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High prices of new drugs: we are ready to do whatever it takes

Stefano Capri*

Abstract
Debates over pricing and reimbursement of new and innovative drugs have become increasingly dominated by the excessive high prices and the challenges to the sustainability of the public expenditures. This paper examines the phenomenon of raising prices through the examples of oncology and hepatitis C drugs. In many cases the cost is not related to the benefit promised by the treatment. The costs of R&D of a drug seem to be shrouded in a cloud of mystery, while pharmaceutical companies are still struggling to provide their real R&D costs. The hostage theory is described here in order to explain the lack of instruments which are currently applied to evaluate a new drug. Finally some tentative algoritms are revised, and the need for a combination of cost-effectiveness and budget impact is proposed, trying to combine the private interest with the public interest.

Keywords: Innovation, R&D cost; Pharmaceutical drugs, Italian National Health Service, Health expenditure, Cost-effectiveness.

JEL Codes: D40, G35, H51, I11, I18, L11, L65.

1. Introduction

Let's imagine calling a plumber for an emergency following a water leak in our washing machine. The plumber arrives promptly, repairs the fault and asks us to pay 3,000 euros because thanks to his intervention we avoided the flooding of the kitchen, the collapse of a wall, and the damage to the room downstairs to ours, a set of damages that would have cost us probably 6-7,000 euros. Obviously we would be astonished by such a request and we would be convinced that we would only have to pay him the price of the intervention, that is to say a much lower amount, and not a proportion of any damage avoided. When we talk about the value of a medicine, we often use this avoided event logic to justify its high price, forgetting that this is only one of the components that must be taken into account when forming the price (Arzymanow and Manning, 2013).

As we will see later, certainly the value of the drug is represented by the effectiveness it deploys (the years of life it saves, the infections it solves, the cardiovascular events it avoids, etc.), but this value must be contextualized in a more complex evaluation process. It is impossible not to recall here the difference between the value in use and

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the exchange value of a good: the exchange value of a bottle of water can be a few cents, but if we are in Death Valley with a dehydration principle, its value in use is extremely high, but a price of a thousand dollars would not be justified!

This is what pharmaceutical companies often claim to justify the high prices of new drugs, as well as the high costs incurred for research and development (R&D). But in order to address the problem of high prices and therefore high expenditure, the phenomenon must first be described.

At the end of 2017, a drug with a price of US$475,000 (about €410,000) was introduced in the USA for a single treatment in oncology (acute lymphoblastic leukaemia), compared to a probable life extension of 1 year in 80% of cases (Bach and Giralt, 2017). This is to date the most expensive drug ever appeared in oncology, and not only in oncology, except for some drugs used for rare diseases (for rare diseases there are now many treatments that cost one million euros and even more per year, and this figure is spent throughout the patient's life) (Medica et al, 2017) . Does it make sense to spend similar amounts? Is it sustainable for a health system, even imagining that in Italy the price could be, when it is approved, slightly lower? Is the road opening up to a scenario in which only those able to pay will be able to live a few months longer, while all the others, that is, the majority, will remain watching the new technologies without being able to use them?

Certainly, drugs are the technology that more than any other contributes to saving lives, to restoring good health, to increasing life expectancy. Today it is quite normal to be treated with antibiotics, but before their discovery the probability of dying from a trivial surgery due to an infection was very high and almost always an episode of pneumonia led to the death of the patient. As for diseases that were once incurable, such as tumors, today in some cases there is a cure (i.e. the patient heals), and for many tumors survival has been significantly prolonged.

While some new drugs are very effective, to the point of being considered innovations, many others do not add significant advantages over the drugs already available. However, new drugs almost always have increasing prices, as if novelty and not innovativeness could be a good justification. Thus, in recent years, there has been a sometimes limited increase in efficacy, except in rare cases, but a generalised increase in drug prices, which immediately translates into an increasing cost to the healthcare system for the treatment of a specific disease. Apart from the example just reported,

cancer drugs now often exceed €5,000 for one month's treatment in Italy and US$10,000 in the USA (OECD, 2018).

The high prices of some drugs are reflected in the entire pharmaceutical expenditure. In the countries of the OECD area pharmaceutical expenditure absorbs about 20% of the total health expenditure and in Italy it amounts to 19.7% (€29.8 billion) (Osservatorio Nazionale sull'impiego dei Medicinali, 2018), equal to 1.75% of GDP (ISTAT, 2017).

The following is the case of drugs to treat cancer, with high prices and sometimes low efficacy, and that of hepatitis C drugs, which are extremely effective but excessively expensive.

2. Oncology drugs could cost about €100,000 for one year treatment

With therapy costs ranging from €40,000 to €100,000 per year for a single patient, in Italy public spending on drugs in oncology has more than quadrupled in just eight years, reaching €5 billion in 2017, when it was only €1 billion in 2007 (Osservatorio Nazionale sull'impiego dei Medicinali, 2018), making it the first therapeutic category with the highest public spending. More than US$ 133 billion is spent each year on cancer therapies worldwide, and it is estimated that it will reach US$ 180-200 billion in five years (IQVIA Institute).

This unprecedented increase in drug prices in history has been accompanied from the outset by the recognition of therapeutic benefits and, above all, by the justification for high investment in research and development and, of course, by the attribution of high prices for what is scientifically complex and innovative. As it cannot escape the reader, in other industrial sectors these elements that justify high prices are translated into low prices: technological innovation tends to reduce costs and prices. Certainly in health care, due to various factors summarized in the market failure (in short, the price of a good is not determined by the simple encounter between supply and demand, and similarly its consumption), costs tend to increase. However, the pharmaceutical sector has many similarities with other industrial sectors, while recognising on average higher R&D costs, and therefore this price shift can be corrected, as we will see. At this point, the recent price history of the oncology case, the development of the effectiveness of these drugs, R&D cost considerations should be analysed.

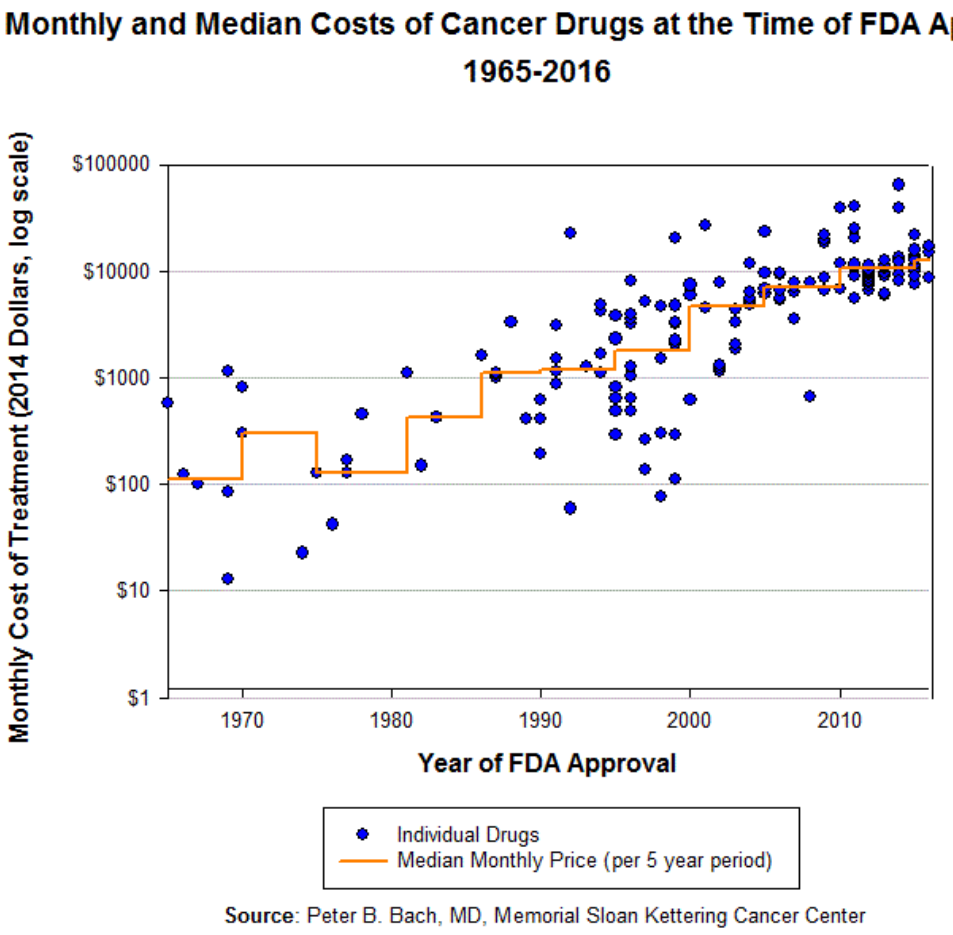
Contrary to what we should have expected, it was not we economists who raised the alarm about the rising prices of drugs for cancer treatment, but oncologists, and not in Europe, where there is certainly greater sensitivity to health spending, given the prevalence of public systems, but in the United States, the country with the highest share of private spending (a total public health expenditure that could absorb 20% of GDP in 2026) (Centers for Medicaid & Medicare Services, 2017).

Some American oncologists, in a country where drugs have always cost more than in any other country in the world, realized that the soaring prices were beginning to be unexpectedly exaggerated, especially taking into account how, in most cases, it was not justified by a proportionate increase in the effectiveness and safety of the drugs themselves (Kantarjian et al, 2013; Light and Kantarjian, 2013). Also the Trump Administration, often not very attentive to the real problems of the country, has published a document (U.S. Department of Health & Human Services, 2018) in which the prices of medicines are requested to be reduced (indeed, without providing the instruments).

Since 2012, 78 new cancer therapies have been launched on the market for 24 types of cancer, many of them with more than one indication. In the United States alone, US$50 billion was spent in 2017, and this figure is set to double in 2022.

Figure 1 illustrates the phenomenon well.

Figure 1



Peter B. Bach, Memorial Sloan-Kettering Cancer Center, available at: www.mskcc.org/research-areas/programs-centers/health-policy-outcomes/cost-drugs

The same trend is recorded proportionally in all advanced countries, including Italy.

In the UK, before 2000, there were 69 cancer treatments available. The median duration of treatment with the new drugs increased from 181 days to 263 days. The average cost per treatment rose from £3,036 (equivalent to 20.6% of UK GDP per capita) to £20,233 (89% of GDP per capita) in 2005-2009, and to £35,383 (141.7% of GDP per capita) in 2010-2014 (Savage and Mahmoud, 2015).

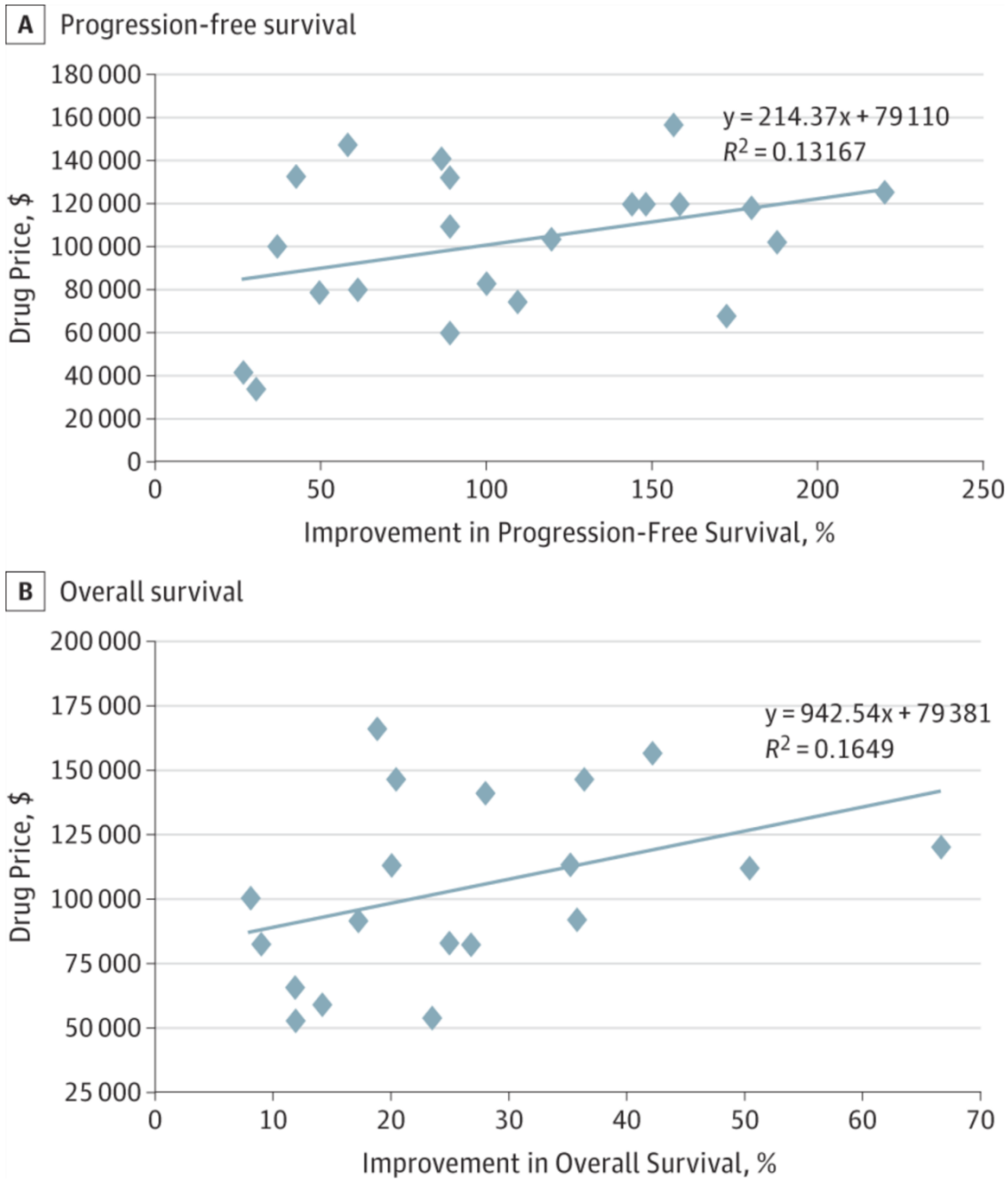
The correlation between health expenditure and life expectancy at birth has been verified for a long time, but not the same for medicines. In countries where more is spent on health care, individuals live longer (in the period 1995-2015 it is estimated that 35.2% of life expectancy is determined by health spending, 22.4% by income, 23.8% by the level of education and the remaining 13% by the reduction in tobacco

and alcohol consumption) (OECD, 2017). This was one of the first elements of empirical analysis of the health economics, when since the 1960s this positive correlation was identified. Health expenditure is not the only important variable, even if it is the dominant one, and its weight varies from country to country. The borderline case is represented by the USA which, spending more than any other country in relation to its GDP, has a life expectancy lower than the majority of the countries they are confronted with.

In the case of drugs, on the other hand, there seems to be no relation between the number of deaths from cancer per 100.00 inhabitants and the per capita expenditure for cancer treatment. This seems to be true for tumors in general, but also for the most common tumors such as lung, breast, colorectal and prostate cancer (Uyl-de Groot et al, 2014). A possible explanation, in addition to the weak correspondence between cancer drug prices and survival, seems to be the different conditions of access to treatment and lifestyles in different countries. A problem therefore of equity in health systems and health education.

The way to verify how reasonable is a cost, and the price of the drug, is to relate it to the benefit it promises. First of all, the benefit: the prices of oncological drugs are rising, but not so much in proportion to total survival or disease-free progression (the so-called PFS-Progression Free Survival, the period of time during which the patient does not experience a worsening of the disease, an indicator widely used when survival data is not available) (Wait et al, 2017). In Figure 2 the poor correlation between treatment costs and progress in survival and PFS is clearly visible (Mailankody and Prasad, 2015).

Figure 2



Mailankody S, Prasad V. Five Years of Cancer Drug Approvals: Innovation, Efficacy, and Costs. JAMA Oncology July 2015 Volume 1, Number 4.

Therefore, after having seen the increase in prices, it is good to investigate the increase in efficacy achievable through new cancer drugs.

It is also true that some drugs have recently shown good efficacy, both in the prolongation of survival and PFS, such as those belonging to the new broad class of

immune oncology drugs. These are drugs that stimulate the immune system to attack cancer cells, so they are not like the other cancer drugs that target cancer cells themselves (the most famous immuno-oncological drug is undoubtedly nivolumab) (Borghaei et al, 2015). Unfortunately, there are many cases of drugs in which the benefits are modest or almost zero. A quite recent study has analyzed the 51 drugs approved in the USA by the FDA (the Food and Drug Administration is the federal agency in the United States that oversees the safety of food and drugs as well as medical devices, verifying their safety and effectiveness and thus allowing them, when appropriate, the sale) for solid tumors in the period 2000-2015 (Vivot et al, 2017).

No relationship was found between the price of the drugs and their value, measured according to two scales (ASCO-VF and ESMO-MCBS) (they are scales that attribute scores to some important characteristics of oncology drugs, such as increased survival and disease-free progression, quality of life of patients). Not only that, but no drug was found with a significant relationship with at least one clinical benefit: only 5% of drugs obtained the highest level of evaluation according to ESMO-MCBS, i.e. level 5, 65% between 1 and 3, and 30% level 4. Another study (Salas-Vega et al, 2017) examined the 62 new cancer drugs approved by the FDA and the EMA (the European Medicines Agency, the equivalent of the FDA for EU Member States that centrally approves drugs with effect for all countries) in the period 2003-2013 and analyzed the 53 evaluated by the British, French or Australian HTA (Healthcare Technology Assessment) agencies. Conclusions: of these 53 drugs only 5 % extended the overall survival of patients compared to the drugs available at the beginning of the period, 2003, by about 3.43 months on average (with a very small standard deviation of 0.63, confirming the high representativeness of the average value). The remaining 45% of the drugs, i.e. 24, had no survival data or no evidence of higher survival compared to the compared drugs.

Surprisingly the authorities deciding on the safety and efficacy of new drugs grant approval to drugs that were poorly or not at all effective, but also institutions specifically responsible for funding expenditure on cancer drugs introduced poorly effective drugs. This is the case with the Cancer Drug Fund (CDF) in Great Britain. Of the 47 indications approved by the CDF in the period 2010-2015, only 18 (38%) had statistically significant survival data, with a median gain of 3.1 months (from a minimum of 1.4 months to a maximum of 15.7 months) (Aggarwal et al, 2017). Using two clinical benefit scales (not only survival, but also quality of life and other clinical indicators), only 23 (48%) and 9 (18%) met the criteria of the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncolgy (ESMO) scales,

respectively. It should be noted that NICE (National Institute for Health and Care Excellence), the agency that recommends NHS drugs in England and Wales, after careful evaluation of cost-effectiveness, had previously rejected 55% of these drugs because they did not meet the criteria of cost-effectiveness. In this case, unfortunately, it has been shown that even where the criterion of cost-effectiveness is so important, space has unexpectedly been given to oncological drugs that are little or not at all effective and very expensive: the authors of the study concluded, not without a hint of bitterness, that the CDF had not delivered meaningful value to cancer patients.

From 2009 to 2013, the EMA approved 48 oncological in 68 indications. The 12% of these indications had insufficient studies (i.e. they were lacking in comparison with other therapies). In 35% of the cases, there was a prolongation of survival judged significant (with a median of only 2.7 months, from a minimum of one month to a maximum of 5.8 months), while the remaining indications did not show even a survival gain (Davis et al, 2017).

The prices of oncological drugs, but this also happens in other therapeutic areas, therefore risk reaching levels that are increasingly unsustainable for healthcare systems, and in many cases without even the justification of bringing extraordinary benefits to the patients. The dynamics of prices, however, need to be changed even in cases where drugs bring great benefits to patients, and this is because comparing costs to effectiveness is not enough when the number of patients to be treated is so high that they have to bear an excess cost that would quickly lead to the collapse of any healthcare system. The case of the new hepatitis C drugs is the first sign of this further phenomenon.

3. Hepatitis C: drugs too expensive to treat all patients

In December 2013, the FDA approved Sovaldi, the first drug obtaining an overall sustained virological response of 95% in cases of hepatitis C, which for the first time made it possible to heal almost all patients affected by this serious infection (Lawitz et al, 2013; Fathi et al, 2017). The hepatitis C virus (HCV) spreads through blood contact, sexual intercourse, or during childbirth. The infection does not show symptoms for years, but it can cause chronic liver inflammation, and because there is no vaccine as for other liver infections, many infected individuals evolve towards cirrhosis of the liver, liver cancer, with a high risk of death. The proportion of patients evolving towards cirrhosis is very variable: from 4% to 24% and depends on the genotype. Of the

infected subjects, 50%-80% develop chronic infections, of these about 50% will develop cirrhosis and 1%-5% will develop liver cancer within 20-30 years (this means that out of 1,000 infected subjects after 20-30 years about 7 will have liver cancer) (European Centre for Disease Prevention and Control, 2016).

It is estimated that there are over 177 million hepatitis C patients worldwide (Petruzziello et al, 2016) and 2.4 million die each year (Mohamed et al, 2018). The most affected countries are the so-called developing countries and some large emerging countries, such as China and India.

However, even in the countries of the European Union there are 5.6 million inhabitants with hepatitis C, and in Italy there would be almost 3 million (part of which has not even been diagnosed, and this is due to the fact that for many years the disease does not show symptoms) (European Centre for Disease Prevention and Control, 2016).

Sovaldi therefore quickly becomes one of the most effective drugs ever introduced in the market, a drug that will quickly be followed by others with similar characteristics, able to heal with one tablet a day for only 12 weeks of treatment. But since its appearance, there is a problem: the initial price of Sovaldi requested and applied in the USA is US$84,000 for 4 months of therapy (in some cases the therapy must last twice as long, obviously doubling the cost), that is US$1,000 per pill! For this price there is an estimated production cost of US$68-US$136, almost a thousand times lower! In fact in India, thanks to an agreement between the manufacturer and the government of that country, the treatment is available for US$300.

As we explain in the following paragraph, the price of a drug always needs to be higher than production costs in order to be able to recover the investment made in R&D on the one hand and to guarantee a profit margin on the other. However, compared to many other drugs, even more expensive ones, the number of patients with hepatitis C requiring treatment has been extremely high, so much so that in all countries where it is available a small part of them are treated, those defined as more serious, i.e. those at immediate risk of liver transplantation and/or cirrhosis close to cancer. The argument in defence of Gilead's price range has always been that Sovaldi's R&D expenditure has had to be covered by a large amount of money. According to the manufacturer, this expenditure amounted to US$11.2 billion, the amount spent by Gilead for the acquisition of a small biotech start-up, Pharmasett, the company that had actually invested in the research and development of the molecule (for R&D, therefore, it is estimated that no more than US$300,000 was spent) (see in this regard the letter of

the U.S. Senate sent to Gilead, the beginning of a controversy focused on the excessive price of Sovaldi, United States Senate, 2014). In the first year of Sovaldi's sale in the United States, the revenues amounted to US$12.4 billion. This opens up two further issues: first, after only one year of sale and in one market only, the investment has completely returned; second, the expenditure for the acquisition of Pharmasett does not exactly qualify as research and development expenditure. But even assuming it was R&D expenditure, Gilead's revenues were already US$32.6 billion in 2015 and US$30.4 billion in 2016, almost entirely derived from Sovaldi and the subsequent molecule launched on the market (Gilead Sciences, 2017). On the basis of these astonishing data, the aforementioned US Senate document identified Sovaldi as the best and the worst for the US health care system. The best, as a result produced by the science of that country, and the worst, as a potentially destructive element of the healthcare system. The fact also remained that a large part of scientific research in the medical field is financed in the USA with public money, while in this case there would arbitrarily be a great return in private profits. The US government therefore strongly advocated the need to adopt a drug pricing system that would avoid situations such as this one that put the private interest on a collision course with the public interest. To date, prices in the US are still freely determined by the manufacturers, but unusual for the US market, Sovaldi and other similar drugs have progressively enjoyed strong discounts of up to 40%, but still remain very expensive, especially in view of the large number of patients to be treated.

In Europe Sovaldi was launched in the following year at an average price of around €45,000, and currently each country has obtained significant discounts, but not enough to offer the treatment to all HCV infected patients.

The Italian case is an exception in the ability to impose more reasonable prices by public authorities (AIFA, the Italian Medicines Agency), although high enough to prevent treatment for all patients. In fact, progressively the price per treatment with Sovaldi has fallen to less than €15,000, and taking into account the progressive mechanisms that in fact bring further discounts has come to less than €10-8,000 (there are no official published data, and these values are based on some calculations made on the total cost and on some interviews carried out over time by AIFA managers). This is certainly the lowest price obtained in an advanced country.

This example adds an important element to the problem of rising prices already seen in cancer drugs. Actually, if it is easy to correct the excessive price of a drug when it is

little or not at all justified by its effectiveness, and in this regard the instrument of cost-effectiveness is the solution, a drug with high effectiveness but also high price requires additional tools. A difficult balance has to be found between the return on investment in R&D, how much this affects the price and, above all, how much profit the pharmaceutical company should earn. A given profit can be achieved by selling a few packs of a high-priced drug or many packs at a lower price, the important thing is to avoid that effective drugs resulting from excellent scientific research remain at a high price with the justification of innovation, regardless of the number of patients that can be treated. As we will see later, it is possible to propose algorithms to calculate the "right price".

The combination of two criteria, cost-effectiveness and impact on expenditure (the so called budget impact), allows a balance to be found. If in fact a drug is cost-effective, and the number of patients is not so high as to damage the public budget, the proposed price could be accepted. If a cost effective drug causes an excessive deficit given the high number of patients, then the price should be reduced and the profit, with a high number of sales, would be guaranteed anyway, although obviously lower than expected.

But before moving on to the profit component of the price, let's take a look below at the alleged R&D costs of a new drug.

4. How much does it cost to bring a drug to market

Regardless of the effectiveness results, sometimes encouraging and sometimes less so, medicines to reach the market require investment in R&D, obviously of varying intensity. In many cases, especially in the USA, basic research is carried out with public expenditure, while the subsequent stages are almost always left to the private initiative of pharmaceutical companies in each country. When a high price is asked for a new drug, normally the main justification is precisely this: a lot of money has been spent to obtain the drug, and of course this expenditure has to be recovered. It is therefore important to know how much the cost of R&D is, if it is the public authority that intervenes in formulating the price and then bears the cost.

A 2011 review (Morgan et al.) identified thirteen studies with average R&D cost results for a new drug ranging from US$92 million to US$883 million, a nine-fold difference! The most recent study available (DiMasi et al, 2016) estimated the cost of R&D for a new drug at US$1,395 million in terms of direct costs, which would increase to

US$2,588 million if opportunity costs were taken into account (the authors add the lost revenue from not investing the sum of R&D in equity investments, a calculation difficult to trace back to economic theory). This is the latest in a series of studies aimed at estimating the cost incurred by a pharmaceutical company to bring a new drug to the market, but none of these can be considered reliable as there is a lack of transparency of sources, independent review of the study, and above all, an average cost is estimated without any reference to a specific drug; moreover, the methods vary considerably, as do the data sources (Light et al, 2011; Avorn, 2015). R&D expenditure thus remains an approximation without a solid basis, left to the pharmaceutical industry to complain about the sharply rising cost to justify the demand for ever higher and often unsustainable prices by healthcare systems. More and more studies show that newer drugs are not associated with the greatest benefits when compared to older drugs (David et al, 2015).

Also, even in the UK, where there is a system that should guarantee access to only cost-effective drugs (NICE), expensive and dubious drugs are available because of the emotionality that accompanies any cancer decision (Hill et al, 2017). Ultimately, the costs of R&D of a drug seem to be shrouded in a cloud of mystery, while pharmaceutical companies are still struggling to provide their real R&D costs (Daemmrich, 2011; Light and Warburton, 2011; Scherer, 2011; Scherer, 2000; Broekhof, 2002; Adams and Van Vu Brantner, 2010; Light and Lexchin, 2012).

The difficulty of access to R&D data, i.e. the lack of transparency, is such a serious problem that the Council of Europe has also dealt with it. In one of its resolutions (Council of Europe Resolution, 2016), it calls for pharmaceutical companies to be obliged to be completely transparent about the real costs of R&D, in order to safeguard the common interest and to be able to guarantee access to effective medicines while maintaining the sustainability of healthcare systems.

5. Hostage Theory

Let's assume that a new drug with a price of €100,000 per therapy/patient can saved €1 million in hospital admissions. For the healthcare system would certainly be advantageous to purchase, since it would save as much as €900,000. Would the price be reasonable? In the absence of information on the real costs of R&D, it may not be. Let's assume that for each individual package, as much as €20,000 would pay for R&D and production costs, there would remain €80,000 for profits, promotion, management

bonuses and shareholder payments. Would such values be acceptable for a production factor in a publicly funded system? Anyone can give their answer, but the industry would normally justify it by supporting the value of such a drug, which is equivalent to at least €900,000 saved by the health service, and therefore acceptable. Without going into technical details, this formulation of the problem is recurrent and goes under the name of price-value-based, i.e. the price justified by the value it produces. But once again we forget not only the spending constraints of the system (once this price has been granted, subsequent medicines would obtain a higher one even in the absence of such a great saving in hospital spending, which is also difficult to estimate), but above all the fact that the price is the result of a negotiation between the manufacturer and the regulatory authority, which, when faced with a medicine deemed necessary, will have a small margin of manoeuvre, i.e. a reduction in the proposed price. In essence, we have been seeing drug prices with little downward variability for some time. To explain it, we can here define the "hostage theory", taking as our starting point some considerations of an American professor of international law who has been studying for some time the prices and patents of medicines (Abbott, 2016). Imagine a consumer asking for a good or a service strongly influenced by the time available to consume it. It could be the case of a manager of a large company who shows up at London Heathrow airport to take the plane for Japan where on arrival he will have to sign a very important contract, vital for his company. When he shows his ticket for check-in, the desk clerk tells him that the airline knows how crucial his journey is and therefore with his ticket he cannot board, because the price is too low in relation to the great benefit his company will get. He then proposes to buy a new ticket ten times more expensive than the one he has already bought. An honest price, given the enormous gain his company will be able to make, and which he would lose because the flights available from other airlines would not get him there in time. It would obviously not be an honest and reasonable price. Similar examples are easily conceivable in health care for many medicines, particularly for lifesaving in rare diseases. The consumer is like being taken hostage, and the ransom must and of course will be paid. Of course, the illustration of this theory is a little strong and perhaps applicable at present to a few medicines, but we believe that it faithfully sums up the terms of the problem: on the one hand there is the pharmaceutical company, a monopolist, and on the other a public payer whose institutional objectives include providing the best care for citizens. The price will result from the ability of the two players to push towards their respective

interests, without a real and transparent relationship between R&D costs, profits and the actual value of the drug.

It should be borne in mind that a lower price for a larger volume guarantees much higher turnover for the pharmaceutical company, while at the same time making it possible to treat many more patients. But one of the reasons why companies are resisting lower prices is to prevent new drugs from undercutting existing drugs, thereby sending a negative message to investors. However, this motivation is underpinned by investors' desire to be guaranteed immediate returns. High prices, albeit for small volumes, lead to very high profits in the short term, while profits in the long term are of little interest. This logic needs to be changed: the public interest is always long-term, while investors' interest is short-term. The two interests must therefore be aligned, the private interest and the public interest. If a new drug obtains a high price, the shares will rise, while if it obtains a low price, or lower than expected, the shares risk losing value. Since in our country, as in all of Europe (and marginally it is beginning to happen also in the USA with the new regulations for Medicaid and Medicare, the public health spending programs), the public acts like the monopsonist, that is, it is the only buyer of the drugs (drugs are reimbursed only by the public system, even if privately the citizen can buy them at the non-reimbursed price), it has the power to face the monopolist, but always within a narrow margin of variation of the price proposed by the pharmaceutical company.

6. Algorithms for setting drug prices

Uyl-de Groot and Löwenberg (2018) proposed to calculate the price of cancer drugs, as has often been seen to be extremely expensive, taking certain variables into account:

$$\left(\frac{R\&D}{Number\ of\ Patients\ treated * Years\ covered\ by\ patent}\right) + production\ costs * [1+ \text{profit margin}]$$

The variables are the following: the costs of R&D, the expected sales (the number of patients who will consume it in each year of patent protection), the production costs (these also take into account other costs, such as those for the promotion or marketing of the drug), and finally a percentage increase is applied to the result which is nothing other than the profit share for each unit of the drug sold. This percentage would be

more or less high in relation to the benefit/effectiveness of the drug. This is a formulation that is certainly incomplete and lacks many fundamental elements, for example, not taking into account price relationships between countries or the absence of an economic criterion that better reflects the costs of a drug, the capital invested, etc.. The path indicated is interesting, but still very uphill in order to make the profits of pharmaceutical companies compatible with public expenditure, increasing access to medicines, without inhibiting them from investing in new medicines. On the one hand, this proposal stimulates the implementation of different algorithms and, on the other, it meets certain limits that only new market rules could overcome. The improvements concern a specification of the formula that takes into account the period over which revenues and consequently profits are calculated. It will be a matter of discounting the values according to a given discount factor over a fixed period, which could be the duration of the patent coverage. The first point is a difficult decision and there are two possibilities. The first is to use the discount rate (which goes into the calculation of the discount factor) commonly used in economic evaluations of medicines by the major HTA authorities. It could be 3%, which is widely accepted in the literature. The second, more complex to define, to apply a discount rate as the market average for pharmaceutical investment. In this case there is no reference rate, and above all it would vary significantly over time. But the real problem is the second point, that is the difficulty, or rather, the impossibility at present to know the R&D costs associated with a single drug. Only an obligation of transparency imposed by government authorities on pharmaceutical companies could attempt to resolve this difficulty. As pharmaceutical companies are multinationals, it is clear that only an agreement between countries could be successful. In this respect, R&D costs could be envisaged, looking as far as possible for an agreement with the multinationals, broken down by different therapeutic areas. Also the presence of partly similar drugs on the market could lead to consider lower R&D expenditures of companies coming second, third, and so on to the market. However, it is necessary to open a debate that has long been left hidden in the name of protecting private interests and the need to finance innovation. The third lack of the formula proposed in the literature to date is the failure to take account of another fundamental aspect that drives the dynamics of drug prices, and not only that: price discrimination. The same medicine cannot have the same price in Greece and Germany simply because the capacity to spend is significantly different between the two countries. In the economy, this phenomenon is represented by the so-called price elasticity with respect to demand: for the same price of a given medicine in

Greece and Germany, the quantity that can be purchased in the first country will be much lower than in the second, because Germany is a richer country than Greece (Danzon and Towse, 2003). This is normal, widely accepted and happens for any good. This mechanism allows countries with different incomes to buy the same good on the one hand, and thanks to the higher prices for 'rich' countries, companies can recover their R&D investment on the other. This happens even more significantly when you look at the prices of expensive drugs, such as those mentioned here for hepatitis C, whose prices for a treatment cycle can be 30,000 euros in Europe and 600 euros in India and Egypt. We must certainly reject the principle, which has no economic basis, that the same good should have the same price everywhere, because this would have a perverse result: in rich countries, prices would be lower than at present, and in poor countries, prices would be too high, probably unsustainable This would have the opposite result, benefiting the rich and penalising the poor, precisely what the starting principle, referring to the equality of situations, wanted to avoid.

Another example, again in the field of health, is that of mosquito retinas for cradles distributed in some African countries where malaria continues to claim victims (Killeen et al, 2007). Initially, according to the ideological principle of gratuitousness, which of course can work in many other situations, women with small children were given these mosquito nets to put on their babies' cribs. After a certain period of observation, however, it was seen that most women did not use these nets. It was then decided to give them at a very low price. Since women had to pay for a good, they attached greater value to the anti-mosquito nets, they felt responsible to use them, and in fact the number of women who applied the nets daily to their cots and beds increased. The result was therefore a greater benefit than that obtained previously to follow the principle of gratuitousness in a fallacious way.

And once these difficulties were solved, the question will remain, never solved by economists (perhaps unsolvable): what should be the "right" profit margin for a company, in this case pharmaceutical.

A formula that takes into account the variables listed above would have two fundamental consequences: reducing the prices of medicines and directing the investments of pharmaceutical companies towards specific therapeutic sectors. The second effect could lead to a reduction in investment for rare diseases, the number of patients that can be treated being a key variable for the price calculated in this way: the lower the number of patients the higher the price, as is already the case today. But in a

scenario where exaggerated prices would be less and less acceptable, it would be unprofitable to invest in orphan drugs. Finally, whatever formula may be used to calculate the price of a drug, this price will only be the maximum price from which the cost-effectiveness assessments discussed here can start. In fact, it is well known that often pharmaceutical companies, where the cost-effectiveness criterion is used to grant the marketing and reimbursement of a drug (unfortunately not yet in Italy and in many other countries), are called upon to reduce the price, even considerably, in order to be able to fall within the cost-effectiveness ratio considered acceptable from time to time. market clearing price describe where supply and demand meet

The price of an I-phone is determined when supply and demand meet, it is sufficient that millions of consumers are willing to pay an exaggerated amount of money for a product with a production cost of a few euros, and here no criticism is made because consumers are free to choose with their own money. For medicines, first of all, it is mainly public expenditure, i.e. the choice must be informed by the principle of an efficient allocation of resources, resources that are in competition with many medicines, hospital care, family doctor care, etc. The effort of the public decision-maker is therefore to achieve maximum results in terms of benefits for patients with minimum costs. In addition, the consumer/patient does not express a preference according to his or her preference and ability to spend. The physician decides the therapy in relation to the need (diagnosis) without any regard, rightly so, for the economic condition of the patient himself. In this context it is clear that while the price of the drug must take into account a sufficient profit margin to attract future investment in R&D, it must also promise value (to a large extent this will be therapeutic and other side benefits such as possible reductions in the cost of alternative therapies and benefits for the patient and the doctor represented by the convenience of using the drug). We then return to the cost-effectiveness of the drug, i.e. to identify at what cost to the healthcare system a given therapeutic benefit is obtained.

In conclusion, what is proposed here, even if further study and modifications are necessary, is the following logical-decisional path.

1. Formulation of an algorithm to establish the maximum price of the drug. The R&D costs attributable to the specific drug remain difficult to estimate, and it will probably take a long time to agree with the pharmaceutical company on an "estimated" cost . relatively easy is the estimation of the number of

patients to be treated, the period covered by the patent, and the weight of each country's GDP.

2. Once the maximum price has been set, it is up to the company to propose the price, which may even be lower. At this point the cost-effectiveness of the treatment is evaluated, having previously identified a threshold value, i.e., for example, a maximum of €30,000 Euro per year of life saved (more precisely for QALY: Quality Adjusted Life Year). If it goes out of the threshold, the price will be adjusted downwards accordingly.

3. On the basis of the number of patients to be treated over time (generally we can estimate the trend in the first 3-5 years of use) we calculate what would be the budget impact.

4. Finally, from the combination of the criteria mentioned in point 2 and 3, the final price is obtained. If the impact on spending were considered excessive (here we obviously open some space to the subjectivity of the public decision-maker, a subjectivity tempered by objective public spending constraints), even in the presence of an acceptable cost-effectiveness ratio, the price would be reduced. In this sense, the Sovaldi case described here above could provide a good example.

7. Balance between private and public interest

On the one hand, pharmaceutical companies are pushing for the introduction to the market of a drug whose sale can make them recoup their investment in R&D and also make profits (of course, over and above social objectives such as improving health, increasing consumer welfare, solving citizens' health problems more and more effectively in general, the primary objective of any company is to maximise profits). In order to do this, they are encouraged to improve their medicines to the best of their technical and scientific capabilities, find the most appropriate uses for them, study all aspects of a given disease, find the implications of a given disease that are beyond the clinicians' control, and in so doing sometimes make better medicines available than existing ones. It is therefore the result of technological progress. This incentive scheme can bring profits to the company, but it can also bring benefits to patients. The public is not able, or not so incentivised, to produce such a large amount of studies and insights that pharmaceutical companies are currently doing for new drugs. On the other hand,

the second incentive scheme is for the public (the State) which has as its objective the welfare of the population by trying to satisfy its spending constraint. The regulatory authorities (e.g. AIFA for Italy) do everything possible to pay as little as possible for the new drug by seeking the limits of its effectiveness, restricting its use to the patients who will benefit the most, safeguarding the safety of the drug, and so on. Therefore, the challenge is to dynamically seek the difficult balance between public and private interests, with continuous adjustments where one now has the upper hand. The goddess of building a price algorithm seen in the previous paragraph goes in this direction.

But there is another dangerous outcome, apart from the imbalance between interests, nested in this phenomenon of rising drug prices. An analogy with the 2008 financial bubble could be used to explain this. In that year, the real estate and financial markets produced the recent economic crisis. The growing optimism in the real estate market opened the door to further easy financing (the famous subprime mortgages) for the purchase of new homes. This led to an increase in the prices of the houses themselves with the consequence of believing in a real estate market with increasing values, and therefore with prospects for excellent investments in the sector.

There was an euphoria: high prices, increasingly favourable financing, higher and higher share prices of lenders and property groups. But, as always happens in periods of euphoria, peoleare is under the illusion that these increases are necessarily the result of developments in certain sectors of the real economy, that is, those that produce goods, innovations, technologies (Reinhart and Rogoff, 2009). High prices are accepted as the countervalue of new technological developments. And finally one is forced to bow to reality: it was a bubble. And then comes the collapse. The mechanism adapted to the pharmaceutical market could be as follows.

1. Pharmaceutical companies propose and obtain ever-increasing prices, justifying them with as many increases in R&D costs.
2. As prices are accepted by the 'market', in this case by public spending decision-makers, they are thought to be justified by the technology embedded in them.
3. Pharmaceutical companies' shareholders therefore see the value of their shares grow, and by giving more and more confidence to the companies they increase the price of their shares.

4. Pharmaceutical companies are increasingly capitalised and invest in a large number of R&D projects (in oncology alone, in 2017 the pharmaceutical industry reached an amazing 700 molecules in the final stages of study, about 60% more than in 2007) (IQVIA Institute, 2018).

5. At a certain point the growth in share prices no longer corresponds to the technological increases, and numerous "failures" of new drugs previously considered very promising begin: the bubble is revealed for what it is and the process “high prices drugs →funding high prices shares → high prices drugs” stops.

If this scenario were to occur, we would see the collapse of many pharmaceutical companies. But beyond this vision, which is probably a bit bold, there is another key component in this context. While in the financial bubble that led to the economic crisis of 2008, the protagonists who put their money on the table were private individuals and, to a large extent, private financial institutions, in the case described here of drugs, it should not be forgotten that it is the public entities that pay for the prices of drugs on a daily basis.

8. Conclusions

In conclusion, it is a question of summarising the fundamental steps in the balance between private and public interests, between R&D and public pharmaceutical spending, and how to turn the legitimate interest of profit to the common interest. In fact, it would be an announced tragedy if R&D were entrusted to the public (at least in its entirety, given that part of basic research already is, but it is the development of the individual drug that remains the prerogative of pharmaceutical companies and fortunately), the healthy contrast of incentives being lost: the company must produce the best drug otherwise it does not earn money, the state must adopt the best drug but compatibly with its effectiveness and costs (price). This healthy opposition, if properly regulated by the State (the market has shown that it cannot do so) produces benefits for society as a whole (for patients, the State and pharmaceutical companies).

If we restrict approval to only the most effective drugs (Howard et al, 2015), we will have more of them in the future, and this will be one of the results of a new balance between private and public interest.

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