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PERSPECTIVE

Non-profit Drug Research and Development at a Crossroads

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ABSTRACT In wealthy nations, non-profit drug R&D has been proposed to reduce the prices of medicines. We sought to review the ethical and economic issues concerning non-profit drug R&D companies, and the possible impact that their pricing strategy may have on the innovation efforts from for-profit companies targeting the same segment of the pharmaceutical market. There are two possible approaches to pricing drugs developed by non-profit R&D programs: pricing that maximises profits and "affordable" pricing that reflects the cost of manufacturing and distribution, plus a margin that ensures sustainability of the drug supply. Overall, the non-profits face ethical challenges - due to the lack of resources, they are unable to independently commercialize their products on a large scale; however, the antitrust law does not permit them to impose prices on potential licensees. Also, reduced prices for the innovative products may result in drying the for-profit R&D in the area.

KEY WORDS biotechnology · drug industry · non-profit drug development · orphan drugs · rare diseases

ABBREVIATIONS

AFM-Telethon	Association Française contre les Myopathies
CFF	US Cystic Fibrosis Foundation
DNDi	Drugs for Neglected Diseases initiative
MA	Marketing authorization
PDP	Product development partnerships
R&D	Research and development

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INTRODUCTION

Non-profit drug research and development (R&D) is of growing interest globally. In terms of developing countries, this field has focused on developing drugs and vaccines for neglected tropical diseases, in which the for-profit industry has little interest, due to the low purchasing power of the concerned nations (1,2). Since the early 2000s, several product development partnerships (PDPs) have been established as collaborative efforts between research agencies, donors, and biotech and pharmaceutical companies, to develop drugs, diagnostics and vaccines for the developing world (2,3).

In wealthy nations, where the high cost of novel treatments has put increasing strain on the budgets of health care insurers and patients, non-profit drug R&D has been proposed as a way to reduce the prices of medicines (1,4,5). Further, certain rare diseases had been traditionally omitted by research programs of the for-profit pharmaceutical industry, as the small size of the affected population results in few anticipated users of the product. This trend has been reversed by policies that encourage innovation in the area of rare diseases, by allowing expedited drug approval and thus reduced R&D costs, and by extending market exclusivity compared with more common indications, in order to allow for a longer return on investment time (5). This has led to the development of many so-called 'orphan drugs' for rare diseases, but has also resulted in extremely high prices of these drugs (6–8).

Non-profit drug R&D has been increasingly proposed as a possible way to address the price issue (5); however, it faces two prominent challenges. Firstly, small ventures established for a single R&D program do not have the expertise or resources to obtain the marketing authorization (MA) for their

product, or to subsequently manufacture and distribute it (2). Secondly, given the high cost of R&D activities, many donation-funded R&D programs that wish to sell their products at lower prices are not sustainable, and their successive R&D undertakings depend on the flow of fresh donations (2).

DISCUSSION

Pricing Models, Ethical Considerations

Generally, there are two possible approaches to pricing drugs developed by non-profit R&D programs (Fig. 1.)

a) The first approach involves pricing that maximises profits, likely leading to a very high price. This can be achieved via licensing the drug to a large for-profit pharmaceutical company, proficient in obtaining MA for similar products, as well as in manufacturing and distribution.

An example of the 'profit-maximizing pricing' approach comes from the US Cystic Fibrosis Foundation (CFF), which spent $150 million to develop ivacaftor – a cystic fibrosis medication – and subsequently sold the sales rights to a private company for $3.3 billion. Ivacaftor is one of the most expensive drugs available, being priced at $300,000 per year. While CFF expressed concerns regarding the drug's price, they stated they could not affect it (9). The ivacaftor example is one of several similar stories – ranitidine, acyclovir, captopril, enalapril and fluoxetine are further examples of US government-funded discoveries that were licensed to the for-profit industry, which later sold the final medicines at high prices (10,11). Similarly, other costly drugs, such as abiraterone, alemtuzumab and adalimumab, originated from UK government-funded institutions (12).

Further, the prices of recently approved rare disease therapies that had initially been developed in academia continue to be high. For instance, in the US, voretigene neparvovec for the treatment of Leber's congenital amaurosis (blindess) was priced at $850,000 per patient and tisagenlecleucel for

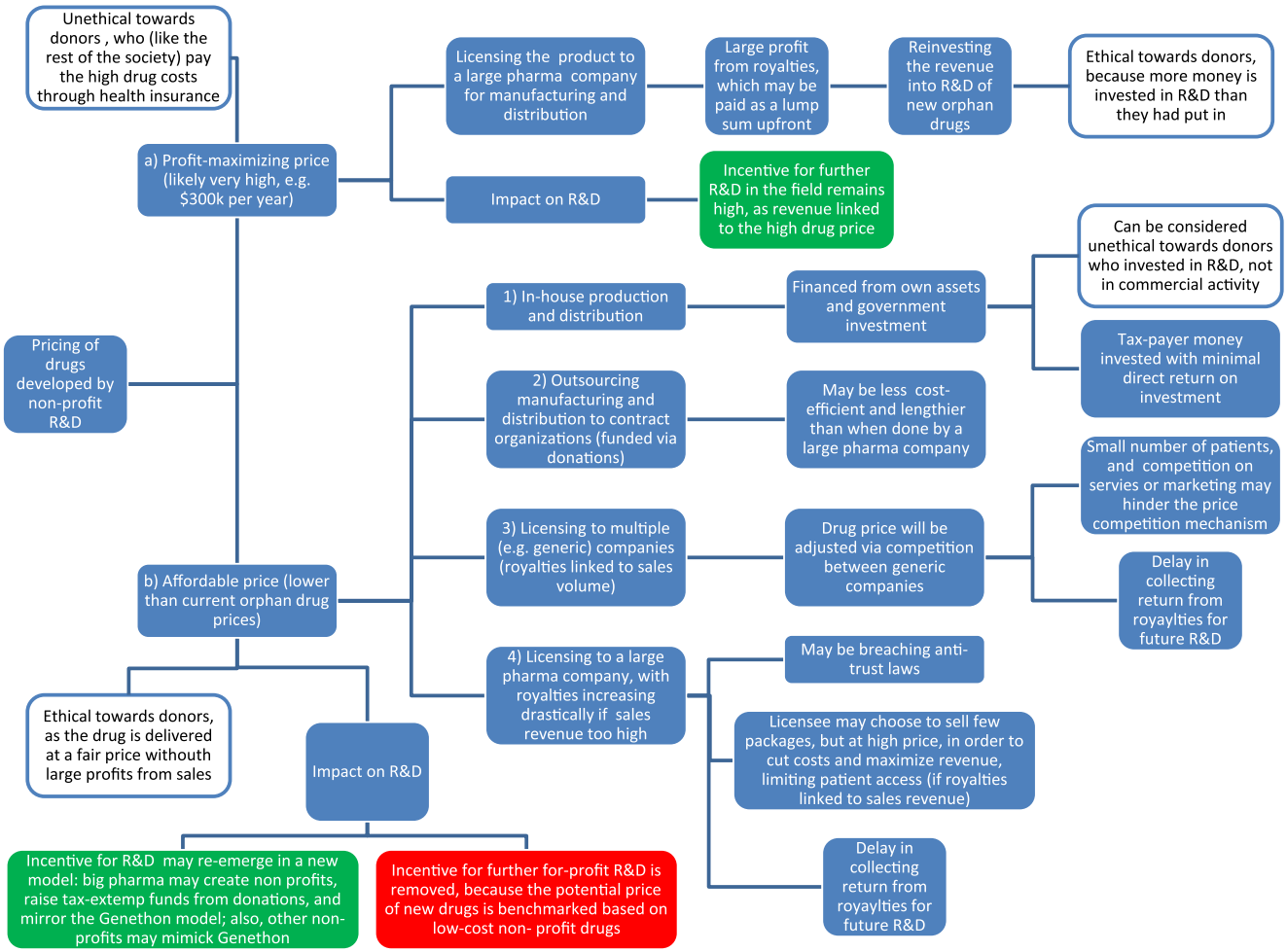

Fig. 1 Pricing and ethical considerations for drugs developed by non-profit R&D.

treatment for B-cell acute lymphoblastic leukemia was priced at $475,000 per treatment. Both treatments were licensed from the University of Pennsylvania and originated from research that received US government funding (13). Additionally, it has been speculated that the cost of clinical development of tisagenlecleucel by Novartis was relatively low, due to the accelerated route to market granted by the FDA, small trial populations and a tax credit (14).

Nevertheless, the contribution of non-profit sources towards the cost of drug development can be considered by public payers when negotiating prices in certain European countries. Illustratively, the Italian pricing authority argued that the drug strimvelis approved to treat a rare disease called severe combined immunodeficiency due to adenosine deaminase deficiency (ADA SCID) was developed with significant contribution from local charities. As a result, GlaxoSmithKline had to agree to price the drug at $665,000 per treatment, which was nearly a half of their initial pricing bid (15). Of note, the prices of drugs for rare diseases in Italy and other European countries have been shown to be inversely correlated with patient population sizes (16,17), but a similar association was not observed in the US (18). This suggests that orphan drug pricing in Europe may be influenced by additional commercial factors, such as prospective market size or R&D costs, to a larger degree than in the US. However, more research is needed to confirm this hypothesis.

Since non-profits are funded by donations from the public, they have a moral obligation to deliver the drugs to the society at an affordable and fair price. Thus, licensing the product to a for-profit company, which aims for profit-maximizing pricing, may be considered unethical. However, the substantial royalties obtained by the non-profit from the transaction could be reinvested into R&D on novel drugs, or used to support patients. Because the royalties exceed by far the sums donated by the society, more money will be invested into new drugs than the donors had put in. Through this 'return on investment', one may consider this approach to pricing to be indirectly ethical towards the donors. However, it is hard to assess who would benefit the most from the initial donation that allowed the research to materialize: the donors and the patients, the for-profit pharmaceutical company, or the non-for-profit organization.

b) The other approach to pricing is to set an affordable price that reflects the cost of manufacturing and distribution, plus a margin that ensures sustainability of the drug supply. This approach can be considered ethical, because the society pays a fair price for the drug, without generating extremely large profits for a for-profit entity. Multiple solutions for implementing this approach are possible, and these are outlined below.

1) The owner of the French non-profit biotherapy R&D organisation Genethon has opted for in-house production and distribution in order to maintain control over the supply of its products and sell them at a 'fair and controlled price'. The company was created in 1990 by the French Association Against Myopathies (Association Française contre les Myopathies, AFM-Telethon). The Association also supports patients and their families, and organizes the country's annual fundraising campaign called Telethon (http://www.afm-telethon.fr). In the early 1990s, Genethon made its mark by publishing the first map of the human genome, and took part in identifying the genes involved in several hundred genetic disorders (19–23). Currently, the company has 10,000 m^2 of laboratories and the largest human genetic disorder DNA and cell bank in Europe. In 2015, Genethon had a budget of €42 million, of which nearly 60% was funded by AFM-Telethon.

On November 2, 2016, AFM-Téléthon and the SPI fund, managed by a subsidiary of the French Caisse des Dépôts Bpifrance under the French government's investment program Avenir, created YposKesi. YposKesi is a company dedicated to obtaining MA, manufacturing and distribution of gene and cell therapy drugs developed by Genethon and targeting rare diseases. AFM-Téléthon would contribute its R&D assets and invest 37.5 million euros between now and 2022, while the SPI fund will invest a total of 84 million euros as part of the Avenir program. AFM-Téléthon has a majority holding in the new venture, allowing it to control the prices of the marketed products.

Currently, private pharmaceutical companies take the lead in drug discovery, development and manufacturing, while publicly funded research organizations excel in basic research. A study from the Tufts Center for the Study of Drug Development revealed that 54% of basic science milestones were achieved by the public sector, and 27% by the private sector (24). The private sector was dominant in achieving the major milestones for the chemistry/manufacturing/controls, drug discovery and development phases in 81%, 73% and 58% of the drugs reviewed, respectively. Unusually for a publicly funded organization, Genethon has decided to occupy the whole chain of value creation, from discovery to large-scale manufacturing and sales, in order to fully recoup the public funds invested into research, and offer its products at affordable prices. However, they lack the experience in launching, selling, and distributing medicines – and the learning curve for building teams in new functional areas – mean that it will take time for even the most talented people to become efficient in performing their tasks, which may delay or jeopardize patient access to Genethon's innovative therapies.

Overall, the 'affordable pricing' approach has several ethical issues. Firstly, funds donated by the public for R&D are spent on commercial sales activity. Secondly, building new infrastructure for manufacturing and distribution, rather than using the resources of established companies, can delay or jeopardize patient access to treatment and result in cost inefficiencies.

Finally, investing public funds into a sales venture that will bring a return on investment much below the potential return in the for-profit sector could be considered inappropriate towards the tax payer. However, indirect returns – such as creating jobs and increasing the competitive edge of the local industry – are possible mitigatory factors in this lattermost issue.

2) An approach alternative to marketing the product independently relies on outsourcing manufacturing and distribution to contract organisations already established in this field. This solution has been employed by organizations that focus on treatments for the developing world, such as the Drugs for Neglected Diseases initiative (DNDi, www.dndi.org). DNDi's antimalaria drugs are manufactured and distributed by GMP-compliant contractors that were not involved in the R&D of the products (25). We are aware that R&D and commercialization of treatments for neglected and rare diseases have their specific challenges; however, we have not identified similar examples in the developed countries.

Overall, this option could be more cost-efficient than in-house activities, providing that established contractors, who will enable timely access to the medicine for patients, exist. However, this may not be the case for technologically advanced treatments, such as gene and cell therapies. Another challenge lies in orchestrating the efforts of multiple organizations involved in various activities. Finally, the time needed for the drug to reach the market may still be longer than if the product is licensed to a large for-profit company, thus delaying patient access. Further ethical challenges are related to the use of public funds to cover the costs of outsourced activities, resulting in the same concerns that were discussed in point 1).

3) Yet another approach to achieving an affordable price involves licensing the new product for manufacturing and distribution to multiple for-profit (e.g. generic) companies. For instance, Janssen R&D Ireland (formerly Tibotec Pharmaceuticals) granted multiple non-exclusive licenses to generic companies to manufacture, market and distribute its HIV drug rilpivirine hydrochloride in lower-middle-income countries and sub-Saharan Africa (26). Like in the point above, we are not aware of similar examples in the developed countries.

This approach allows to avoid monopoly for selling the drug, so that its price would remain controlled by competition among the licensees. However, in the setting of a rare disease, the small size of the patient population could hinder this control mechanism. Further, royalties distributed in time, rather than paid as a lump sum upfront, will delay the flow of cash needed for further R&D activities. Also, there is a risk that the licensees may compete not on price, but rather on services and marketing strategy, while keeping the drug prices high.

4) Finally, one could consider licensing the new product to a single for-profit pharmaceutical company – in this case, however, the price of the drug is generally expected to be very high (as in point 0 above). On the other hand, the time- and cost-efficiency of obtaining MA and commercialization can also be very high. For instance, DNDi used the expertise of the established multinational pharmaceutical company Sanofi to register, manufacture and distribute in developing countries the antimalarial fixed dose formulation of artesunate in combination with amodiaquine (ASAQ) (25). Further, the industrial partner agreed to make the treatment available at cost for the public sector, at prices lower than those available at the time. However, similar examples are lacking in the developed world.

Importantly, because the antitrust law in many countries forbids discussing price in licensing deals, the licensor will not be able to control, prices directly. However, to ensure affordable pricing of the drug, the licensor could place a clause in the licensing deal, stating that if the drug sales revenue exceeds a certain threshold, royalties would increase drastically, rendering further sales unprofitable. In practice, however, this approach can lead to the licensee selling the drug at a high price but in smaller volume, so that the total sales revenue does not exceed the threshold set in the licensing deal. To overcome this, the licensor could link the royalties to sales volume, so that beyond a certain number of packages sold the royalties would become smaller. This would ensure that the company is efficient in marketing and distribution, aiming to reach the largest number of patients, rather than to maximize profits by selling at a higher price via limited distribution channels. However, any such clauses may still be considered a breach of the antitrust law, therefore proving unfeasible to implement. As such, fast patient access achieved through licensing to an established, experienced company, may be counterbalanced by restriction of access due to high price and limited distribution.

Incentives for Future Innovation

The two pricing models differ in their impact on the future of R&D in the field where the non-profit is active (e.g. orphan drugs). Assuming that, without price control, drugs are priced by the industry by benchmarking to the most recently approved drug in a similar disease area, novel orphan drugs would be priced at least on a par, or higher, than the currently approved ones.

The absence of R&D into unprofitable third-world diseases, and the increase in R&D for certain rare diseases after the US Orphan Drug Acts suggest that high drug prices are indeed a real incentive for R&D investment (27). Therefore, the 'profit-maximizing pricing' approach described above

seems to maintain the traditional incentive for further R&D, because of the potential for large revenues from the sales of expensive novel treatments.

However, the 'affordable pricing' model assumes that the new product is priced lower than the most recent orphan drugs. This means that future products in the same area, which may be significantly better than the existing ones developed by non-profits, will be priced based on the low price of the non-profit product, plus a premium. This constitutes a disincentive for the for-profit sector to develop further products in the same disease area, potentially limiting the range of therapeutic options available to patients. Therefore, in the short-term perspective, the risk of drying out the for-profit sector R&D in the therapeutic area is high. Nevertheless, the pricing of orphan drugs is a non-transparent process and more research is needed to reveal the underlying factors (28). In the long-term perspective, however, more non-profit organisations could take over the leadership in orphan drug development and invigorate the field, if it is disregarded by the for-profit sector. Subsequently, the for-profit industry may choose to mirror them and create their own non-profit affiliates, raising tax-exempt funds from donations in order to pursue R&D activities in neglected diseases. A similar scenario was observed in the past decade, when most large pharmaceutical companies acquired or established generic firms to compete with the growing generic sector. Moreover, single-product companies may be more time-efficient in drug development than the multi-drug big pharma. Also, some evidence suggests that large for-profit companies are less cost-efficient than non-profit organisations in developing new products, although limited examples exist (1). However, these efficiency aspects deserve further research in order to be validated.

CONCLUSION

Historically, donation-funded R&D used to be specific to diseases affecting the developing world. These drugs were priced affordably, reflecting the cost of manufacturing and distribution, and ensuring sustainability. The new initiatives for donation-funded R&D in diseases relevant to the developed countries will likely also deliver innovative products. These non-profits may be willing to adopt an ethical attitude toward their donors by pricing their products affordably. In the process, they are bound to face a pricing challenge – due to the lack of resources, non-profits do not have the opportunity to independently commercialize their products on a large scale; however, the antitrust law does not permit them to impose prices on potential licensees. An attempt to circumvent the antitrust regulation is likely to be considered illegal, as the successful outcome of such attempts would be to control the price indirectly. Alternative solutions, such as preventing market monopoly by signing deals with multiple licensees, in order to generate price competition, may also fail – for instance due to the companies competing on marketing strategy rather than price. Finally, the non-profits face a dilemma whether to adopt an ethical, affordable price for the innovative products – and possibly dry the for-profit R&D in the area – or an unethical, unaffordable price, and maintain the incentive for further R&D efforts from the commercial sector.

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REFERENCES

1. Maxmen A. Busting the billion-dollar myth: how to slash the cost of drug development. Nature. 2016;536(7617):388–90.
2. Hale VG, Woo K, Lipton HL. Oxymoron No More: The Potential Of Nonprofit Drug Companies To Deliver On The Promise Of Medicines For The Developing World. Health Aff. 2005;24(4): 1057–63.
3. Butler D. Neglected diseases fund touted. Nature. 2010;465(7296): 277.
4. Dougherty G, Harjivan C. Drug Development for Government, Nonprofit, and Developing-World Markets. Pharmaceutical Technology Sourcing and Management. 2011;7(3). http://www.pharmtech.com/drug-development-governmentnonprofit-and-developing-world-markets. Accessed 29 Jan 2018.
5. Conti RM, Meltzer DO, Ratain MJ. Nonprofit biomedical companies. Clin Pharmacol Ther. 2008;84(2):194–7.
6. Murteira S, El Hammi E, Toumi M. Fixing the price of the orphan drug Siklos®: The Council of State takes over the decision. European Journal of Health Law. 2014;21(5):505–15.
7. Meekings KN, Williams CS, Arrowsmith JE. Orphan drug development: an economically viable strategy for biopharma R&D. Drug Discov Today. 2012;17(13–14):660–4.
8. Morel T, Arickx F, Befrits G, Siviero P, van der Meijden C, Xoxi E, et al. Reconciling uncertainty of costs and outcomes with the need for access to orphan medicinal products: a comparative study of managed entry agreements across seven European countries. Orphanet J Rare Dis. 2013;8:198.
9. Pollack A. Deal by Cystic Fibrosis Foundation Raises Cash and Some Concern. The New York Times 2014. https://www.nytimes.com/2014/11/19/business/for-cystic-fibrosis-foundation-ventureyields-windfall-in-hope-and-cash.html. Accessed 29 Jan 2018.
10. Young B, Surrusco M. Rx R&D Myths: The Case Against The Drug Industry's R&D "Scare Card". Public Citizen Congress Watch; 2001. Available from: https://www.citizen.org/sites/default/files/rdmyths.pdf.
11. NIH Contributions to Pharmaceutical Development, Administrative Document,. National Institutes of Health; 2000. Available from: https://www.citizen.org/sites/default/files/appc.pdf.
12. Pills and profts. Stop AIDS. Global Justice Now.; 2017. Available from: https://www.globaljustice.org.uk/sites/default/files/files/news_article/pills-and-profits-report-web.pdf.
13. NIH Director's Blog. What a Year It Was! A Look Back at Research Progress in 2017. National Institutes of Health 2018. Available from: https://directorsblog.nih.gov/2018/01/02/what-a-year-it-was-a-look-back-at-research-progress-in-2017.

14. Silverman D. At $475,000, new cancer drug raises thorny questions about drug pricing — and value.; 2017. Available from: https://www.statnews.com/2017/09/04/cancer-drug-pricing-novartis/.
15. Regalado A. Gene-Therapy Cure Has Money-Back Guarantee. MIT Technology Review 2016.
16. Medic G, Korchagina D, Young KE, Toumi M, Postma MJ, Wille M, et al. Do payers value rarity? An analysis of the relationship between disease rarity and orphan drug prices in Europe. Journal of Market Access & Health Policy. 2017;5(1):1299665.
17. Messori A, Cicchetti A, Patregani L. Orphan drugs. Relating price determination to disease prevalence BMJ. 2010;341:c4615.
18. Jarosławski S, Auquier P, Toumi M. No correlation between the prices of oncology orphan drugs in the US and their patient population sizes. J Cancer Policy. 2017;14:1–4.
19. McPherson JD, Marra M, Hillier L, Waterston RH, Chinwalla A, Wallis J, et al. A physical map of the human genome. Nature. 2001;409(6822):934–41.
20. Chumakov I, Rigault P, Guillou S, Ougen P, Billaut A, Guasconi G, et al. Continuum of overlapping clones spanning the entire human chromosome 21q. Nature. 1992;359(6394):380–7.
21. Cohen D, Chumakov I, Weissenbach J. A first-generation physical map of the human genome. Nature. 1993;366(6456):698–701.
22. Bellanne-Chantelot C, Lacroix B, Ougen P, Billault A, Beaufils S, Bertrand S, et al. Mapping the whole human genome by fingerprinting yeast artificial chromosomes. Cell. 1992;70(6):1059–68.
23. Butler D. Genethon builds up 'genetic valley'. Nature. 1994;370(6484):4.
24. Chakravarthy R, Cotter K, DiMasi J, Milne CP, Wendel N. Public and Private Sector Contributions to the Research & Development of the Most Transformational Drugs of the Last 25 Years. Boston, MA: Tufts Center for the Study of Drug Development. Tufts University School of Medicine; 2015. Available from: http://csdd.tufts.edu/files/uploads/PubPrivPaper2015.pdf.
25. Pioneering ways of working through innovative partnerships 2002–2015. The successful development of a fixed dose combination of artesunate plus amodiaquine antimalarial. Drugs for Neglected Diseases initiative; 2015. Available from: https://www.dndi.org/wp-content/uploads/2014/11/DNDi_ASAQ-story_2002-2015.pdf.
26. Janssen Global Public Health: HIV Medicines Access & Partnerships Program. 2014. Available from: http://partnerships.ifpma.org/partnership/janssen-generic-arv-licensing.
27. Goldman DP, Jena AB, Philipson T, Sun E. Drug licenses: a new model for pharmaceutical pricing. Health Aff (Millwood). 2008;27(1):122–9.
28. Simoens S. Pricing and reimbursement of orphan drugs: the need for more transparency. Orphanet J Rare Dis. 2011;6:42.