Opinions expressed are solely my own and do not express the views or opinions of my employer

How is pricing for prescription drugs determined?

1 A short description of Drug Pricing mechanisms in the world

Drug pricing is always a balance between rewarding innovative drug developers and catering to the needs of budget-strained health systems, whether strict government-level price control is in place, like in most European countries, or a more free-market system, as in the US. In developing countries, where medicines can represent up to 60% of healthcare spending and the vast majority of people pay out-of-pocket for prescription drugs, the needs for a strict price control to maintain access to drugs is a critical issue.

1.1 US: the high price of innovation

The US system of pharma reimbursement is multi-faceted and somewhat opaque, and often results in different prices for different buyers. The US doesn't directly regulate drug prices, meaning that drug companies can set whitchever sticker price they deem fit, as Gilead did in 2013 when it set a price of $84,000 for a 12-week course of its breakthrough hepatitis treatment Sovaldi, kicking off a sustained backlash on drug pricing that rages on today. Medicaid, the federal programme to cover the medical costs of low-income individuals, receives a mandated discount, but Medicare, which provides insurance for Americans over 65 and is the pharma industry's biggest single customer, spending $135bn on prescription drugs in 2015 over a Total spent of $317bn[1] is not allowed to negotiate at the federal level. Insurance companies that have been contracted to administer Medicare are able to negotiate, but with limitations such as having to cover all treatments across six broad drug categories. The private insurance system, which covers many Americans who are not on Medicare or Medicaid, is fragmented into hundreds of different employers and insurance providers, limiting their ability to negotiate steep discounts. The current debate among US legislators is the sign that new measures will take place in the US, in a form or another, in the near future and that the Pharma industry should be wise to rethink its business model as the US is considered as accounting for half of the revenue of Pharma companies.

1.2 China: ongoing drug pricing reform

For the past few years, Chinese authorities have been working to pursue the twin goals of creating a less centralised, more market-driven drug pricing system, as well as combating monopolies and ensuring that new, branded drugs are made available at affordable prices. The National Development and Reform Committee has traditionally set medicine pricing policy and has final approval on the national product price list, while provincial committees compile a list of reimbursable products for different regions. The Drug Price Policy implemented by the government in June 2015 is intended to gradually transition from a centralised, double government-controlled system to a more indirect, incentive-driven market. New mechanisms introduced reimbursement standards for drugs included in the Health Insurance formulary and a move towards greater reliance on tendering processes with local buyers. The introduction of the Volume Based Procurement (VBP) in China in 2015 has led to major savings every year; as an example in August 2020 the VBP covered a total of 55 products with an average price reduction of 72% across the board and led to a savings of around 15.2 billion yuan. Combined with the VBP January 2020 round, 27.6 billion yuan were saved it is important to notice that the VBP is focusing on generics and biosimilars rather than innovative drugs.
While the country is in the process of moving away from a centralised drug price regulation, the government has shown its willingness to negotiate aggressively with companies, leveraging the size of state health insurance schemes and its broader pharmaceutical market to bring prices down. In early 2018, China reduced the prices

[1] https://www.statista.com/statistics/184914/prescription-drug-expenditures-in-the-us-since-1960/

of 36 drugs, predominantly branded medications developed by multinational Pharma companies, by an average of 44% as a condition of being made reimbursable under government health insurance. In 2021, the current trend is to combine some private coverage with this national reimbursement, the "How" has still yet to be defined. Access to Orphan diseases treatments remain a burning issue as few of them were included in the last NRDL list in the past few years, this is slowly changing with one of the first drug for an Orphan disease (Neuro Muscular Diseases) introduced in 2021. It is important to remember that a very strict cost threshold is still unformally applied before including any drugs in the yearly negotiation round.

1.3 Germany: a combination of free pricing and clinical evaluation

Health insurance is mandatory in Germany. The vast majority of Germany's population (90%) get coverage from statutory health insurance (SHI). The other 10% are covered by private insurance or special schemes. The basket of goods and services covered by SHI is defined at the national level by law, in terms of general principles, and by the Joint Federal Committee (Gemeinsamer Bundesausschuss - G-BA), through decisions on individual products or services that should be excluded from or included in the basket. Private health insurers generally cover a more or less similar basket though they are allowed to extend or restrict benefits. Patients are generally required to contribute to the costs of pharmaceuticals through a 10% co-insurance rate. Pricing and reimbursement policies are based on the following principles: prescription drugs are reimbursed by health insurance unless included in a negative list maintained by the G-BA; manufacturers are free to set their price at launch; a systematic and formal assessment of the "added therapeutic benefit" of new medicines in order to negotiate the price according to the therapeutic value of the drug takes place within twelve months after market launch. If a new drug has some added therapeutic benefit over existing standards of care, a reimbursement price is negotiated based on the prices of appropriate comparators (the current standard of care). If no additional therapeutic benefit is found, the new drug is included in a reference price cluster (Festbetrag) or price is negotiated to be equal or lower than the price of the appropriate comparator.

1.4 France: clinical effectiveness balanced by market competition

In France, the level of improvement in medical benefit, determined by the transparency commission, is a central element of the approach to price setting for reimbursable outpatient drugs; in fact it determines on one hand the type of procedure which will apply to a drug in order to obtain a price, and on the other - and related to this - the time it will take to obtain a price: the better the evaluation, the quicker the negotation and the faster access is granted to the French market. Indeed, a scale of 5 levels (namely the ASMR scale, 1: excellent to 5: no benefit) defines the relative therapeutic value of a drug. Economic evaluation and/or absolute therapeutic value are marginally used. The categories 1, 2, 3 will define drugs as being innovative. In this situation, the procedure for price registration established in 2003 has liberalised the pricing of these products for which now the only requirement is coherence with prices in Germany, Spain, Italy and the UK. For Non-Innovative drugs (categories 4 and 5) the regulator's intervention (specifically for some drugs with a very small increase in medical benefit) is drastic with the need to discount the price versus comparators. The ongoing debate in France lies on the low probability to get the ASMR grade granting the innovative status and thus stopping many drugs, evaluated as innovative in the rest of the world, to be granted access to the French market. This introduces patient unfairness to access as the French market, being highly managed by the government trough the Social Security authority, does not allow for alternative access routes such as private insurances.

1.5 UK: strict cost-effectiveness analysis

A voluntary system called the Pharmaceutical Price Regulation Scheme (PPRS) is the primary touchstone for setting drug prices in the UK. The PPRS is a non-contractual agreement between the UK Department of Health and the members of the Association of the British Pharmaceutical Industry (ABPI), and is usually reviewed every five years. The current iteration uses a value-based pricing mechanism and limits the profits that Pharma companies can make from drug sales to the National Health System (NHS), rather than the prices themselves. The main body tasked with determining the value of new branded drugs in the UK is the National Institute of Health and Care Excellence (NICE). This non-departmental body of the Department of Health evaluates the cost-effectiveness of drugs based on quality-adjusted life years (QALY), which measure the ability of a treatment to both extend and improve a patient's life. Generally, NICE will not approve any drug for sale to the NHS that costs more than £30,000 per QALY, although exceptions have been made. The UK Government also implemented a budget impact test, which stipulates that any treatment that would cost the NHS more than £20m in any of its first three years of use would trigger additional negotiations with the health service to mitigate the financial burden on the public health system. One of the most despised downside of the

UK's strict value-based approach to drug pricing, is that it does not support innovation and leaves patients waiting longer for innovative new treatments. It is not uncommon to see drugs reaching patients in the UK, when they have already been available to patients in the US for two years or more.

1.6 Japan: strict budget impact containment through a complex set of pricing rules

In Japan, a drug pricing organization, within the Ministry of Health, undertakes the scientific evaluation of new drugs. This organization is specifically in charge of the publication of the National Health Insurance (NHI) Price List: all drugs available on the Japanese market are listed in this list.
Complex pricing and repricing rules are applied from launch and during the entire life cycle of the drug on the Japanese market:

1. Two systems coexists depending on the existence of similar drugs available on the market: a "comparator pricing method" or a "cost calculation method",
2. The status of "innovator" will be rewarded by a premium regardless of the method used,
3. The price is adjusted on the "overseas" situation *i.e.* comparison with the US and a list of European countries is used,
4. A budget threshold of $1bn is applied, triggering a price decrease of 25% at any point of time after the entry on the market: each time this threshold is attained the price cut takes place,
5. Following the same logic, if the budget impact exceed by 1.5 the forecast provided by the company at the time of entry, a price decrease of 25% is applied.

Since 2015, a set of new rules were introduced to:

1. Allow for a strict selection of innovative and useful drugs with a premium defined in accordance to the level of innovation and usefulness. A clear clinical mechanism, superiority and greater efficacy compared with the standard of care and an objective improvement in treating the disease will guide the qualification for a drug to be innovative triggering a premium price allocation,
2. Develop a cost-effectiveness approach,
3. Harmonize price between generic and originator drug.

The system has the vocation to be transparent with all prices published in the list and a clear qualification of all the purchase prices by the healthcare providers. Two main principles guide this pricing system: transparency and cost-containment. These principles are combined with the "access for all" without delays.

2 Mitigating drug costs: what levers are currently being used by Health Authorities ?

2.1 Generic impact

A generic drug is identical, or bioequivalent, to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use[2]. Since the 90s, it has been widely considered that substituting generic medicines for more expensive brand-name versions is a clinically acceptable and likely among the most cost-effective interventions in health care systems. Originally, this approach was considered critical to support access to medicines in emerging countries; However between 2008 and 2015, in the wake of the global economic recession, several European governments implemented generic drug policies to help control costs[3]. Various approaches were implemented like voluntary or compulsory generic prescribing or internal reference pricing. Yet, there remain large differences in the usage and prices of generics in the world as the barriers to market entry for generic companies vary between countries, as do pricing and reimbursement policies. There are interesting examples from some European countries like Denmark, Norway and Sweden which have achieved low generic drug prices and very efficiently leverage generic entry to lower the impact of drug cost on the health system. There is no one-size-fits-all solution, though, and there are different ways of achieving similar results. The perception of the unacceptable burden of drug costs on the health systems as well as delays in negotiating adequate prices to enable access to drugs were some of the drivers behind a greater use of generics. However, regulation is highly politicized and adversarial and highly dependent on how healthcare is seen as a basic human right or more of a consumer need. Such political and cultural factors help to explain differences in generic drug policies among countries. Despite effective policies to reduce delays in

[2]US Food and Drug Administration, Center for Drug Evaluation and Research. What are generic drugs? April 16, 2002.
[3]Mrazek MF, Mossialos E. Increasing demand while decreasing costs of generic medicines. Lancet 2000;356: 1784-5.

generic availability, stimulate price competition, and increase generic drug use, we do not see yet a sustainable pricing model giving access to innovative drugs as well as using generic to optimize the economic impact on the health system. Indeed, in the past years many Pharma companies tend to delay generic entry by artificially maintaining patent rights[4]. However, patents are forward-looking policy tools meant to signal to firms that the potential return on innovation will be in proportion to the social value of the discovery, but never in excess of that value. On the contrary, generics are a mean to increase value to health systems by optimising the economic return for the system. Pricing at costs with a fair return for the generic manufacturer is the most efficient way to optimise this return. This concept of the maximum value of a medicine to a health system should become central to any future drug pricing system. However this is not currently the case as the growth in off-patent pharmaceutical prices has been demonstrated in recent works where some WHO essential medicines have been found to be sold at prices significantly higher than those estimated from production costs. Such prices suggest that market power is being exercised in ways that are inconsistent with the notion that off-patent pharmaceuticals should be available at prices close to the cost of production[5] [6].

Since the last 10 years, all developed countries have implemented severe cost-containment measures through a combination of:

1. medical evaluation assessing the level of innovation of the drug with stricter criteria than in the past,
2. cost-effectiveness measures of different forms,
3. mandatory price cuts depending on competition entry or time on the market,
4. mandatory budget cap for new drug.

A different mix of these measures is used between countries with always the same intent: to manage the increasing burden of the drug budget on the health budget.

2.2 International Reference Pricing: is that optimal ?

A principle is central to the current drug pricing system: the price secrecy and discrimination between countries. The difference between list prices *i.e.* the price visible to the public, and the confidential discounts negotiated with payers is the key element of this discrimination[7]. In theory, the final prices negotiated confidentially reflect each health system's ability to pay; however, due to the secretive nature of the negotiations as well as the absence of external references *i.e.* prices are always compared between comparators and within country, the final price is just as likely to reflect the negotiating power of the health authority in a given country. This leads to inequalities with some low and middle income countries having higher price than high income countries[8] [9]. Secrecy makes it virtually impossible to guard against such inequity in final pricing. The International Reference Pricing mechanism has been introduced as a mean to minimise such differences; however, only list prices are concerned.

2.2.1 Definition

International Reference Pricing (IRP) also called international price comparison, external reference pricing (ERP) or cross-reference pricing is:

> *"the practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country".*[10]

IRP has been widely used across the world since the 1990s, focusing on the management of individual drug prices, rather than the average price level for drugs.This approach aimed to reduce price difference with the purpose to help the countries with lower bargaining power to obtain fairer prices from pharmaceutical companies.

[4]https://blog.petrieflom.law.harvard.edu/2021/01/06/abbvie-humira-antitrust-patent-thicket/

[5]Ljungkvist M, Andersson D, Gunnarsson B. Cost and utilisation of pharmaceuticals in Sweden. Health Policy 1997;41 Suppl:S55-S69

[6]Garattini L, Tediosi F. A comparative analysis of generic markets in five European countries. Health Policy 2000; 51:149-62.

[7]Morgan SG, Vogler S, Wagner AK. Payers' experiences with confidential pharmaceutical price discounts: a survey of public and statutory health systems in North America, Europe, and Australasia. Health Policy 2017;121:354-62. doi:10.1016/j.healthpol.2017.02.002

[8]Health Action International. Life-saving insulin largely unaffordable—a one day snapshot of the price of insulin across 60 countries. 2010. http://apps.who.int/medici

[9]Goldstein DA, Clark J, Tu Y, et al. A global comparison of the cost of patented cancer drugs in relation to global differences in wealth. Oncotarget 2017;8:71548-55. . doi:10.18632/oncotarget.17742

[10]European Federation of Pharmaceutical Industries and Associations.Glossary of terms. 2012. http://www.efpia-annualreview.eu/index.php?page=glossary-of-terms. Accessed 4 Oct 2012.

2.2.2 Limitations related to IRP

Even if IRP is a widely accepted and used cost-containment tool, several limitations to its methodology were reported in the literature[11]:

- First, it is characterised by a "path dependence", which means that the observed price levels are influenced by the rules of the systems itself (*e.g.* country selection, price taken from the basket, and revisions dates) and other aspects of the market, such as health needs, income and healthcare costs, as well as their fluctuations across countries are ignored.
- Price heterogeneity (e.g., ex-factory prices, PPPs, PRPs) making the price comparison difficult (price derived from calculation, proxy of true price).
- Publicly available prices are often facial prices that do not take into account the managed entry agreements, as these agreements are often confidential.
- Lack of transparent price databases that may lead to mistakes in published prices and thus distort IRP-based systems (such as recently seen in Greece where published prices were miscalculated).However, this may be an exceptional case.
- IRP-based price revisions occurring on irregular basis after the initial price has been set, price reductions in reference countries are not automatically translated into price decreases in referencing countries.
- Exchange rate volatility affecting prices denominated in local currencies.

Due to these limitations, there are potential consequences to use IRP such as:

- A spill-over effects and a price convergence which does not truly reflect the ability to pay of health systems or patients.
- The possibility to use inadequate list prices if the Pharma industry seek to maximise revenue by artificially increasing list prices in developed economies and used these prices as anchor for future negotiations.
- The absence of true recognition of innovation when the basket of prices is unbalanced or when the prices (after the IRP process) in developed economies do not consider the need to maintain a certain level of spent to finance innovation.

These limitations call for different pricing mechanisms such as differential pricing, tiered pricing or risk-sharing agreements to be considered in the future. These new approaches have their own downsides as there is no straightforward, equitable way to set differential pricing to achieve affordability[12]. The present work below advocate for a more radical approach considering that a clear cut has to be made between innovative drugs and generic drugs: the former being priced using a value-based pricing approach, the latter being considered a "common good". Indeed, the ultimate goal of any pricing system is to assess the maximum value of a medicine for a health system while at the same time adjusting on the economic burden for this system. IRP does not permit this balanced approach and is intrinsically biased by the market.

3 Between scientific and economic evaluation: does an optimal trade-off exist ?

The balance between price and budget impact is the burning topic between pharmaceutical companies and pricing authorities: the current pricing systems makes price central to any discussion and does ignore the impact of organisation of care or non-drug related interventions on the overall cost of the disease. This evaluation in silos makes difficult to evaluate the real economic burden of the introduction of innovative drugs and very often introduce evaluation biases leading to delayed access when Pharma companies and payers can't find a common ground either on the real impact of the new drug on the disease or on its cost to the health system. These two dimensions are closely interconnected (as shown above in the description of some drug pricing systems). The introduction of Health Economic metrics such as incremental cost-effectiveness (ICER) is a very efficient way to maintain the drug budget impact manageable while using some broader metric than a pure comparator comparison; however, there is a need to assess the value of medicines that cannot be expressed numerically such as ethical and social value. Some orphan drugs, cancer drugs or even some innovative drugs developed in prevalent disease such as Alzheimer will rarely pass the test of the ICER. Two main reasons can explained this effect: the impossibility to include all indirect costs in the ICER calculation and the need to assess these drugs on a longer period of time than the one usually considered. The distinction between evaluation bodies (such as HAS, NICE, FDA,..) in charge of the scientific evaluation and payers running price

[11]The End of the International Reference Pricing System? Ulf Persson, Bengt Jönsson. Appl Health Econ Health Policy (2016) 14:1–8

[12]Moon et al. Globalization and Health 2011, 7:39 http://www.globalizationandhealth.com/content/7/1/39

negotiations with pharmaceutical companies seems to be a virtuous concept; However, in practice the lack of connection between price and value at the start of the price discussion leads to lengthy delays, this is mainly related to an important gap between the price designed by the companies to fulfill their financial goals and duties to shareholders and the price acceptable for payers *i.e.* maintaining the budget impact bearable by the health system. The absence of definition of any "anchor price" strongly connected to value by the evaluation bodies is a major issue. Most evaluation bodies will make a recommendation on the relative value of the product versus standard of care (ASMR in France, cost per Qualy in UK,...) but will very rarely acknowledge a true absolute value that could be translated in an "anchor price" or a "reference price".

4 Current debate on how to develop a sustainable pricing approach

Peter Kolchinsky[13] defined the Biotech Social Contract as follows:

> *"The drug development industry's commitment to developing new medicines (and other technologies) that will go generic without undue delay is reciprocated by society's commitment to providing universal health insurance with low/no out-of-pocket costs so that patients can afford what their physicians prescribe"*

This concept of a social contract between Pharma companies and society was the cornerstone to the development of the drug industry, patents were, from the beginning, the visible symbol of this contract allowing a fair return on investment with the possibility to support research onward. This contract was built on the understanding that behind each drug is a story of risky and expensive innovation but coupled to the possibility, after an agreed period to reward this innovation, to make this drug less expensive over time. This unique characteristics is not shared by the other healthcare services as most of the other costs either remain stable or increase.

It also should be remembered that a medicine is a proprietary good, in the sense that it is the subject of exclusive rights. It is sold on a market and must be profitable. Pharmaceutical companies are not humanitarian organisations and do not pursue the same objectives as the latter. They rely on the profitability of the patents they hold on the active ingredients - molecules - of the drugs they have invented.

When it takes nearly ten years to bring a new molecule to the market, and around twenty "drug candidates" have to be tested before one is finally approved for marketing, it is crucial to ensure maximum profitability for this "Winner". However, the active medicinal ingredient can also be seen as a common good, or a public good, in the sense that every individual has a virtual right to access, based on the right to be treated that is itself non-commercial or inalienable. The concept of a "fair price" for such a good could be to combine a retribution for innovation during the patent-covered period and then make the active ingredient a non-commercial good at the end of the patent period.

Explaining the price of a drug is a complex exercise that involves taking into account many dimensions: development time, repeated failures, multiple and increasingly expensive investments throughout the development chain. However, beyond this explanation, the question remains: who benefits most from this commercialisation? The pharmaceutical company? The civil society? The shareholders? This last category (shareholders) seems to be the least legitimate to benefit from a gain linked to the drug. This is to quickly forget the risk involved in financing a risky industry and the need to give a return commensurate with the risk. The problem comes when a pharmaceutical company no longer takes risks, is no longer innovative, but still constitutes a high expense for the community while handsomely paying the investors who supported it. Our analysis of the P&L of Big Pharma has shown the need to isolate marketing investment, research investment and fair return to investors. The market has the power to regulate itself (in a socially responsible way) by adopting ESR indicators that allow for a balance between a fair valuation of risk and a fair return on investment for society.

This vision will fall into a Corporate Social Responsibility approach of the Pharma business by managing to produce value for all associated stakeholders throughout the value creation chain with the result that performance gains are greater over time: in the patent period investors and pharma companies will have the highest return, after this period the society and all stakeholders will have access to the drugs defined then as a common good. Such an institutional agreements between users can lead to rational management of drugs seen as a common resource. The current debate around the Pharma and the commercialization of drugs is leading the debate in the direction of a Nash equilibrium (as illustrated by the prisonner dilemna example[14]), which is a non-zero-sum game in the form of a non-cooperative game, *i.e.* with no possibility of communication between players. This non-cooperative approach is positioning the Pharma industry in this Nash equilibrium

[13]The Great American Drug Deal. A new prescription for Innovative and Affordable Medicines

[14]Fehr, Ernst; Fischbacher, Urs (Oct 23, 2003). "The Nature of human altruism" (PDF). Nature. 425 (6960): 785–91. Bibcode:2003Natur.425..785F. doi:10.1038/nature02043. PMID 14574401. S2CID 4305295. Retrieved February 27, 2013.

which makes the Pharma Business model less and less viable. On the contrary, if each stakeholder chooses the cooperative strategy, the gains would be greater than those obtained in this Nash equilibrium.