Drugs and therapeutic advances:
GUARANTEEING ACCESS, BRINGING PRICES UNDER CONTROL

Civil society's contribution to the debate in France

DRUG PRICES, THERAPEUTIC VALUE AND ACCESS TO MEDICINES: CIVIL SOCIETY ADDS ITS VOICE TO THE DEBATE IN FRANCE, TO DEFEND THE PUBLIC INTEREST

Faced with significant price increases for new drugs, in North and South alike, particularly drugs for cancer, hepatitis C and rare diseases, civil society in France is taking action to defend access to best-quality care for all, and to safeguard the public healthcare system. Several organisations representing patients, healthcare users, healthcare professionals and students have joined together to publish a White Paper (in French) entitled: ***"Drugs and therapeutic advance: guaranteeing access, bringing prices under control" ("Médicaments et progrès thérapeutique: garantir l'accès, maîtriser les prix").***
Based on our shared position, our 8 organisations contributed 12 texts, collected together in this White Paper, which aims to speak on behalf of civil society in the public debate.
The texts address two key concerns.

Analysis and proposals to move beyond false ideas.

The various organisations, within their respective areas of expertise, have observed that medicines policy has gone seriously astray. They have spoken out against the opacity of drug prices and their components, the lack of transparency in negotiations between government and industry, and the dangerous budgetary and financial consequences for France's national health insurance system. They have alerted the authorities about the threats hanging over the access to new and costly treatments, while some older drugs are plagued by intolerable shortages.

They have criticised talk of "innovation" which above all serves to justify exorbitant prices, without properly defining just what innovation means, and without any guarantees that it provides any actual improvement in the quality of care for those who are most affected, the persons living with these diseases.

Based on analysis of public data, documented practical situations and intellectual property issues, on research, on clinical trials and on transparency, the texts brought together in this White Paper aim to provide citizens, policy makers and elected officials with information that goes beyond certain commonplaces that are too often mistaken for established and intangible truths.

Transparency and democracy: needed for the maintenance of a universal healthcare system

The constant price inflation for new treatments is a threat to equal access to healthcare, and to the survival of France's universal healthcare system. By speaking out together, our organisations, in all their diversity, proclaim that this is not inevitable. Innovations whose efficacy has been demonstrated must be made accessible, and their appropriate use must be guaranteed. Prices must be better controlled so that therapeutic progress first and foremost benefits patients, but without discouraging innovation. To do that, we call for real transparency at all levels: from medical research and its funding to the pricing and marketing of healthcare products, along with transparency regarding the level of therapeutic advance a healthcare product actually delivers.

We also wish to be more involved in decision-making regarding medicines policy, and we call for a truly democratic debate to be held. This democratic debate must be structured so as to fulfil the requirement that all of our organisations agree upon: **based upon drug prescriptions justified solely by health considerations, France's universal healthcare system must guarantee access to therapeutic progress to all those who need it** ●

CONTRIBUTIONS

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FRENCH MYTHS (1): ‘THE DRUGS BUDGET IS UNDER CONTROL’

Between 2008 and 2016 expenditure on drugs in France as a proportion of total health spending remained relatively stable, amounting to 17% of spending on medical goods and services (1). Thus, in 2016, with overall health expenditure at EUR 198.5 billion, a total of EUR 34 billion was spent on drugs, representing 11% of GDP (2). Of every EUR 10 spent on medicines, around EUR 7 was covered by Social Security, the rest being financed by supplementary insurance and households (3).

In recent years, public authorities on both right and left have regularly boasted about their policies for managing drug expenditure with cost-saving measures, such as increasing penetration of generic drugs, better organisation of care pathways and prescriptions, delisting items from reimbursement, negotiating rebates with manufacturers, and compensation mechanisms, based on changes in sales volumes.

Ultimately, drugs have become the ‘star pupil’ of the health insurance budget, through a focus on near-zero growth in reimbursements for drugs in general practice ‘whereas this was not the case in the early 2000s’ (4). In addition, manufacturers were not mistaken when their industry body, the French Pharmaceutical Companies Association (Les entreprises du medicament – LEEM) regularly condemned the fact that they directly shouldered the burden of ‘half the Social Security savings’ (5). This continuous focus on drug spending, with some congratulating themselves and others condemning the system, helps to sustain a myth about the Social Security budget that fosters a sense of certainty. Yet tomorrow may bring a painful wake-up call...

In fact, since 2008 this relative stability has concealed a significant and worrying development in spending trends within the funding envelope for medicines. This funding envelope comprises two groups of medicines: expensive – if not exorbitant – drugs, often described as ‘innovative’, and other drugs. Virtually all the cost-saving measures mentioned above have affected everyday medicines, thus creating a financial margin which, until now, has been able to compensate for the explosion in prices of expensive drugs – and thus also the burden on health insurance. The worrying trend is illustrated by the development of a specific budget line within the drugs envelope: reassignment. Reassignment allows drugs prescribed in hospital but for outpatient treatment to be billed to the health insurance system under the budget for ambulatory care. This applies, for example, in the case of antiviral drugs for HIV and hepatitis C.

Thus the launch on to the market in 2014 of new treatments for hepatitis C was very revealing. That year Social Security paid EUR 2.9 billion for reassigned drugs, an increase of 80% compared with the previous year – an increase which was essentially due solely to new hepatitis C drugs.

In fact, the growth in expenditure on reassigned drugs appears to have spiralled out of control: between 2008 and 2016 the amount spent by health insurance due to reassignment increased by 141.7%, while total consumption of medicines for the same period grew by just 2.7% (6). Who could reasonably continue to assume that the budget is under control? It took cost-saving measures and cutbacks to maintain the famous ‘stability’ of the drugs budget at a level of 17% of healthcare spending (7).

More worryingly, the Social Security accounts for 2017 seem to reveal a new situation: while the cutbacks have for years manifested as virtual stagnation or sometimes a fall in expenditure on drugs from retail pharmacies, this expenditure is rising again with the introduction to retail pharmacies of drugs which were previously on the reassigned list. After the hepatitis C shock, the inflationary growth of reassigned medicines is now being fed by cancer drugs and cystic fibrosis medicines.

Thus the relative overall stability has until now concealed a significant increase in expenditure on increasingly expensive drugs described as ‘innovative’, which may cost tens of thousands of euros per year per patient. The imminent arrival of a number of new treatments, especially in oncology, some of which may cost hundreds of thousands of euros per patient, is likely to lead very quickly to another huge increase in drug spending. The medicines budget is therefore far from being under control; or it must be assumed that ‘control’ will mean rationing access to new drugs.

Since new hepatitis C treatments came on the market, we have come to realise that the concept of ‘rationing’ is not a figment of the imagination. ‘Rationing’ means access to a particular

treatment is restricted to just a proportion of those eligible for it. In France, this kind of rationing was made explicit by a ministerial decree of 18 November 2014 which defined the conditions for treating hepatitis C patients based on clinical and behavioural criteria. This was a first in the history of the French social security system since 1945. It was also a first for almost all wealthy countries which faced a budget deficit (8).

The apparent calm underpinned by the famously stable figure of drug consumption as 17% of healthcare spending conceals relentless plate tectonics presaging powerful tremors for our statutory health insurance system ●

(1) This refers to ambulatory medicines, that is those prescribed in general practice and delivered by external pharmacies as well as those that the hospital bills to the statutory health insurance system. It also includes non-reimbursable drugs, which make up around 10% of the total. It does not include medicines prescribed in hospital during a patient's hospital stay: these are included in the hospital's budget as part of the budget allocated on the basis of the tariffs for diagnosis-related groups, fixed by activity-based costing (T2A) established by the Social Security Financing Law (Loi de financement de la Sécurité sociale – LFSS) for 2004.

(2) Ministry of Health, DREES, Les dépenses de santé en 2016, résultats des comptes de la santé [Healthcare expenditure in 2016, healthcare accounts results], 2017.

(3) In 2016, the statutory health insurance system covered 68.9% of drugs spending, the government (including CMU-C) accounted for 1.5%, supplementary insurance organisations 12.5% and households 17.1% (DREES 2017). The highest contributions paid by households are for medicines.

(4) Maurice Pierre Planel (President of CEPS), Le Prix des médicaments en question(s) [Questions on drug pricing], Presses de l'EHESP, 2017, p. 78.

(5) J.-Y. Paillé, « Sécu : le lobby pharmaceutique juge les économies «irréalistes» et contre l'innovation » ['Social Security: the pharmaceutical lobby sees cost-savings as "unrealistic" and anti-innovation'], La Tribune, 4 October 2016, www.latribune.fr/entreprises-finance/industrie/chimie-pharmacie/secu-le-lobby-pharmaceutique-juge-les-economies-irrealistes-et-contre-l-innovation-604707.html

(6) Change in the proportion represented by medicines in the consumption of healthcare and medical goods (CSBM) and the reassigned medicines budget line as shown in the national health accounts published by DREES.

(7) This is recognised by DREES itself in its latest report on the national health accounts for 2016: 'The spread of innovative and expensive specialties thus offsets the effect of price reductions for older medicines, medical control measures and the promotion of generic drugs.' (DREES, National health accounts 2016, overview).

(8) OECD, New health technologies. Managing access, value and sustainability, January 2017.

FRENCH MYTHS (2): ‘OUR PRICE-SETTING SYSTEM IS EFFECTIVE’

Away from the loud protests of the pharmaceutical industry, the relative stability of spending on drugs actually conceals a value increase. Between 2001 and 2016, total annual spending on medicines rose from EUR 26.1 billion to EUR 34 billion (1). In fact, the ‘cost savings’ in this area relate more to a desire to manage rising prices rather than to efforts to achieve spending reductions. Furthermore, why should we automatically accept the dogma of health expenditure reduction? This is especially relevant in the light of projected future needs associated with an aging population and the health consequences of harmful environments.

Instruments currently used by the public authorities

We now return to the cost-saving myth by looking at the work on medicines undertaken over a number of years by the French national audit office (*Cour des comptes*) through its annual report on the application of the Social Security Financing Laws (*Lois de financements de la sécurité sociale – LFSS*) (2).

In order to understand what the *Cour des Comptes* is saying, we must revisit the framework within which the government operates to set drug prices. It chose what it calls a contractual policy, which means it negotiates with manufacturers. This negotiation is organised by means of the government and manufacturers defining rules and adopting regulatory provisions. Below are several examples.

The ‘European price guarantee’

In the French system, as in the majority of France’s European neighbours, the government negotiates, through the Economic Committee for Health Products (*Comité économique des produits de santé – CEPS*), what is known as a ‘list’ price (prix facial). This means the public price which will be found on the medicine packet. Parallel to this price, the CEPS also negotiates confidential rebates which depend, for example, on sales volumes, to reduce the bill for the health insurance system. However, the country negotiating does not have any precise information on the real prices in other European countries after rebates, unlike the manufacturer, who has a very clear picture of its global market. Governments are thus forced into an unequal power relationship from the start of the negotiation, due to this information imbalance. Yet the rules established often require prices to be consistent with those which exist in other reference countries. This is known as the international reference price. Thus the public price in France is referenced in over 50 countries globally and manufacturers will use this reference in their negotiations with the administrative authorities of these countries. Consequently, strategically, manufacturers need to ensure the price is as high as possible in France. In contrast, for price setting in France a framework agreement between the CEPS and the French Pharmaceutical Companies Association (*Les enterprises de médicament – LEEM*), which represents pharmaceutical firms, introduced a very restricted reference system for medicines defined as innovative treatments. This is the ‘European price guarantee’. Agreed by the government, this regulation requires the French price for innovative treatments to be consistent with the Spanish, British, German and Italian prices.

As a result, the *Cour des Comptes* has for a number of years been fiercely critical of this ***‘European price guarantee [which] creates unearned income for the industry: the systematic extension of this provision leads to the public authorities, in their relationship with pharmaceutical companies, repeatedly consenting to the granting and maintaining of increased list prices for innovative medicines’***. Apart from the price of innovative medicines, the whole drug pricing chain in France is subject to inflationary pressure with the European price guarantee system. When a new drug in an existing treatment class comes onto the market, the associated improvement to the medical service provided is by definition less significant than that of an innovative medicine which has come onto the market for the first time and with which it will be compared. The Social Security Code clearly establishes that, for this reason, the price must be lower or at least the same, depending on the individual case. However, since the baseline for the negotiation consists of the high list price of the first-in-class drug, there is inevitably limited room for manoeuvre in terms of cost savings. This has led the *Cour des Comptes* to point out the ***‘risk of escalating list prices’*** even for drugs which offer poor added therapeutic value.

Secret rebates

For their part, the public authorities have come to justify their

consent to high public prices by negotiating rebates, some more substantial than others, but all confidential. The reasoning is simple, even simplistic: 'Of course, the prices are high, but in the end it costs less overall, because we get rebates'. However, this system of rebates has been diverted from its original principle by also being used for drugs which offer limited improvements on existing drugs – something which was not meant to happen. Rebates have been deflected away from delivering their original intended benefit and, now used routinely, they have contaminated the clear, rational and transparent management of drug spending with several undesirable effects.

Firstly, and very specifically, for drugs which provide no improvement to medical services, the cost savings obtained by means of rebates negotiated on the basis of a high list price are always lower than the cost savings which would be made if the price was lower from the start and aligned with the comparator! The *Cour des Comptes* provides a very concrete example of treatment for multiple sclerosis where cost savings could have been three times higher if the principle of a lower list price had been applied.

Secondly, the rebate principle leads very directly to extra costs – of varying magnitudes – for the health insurance system. For example, medicines provision is subject to regulated mark-ups which compensate the different parties involved (wholesale distributors, retail pharmacists), yet these mark-ups are based on the list price and not the net post-rebate price.

Less substantial cost savings, extra costs: ultimately, used widely in pricing policy, these rebates lead to greater opaqueness as well as to rises in spending. In the words of the ***Cour des Comptes: 'While on first analysis the rebates may seem to have the same impact as reductions of manufacturers' prices, in reality they involve extra costs for the health insurance system and the people covered by it'.***

Safeguard clauses

The last tool used by the public authorities in an effort to reduce the bill resulting from high prices is compensation mechanisms. Adopted as part of the social security financing laws (LFSS), this provision allows manufacturers to be re-invoiced, the following year, for a proportion of the amounts received. The mechanism is triggered above a certain threshold of sales volume billed to the health insurance system. This instrument for retrospective regulation of drug spending was introduced by the 1999 LFSS. It is known as the safeguard clause In response to the explosion in spending generated by new hepatitis C drugs, the 2015 LFSS introduced a specific safeguard clause based on the sales volume for hepatitis C drugs. As with the rebates, these safeguard clauses have no effect on the inflationary logic fed by the high list prices. They put the government in the position of someone driving a car while looking in the rear view mirror...

Sometimes there are even more bizarre arrangements to make believe that the government is in control. One example is the Innovative Treatment Financing Fund (*Fonds de financement de l'innovation thérapeutique*) introduced by the 2017 LFSS. Put forward as a tool to spread expenditure on innovative and costly medicines, the *Cour des Comptes* noted that it amounts, for the government, to presenting pharmaceutical companies with a new source of financing to loosen price-setting restrictions. Apart from this message which feeds the inflationary spiral, the Fund fundamentally resembles an accounting trick. The 2017 Social Security Accounts Committee provided indisputable proof: charging a large proportion of the volume of reassigned medicines to this Fund meant the annual increase could go from 6% to 1.8% (3), which looks much more presentable in the annual accounts!

Alternative tools for managing drug spending

A contractual and regulatory framework is not intrinsically a bad thing. The parties – the manufacturers and the government – must play the game and the dice must not be loaded. Yet this is manifestly not the case. Fundamentally, the government has accepted a contractual and regulatory framework which reduces the public payers' room for manoeuvre. In other words, the rules the government has approved and which are established for drug price setting mean that the payers are unable to negotiate better use of public funds.

But why would the government accept this? The *Cour des Comptes* provides two interesting points in response to this question.

Firstly, it notes that the practice of high prices approved by the government relates to a policy which aims to promote economic attractiveness and stimulate employment in the country, thereby diverting the statutory health insurance from its core objective, health, for the sake of industrial policy. It is a major peculiarity of the public authorities to consider Social Security as a means of supporting other public policies apart from health. This peculiarity has long been illustrated by the impact on Social Security resources (and thus on financial stability) of social security contribution exemption measures for low wage earners to underpin policies to tackle unemployment among low-qualified workers.

More generally, the *Cour des Comptes* expressed a concern: ***'Interventions targeted at the public authorities which are motivated by industrial considerations sometimes lead to the setting or maintaining of abnormally high prices'***. At a time when the government is about to bring together manufacturers through the Strategic Board for Health Industries (*Conseil stratégique des industries de santé*) on 9 July 2018 to update various regulations for the sector, including those relating to negotiating price setting, we largely share this concern regarding the burden of these ***'interventions'***.

This concern is all the greater since there are many of us who observe that governments are obstinately refusing to use other regulatory tools at their disposal, which would strengthen their position in pricing negotiations. There are many such tools and, in some cases, they have been established in law for a long time. One such example is the licence of right (*licence d'office*) introduced in France by General de Gaulle in 1959 as a firewall against the situation where access to a medicine might be jeopardised for price reasons due to a position of dominance. Article L 613-16 of the Intellectual Property Code clearly states that, in the case of an 'abnormally high price', the French government can trigger this provision which opens the door to less expensive, high-quality competition. There are also other tools, which are administrative in nature, such as unilateral price setting by the public authorities if price negotiations with manufacturers fail.

Here is not the place to define a new mantra for price-setting policy, instead our aim is to provide a reminder that these legal tools exist and can be triggered when the public authorities reach an impasse. These tools, with other instruments for managing spending on drugs and on health in general, are a response which aims to rebalance the negotiation between the government and manufacturers at a time when, according to the ***Cour des Comptes, manufacturers are developing 'price demands based on the public purchaser's ability to pay. These new, more aggressive strategies exert unprecedented pressure on funders'*** ●

(1) DRESS, Comptes nationaux de la santé – base 2010 [National health accounts – 2010].

(2) Cour des Comptes (national audit office), reports on the application of the Social Security Financing Law (LFSS). This annual report is published in the September of the year N+1 for the LFSS for the year N. In addition to a number of standard sections, each year the Cour des Comptes also examines specific issues which have an impact on the Social Security budget. Medicines appears regularly in these reports as a topic of specific concern for the Cour des Comptes – see the reports for 2001 (pp. 85-110), 2002 (pp. 368-382), 2003 (pp. 213-216), 2004 (pp. 305-355), 2007 (pp. 257-304) and 2011 (pp. 109-145). The most recent investigation into medicines can be found in the September 2017 report, in Chapter VIII, entitled 'Drug price setting: significant results, ongoing major efficiency and sustainability challenges, a policy framework requiring substantial readjustment', from which the quotes in this text are drawn.

(3) Social Security Accounts Committee (Commission des comptes de la Sécurité sociale), Résultats 2017. Prévisions 2018 [Results 2017. Forecasts 2018], June 2018.

NEW CANCER DRUGS, BUT AT WHAT PRICE?

New cancer drugs have brought progress, but sometimes at the cost of serious side effects. However, increases in survival duration (sometimes only minimal) seem to be enough to incite pharmaceutical companies to demand astronomical prices – even when there has been no major investment in R&D.

Unlike the US, France has no free pricing system for reimbursable drugs, with prices controlled and set by the CEPS (France's Economics Committee for Health Products). In introducing cost-effective measures, the HAS (French National Authority for Health) is now trying to curb the prices of innovative pharmaceutical products that weigh heavily on the state's health insurance budget. These measures involve establishing for each innovative and expensive product the additional cost of one year of life in good health. With the CEPS holding completely un-transparent closed-door discussions, it is clear that during negotiations where the payer is on a far from equal footing pharmaceutical companies are able to impose their arguments and obtain very favourable prices.

Examples of exorbitantly priced cancer drugs

Glivec® (imatinib, Novartis). Imatinib has revolutionised the treatment of rare blood and bone marrow cancers. A life-long treatment costs, depending on the dosage, €2,270 to €3,400 euros a month, which can amount to as much as €40,000 for one year of treatment. Since its arrival on the market as an orphan drug in 2001, it has been approved for the treatment of other conditions, which include some gastrointestinal tumours. *Glivec®* is a textbook case: despite increasing profitability gained from these additional conditions, its price has not fallen. Far from it in fact, as in the USA it rose from US$30,000 in 2001 to US$92,000 in 2012.
Good to know: introduced in 2017 after the patent expired, the generic form of imatinib costs half the price of the brand product, the price of which has now seen a decrease of 20%.

Kadcyla® (trastuzumab emtansine, Roche). Prescribed when an initial treatment for a specific form of breast cancer (HER2-positive) fails, its therapeutic benefit has been recognised by the HAS. *Kadcyla®* increases survival duration by six months in comparison to the previously preferred treatment. It costs €4,361 per three-week cycle, i.e. over €6,000 euros a month and €72,000 a year.

Revlimid® (lénalidomide, Celgène). Used to treat myeloma and myelodysplastic syndrome and costing between €3,900 and €5,000 a month, this drug is a derivative of thalidomide, a very old compound infamous for causing severe birth defects in the 1960s. So, *revlimid®* is nothing new, it has required no substantial investment, and yet it is expensive! From the therapeutic perspective, it is one option among others, but its benefits have not proven conclusive.

Tarceva® (erlotinib, Roche). Used as a first-line therapy in non-small cell lung cancer, this drug does not improve overall survival. It has not been subjected to comparison as a second-line therapy with the reference treatment. Only when used as third-line therapy does it deliver a minor benefit. It costs €2,195 a month.

Keytruda® (pembrolizumab, Merck). This brand new drug is used to treat non-operable or metastatic melanoma. The HAS considers it offers only a minor improvement in therapeutic benefit (ASMR) compared to existing treatments. Administered every three weeks, the treatment still costs close to €6,000 euros a month, i.e. €72,000 a year. It has now been approved for use with other conditions.

Avastin® (bevacizumab, Roche). Approved in France for the treatment of metastatic cancers of the breast, ovary, kidney and lung, *Avastin®* is controversial. According to independent French medical journal Prescrire, its side effects are too severe compared to a few more weeks of survival. Given its price, the UK's national health insurance system has disqualified it from reimbursement. In France, its cost varies between €1,633 and €3,270 a month.
Good to know: for more than 10 years Avastin® has also been used in ocular injections to treat wet age-related macular degeneration (AMD), i.e. to treat a disease for which it was not initially approved. While its cost is prohibitive when used in cancer treatments, it still represents a substantial economy in treating AMD in comparison to Novartis' Lucentis® – the officially approved drug. One ocular injection of one dose of

Avastin® costs €10, as compared to €739 for the same injection with Lucentis®, i.e. 80 times less! It is for reasons of cost that hospitals have begun, outside any regulatory framework, to use Avastin®. It was only in 2015 that France's Ministry of Health temporarily approved the use of Avastin® in the treatment of AMD. In the wake of this decision, Roche (the owner of Avastin®) applied to the administrative tribunal for the annulment of this temporary authorisation, preferring to forego a market than sanction a drastic price reduction in a treatment for another condition. There were suspicions that the two pharmaceutical companies had entered into an illicit agreement that left the AMD market to the more expensive drug. This was the verdict of the Italian Competition Authority in March 2014 when it fined the two companies a record €182.5 million. In April of the same year, consumer organisation UFC-Que Choisir referred the matter to the French Competition Authority for the same reason of a possible illicit agreement between the two pharmaceutical companies. While the inquiry was still continuing at the time of writing, a State Council decision of September 2017 confirmed the validity of the temporary recommendation for the use of Avastin® in the treatment of AMD ●

Calculated on the basis of the most common average dosages (data supplied by the Curie Institute), the above prices are based on unit list prices set by the CEPS and published in the French Official Gazette. They are therefore exclusive of all possible discounts.

Prescrire

THE MISSION OF PHARMACEUTICAL COMPANIES IS, FIRST AND FOREMOST, TO PRODUCE, AND MAKE AVAILABLE, CLINICALLY USEFUL DRUGS WITH THE REQUIRED QUALITY AND IN THE REQUIRED QUANTITY

According to a media-wide European publicity campaign, pharmaceutical companies claim that they "never sleep".

Conditions that must be fulfilled for research to be useful to patients.

This campaign is centred on the activity of pharmaceutical companies in terms of research and development of new drugs, an activity which is important for society and for patients, provided that the following conditions are met. Firstly, it must be directed towards the most important health needs in terms of public health. Secondly, the new drugs must represent real clinical progress for patients. Thirdly, they must be robustly evaluated before and after marketing authorisation (so that the risks of harms incurred by patients are not disproportionate in relation to the expected benefits). Fourthly, the price of new useful drugs should allow access by all who need them and finally, pharmaceutical spending should not develop at the expense of social welfare spending and other spending which is equally useful for public health (prevention, diagnosis, hospitals, social care, nutrition, housing etc.).

Given these conditions, the research and development activity of pharmaceutical companies (which often follows on from publicly funded or university research) is most valuable when it enables the development, production in sufficient quantity, and provision, of medicines for diseases which are currently difficult if not impossible to treat.

However, many diseases these days are well, or even very well, managed with drugs and many patients have to take drugs regularly and sometimes without fail. Their drugs must be available, though!

Development ... of stock shortages!

Every year, more and more drugs are lacking in pharmacies or even hospitals. The French Health Products Agency (ANSM), for example, noted more than 500 cases of drugs which it considers ***"of major therapeutic value"*** for which unacceptable ***"supply pressures"***, or even stock shortages, occurred in 2017 (1). ANSM found that, among these, 20% were antibiotics or vaccines (1). Long term stock shortages of several vaccines have on several occasions forced the Technical Committee on Vaccinations (CTV) of the French National Authority for Health (HAS) to revise vaccination protocols, which should, however, be procedures entirely guided by scientific considerations (2)!

This failure by the companies is not new, but it is becoming worse. In 2011, the so-called Safety of Medicines Act had stipulated that companies should announce any predictable stock shortages a longer time in advance (1 year) (Article 46) and that wholesale distributors should specify the amounts of medicines which they intended to export (Article 45) (3). In 2016, the so-called Public Health Act reinforced these obligations by stipulating that firms should put in place "plans for management of shortages". ***"These shortage management plans should, in particular, provide for the establishment of stocks of drugs destined for the national market, depending on the market share of each pharmaceutical company, other sites of manufacture for pharmaceutical raw materials, other sites of production of the proprietary drugs, as well as, if necessary, identification of the proprietary drugs which could represent an alternative to the brand which is lacking"*** (4,5).

It has to be concluded that these measures are insufficient and that the companies have not effectively resolved this public health problem.

This problem is not confined to France. Many countries are affected by it and in the United Kingdom, for example, these shortages are leading to additional expenditure (6). Across Europe, health authorities are becoming more and more concerned by this problem (1).

Production under threat

What are the causes of these stock shortages? The ANSM blames production problems relating to the quality (detected in particular during inspections) or the quantity of pharmaceutical raw materials, particularly when they are produced in just a single factory in the world.

Is there any scientific or technical necessity to explain why just one factory should be capable of producing these raw materials? No. It is purely a question of economic motives, the pharmaceutical firms preferring to pare down production costs and, in particular, to buy their raw materials in China. However, these drugs are at risk of stock shortages, because the Chinese

pharmaceutical factories are having to close as a result of China's anti-pollution policy (7). This ends up creating situations which are a major threat to health, in which pharmaceutical companies seek, first and foremost, to reduce their costs and to improve profitability for the benefit of their shareholders, while relegating patients and their care to second place.

The French and European public authorities must take proactive measures to force companies to guarantee the permanent availability of the vital drugs they produce. It should be remembered, for example, that compulsory licensing exists in France to provide for situations where companies are not supplying drugs in the necessary quantities (8).

Companies must guarantee their core business.
Firms make announcements about thousands of drugs under development, dangling the promise of successes tomorrow, whereas in reality, for many years, drugs coming onto the market which bring real progress for patients have been rare. Meanwhile, patients are losing access to the drugs which they need every day and factories producing drugs in Europe have closed, or are in the process of closing.

Companies must maintain their core mission, which is to produce, in sufficient quantity and in a sustainable manner, high quality drugs with demonstrated therapeutic value ●

(1) "Médicament : les signalements de rupture et de risque de rupture en hausse de 30 % en 2017 (ANSM)", APM press release 13 February 2018: 2 pages.
(2) Ministère des solidarités et de la santé, Calendrier des vaccinations et des recommandations.
(3) Article 46 de la loi n° 2011-2012 du 29 décembre 2011 relative au renforcement de la sécurité sanitaire du médicament et des produits de santé, Journal Officiel 30 December 2012: 1 page.
(4) Article 151 de la loi n° 2016-41 du 26 janvier 2016 de modernisation de notre système de santé, Journal Officiel 27 January 2016: 1 page.
(5) Décret n° 2016-993 du 20 juillet 2016 relatif à la lutte contre les ruptures d'approvisionnement de médicaments, Journal Officiel 22 July 2016: 3 pages.
(6) "Drug shortages derail CCGs' budgets", BMJ 2018; 360:k331: 1 page.
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Prescrire

"INNOVATION", UNFORTUNATELY AN OFTEN MISLEADING WORD IN THE FIELD OF DRUGS

«Early access to innovation» : such is the slogan hammered home these days by pharmaceutical companies, some medicines agencies (notably the European agency, EMA) and some patient organisations.

Who could possibly be against "early access to innovation"? No-one, if the innovation always represented progress, but in reality, innovation does not mean progress.

It often takes time to make the distinction. Some stakeholders believe, or tend to make us think, that health authorities, i.e. medicines agencies and those charged with evaluating the therapeutic value of drugs, are causing time to be lost through their "bureaucratic" activities. They also consider that comparative clinical trials themselves are too long and are slowing access to new drugs.

Quick and dirty

In reality, today there are already numerous accelerated routes to marketing (conditional marketing authorisation (MA), adaptive pathways etc.) not to mention temporary authorisation for use before MA. However, this speed usually comes at the expense of the quality of assessment, because the drugs have been evaluated using rough and ready efficacy endpoints, for a short period of time, or in a reduced number of often poorly representative patients. It is not surprising, therefore, that the authorities subsequently have difficulty in determining the therapeutic value of the drug, which can also delay decisions regarding reimbursement and price setting.

The word "innovation" is misleading. If all new drugs represented real progress for patients, then yes, it would be legitimate to do everything to accelerate access to them.

Innovation: with no guarantee of added therapeutic value.

Unfortunately, however, this very positive word "innovation" is used in place of the more factually correct word "novelty". Indeed, the European Medicines Agency has clearly recognised this: ***"We recognise that "innovative" means nothing more than "new". This term is neutral in relation to whether the "innovative" product is more (or less) effective and/or safe than already existing treatment options"*** (1).

In practice, numerous studies published in international journals have shown that many new drugs, particularly for cancer and rare diseases, are marketed on the basis of very limited knowledge. Even worse, this knowledge is still very limited some years later. In practice, this means that we know too little about the efficacy of these drugs even after they have been marketed for several years (2 à 6).

A real innovation: better evaluation today for better care tomorrow.

Patients have the right to be hopeful, and they can accept uncertainties, provided that these are not disproportionate and that the lack of evaluation of drugs today does not harm the patients of tomorrow ●

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Prescrire

DRUGS: UNJUSTIFIED AND UNACCEPTABLE PRICES

The exorbitant prices of many new drugs are causing concern across the world.

Unjustifiable growth in prices

Researchers in public health and health economics institutes in the United States studied the price of 58 anti-cancer drugs authorised in the USA between 1995 and 2013 (1).

According to this study, the most recent drugs have not increased survival compared to older drugs. On the other hand, the price of the drugs has markedly increased: by +12% per year. Hence, an additional year of survival cost 54 000 dollars in 1995, 139 000 dollars in 2005 and 207 000 dollars in 2013 (all figures adjusted to 2013 dollars) (1). What logic have the firms been following?

"Willingness to pay"

These researchers noted that the price of anti-cancer drugs increased up to the point where it corresponded to the "willingness to pay for an extra year of survival", as determined by surveys carried out by health economists (1).
This amounts to an application to health of a concept in economics: "willingness to pay" (2). One can easily imagine that a person would say that they are prepared to spend a large sum to stay alive for an extra year.

But at what age? In what state of health? With whose money, the community's or their own? The application of this concept to health is both dangerous and absurd. If one applies this concept to drugs, why not also to procedures carried out by healthcare professionals? So how much would one be prepared to pay for a midwife to remove an umbilical cord from around the neck of a newborn baby? How much to survive thanks to a tracheotomy? etc.

At the end of the day, it is an illusory application, because the extortionate prices, which are all too real, are all too often based on scarcely more than the hope of progress. For example, for 36 of the 54 anti-cancer drugs authorised between 2008 and 2012 in the United States, this authorisation was based on intermediate efficacy endpoints. After several years of follow-up, for 86% of these 36 drugs there was still no proof of an improvement in survival (3).

What is the value of a drug which one cannot buy?

To cite just one example from many, if the community accepted the price of nusinersen requested by the company for some types of spinal muscular atrophy (a rare disease), the excess cost of treatment per patient would be between 1 and 2.5 million euros (depending on the type of disease) per life-year gained compared to current treatment (4). The committee of the French National Authority for Health (HAS) charged with health economics assessment questions the sustainability of this price for the national health insurance system (4). The AFM (French Muscular Dystrophy)-Telethon organisation is also alarmed at the possibility that the price of this drug could undermine access, not only to it, but also to other drugs (5).

Such prices make access to treatment impossible in many countries. A drug can be so expensive that, in practice, it effectively does not exist for patients.

The "value" of a drug for healthcare rests, first and foremost, on the assessment of its benefits, harms and ease of use. However, price also comes into consideration when estimating its value, because the price determines access to the drug. A drug with a favourable harm-benefit balance, but which is offered at a price which is unaffordable for a large proportion of patients, is a drug which is worth little (or nothing if it is not accessible at all).

When new drugs for hepatitis C came onto the market around 2015, some stakeholders heralded the eradication of the disease. In practice, however, as of 2018, only a tiny minority of people infected by the hepatitis C virus worldwide have access to these new drugs. The prices of these drugs are such that large-scale access to treatment of this disease can only be implemented by the richest countries and the poorest countries (the latter through discounted prices offered by companies, or access to generics). In countries with intermediate income (China, Mexico, Turkey etc.) where around 40% of infected people live, access to the drugs is virtually non-existent as a result of their unaffordable price (6).

A realistic and effective solution: generic drugs

Against this globally very unsatisfactory background, the World Health Organization (WHO) applauds the counter-example provided by Egypt, which has adopted a vigorous policy for

combatting this disease and where 1.5 million people received treatment between 2014 and September 2017. Thanks to locally-produced generics, Egypt should be in a position to eradicate hepatitis C between now and 2030, according to the WHO (6).

As in the case of AIDS since the beginning of the 21st century, it will be generics, including use of intellectual property flexibilities, which will allow most of the world to combat hepatitis C, not the originator brands which will be reserved for the "happy few".

Reject prices which are damaging to public health

As AFM-Telethon emphasised in relation to nusinersen, the exorbitant price of some drugs is also threatening access to other drugs in France (5). Even with very limited volumes of sales, paying for these drugs assumes that either new sources of income for the health insurance system can be found, or more probably, that other health related expenditure will be reduced. Which? Spending on hospital staff? Care for other patients?

The exorbitant price of drugs can be analysed in various ways: moral, political, industrial, but there is one which has the merit of being understood by everyone: when money is used for something or someone, it is no longer available for something or someone else. This is what economists call "opportunity cost" or "alternative cost".

Throughout the world, the exorbitant price of new drugs, and their opportunity costs, considerably reduce their value for healthcare, both for the patients who need them and for the community. The price of these new drugs is unjustified and unacceptable ●

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(5) AFM-Téléthon, "Spinraza: l'AFM-Téléthon se réjouit de cette avancée majeure pour les malades mais demande à Biogen de faire toute la transparence sur le prix revendiqué", 10 January 2017: 2 pages.
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CAR-T CELL THERAPIES: SURVIVAL, BUT AT WHAT PRICE?

What are CAR T - cell therapies?

A T-cell, or T-lymphocytes, have a central role in the immune system. They are distinguished from other lymphocytes by the presence of a T-cell antigen receptor on the surface of the cell that is responsible for recognising fragments of foreign antigens. Frequently produced by cancer or virus-infected cells, an antigen is a molecule capable of stimulating an immune response. Once a cancer cell is recognised, the T-cell destroys it.

In the case of CAR T-cell therapies, T-cells are subtracted from the patient's blood and modified genetically to express a Chimeric Antigen Receptor (CAR), an engineered receptor capable of targeting specific cancer cells.

An old concept with brand new ambitions

Publications and research on CAR-T have grown exponentially, from 16 in 2012 to more than 391 in 2017. More than 200 clinical trials on CAR-T therapies are underway, primarily to cure haematological cancers (lymphoma, leukaemia and myeloma) but also solid tumours (e.g. lung cancer, breast cancer, cervical cancer, etc.). CAR-T technology may also be effective in treating HIV/AIDS.

This renewed interest has also stimulated public funding. According to NGO Knowledge Ecology International (KEI), between 1993 and 2017, the US National Institute for Health (NIH) invested over US$200 million in CAR-T R&D and, by March 2017, 91% of CAR-T trials were sponsored by an academic institution.

Similarly, CAR-T therapies attracted private funding and investor interest. In August 2017, Gilead Sciences acquired a leader in CAR T-cell therapies, Kite Pharma, for US$11.9 billion and in January 2018, Celgene made a US$9 billion deal with the acquisition of Juno Therapeutics Inc. Both Celgene and Juno Therapeutics Inc. are very advanced in CAR T-cell therapy development.

Are CAR T - Cell technologiesworth the price?

The US Food and Drug Administration (FDA) approvals of the first two CAR-T therapies were based on robust clinical benefits data, despite the fact that the trials included small numbers of young, lower risk patients. Novartis' Kymriah® was approved for Relapsed/Refractory B-cell ALL in children and young adults after the phase II study submitted to the FDA showed 82% of patients infused with the treatment had achieved complete remission. For Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL), the complete remission rate was 32% at month 3. As for Gilead's Yescarta®, of 101 patients infused with DLBCL and other B-cell lymphomas, 51% achieved complete remission.

However, CAR T-cell therapies pose serious safety risks to patients. Kymriah® and Yescarta® can cause adverse events and toxicities, such as cytokine release syndrome and neurologic toxicity (e.g. delirium, expressive aphasia and seizures).

But, with no treatment alternatives existing for patients with ALL and DLBCL, CAR T-cell therapies have generated tremendous excitement and inspired hope among physicians and patients alike... but at what price?

CAR T therapies - the princing issue?

Novartis' Kymriah® was approved by the FDA in August 2017 at a list price of US$475,000. The company introduced an outcomes-based contract, with payment due only if the patient responds to Kymriah® by the end of the first month.

Approved two months after Kymriah®, Gilead/Kite's Yescarta® was priced at US$373,000, with no outcomes-related stipulations.

Both Gilead and Novartis justified these prices with the value-based pricing model. The model sets the price on the value of the treatment generated by patient outcomes (such as clinical benefits, response rate, toxicity, safety, adverse events and quality of life indicators) and the cost to society (e.g. cost of treatment, therapeutic alternatives and illness burden). As Kymriah® and Yescarta® can enable complete remission for patients who have no treatment alternatives, the high value they deliver is undisputable.

Whereas pharmaceutical companies laud value-based pricing, it is not without societal concerns. Marie-Paule Kieny, WHO's Assistant Director-General for Health Systems and Innovation, labelled value-based pricing as 'very dangerous', stating, "What's the value of life? This structure is good for luxury goods because you have a choice...if I'm sick with cancer, what's the choice?

We think value-based pricing is not feasible for products that are indispensable."

Moreover, many factors influence the results of the analysis, such as the set of relevant patient outcomes, available clinical and quality data, the data used to estimate costs, the choice and price of comparator and target population. Regrettably, most data used for assessments are confidential and therefore concealed from the necessary public scrutiny.

Controversies over CAR T price?

Even though no CAR-T therapies are available on the European market yet, their price has already given rise to some controversy. The first issue relates to the price itself. Even if cost-effective, US prices are too high. With the way health care systems function today, it will be a challenge (if not impossible) for European payers to ensure all patients have access to CAR-T-cell therapies.

Other controversies stem from explanations the pharmaceutical industry puts forward to justify high prices – mainly associated with costs of production and public sector involvement in R&D. The public sector has invested heavily in CAR-T development, and research has been and still is supported by public spending, but alas, this is not reflected in the price. According to Novartis, the company paid over one US$ billion to bring Kymriah® to market. However, NGO Patients for Affordable Drugs has calculated that the NIH (National Institute of Health) alone has poured US$200 million into research on CAR-T therapies.

Yet another controversy are the manufacturing costs. With the new technology based on each patient's immune system, CAR-T therapies are personalised and thus expensive to manufacture. However, there are many different cost estimates that tend to grow as time passes. Dr June, a major contributor to the use of CAR-Ts in cancer care, told the New York Times in 2012 that producing engineered T-cells would cost about $20,000 per patient. In 2015, Kite CFO Cynthia Butitta said that their financial model set a base case-price at $150,000 per treatment but, by 2017, the cost of Novartis' Kymriah® was reportedly around $200,000.

The latter two controversies underscore a clear lack of transparency. R&D investments and production costs are for the most part based on only partial information and estimates. Therefore, measures must be taken to make the price understandable – if not acceptable – and ensure more transparency in the pricing of CAR-T therapies ●

Source, CAR T-Cell therapies : How muche for survival, ECL Access to Medicines Task Force, 06/20/2018

THERAPEUTIC INNOVATION: CONTROLLING PRICES TO ENSURE ACCESS

Innovation and medical progress

Widely used by drug companies to support their marketing and fundraising strategies, the concept of therapeutic innovation has a variety of meanings. Innovative drugs can designate new therapeutic indications of an already commercialised product, galenic formulations or methods of treatment or use.

France-Assos-Santé promotes the notion of therapeutic progress as the delivery by new treatments of improved outcomes (efficiency, tolerance, quality of life improvement) for patients in comparison to already available drugs along with benefits to public health.

Public funding of research and cost of innovation

Financing innovation is essential, and research to address unmet medical needs should be supported and adequately funded. But equally vital is ensuring that all those concerned have effective access to the progress it brings.

The criteria for setting drug prices are being contested, due notably to the lack of transparency around the cost of developing molecules and the increasingly common use of a model based on a financialisation of research outcomes. Furthermore, public investment in basic research and public subsidies benefiting the pharmaceutical industry are not taken into account.

Many stakeholders suggest delinking support for research and development from drug pricing, often still seen by the public authorities as a legitimate and essential element of support for innovation (1). There is, however, no established causality between high drug prices and effective funding of research (2). The often exorbitant prices asked by manufacturers for innovative treatments pose a serious threat to our health system and call into question our fundamental right to access to care, especially when the government uses rationing to curb increases in spending. The demands of manufacturers also result in lengthy price negotiations, which delays patients' access to new molecules.

Our organisations are aware that the issue of access to innovation is intrinsically linked to that of price. The recent mobilisation of our organisations on the price of new hepatitis C and cancer treatments has contributed to raising awareness among citizens. In June 2016, France Assos Santé held an interactive conference on the price of innovative medicines. Considering their price posed a threat to access to health care, the 110 participants spoke out strongly in favour of new mechanisms for setting drug prices and improving the adequacy of prescriptions to release funding for innovation.

As representatives of patients and users of the health care system, we are constant witnesses to unfulfilled therapeutic needs and the hope innovations give to patients, especially those with therapeutic failure or suffering from orphan diseases. We call for a fair balance between supporting the development of bona fide therapeutic innovation and protecting the sustainability of our health insurance system that is based on the principle of solidarity. There should be no restrictions on access to medicines, and a new pricing model is required.

Activists have been campaigning for decades for access to care in countries in the South; now the North is also affected by the issue. Studies have shown there is no valid evidence of a causal link between a high drug pricing policy and effective research funding and we consider the lack of transparency around drug price negotiations unacceptable.

We urge the authorities to revise the drug pricing policy to secure sustainable access for all patients to essential drugs ●

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(2) James Love, Knowledge Ecology International, « Delinkage of R&D Costs from Product Prices », International AIDS Society, Durban, 2016. http://www.ip-watch.org/2016/09/15/delinkage-of-rd-costs-from-product-prices/

FOCUS ON EARLY ACCESS TO INNOVATIVE TREATMENTS IN FRANCE

The system of temporary authorisation for use (ATU) is particular to France. It allows patients to benefit quickly from medicines that at first sight appear to be particularly innovative, even though they have not yet received a marketing authorisation (MA). The system was expanded in 2014 to allow the continued access to a drug in the interval between the marketing authorisation and the setting of its price. This period, known as post-ATU, can be lengthy and may sometimes last more than 18 months. During this period, the pharmaceutical company holding the exploitation rights can supply the medicines to healthcare facilities either free of charge or sell them for an amount which it is free to determine. The Public Health Code provides for a system of reimbursement to the Health Insurance Fund in the event that the price set by the Economic Committee for Healthcare Products (Comité Economique des Produits de Santé – CEPS) turns out to be lower than the amount set by the pharmaceutical company.

Because it recognised that allowing the pharmaceutical company to freely set the amount would result in a loss of bargaining power for the CEPS, the 2017 Social Security Finance Act imposed a ceiling of €10,000 on the annual average cost per patient of any product marketed under the ATU and whose projected turnover would exceed 30 million euros (once the adjustment has been made after the final price is set).

- **The ATU system is essential to allow rapid access to innovative medicines for patients not benefiting from any therapeutic or alternative treatment. The system of free pricing by the pharmaceutical companies during this period, however, is used by some of those companies as a lever in price negotiations and to generate excessive profits.**

- **France Assos Santé supported the latest changes to the 2017 Social Security Law which, in our view, meet in a proportionate manner the various objectives that are of greatest concern to us: the rapid access to new therapies, cost control, and the encouraging of companies to quickly reach agreement with the CEPS. We call on the public authorities to assess the practical application of these new rules and to make sure they respond to the three complementary objectives mentioned above.**

RETHINKING THE MEDICAL RESEARCH ECONOMY SO THAT WE CAN TREAT THE SICK

Is it acceptable when the treatment that might save your life costs more than a year of your salary?
MSF has been engaging in the issue of unaffordable, non-existent or inadequate healthcare products for nearly 20 years, through its campaign for access to essential medicines. The realities encountered by MSF in carrying out its operations have prompted it to probe two major factors. Firstly, the way in which intellectual property rules impact prices and hinder access to medical products. Secondly, how innovation can be promoted by analysing the workings and limits of the current system for funding medical research, in order to generate medical products, treatment or diagnostic tools that are adapted to the needs of patients in countries with limited resources.

The diagnosis that has emerged in recent years points to numerous failings in this system: little or no investment in, or even the halting of production of, treatment for diseases that the pharmaceutical industry deems not profitable; research or development priorities which do not reflect public health needs or the burden of the diseases; insufficient use of resources encouraging silo research precisely in areas where collaborative working would bring about greater progress, such as the development of combination therapies; and the increasing, systematic and persistently high prices due to the proliferation of monopolies created by patents, wrongly thought to be the only or best way of encouraging research and development (R&D).

MSF has born witness to countless examples illustrating these points. Ebola was discovered 40 years ago and yet when the 2014 epidemic struck West Africa, we had nothing to treat it. In 2010, Sanofi stopped the production of a rare anti-venom product for the treatment snake bites in Africa (1), taking the view that the market wasn't profitable enough. Last but by no means least, despite almost 10 million cases of tuberculosis and increasing numbers of cases of multi-drug resistant tuberculosis, we still don't know how to use the only two new treatments developed to combat this disease in the last 50 years in combination. Elsewhere, although one million children die of pneumonia every year, the existing vaccine remains inaccessible because of its high price – almost a third of countries are unable to introduce it into their vaccination schedule. 20 years ago, the AIDS epidemic focused attention on the existence of very high prices making vital treatments unaffordable in the poorer, Southern hemisphere countries that were hardest hit. In recent years, new treatments for hepatitis C that are chemically very similar to the antiretrovirals used to treat AIDS, have exposed wealthier Northern hemisphere countries to prices that have caused a crisis in these public health systems.

Investigations and studies conducted over almost two decades that have documented the experiences and challenges of access to medical products in middle income countries and resources limited settings mirror some of the same challenges now facing healthcare professionals, patients and healthcare organisations in France, Europe and the United States. In 2016, a 'high-level' panel of experts, mandated by the United Nations Secretary-General, published a report on 'Promoting innovation and access to health technologies' (2). The report emphasised that problems with access due to high prices exist across countries despite their income level. It highlighted the 'inconsistencies between international human rights, trade, intellectual property and public health objectives' and stressed the existence of research needs that are not being met by the current patent system. In line with the work carried out under the auspices of the World Health Organization (WHO) since 2004, the report underscores the need for new funding mechanisms for medical research which do not rely on the granting of monopolies, thereby uncoupling the cost of R&D from the price of drugs.

During the G7 in Japan in 2016, health ministers recognised the need to address the shortfalls of a biomedical research model that is based solely on profitability. Since 2017, the fight against antibiotic resistance and the inability of the current system to address these challenges has been at the centre of G20 debates. Finally, at the World Health Assembly in May this year, after 20 years of deliberations and reports, countries unanimously approved a decision instructing WHO to establish a road map specifically addressing the system failures that have been the subject of analysis since 2004 (3,4).

A public debate on this issue, involving all of the relevant players, is urgently needed in France. It needs to be based on the studies, observations and proposals for alternative systems that would support a more efficient, transparent, less costly biomedical research system that could provide return on investment for society as a whole ●

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(2) United Nations Secretary-General's High-Level Panel on Access to Medicines. The United Nations Secretary-General's High-Level Panel on Access to Medicines Report: Promoting Innovation and Access to Health Technologies. [Online]. 2016 Sept 14 [Cited 2018 Nov 09]. Available from: http://www.unsgaccessmeds.org/final-report/

(3) World Health Organization. Addressing the global shortage of, and access to, medicines and vaccines: WHA71(8). [Online]. 2018 May 25 [cited 2018 Nov 9]. Available from: http://apps.who.int/gb/ebwha/pdf_files/WHA71/A71(8)-en.pdf.

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INTELLECTUAL PROPERTY RIGHTS: ACCESS BARRIERS TO INNOVATIVE MEDICINES

In 2014, the arrival on the market of Sovaldi® – a new hepatitis C treatment sold by Gilead at the price of €41,000 for a three-month course of treatment – led AIDES and other organisations to investigate the links between intellectual property, price and access. This paper seeks to show how misuses of intellectual property rights maintain high prices that threaten access to new medicines for all. Three mechanisms illustrate this distortion: misuse of patents, improper recourse to Supplementary Protection Certificates (SPCs) and questionable legal protection, i.e. data exclusivity.

1. Abusive monopolies: misuse of the patent system

What are the links between patent and price?

A patent is a right granted to an inventor. It prevents or excludes others from making, selling or using the invention for a period of twenty years. As a tool to foster research and development, its purpose is to protect industrial property and ensure return on investment. When a patent expires, the invention becomes public, it can be used freely and the generic form can be produced and distributed. The expiry of a patent results in a drop in price – in France, generic prices are 60% less than that of the original patented drug.

Patents are not always filed and granted for genuine innovations. In some cases, they are misused for the purpose of profit and control of drug markets. Some companies use patents merely as tools to exclude the market entry of generics and maintain high price levels.

Gilead's patent on Sovaldi®: a questionable monopoly

Some companies are granted patents on products that are not inventions, which is the case of the patent on Sovaldi®. Even though the molecule (sosfosbuvir) is highly effective, its innovative character is insufficient to be patentable. Following the patent opposition filed by Médecins du Monde (2), the European Patent Office (EPO) called into question the compliance of one of the patents on Sovaldi® (1) and, in March 2017, a second patent opposition was filed by over 30 European organisations, including AIDES, Médecins du Monde and Médecins sans Frontières (3). The verdict is pending.

A threat to universal access and health care sustainability

Facilitating the setting of a prohibitive price, the patent on Sovaldi® jeopardised the sustainability of the health care system. Subject to budgetary constraints, the French government challenged access to Sovaldi® for all by limiting access to the most severely affected patients (4). In response to this "selecting of patients", several organisations demanded access for all and, on May 25th 2016, former Minister of health Marisol Touraine announced that universal access would become effective as of January 2017 (6).

2. SPCs: questionable monopoly extensions

Since 1992, European Union pharmaceutical companies have been able to benefit from a monopoly extension beyond the twenty years granted by the patent (7). An SPC has a maximum lifetime of five years after the expiry of the patent, so a combination of a patent and an SPC allows companies to benefit from a monopoly lasting 25 years. While SPCs can be seen as a way of compensating for the period between the filing of a patent and granting of the Market Authorisation (MA), SPCs are often used as a tool to postpone a patent's expiration, thereby effectively delaying market entry of generics.

Gilead's SPC: a strategy to extend market exclusivity

AIDES found out about Gilead's Truvada® SPC in early 2017. A combination of tenofovir disoproxil fumarate (TDF) and emtricitabine, Truvada® is used to treat HIV. However, since January 2016, it has also been used as PrEP (pre-exposure prophylaxis) to reduce the risk of HIV infection (8). Because of the SPC, the market entry of generics that had been projected for July 2017 when Gilead's patent was to expire could potentially have been postponed until February 2020.

Delayed market entry of generics and increase in public health spending

By delaying the market entry of cheaper generics, the SPC could have engendered an additional cost of €760 million (9), which would have slowed down roll-out of PrEP and funding of its cost by our health care system in order to safeguard the public health budget. Gilead's SPC could thus have impeded

access to a prevention tool with proven efficacy (10).

Validity of SPC challenged before the CJEU

The English High Court has referred a SPC dispute over Truvada® to the Court of Justice of the European Union (CJEU) to rule on the validity of Gilead's SPC (11). The verdict is expected during the summer of 2018. Further to the market entry of generics in France in July 2017, the Paris High Court of Justice ruled in favour of generic competitors and the SPC was deemed "probably null" (12).

3. Data exclusivity: one more barrier to generic competition

Data exclusivity: limited right to clinical trial results

In order to obtain a MA for a new medicine, a company must provide the European Medicines Agency with data relating to pre-clinical tests and clinical trials that demonstrate a product's efficacy and safety. Under World Trade Organization (WTO) agreements, originator companies can benefit from protection of this data for purposes of business secrecy. Some governments and inter-state organisations, such as the European Union, decided to go a step further by granting originator companies with additional protection, namely data exclusivity, not provided in WTO agreements.

A deterrent to generic competitors

A generic is an equivalent to the originator pharmaceutical product, so generic competitors can avail themselves of the original manufacturer's clinical trial results for the granting of an MA. However, if the originator is protected by data exclusivity, competitors are not allowed to use the data for a period of between 8 and 10 years after the granting of the first MA. Competitors have two options open to them: repeat the same tests to obtain an MA or wait for the end of the period of exclusivity. The objective of data exclusivity could not be clearer: maintain the monopoly of an originator company to delay and deter generic competition.

A barrier to the use of the compulsory licence

According to TRIPS (Trade Related Aspects of Intellectual Property Rights) flexibilities, a government can decide to override a drug's patent to protect public health by using the compulsory licence that enables market entry of generics. But, should the drug be protected by data exclusivity, competition is still prohibited because, although the patent is cancelled, data exclusivity prevents generic competitors from using the clinical trial results to obtain an MA. Current European legislation on data exclusivity does not include any provisions allowing for a "data exclusivity waiver" in the case of a compulsory licence (13).

Conclusion

Pharmaceutical companies have the advantage of a broad range of protection tools that strengthen their monopolies, hamper competition from less expensive generics and maintain high prices. The intellectual property mechanisms outlined in this paper show how companies exploit them to serve their own commercial interests at the expense of patient needs and sustainability of health care. The effects of such distortions can be damaging:

1. increased drug prices and public health spending due to delayed market entry of cheaper generics;

2. increased health expenditure on drugs to the detriment of human resources, updating of technical infrastructure and implementation of health promotion programmes;

3. risk to the sustainability of our healthcare system: increase in prices now affects not only niche drugs but also medicines used by thousands of patients;

4. access to new drug innovations is undermined because of financial constraints ●

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(7) Council Regulation (EEC) No. 1768/92 of 18 June 1992 concerning the creation of an additional protection certificate for medicinal products.
(8) For HIV-negative people at high-risk of becoming infected with the HIV virus.
(9) Calculations made from two French cohort studies (FHDH ANRS CO4 and AQUITAINE ANRS CO3) and the price difference between Truvada® (€406.87 a box) and the generic version (€179.90 a box).
(10) Results of the ANRS Ipergay study: http://www.croiconference.org/sessions/demand-prep-oral-tdf-ftc-msm-results-anrs-ipergay-trial
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(13) For further details: https://medicineslawandpolicy.org/2018/05/european-pharmaceutical-legislation-needs-exceptions-to-data-and-market-exclusivity-to-protect-european-patients-from-high-drug-prices/

France Assos Santé
La voix des usagers

DRUG PRICES: SHOULD WE RESIGN OURSELVES TO ACCEPTING RISING INEQUALITIES?

The US drug market: an unparalleled/unequalled supremacy

Despite spending a record 17% of GDP on health, the US health care system is ranked 25th in the world by the OECD. At $ 500 billion, pharmaceutical spending accounts for 17% of these health expenditures and represents half of the global drug market (all products combined). Access to the US market is therefore clearly a priority for all manufacturers and start-ups, and the price that is first set on the US market is now used as the reference price throughout the world. The pharmaceutical industry has applied a sophisticated strategy of differentiating prices by country using the price at which the drug is made available to the US public as a basis for calculating each country's "propensity to pay". The price varies according to the size of the country, its wealth, and depends largely on the time it takes to access a therapeutic innovation. In addition, the US has been responsible for 80% of pharmaceutical innovations (biological drugs) for at least the last ten years (1). A French pharmaceutical industry executive recently wrote that "the price of an innovative medicine is what the US market agrees to pay" and that "prices in other countries ... are mere derivatives of that price" (2).

Yet, in the United States, illness has become the first cause of personal bankruptcy in a country that has already experienced the subprime crisis in the real estate market in autumn 2008. A recent study has shown that American patients are increasingly likely to face difficulties and the middle-class is now affected. One in three American patients taking more than 4 drugs is struggling to pay the share at their charge (one patient in five for those taking between 1 and 3 drugs). Still in the US, 35% of patients are forced to skip shots, cut their tablets in two, or not to go to the pharmacy to pick up drugs prescribed by their doctors. This explains why the issue of drug price controls was so high on the agenda during the last US presidential campaign. In one of his first public speeches, President Donald Trump also criticised in a rather explicit way the behaviour of pharmaceutical companies: "drug companies are getting away with murder" (3).

The measures employed by the US government seek to divert attention and will not result in price control, on the contrary...

But, contrary to the sensationalist statements of Donald Trump, the US government's recent measures have, if anything, tended towards strengthening the position of the pharmaceutical industry. This is clearly the case when the US government seeks to prevent "socialist economies" from continuing to act as "free loaders" (4). In other words, in this administration's view, many countries including EU countries, benefit from access to innovation without paying the right price for the drug and thus without contributing to the US R & D effort, which has been responsible for the vast majority of recent pharmaceutical innovations. This way of presenting the situation actually makes it possible to divert attention from the true causes of why drugs prices have soared in the United States: the intermediaries - logisticians, insurers and their subcontractors – cream off up to 30% of the net price (which unlike the reference price, remains a secret, as indeed it does in most countries); marketing and advertising expenses are estimated at $ 120 billion a year, with the US being the only major country in the world to allow the public advertising of drugs to the consumer; the remuneration of senior executives from the largest groups including start-ups, is on the rise, while shareholder remuneration and the repurchase by corporations of their own shares often cost more than the R & D effort (5, 6).

Since the adoption of the Bayh-Dole Act in 1980, research promotion practices have allowed American university hospitals to cede intellectual property and patents resulting from publicly funded research for no consideration. The current market overvalues the price for acquiring patents and the buy-out price of start-ups by betting on the ability of multinationals to offer rates of return on capital invested that are not commensurate with other sectors of economic activity. The net profitability of publicly traded drug companies increased from an average of 10% between 1954 and 1986, to 20% in 2010 and 28% today for proprietary drugs (it is 18% for generics). This makes the pharmaceutical sector the most profitable industrial sector in the world, ahead of the tobacco and alcohol industry, which are in second and third places respectively. Overall, it is this quest for hyper-profitability that explains the soaring prices much more than the return on investment on R & D, which is often financed upstream by public spending.

...which could have as a consequence the risk of exporting this inegalitarian model from the US to Europe.

This quest for American supremacy must be taken into account

to understand the mechanisms behind the recent surge in global drug prices. Demanding, as the Trump administration does, that European prices move closer to the current reference prices on the US market would, as in the United States, lead to greater inequality. In the context of the tight management of public spending and especially taking into account the fundamental characteristics of European social protection systems, the soaring prices of innovative medicines would have rapid and far-reaching repercussions, particularly in France. Starting with the example of Sovaldi®, France Assos Santé, at its seminar in June 2016, identified two possible and probably unavoidable developments in the absence of price controls: restrictions on the access to innovation (explicit rationing) and the increase in the remaining burden (implicit rationing). This trend was dubbed the "American scenario" by France Assos Santé. Under this scenario, countries will only be able to offer rapid access to innovation if this is reserved for patients who are rich enough and able to pay a very high share, as in the United States today.

In the absence of measures to reduce distortions and adverse effects on its own market, the Trump administration's preferred approach will ultimately be to seek to export its "inegalitarian model" to Europe in order to allow large publicly traded corporations to maintain record profitability. Paradoxically, in a country like France, higher prices could even allow the pharmaceutical industry to count on significantly higher profitability than is the case in the United States given the comparatively much lower marketing costs ●

(1) Many innovations marketed by European groups were initially developed by their US subsidiaries and are the result of business or joint development agreements, or may be based on acquiring patents held by US university hospital centres.

(2) « Médicaments : l'impossible contrôle des prix », Les Echos, 25 novembre 2017.

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(4) Press conference by Alex Azar, the Trump administration's health minister, 11 May 2018. https://www.c.-span.org/video/?c4729092/socialized-medicine. Alex Azar is the former president of the US branch of the American pharmaceutical corporation Eli Lilly and ex-member of "Biotechnology Innovation", a pharmaceutical industry lobbying organisation.

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UAEM
Universités Alliées pour les Médicaments Essentiels

TRANSPARENCY – PUBLIC DEBATE URGENTLY NEEDED

The failures of the biomedical innovation model based on profit maximisation have placed transparency centre stage in the public debate on health research and development (R&D). An exponential increase in prices of essential and new medicines, proliferation of innovations without any progress in actual therapeutical benefit and lack of breakthrough innovations for neglected populations are just some of the consequences of inadequate regulation of mainstream R&D. In view of the lack of transparency and/or inaccessibility of data at all levels of the pharmaceutical chain, neither health professionals nor civil society organisations are able to measure the societal impact of incentives on health innovation. It is therefore impossible to assess the capacity of the current model to ensure that health care recipients have affordable and sustainable access to essential medicines.

Transparency is the best method to rectify this lack of dialogue among the various stakeholders that hinders informed democratic debate and undermines the role of the state in coordinating R&D for the benefit of the public interest. Pivotal to our public health policy, transparency is structured around three pillars.

1. Transparency of R&D costs

How much does research and development cost?

At present, the public has only very conflicting estimates of the R&D costs of a drug. Whereas the industry fixes the cost at US$4 billion (1), other entities estimate it to be somewhere between US$116 and US$170 million (2). Studies, such as the one conducted by DiMasi (3) and sponsored by the pharmaceutical industry, lack transparency as to the parameters used to estimate the cost of R&D thereby creating confusion in the collective debate on public policy. Furthermore, several studies show that pharmaceutical companies invest more in marketing than in R&D (4). It would seem that the pharmaceutical industry has found that the return on investment of R&D does not meet the short-term expectations of its shareholders. The consequence is the putting up of smoke screens around the issue of R&D funding and channelling of resources into marketing designed to persuade doctors to prescribe their drugs and convince patients they need medication – regardless of the cost.

There is now an urgent need for independent and detailed data on the cost of R&D. This is justified by the many concerns over the absence of crucial information:

- Lack of transparency and traceability regarding direct public funding and subsidies afforded to the entire pharmaceutical innovation chain – from basic research through to production. It is estimated that almost 30% of total worldwide R&D health expenditure is funded from the public purse (5). Furthermore, current estimates frequently do not take other relevant factors into account, such as human and public education infrastructure or indirect public subsidies that include tax credits allocated to the funding of health R&D.

- Lack of transparency regarding licensing policies in universities and research institutions with respect to intellectual property clauses, and prices and royalties negotiated with private partners.

- Lack of transparency regarding the cost of pre-clinical research supported by a multitude of stakeholders (universities, independent research centres, biotechnology and pharmaceutical companies) and characterised by the highest rates of failure.

- Lack of transparency regarding the actual cost of the clinical trials required to obtain Marketing Authorisation as these vary significantly according to the therapeutic area and size of the study population.

- Lack of transparency regarding the methods used to evaluate the «cost of capital» paid by companies to banks (interest on loans) and shareholders (dividends), the amount of which is included in the cost of R&D and, by the same token, the controversy over the very principle of including this cost in calculating the total amount of R&D.

2. Transparency of clinical trials

According to the 1964 Helsinki Declaration, all research involving individuals must be registered in a publicly available database – even before anyone is recruited. Moreover, experience shows that the non-publication of clinical trial results leads to duplicate

research, waste of resources and ethical issues, as patients are not informed of results of studies for which they volunteer. Calls for more transparency in clinical trials are based on several aspects:

- Issue of non-publication of clinical trials that show adverse events. In reality, clinical trials with statistically significant results are always more likely to be published (6).

- Substantial conflict of interest when funding for a clinical trial is reliant on a positive outcome. Trials funded by the pharmaceutical industry are around four times more likely to yield positive results than those funded independently (7).

- Absence of registration of clinical trials, particularly by universities, which precludes an assessment of the total number of trials conducted and the true extent of the data omitted from these trials. Researchers can produce false-positive trials by failing to report results considered negative from preliminary clinical trial results and opting for new findings perceived as more positive (8,9).

- Non-profit institutional donors can assume an active role in promoting transparency policies for clinical trials. Concerning France, INSERM does not yet have any transparency policy regarding the obligation to register clinical trials and share summaries of results and participants' individual data (10).

3. Transparency of prices

As soon as a medical innovation arrives on the market, the question of its cost is raised and whether governments and insurers are able to afford it. But, prices should not be set according to how much a country's government is capable of paying for the innovation or to reward speculative investments. Other criteria should be considered, such as the actual added therapeutic value and the amount of public investment in the drug R&D.

Extremely opaque price setting processes lead all too often to unaffordable and arbitrary prices. Calls for more transparency in prices are therefore based on several aspects:

- Real prices are not publicly available in most countries because of laws and agreements requiring confidentiality on price negotiations and prices agreed on. In general, the official current price is higher than the real effective price negotiated and paid by the government. However, as pricing regulations often impose international referencing, governments are in a situation of total information asymmetry because they do not know the prices paid by their neighbouring countries.

- Since 21 December 1988, the EU's so-called transparency directive (Council Directive 89/105/EEC) has imposed a regulatory framework on European countries for price setting. Provisions mainly concern regulators who have an obligation to make available the criteria used to determine the price of medicines, comply with response deadlines and justify their decisions on price regulation. Holders of Marketing Authorisations must also provide the elements required to inform the regulator's decision. Although a first step towards transparency, it is largely insufficient to allow a proper understanding and assess the reality of the criteria used to determine the final price.

- Since 1994, undisclosed rebates have been customary as part of framework agreements signed by LEEM and the CEPS (France's Economics Committee for Health Products). Drug prices are called «facial» because while France's national health insurance system receives discounts from the industry, it is held to trade secrecy. However, a higher "facial" price continues to be indicated on drug packaging.

- When all is said and done, public decision-makers are extremely poorly equipped to understand and evaluate the public resources actually spent on national drug expenditure. The various administrations tasked with managing these flows do not share access to the same sources of information and drug purchases are subject to different procedures and regulations, according to whether they are hospital or non-hospital prescriptions. With no knowledge of the costs of R&D and production, the government fails to seek out other industrial alternatives to enable it to be in a position of strength during price negotiations with pharmaceutical companies. All this results in not only a lack of visibility but also a lack of management of the public resources allocated to drugs ●

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QUI SOMMES-NOUS ?

AIDES

AIDES is the biggest French community-based organization leading the fight against HIV and hepatitis. Since the late 1980s, it has been fighting for patient access to therapeutic innovations. The concerns of the association have recently shifted from the emergency of early access to misuses of intellectual property, and the resulting price hike, as barriers to access for all.

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students who believe that our universities have an opportunity and a responsibility to improve global access to public health goods.
The network consists of hundreds of university and college students who work towards making medicines more affordable and adequate for all.
Universities and publicly funded research institutions will be part of the solution to the access to medicines crisis by promoting medical innovation in the public interest and ensuring that all people regardless of income have access to medicines and other health-related technologies.

https://uaem.org/
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LIGUE CONTRE LE CANCER

«La Ligue Nationale contre le Cancer» (French League against cancer) is a public interest association founded in 1918 after WWI, when cancer was recognized to be a spreading epidemic. The League's goal is to help cancer patients, their family and friends. Since its founding, the League has developed into a strong network and leads the fight against cancer on three levels; research, promotion of screening and prevention, and care for patients and their loved ones. The League is a federation of 103 departmental committees that are active in relaying the mission of the administrative council and the national scientific council.

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MÉDECINS DU MONDE

Working in France and 64 countries worldwide, Doctors of the World - Médecins du Monde is an independent international movement of campaigning activists who provide care, bear witness and support social change. Through our 355 innovative medical programmes and evidence-based advocacy initiatives, we enable excluded individuals and their communities to access health and fight for universal access to healthcare.

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PRESCRIRE

Prescrire's purpose is stated in Article 1 of the bylaws of the Association Mieux Prescrire (AMP): «To work, in all independence, in favour of quality healthcare, first and foremost in the interest of patients (...).»

Since 1981, Prescrire has provided healthcare professionals – and via them, patients – with the clear, comprehensive and reliable information they need about drugs and therapeutic and diagnostic strategies.

The Association Mieux Prescrire, a non-profit organisation registered under the French law of 1901, manages all of Prescrire's programmes and publications. The AMP is structured so as to be free of any influence from pharmaceutical companies or healthcare institutions.

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MÉDECINS SANS FRONTIÈRES :

la Campagne d'Accès aux Médicaments Essentiels

The Access Campaign is part of Médecins Sans Frontières (MSF), an international, independent, medical humanitarian organisation.

Our work is rooted in MSF's medical operations and supports people in our projects and beyond.

We bring down barriers that keep people from getting the treatment they need to stay alive and healthy. We advocate for effective drugs, tests and vaccines that are:

- Available,
- Affordable,
- Suited to the people we care for, and
- Adapted to the places where they live.

www.msfaccess.org/
contact : Nathalie Ernoult, Head of Regional Advocacy, Acces Campaign
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UFC-QUE CHOISIR

Established in 1951, UFC-Que Choisir is a not-for-profit organisation with a nationwide network of 149 local organisations handling approximately 100,000 consumer complaints a year. Through its monthly publication, UFC-Que Choisir carries out in-depth research and comparative testing for a wide range of goods and services. More than a hundred employees work in the headquarters in Paris on activities related to web and paper publishing, legal issues, policy activities via lobbying and animation of our local network. The three pillars of UFC-Que Choisir are independence, expertise and solidarity.

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FRANCE ASSOS SANTÉ

Bringing together 80 national associations and several million members, France Assos Santé campaigns for the rights of patients and users. Our primary purpose is to give a clear and powerful voice to the views of users on health issues. France Assos Santé denounces the high prices of new drugs while calling for medicines to be accessible to all.

http://www.france-assos-sante.org/
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