GUEST CONTRIBUTION

THE RELATIONSHIP BETWEEN BIOLOGICALS AND INNOVATION

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THE PRICE OF MEDICATION: NOVEL BIOLOGICALS

There are no two European countries with the same –or even similar -health care systems. But they share one common denominator: in all European countries the costs for health care keep on rising faster than their GDP. The growing number of elderly people and the related extra claim to the system can only partly explain this cost increase. There are other drivers as well. Although the increasing use of generic drugs tends to reduce the cost of medicines, there is an upward pressure through the category of novel medicines, in particular biologicals: medicinal product made through recombinant DNA technology. In the list of 10 best-selling drugs (total sales 75 billion US$ in 2013), 7 out of 10 are biologicals (Table 1). All 7 sell between 5 and 10 billion US $ per annum. These biologicals are used to treat serious, often life-threatening diseases, such as cancer and diabetes. And the price for the annualised cost of treatment per patient can be as high 100,000 Euros or even higher (Table 2).

1. **Humira**	6. **Rituxan/MabThera**
2. **Enbrel**	7. **Avastin**
3. **Remicade**	8. **Herceptin**
4. Advair/Seretide	9. Crestor
5. **Lantus**	10. Abilify

*Biologicals are in **bold***

Table 1: Number 1-10 blockbusters in 2013, From FiercePharma, March 25, 2014

Product	Indication	Annualised cost per patient in US	Biomarker	Population testing positive for biomarker (%)	Projected sales (2012-2018)
Erbitux	Colorectal, head and neck cancer	$84,000	EGFR+ KRAS-wt	37.5	$13.42 billion
Herceptin + Perjeta	Breast cancer	$124,800	HER-2+	25	$49.96 billion
Tarceva	Non-small cell lung cancer	$52, 800	EGFR+	10-15	$10.8 billion
Xalkori	Non-small cell lung cancer	$115,200	ALK+	4-7	$4.76 billion
Zelboraf	Melanoma	$112,800	BRAF+	13.5	$4.25 billion

Sources: EvaluatePharma and ThePinkSheet

Note: Projected sales are cumulative and global.
www.pwc.com/pharma2020

Table 2: Targeted medicines with companion diagnostics generate high revenues because they work so well for specific patient segments

Product	Price (US$)	Price/g (US$)	Manufacturing cost * (US$/g)	Cost/price difference
Avastin (bevacizumab)	687.5/100mg	6875	188	2.7%
Enbrel (etanercept)	243/25mg	9706	428	4.4%
Humira (adalizumab)	1816/40mg	45400	308	0.7%
Rituxan (rituximab)	675/100mg	6751	188	2.8%
Herceptin (trastuzumab)	3331/440mg	7570	126	1.7%
Erbitux (cetuximab)	600/100mg	6000	188	3.1%
Soliris (eculizumab)	5122/300mg	17073	135	0.8%
Remicade (infliximab)	784/100mg	7839	188	2.4%
Average		**12877**	**231**	**2.3%**

*Assuming 2g/L yield

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Table 3: Difference between cost of manufacture and price

To explain the high prices of biologicals, two arguments are being used: I) these products are very costly to produce, because of the complex manufacturing process including downstream processing, and /or II) the cost for innovative drug product development is high: 4.2 billion+ euros (period 2006-2012) for a successful product including the money to be recouped for the many failed drug products in the pipeline ('attrition') (PWC, 2012). And, somebody has to pay the bill. In the following I will demonstrate that the manufacturing costs argument is incorrect and that indeed 'big pharma' is –for now- still profitable because of these highly successful biologicals. But there is more to it.

The high cost manufacturing myth

Admittedly, the production process of biologicals is complex. But, experience with generic/follow-on versions of biologicals (the term 'biosimilar' should not be used as it is restricted to EMA/FDA approved biological drug products) in countries such as India, China and Thailand teaches us that indeed the price can be reduced substantially, although there are questions about the quality of these 'bioquestionables' (Hakim et al., 2014). E.g., a follow-on version of Humira® will be sold in India at 20% of the originator's price (1000 $ per injection)(Ail, 2014). Undela (from Gal 2014), published a list (Table 3) where the difference between costs of manufacturing and (whole) sale(s) price is listed for a number of biological blockbusters. On an average, manufacturing costs make up 2.3% of the price. Therefore, the argument that these biologicals are expensive due to the manufacturing process is not convincing at all (cf. Undela, 2014; Gal 2014). In conclusion, manufacturing costs cannot be the reason for the high annual costs listed in Table 2.

The high margins are not specific for novel biological medicines. For some novel small molecule medicines similar situations are encountered. The new anti-hepatitis C medicine Sofosbuvir is sold (wholesale price) for US$ 84,000 for a 12 weeks of treatment course used for genotypes 1 and 2 (about US$ 1,000 per pill) and US$ 168,000 for the 24 weeks course used for genotype 3. But the costs for manufacturing are close to 150 US$/course (Wikipedia). Interestingly, the innovator company (Gilead) will sell the drug for much lower prices in developing countries, e.g. for 300 US$ per course in India (http://en.wikipedia.org/wiki/Sofosbuvir).

Are the biological blockbusters saving 'big pharma' and is the current system sustainable?

The second argument to explain the exceptionally high prices (Table 2) is the sustainability of the current 'big pharma' business model. Many analyses have been published that investigated the costs for the development of new medicines. The PWC report uses a simple calculation (PWC 2012). Between 2002 and 2011 pharma industry spent 1.1 trillion US$ on R&D for the 308 NME (new molecular entities) introduced as medicines in that period. And voila, the average cost per NME over that 10 year time frame is 3.6 billion US$. The questions can be raised: 1) How to recoup these enormous amounts of money and in particular recoup from whom? And 2) Why is drug development such an expensive activity? Is the present business model sustainable?

The research and development investment has to be recouped before the patent expires or within the period of 'data exclusivity and market protection' (cf. EMA 2013). At present, the main source of payment for innovative medicines are the Western world health care systems, in particular in the USA where the prices as listed in Table 2 are being paid.

But, there is a growing concern about the sustainability of this business model with the Western world taking most of the costs of the innovation. Many wonder whether the innovation cost burden should be spread more evenly around the world and include emerging economies.

The second question was (re 2): Why is drug development such an expensive activity? Is the present paradigm sustainable? To answer that question, excellent analyses and recommendations have been published. The PWC 2020 report and the article by Munos, 2009, are mainly dealing with the industry perspective. Eichler et al. 2008 and 2013, are discussing the regulatory position regarding conditional and accelerated approval, the 'risk of risk avoidance' (type II errors) and patient advocacy. What is the big challenge now? All stakeholders in the drug development process (industry, academia, regulatory bodies, patient organizations and political parties) should sit together, critically (re)consider their positions and hammer out a new –global- paradigm for drug development. This could include, e.g. spending less money in clinical phases, in particular phase II/III. That means reduce attrition in a late phase of the development process ('kill' candidate medicines in an early stage) and further strengthen the science base for the regulatory system, e.g. avoid the 'precautionary principle' mind set and continue to work on new, globally harmonized, approval procedures understood and supported by all stakeholders throughout the whole world. These measures should lead to an efficient, economically sustainable and fair system to bring highly needed NMEs to the patient. A formidable task, but a lot of preparatory work has already been done and there is no time to lose!

We need innovation in the pharmaceutical world. Just read the challenges and desired/required new medication listed in the WHO Report on Priority Medicines 2013 (Kaplan et al., 2013). And we, the stakeholders, all have to contribute ideas and commit to make the new, sustainable system work.

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