

New drug pricing: does it make any sense?

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Why are drugs so expensive? A business model going adrift

Specialty drugs, also referred to as niche drugs because they usually target narrow markets, are generally very expensive. What is new, however, is the general trend for these specialty drugs to become the main driving factor for escalating costs in national health systems. A recent example is *sofosbuvir* (Sovaldi®, or combined with *ledipasvir* in Harvoni®), which would more than double the total cost of prescription drugs in the United States if every patient infected with hepatitis C virus were treated with these drugs (a)(1,2).

Although only about 1% of prescriptions are for specialty drugs, they can account for more than one-quarter of total expenditure on prescription medications (1). And spending on specialty drugs is anticipated to quadruple by 2020 (3). Unlike *sofosbuvir*, most new niche drugs often provide only

marginal therapeutic benefits. In oncology for example, they sometimes prolong survival by only a few weeks, but provoke serious adverse effects and can cost more than US\$100 000 per patient per year (b)(4).

The significant and growing disparity between the therapeutic value of many new niche drugs and their price explains why these drugs are at the heart of the pharmaceutical industry's new business model.

Drug prices are not related to their research and development costs

The pharmaceutical industry often tries to justify high drug prices by claiming that they are necessary to fund the research and development (R&D) of new products (5). This would mean that the industry sets its prices at a level where it would recover the cost of its investments. However, in

practice, there is little or no correlation between the price of a particular drug and the company's R&D investment, no more than between a drug's price and the cost of its production (c).

Costs of research and development: putting the industry's own estimates into perspective. According to the estimates of the Tufts Center for the Study of Drug Development, an institute largely funded by the pharmaceutical industry, it costs US\$2.56 billion on average to develop a new drug up to the point where marketing approval is obtained (6).

This estimate is strongly disputed however. It is based on confidential data supplied by pharmaceutical companies, concerns a selected sample from among the most costly drugs, and is marred by a lack of transparency over the data presented. According to Glaxo SmithKline's CEO himself, Andrew Witty, the idea that it costs on average over US\$1 billion to bring a new drug to the market is a myth, and the pharmaceutical industry could certainly be more efficient (7). For example, *Fortune* magazine demonstrated the inefficiency of Pfizer's in-house R&D, which succeeded in bringing only nine new drugs to the market between 2000 and 2008 despite spending US\$60 billion on R&D, making a record average cost of US\$6.7 billion per drug (8). Should patients be willing to pay more for this company's drugs because of its higher R&D costs due to its inefficiency?

Finally, half of this US\$2.56 billion figure corresponds to the estimated "lost earnings" due to the fact that the money invested in R&D was not invested elsewhere (the opportunity cost of the investment). The estimate does not however take into account the generous tax credits generally given to pharmaceutical companies, which can account for up to half of R&D costs (9).

In summary, even using these data as a basis, actual spending would amount on average to about one-



quarter of the claimed US\$2.56 billion for each approved drug.

Costs of research and development are closer to US\$100 million. Other independent estimates of the cost of R&D per drug arrive at very different results from those of the Tufts Center. A North American group of researchers recalculated the Tufts Center figures using a more comprehensive methodology to include cheaper drugs in their calculation and drugs produced in part with public funds or tax credits. According to these authors, the mean cost is closer to US\$90 million per new drug and the median cost US\$60 million (10). Based on 10 years' experience with the non-profit research organisation Drugs for Neglected Diseases Initiative, the non-governmental organisation *Médecins sans Frontières* (Doctors without Borders) considers that the average cost is actually about US\$50 million per new drug, or US\$186 million if drug candidates that fail to make it to the market are taken into account (11). A systematic review of publications on R&D costs shows that in reality it is impossible to get a precise idea of what the R&D of a new drug costs (12).

The exact cost of R&D does not really matter; the goal is to maximise profits. According to Pfizer's CEO, Hank McKinnell, *"it's a fallacy to suggest that our industry, or any industry, prices a product to recapture the R&D budget"* (13). The exact cost of R&D does not really matter: prices are set simply to maximise profits and correspond to the maximum amount health systems are willing to pay.

Some people nevertheless continue to believe that the pharmaceutical industry's profit margins must remain as high as possible, so that it can invest more in R&D. Doctors and pharmacists sometimes even prefer to use brand-name drugs rather than generics, under the misapprehension that this helps increase investment in research (14). This attitude is rather naïve: there is no reason to think that the additional profits will be reinvested in research.

The main incentive for pharmaceutical companies to invest in developing new drugs is the competition created by the arrival of generics when their patents expire. The corollary to this is that, if generics cannot adequately penetrate the market once the originator goes off-patent, the need to invest in the development of new products declines accordingly.



Profits do not lead to investment in R&D. It is an illusion to believe that an increase in profits will lead to increased investment in research.

In the capitalist dynamics at work in the knowledge-based economy, profits are generally distributed to shareholders, through dividends and share buybacks. They can also be used to buy competitors through mergers and acquisitions, often resulting in the closure of research laboratories.

An accounting study based on the annual reports of ten of the largest global pharmaceutical firms over the 10-year period 1996-2005 revealed net operating profits after tax of US\$413 billion and a net return on shareholders' invested capital of 28.7%, a very high return compared with other industrial sectors (15). These firms distributed 77% of net earnings (US\$317 billion) to their shareholders as dividends or share buybacks, used 16% (US\$66 billion) of their net earnings to build provisions for future mergers and acquisitions, and invested 10% of net earnings (US\$43 billion) in tangible fixed assets.

In summary: prices are set at the maximum buyers are willing to pay. If drug prices are not linked to the cost of their development or production, and if profits do not correlate with companies' investment in R&D, how are these prices actually determined? The answer is simple: a drug's price depends on the balance of power between the seller and the buyer. The aim of a pharmaceutical company is not to make drugs but to make profits. The prices of patented drugs are therefore set at the maximum amount that

patients and the healthcare system will accept to pay.

The pharmaceutical industry generated higher profit margins than any other industrial sector in 2013, and likely remained the most profitable sector in 2014 as well (16). 2014 was also a record year in the pharmaceutical sector in terms of share buybacks and mergers and acquisitions (17,18).

The shift from the "blockbuster" to the "nichebuster" business model

To understand why drug prices have risen so sharply in recent years, one has to look at how the new business model that is starting to sweep across the pharmaceutical sector works: the "nichebuster" model.

The blockbuster model dominated the 1990s to the mid-2000s. A blockbuster is a drug that generates annual revenues for the company ►►

a- After acquiring Pharmasset in 2011, Gilead announced that sofosbuvir would be introduced on the market for the treatment of hepatitis C at a price of US\$1000 per tablet, making a total cost of US\$84 000 for one course of treatment. If the 3.2 million people in the United States infected with hepatitis C virus were treated with sofosbuvir (Sovaldi®) or the sofosbuvir + ledipasvir combination Harvoni®, it would cost about US\$270 billion, more than doubling the country's total expenditure on prescription drugs (ref 2).

b- This is the case for 11 of the 12 cancer drugs approved by the US Food and Drug Administration (FDA) in 2012 (ref 34).

c- Manufacturing costs are not a significant factor in drug pricing. For example, a team of researchers estimated that sofosbuvir costs about US\$100 (between \$68 and \$136) per patient to produce, yet it is sold in the United States for US\$84 000 (ref 35).

► that markets it of over US\$1 billion. The blockbuster business model dominated the 1990s and 2000s. It relied on developing drugs to be sold to the largest population possible (d)(19).

In the blockbuster model, purportedly new drugs were often structurally similar variants of existing drugs. These “me-too” drugs had no real additional therapeutic value, but were often priced 20% to 40% higher than the original drug (19).

The success of a new drug depended less on its therapeutic value than on the company’s ability to conduct massive promotional campaigns aimed at convincing doctors to prescribe the drug for the largest number of people possible. The success of these campaigns determined whether the new product became the new blockbuster in its category (19).

Despite the lack of convincing evidence for their greater efficacy, buyers, in particular medical insurance systems, agreed to pay for these new drugs without too much difficulty (19).

The blockbuster model running out of steam for the last 10 years. Around the mid-2000s, this model became a victim of its own success and slowly saturated the “me-too” market (20).

With sales growing faster than gross national product, and with new drugs often offering no therapeutic advantages over older products, the model was unsustainable. During a period when governments were trying to contain health expenditure, the various medical insurance systems became more selective about which new drugs they were prepared to fund and began to demand more value for their money. Clinical superiority over placebo was no longer sufficient, and pharmaceutical companies had to demonstrate the pharmacoeconomic value of new drugs in order to secure reimbursement (21).

Similarly, a higher price could only be justified by greater therapeutic value. The increasing use of health technology assessments in various member states of the Organization for Economic Cooperation and Development (OECD) was a fundamental factor behind the crisis that hit the blockbuster model.

The major pharmaceutical companies responded to this crisis in various ways, specifically with rationalisation (staff cuts, closing R&D departments) and a wave of merger and acquisition deals (21). Other firms sought instead to diversify by moving

into the generics or vaccines sector. After a transition period of 10 years or so, the new emerging business model seems to be based on niche drugs: the “nichebuster” model.

The new nichebuster model. New specialty drugs, often produced through biotechnology, are mainly intended for the treatment of rare diseases and various forms of cancer. Crucially, by targeting specialty markets where no established therapy exists, companies can demand higher prices than they can in already saturated markets.

Some purportedly niche drugs, such as *imatinib* (Glivec®) and *trastuzumab* (Herceptin®), have progressively gained approval in many therapeutic indications, yet their price has not been lowered (22). With sales of about US\$5 billion and US\$6 billion respectively in 2012, they have achieved blockbuster status. Hence the term “nichebusters”, coined for niche drugs that generate annual revenues of over US\$1 billion (19-21).

Nichebusters, or when everyone wants to become an orphan

At the heart of the nichebuster model lie policies introduced to encourage the production of “orphan” drugs. A drug obtains orphan regulatory status when it is indicated for the treatment of a rare disease, i.e. a condition with a prevalence of not more than 5 in 10 000, according to European standards (23).

Significant, mainly regulatory, advantages. In the European Union and North America, when a product is recognised as an orphan drug, the company that markets it enjoys significant advantages, such as an expedited approval process, additional tax credits, financial assistance for research, and longer periods of market exclusivity (23,24).

Choosing to market orphan drugs brings other advantages too. First, the clinical trials required to obtain approval are smaller and therefore tend to be cheaper, even though patient recruitment can take longer. Secondly, orphan drugs are aimed at markets where few or no alternative treatments exist, which limits the negotiating power of health insurers. In particular, society is often more willing to pay higher prices to treat rare diseases and cancer. For example, some countries, including the United

Kingdom, have established cancer drugs funds to cover the cost of these treatments, even when their benefits do not justify their high price tag (e)(25). Finally, because niche drugs are aimed at specialty markets, they are prescribed by a small number of specialist clinicians. This reduces the company’s marketing costs, because small targeted promotional campaigns require less effort than mass campaigns (24).

A growth market. Policies aimed at encouraging orphan drugs onto the market are clearly working. For example, in the European Union, 66 products were granted orphan-drug designation between January 2006 and October 2014 (23,24,26). These policies sometimes favour genuine innovations that benefit patients with rare diseases. However, advances in biotechnology and the development of genetic testing, supposedly enabling a more “personalised” approach to medicine, has meant that the boundary between rare and common diseases is becoming increasingly malleable (27,28).

Salami slicing. In order to obtain orphan-drug designation, it is in pharmaceutical companies’ interests to initially request marketing approval for a narrow therapeutic indication, corresponding wherever possible to a condition with a prevalence of 5 in 10 000 or less. The drug can then be re-submitted, for a new narrow therapeutic indication, and thus accumulate multiple orphan-drug designations.

This practice of “salami slicing” a drug’s indications has become the norm, constituting the main corporate strategy for increasing sales of orphan drugs (24). For example, *imatinib* (Glivec®) has been granted seven marketing approvals for different indications, thus obtaining orphan-drug status seven times over in the United States, while *interferon*, marketed under nine different brand names, has obtained 33 orphan-drug designations (24).

Salami slicing is also an effective means of obtaining an additional period of market exclusivity by prolonging the protection afforded to regulatory data concerning the drug, thus boosting the profitability of a drug that has gone off-patent (23,24,27).

Excessive off-label prescribing. Orphan-drug designation is granted for very specific therapeutic indications, making off-label prescribing

even more common, a practice often encouraged by dubious promotional strategies (29). For example, in the United States, about 50% of oncology prescriptions are off-label (23).

Is the nichebuster market also reaching saturation point? The advantages and exorbitant prices granted for orphan drugs are completely changing the dynamics of research. For example, at the end of 2014, clinical trials were in progress in the United States for seven different drugs for the same indication, lung cancer caused by ALK gene rearrangements (a rare genetic abnormality affecting only a few thousand patients) (30). This situation is worryingly similar to the inefficient concentration of R&D resources observed in the blockbuster model...

In summary: nichebusters, a new business model proving to be another dead-end

The nichebuster model is based on two complementary trends: the "personalisation" of treatment in profitable niches, which also allows companies to obtain marketing approval on the basis of a pared-down evaluation (small trials of short duration); and a pricing level that would have been inconceivable 10 years ago (f).

Accepting astronomical prices for often insufficiently evaluated drugs that have obtained the somewhat mal-leable status of "orphan" drug skews the economic incentives that are supposed to enable efficient medical research that meets patients' needs. And as research has shifted towards the development of orphan drugs, there has also been pressure to reduce the regulatory requirements for obtaining marketing approval, leading to the development of "adaptive licensing" or the "adaptive pathways approach" (20,31,32).

In addition, with rare diseases as the focus of a new gold rush for the pharmaceutical industry, a pricing policy on niche drugs that amounts to a blank cheque is a threat to the sustainability of health systems (25,33).

The excesses of the nichebuster model surely demonstrate the limits of industrial research based purely on profit maximisation. The question now before us is what are we prepared to pay for and what types of clinical research do we want to encourage in order to best meet real public health needs. Indeed, in many respects, the financial incentives in place in the

nichebuster model and the disproportionate prices of new treatments mean that we can no longer properly meet the population's health needs.

In the meantime, it is important to remember that, from the patient's perspective, an unaffordable treatment is no more effective than a non-existent treatment.

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d- Preferred therapeutic categories included, for example, cholesterol-lowering drugs (statins), antidepressants, antipsychotics, antihypertensives, and proton pump inhibitors.

e- In the United Kingdom, it is normally considered acceptable to pay up to about £30 000 per quality-adjusted life year (QALY).

f- This upward price trend shows no signs of abating. On the contrary, the first gene therapies are due to be marketed in Europe in 2015 at a price of over €1 million (ref 36).

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