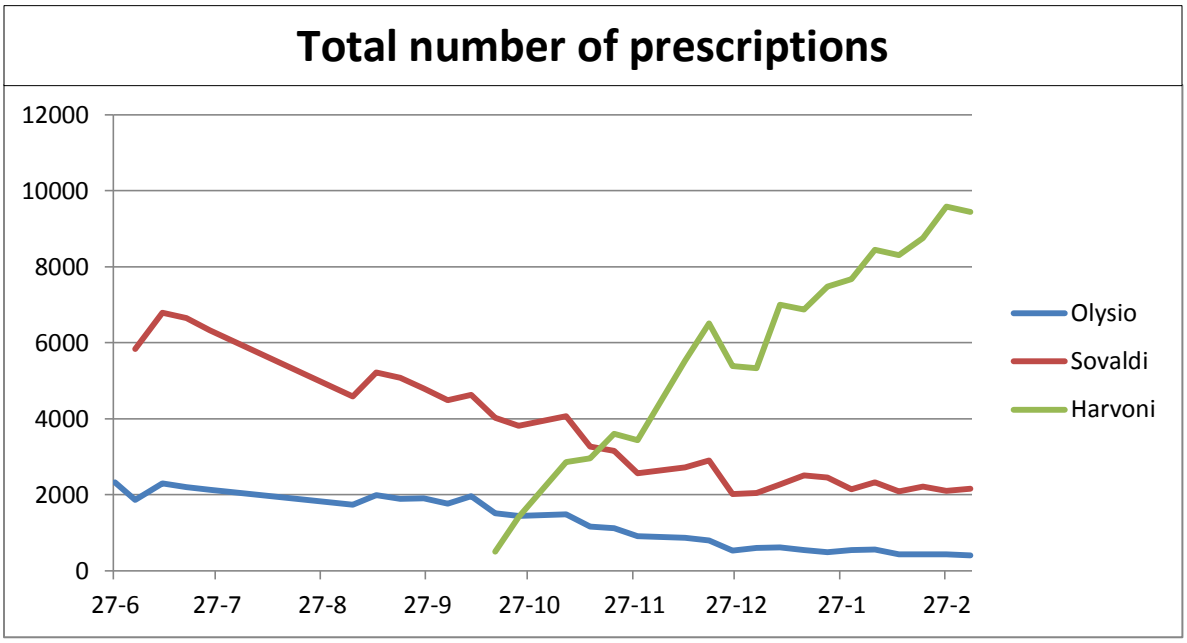
The second trial showed 99 percent of such participants with and without cirrhosis achieved SVR after 12 weeks.

And in the third trial, which examined Harvoni's efficacy in treatment-experienced participants with and without cirrhosis, 94 percent of those who received Harvoni for 12 weeks and 99 percent of those who received Harvoni for 24 weeks achieved SVR. In all trials, ribavirin did not increase response rates in the participants." (FDA news release Oct. 22, 2014).

With Harvoni, Gilead gave a demonstration of authority: one pill per day, for between 8 to 24 weeks, SVR consistently above 90% and first ones to enter the market (remember that

Harvoni was officially approved one month earlier than sofosbuvir-simeprevir combination).

Harvoni came to the market to become the substitute for Olysio-Sovaldi combination, with the addition that both Sovaldi and Harvoni belong to Gilead.



(data provided by Bloomberg)

We can easily see in this figure how Harvoni is conquering the market. How did it happen?

Before Harvoni was launched, the patients faced the following situation: a double monopoly by Sovaldi and Olysio. Both monopolies calculated their prices in an attempt to maximize their profits. However, both drugs have to be consumed together

To explain the consequences of this double monopoly on perfect complementary goods, let us consider a representative consumer that includes the patient wellbeing as well as the costs of the treatment. This representative consumer will have to consume the same quantity of both drugs $Q_T = \min \{q_s^*, q_o^*\}$. Hence, if the patients need to consume both products, the demand of the composite drug will be

$$Q_T = A - B * (p_s^* + p_o^*)$$

And $q_s^* = q_o^*$ = Q_T.

Consequently, Sovaldi (s) and Olysio (o) will respectively look at the demand functions:

$$q_s = A - B * (p_s + p_o)$$

$$q_o = A - B * (p_s + p_o)$$

And face respectively a cost function:

$$C(q_s) = FC_S + VC_S * q_S$$

$$C(q_o) = FC_O + VC_O * q_o$$

When maximizing profits, each firm will obtain the optimal quantity from its point of view at the level where Marginal Cost equals Marginal Revenue, and its optimal prize substituting that quantity in the demand function:

$$[q_s^*, p_s^*]; [q_o^*, p_o^*]$$

Where Sovaldi (similarly Olysio) will maximize with respect to p_s the profit function:

$$Profit_s = (p_s - c_s)\big(A - B\ (p_s + p_o)\big) - F_s$$

From the first order derivative

$$A - B(p_s + p_o) - B(p_s - c_s) = 0$$

This can be written as

$$(A + Bc_s) - B(2p_s + p_o) = 0$$

Similarly, for Olysio we find

$$(A + Bc_o) - B(p_s + 2p_o) = 0$$

And we get

$$p_s^* = \frac{A+2Bc_s-Bc_o}{3B} \qquad p_o^* = \frac{A+2Bc_o-Bc_s}{3B}$$

Substituting these prices in the demand functions, we get $q_o^* = q_s^* = Q_T^*$

$$Q_T = \frac{A - B(c_o + c_s)}{3}$$

And the profits

$$Profits_s = \frac{[A - B(c_o + c_s)]^2}{9B} - F_s$$

$$Profits_o = \frac{[A - B(c_o + c_s)]^2}{9B} - F_o$$

If the two firms merge and decide on the prices of their drugs in a cooperative way or, equivalently, if a single monopolist would be selling the composite drug in the market, then firms will maximize the total profits

$$Profits_M = (p_M - c_s - c_o)(A - B * p_M) - F_s - F_o$$

With respect to p_M which we can understand as the total price for the treatment $p_M = (p_s + p_o)$. Solving this problem we obtain

$$A - B * p_M - B(p_M - c_o - c_s) = 0$$

And

$$p_M^* = \frac{A + Bc_o + Bc_s}{2B}$$

$$Q_M = \frac{A - B(c_s + c_o)}{2}$$

$$Profits_M = \frac{[A - B(c_s + c_o)]^2}{4B} - F_S - F_O$$

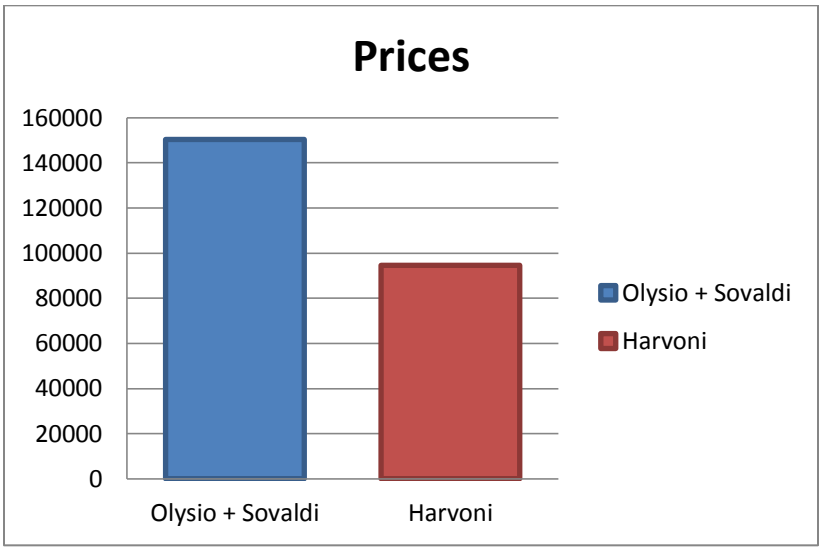
From the previous calculations it is easy to see that $p_M^* < p_s^* + p_o^*$. In addition, at the price $p_M^*$the total profits for the pharmaceutical firms are larger, and more patients will be treated. This is the so call double marginalization problem. In particular it illustrates that a firm

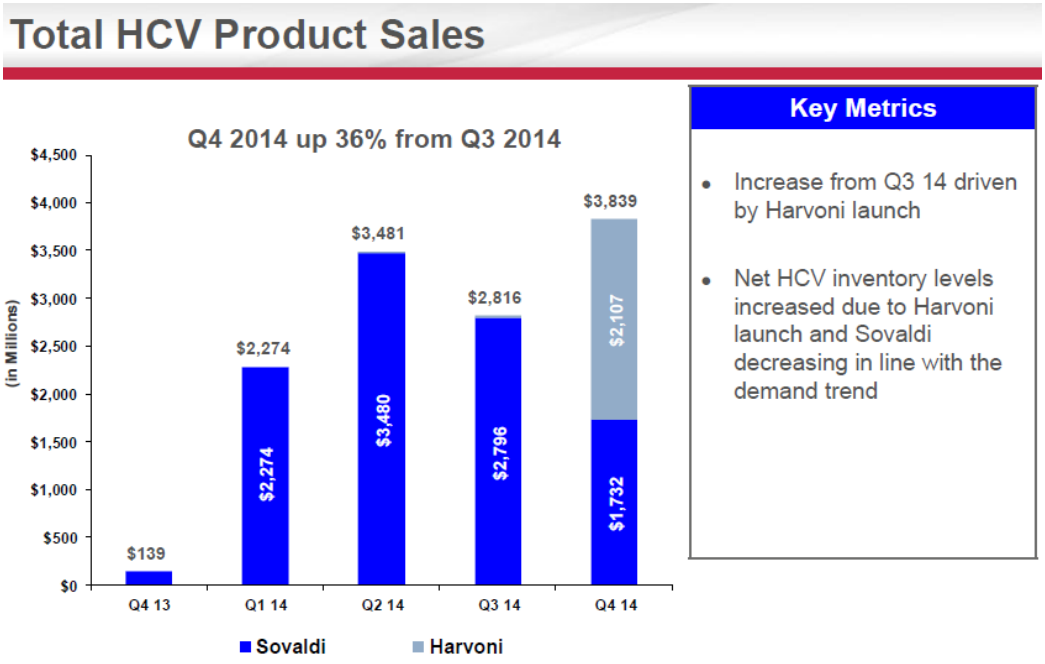
selling a composite drug will make more profits not only than that of the firms selling one component (which is obvious) but also more than both of them together. This provides strong incentives to develop such a composite drug.

Gilead Sciences: they were selling a quantity q_s at a price p_s before, and now they will sell a quantity q_H at a price p_H.

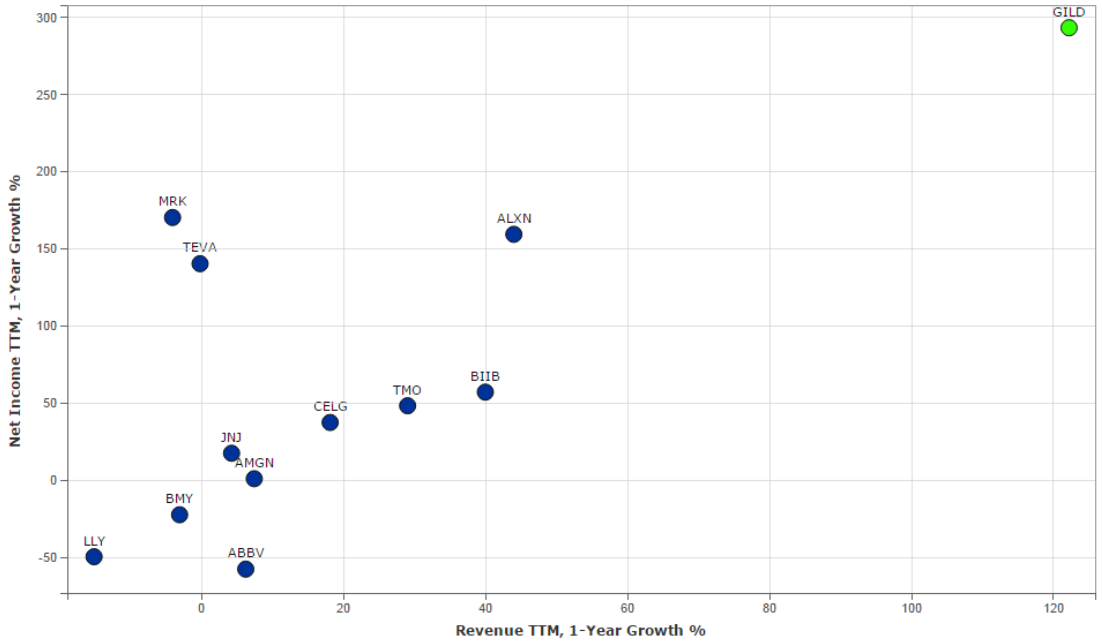
$$q_H > q_s \,;\, (P_s^* + P_o^*) > P_H > P_S^*$$

So we have that Harvoni sells a higher quantity at a higher price than its predecessor Sovaldi, which will be translated in a higher profit. This extra profit obtained by Gilead Sciences is the incentives to R&D which benefits society in a higher surplus due to the creation of value. Next two figures along with previous one about the total number of prescriptions support our previous discussion: that Harvoni would get the whole market (it's on the way), that it would have (It does) a lower price and that its profits are higher:

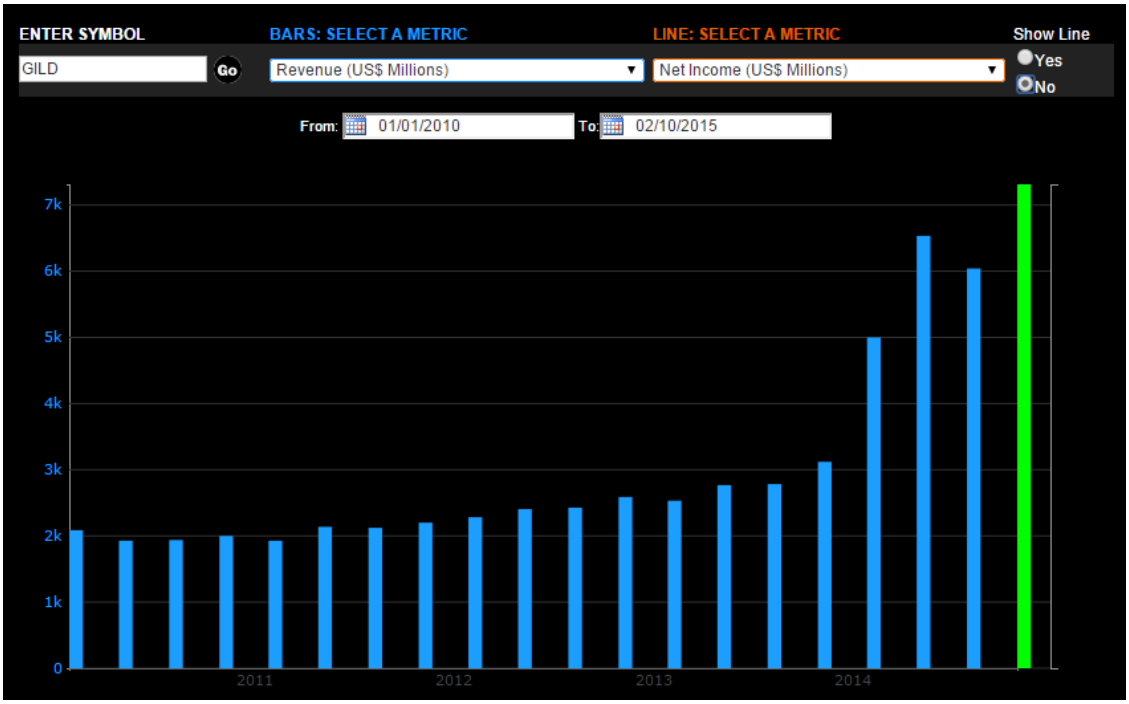




To finish with the data and figures, the next two scatterplots obtained at capitalmarketlabs.com will give us the definite insight about the magnitude of the hepatitis c market. The first one shows the growth in both revenues and net income in percentage terms of the biggest pharmaceuticals in the world during 2014. Astonishing Gilead Sciences has clearly beaten its opponents thanks to Sovaldi and Harvoni.



In the next one we can observe that Gilead's revenues since 2010 to 2014 were steady but it has increased very much in the last year, showing very clearly that these higher earnings don't come from an upward trend but from the spectacular performance of its two star products:



6- CONCLUSION

This report is all about an economic analysis of the appearance of new medicines for the hepatitis C and the shock they have supposed for the society in general and the patients, the Governments and pharmaceutical companies in particular.

The interest lay in that this had become a national issue due to the magnitude of the problem, which affected many people either direct or indirectly. Besides, the reasoning carried out to analyze and explain each part's behavior can be applied not just for the case of hepatitis C but for many other discoveries that may come in the future in the field of the medicine.

The conclusion is clear, and probably obvious without the necessity of developing any studies about the issue: the appearance of new products (in this case Sovaldi et al.) is positive for the society because of the extra value generated. The problem comes when considering how much of this value creation corresponds to each part involved, but that is a discussion related to morality, ideology and personal situations that has no space in here.

This has been an interesting case of study as we have been able to observe the creation of a new market with the situation of a double monopoly and its evolution towards a more efficient form of a unique monopoly. The market is expected to keep changing because of the big returns on investment.

What we could see throughout this work is that Gilead Sciences has been beneficiary of being the first mover to the new market, exploiting its resources at incredible breakthrough levels, recovering its investment during the first year and generating huge profits. They have taken advantage of their monopolistic situation in the market, which allows them to charge higher prices to maximize their profits. This situation is not new at all as it happens very often in our daily lives in different sectors (for example in the supply of electricity). The only way for this situation to change is waiting for the market evolution towards more competitive forms (duopolies, oligopolies, perfect competition). Actually, the pharmaceutical ABBVIE has already developed and commercialized a product named Viekira Pak® which has the intention of competing with Harvoni. This increasing competition will decrease prices and balance the current situation with the patients.

From a different point of view, the same way that, as we have seen, both companies (Gilead and JNJ) would gain if they merged, the European Governments could gain as well by unifying themselves in negotiations with the pharmaceuticals to get a lower price.

Another conclusion that we can extract from this report is the importance of investing in R&D. Nowadays, investments in R&D have decreased substantially due to this never-ending economic crisis because it is considered to be very costly and long-term oriented. However, we can see here how the Governments have to pay now the opportunity cost of not investing before. And it is not cheap.

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