RESEARCH PAPER

Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi

Tarification et coûts des médicaments orphelins : étude de cas sur le Kalydeco et l'Orkambi

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Abstract

Background: A common narrative is that high prices are necessary for "orphan drugs" because of the fewer patients. In the context of state health insurance systems, the high prices create significant challenges because of limited budgets.

Results: This study carefully examines both costs and revenues of two drugs for cystic fibrosis (ivacaftor and lumacaftor), showing that, for this important example, prices are not high because of fewer patients. The study then explores the justifications usually given for high orphan drug prices, including the need to support research and development for new drugs. Each of these standard justifications is shown to be inadequate; instead, it appears that the exercise of market power in the presence of insurance is the dominant driver of high prices.

Interpretation: Insurers need to re-examine how they address high-priced drugs.

Résumé

Contexte : On entend souvent dire que les prix élevés des « médicaments orphelins » sont inévitables en raison du petit nombre de patients. Dans le contexte des systèmes publics d'assurance santé, les prix élevés pausent d'importants défis, notamment à cause des limites budgétaires.

Résultats : Cette étude a examiné attentivement les coûts et les revenus de deux médicaments pour traiter la fibrose kystique (l'ivacaftor et le lumacaftor) et démontre que, dans le cas présent, les prix ne sont pas élevés à cause du nombre de patients. L'étude explore ensuite les raisons habituellement invoquées pour le prix élevé des médicaments orphelins, notamment les besoins en recherche et développement pour les nouveaux médicaments. Il s'avère que chacune de ces raisons est discutable; il semble plutôt que les forces du marché et la présence de modes d'assurance constituent les principaux facteurs des prix élevés.
Interprétation : Les assureurs devraient réexaminer leur façon de traiter les médicaments onéreux.

Introduction

Orphan drugs are at the forefront of pricing pressure in pharmaceutical companies. Numerous new drugs for rare diseases and conditions are priced at over $200,000 per year of therapy; some generate revenues over $1 billion a year (Cohen and Felix 2014; Côté and Keating 2012). Affordability of orphan drugs is a global problem, with high prices limiting access even in the richest of countries, and creating many challenging questions for policy makers (Côté and Keating 2012). Should patient access to new products be sacrificed to create a stronger bargaining position on price? How do we determine that a price is excessive, if ever?

In England and Wales, Vertex's drugs Kalydeco (ivacaftor) and Orkambi (ivacaftor + lumacaftor) have become a *cause célèbre*, as the National Health Service offered a five-year contract of about $650 million (US$ used throughout) to gain access to Vertex's drugs. Vertex has since refused, leading to calls for government intervention to seek a compulsory license (Boseley 2019). In Canada, a class action suit has been launched against a provincial government in a bid to force it to provide insurance coverage for Orkambi (Seucharan 2018).

One of the responses to high drug prices has been the renewed interest in understanding the costs of drug development and supply. In the US, notably, as one of the responses to high prices, there have been many proposals by states that require companies to disclose costs of drug development (Sarpatwari et al. 2016). This paper uses the example of two high-priced drugs used in the treatment for cystic fibrosis (CF), chosen because a credible estimate of anticipated global revenue of the products over their lifetime is available to demonstrate the value of looking at total revenues and costs.

An Illustration: Ivacaftor and Lumacaftor

Ivacaftor (Kalydeco) is indicated for the treatment of CF in patients with certain genetic mutations. Only 2,600 patients globally had the specific genetic mutation that made them eligible for the first approved indication of ivacaftor (Vertex Pharmaceuticals Incorporated

2012). In response, Vertex, the manufacturer, priced Kalydeco in the US at about $300,000 per patient per year of treatment following its Food and Drug Administration (FDA) approval in 2012 (Silverman 2017). Starting in 2016, Vertex marketed a combination product (Orkambi) consisting of ivacaftor and lumacaftor, designed to address a more common mutation. Vertex now indicates that its addressable population globally is over 25,000 patients, which massively increases Vertex's potential revenues (Leiden 2015). Orkambi is priced in the US at $259,000 per patient per year (Weisman 2015). The pricing of these medications has been challenging for insurers (Grant 2017; O'Sullivan et al. 2013; Senior 2015).

Public agencies in various countries have examined the cost-effectiveness of Kalydeco and Orkambi, and the assessments have shown that for the purpose of improving population health, these products have proved to be expensive (Gulland 2016; Haute Autorité de Santé 2016; National Centre for Pharmacoeconomics 2016; Pharmaceutical Benefits Scheme 2013). Indeed, there have been concerns about the effectiveness of Orkambi despite the price (Therapeutics Initiative 2017, 2018). A commonly cited threshold for identifying a drug as being cost-effective is $50,000 per quality-adjusted life-year (QALY) generated (Neumann et al. 2014). The Canadian Agency for Drugs and Technologies in Health (CADTH) estimated that Kalydeco's cost per QALY was $640,000, whereas that for Orkambi was $3.6 million (CADTH 2015; Canadian Observational Cohort Collaboration [CDEC] 2016). Despite the high prices for these products, insurers have felt obliged, in many cases, to insure the products because they did not want to deny patients access to the modest health improvements they promised.

Before exploring the rationale for such high prices, this paper offers a brief analysis of the revenues and costs attributable to these drugs as an important background for understanding the pricing model.

Vertex's revenues

This section calculates the net present value of the expected revenues of Kalydeco and Orkambi. It is possible to turn to a commercial transaction that reveals anticipated revenues with a high degree of credibility. The Cystic Fibrosis Foundation Therapeutics (CFFT) paid for the initial basic research on ivacaftor and lumacaftor, as well as part of Phase 1 clinical trials, in exchange for royalty on the sales of these two products and a third investigational drug (Werth 2014). The complete terms of the royalty are not public; it is in the range of "single digits to sub-teens" (Vertex Pharmaceuticals Incorporated 2014). This means that the upper bound of the royalty is 12.9%. In addition, the royalty is 8% on the first $250 million of annual sales (Vertex Pharmaceuticals Incorporated 2006). A reasonable middle estimate is that royalty averages about 10%, with upper and lower bounds of 12% and 8%, respectively. In 2013, Royalty Pharma purchased CFFT's future royalty stream for these products for $3.3 billion cash. (At the time, Orkambi was still in Phase 3 trials; the third

drug was not approved until 2018, and so, it is reasonable to assume that its value in 2013 was minimal.) This implies that the 2013 net present value of the expected future revenues of these products was approximately $33 billion. This estimate of revenues is highly credible, as Royalty Pharma, a privately held trust with rights to 44 products, would have thoroughly evaluated the royalties for which it paid $3.3 billion. (The amount paid by Royalty Pharma is approximately in line with the following calculation: if Vertex earns $250,000 per patient per year after discounts, and it sells to 25% of the global CF population, the net present value of revenues over 12 years is approximately $37 billion. Twelve years is applied, as this is the exclusivity period assumed for Orkambi by Vertex in its submission to CADTH [CADTH Common Drug Review 2018]. I assume a 10% cost of capital and 2% annual price increase for the products.)

Thus, we can conclude that the net present value of the revenues from Kalydeco and Orkambi, adjusting for discounts granted, risks of competition from alternative therapies, changes in regulatory status, changes in insurance status and the like, was approximately $33 billion as of 2013. It is important to note that by relying on Royalty Pharma's payment, we do not have to rely on confidential prices to estimate Vertex's revenues.

Vertex's production, sales, general and administrative costs

Pharmaceutical companies, including Vertex, have considerable expenses related to production, sales and administration. It is reasonable to use Vertex's 2016 and 2017 financial reports to make an estimate (Vertex Pharmaceuticals Incorporated 2017/2018). The goal in this section is not perfect precision; instead, the desired outcome is to obtain a sense of the scale of production, sales, and general and administrative costs.

According to Vertex's 2017 10-K (a public report filed with the Securities and Exchange Commission), in 2016 and 2017, royalty expenses and production costs averaged 12.6% of revenues, which were derived almost exclusively from the sales of Kalydeco and Orkambi.

In addition, in 2016 and 2017, Vertex's sales and general and administrative (SGA) expenses averaged 24.3% of revenues. I assume all of these costs relate to Kalydeco and Orkambi. (If some related to products in development, this would, if anything, increase the calculated profitability of Kalydeco and Orkambi.) Because Kalydeco and Orkambi were growing in sales in 2016, it seems likely that the selling costs, particularly those related to promotion, will fall relative to sales over time.

The net present value of estimated revenues and costs as of 2013 are presented in Table 1, which shows upper and lower boundaries in addition to a middle estimate. The upper boundary assumes the values that will lead to the largest profits for Vertex (i.e., highest revenue, lowest cost). After deducting royalties, cost of production and SGA expenses, one can calculate "quasi-rents" – the profits of Vertex that are attributable to its investment in developing Kalydeco and Orkambi. The middle estimate is $21.1 billion.

TABLE 1. Vertex revenues and costs for Kalydeco and Orkambi (US$ billion)

	Middle	Upper	Lower
Revenues ($)	33.0	41.3	27.5
Royalties and production costs ($)	4.2	3.3	3.3
Percentage of revenues (%)	12.6	12.6	12.6
Selling, general, administrative ($)	7.7	6.4	8.6
Percentage of revenues (%)	23.3	15.6	31.1
Quasi-rents ($)	21.1	31.5	15.6
R&D cost ($)	2.5	1.3	5.0
Profits ($)	18.6	30.3	10.6

Is $21.1 billion a reasonable return on the investment Vertex made in developing these medicines? To answer this question, we must first consider Vertex's contribution to developing these products and conducting the required clinical trials both before and after regulatory approval.

Vertex's R&D costs

Estimating drug development costs is challenging. A 2011 systematic review of studies on this topic finds little agreement, with estimated average development costs ranging from $160 million to $1.8 billion per drug (Morgan et al. 2011). DiMasi et al. recently estimated that the average cost of drug development, fully accounting for the risk of failure and the cost of capital, and including post-approval requirements, is approximately $2.8 billion (DiMasi et al. 2016). This figure has attracted many criticisms, including the use of confidential data provided by the industry (Avorn 2015; Carroll 2014). If one accepts the DiMasi estimates, a reasonable rate of return on investment in developing a drug would be achieved if a firm earns quasi-rents with a net present value of $2.8 billion. (Estimates of the cost of drug development use a net present value calculation as of the date of approval, which is consistent with the treatment above of revenues, costs and quasi-rents.)

Vertex was not solely responsible for the drug development cost, as CFFT paid for most (if not all) of the pre-clinical expenses and part of the ivacaftor Stage 1 clinical trial (Werth 2014). Pre-clinical costs typically represent roughly 40% of total costs (DiMasi et al. 2010), so Vertex's share of costs is approximately 60%. Given this adjustment, for two new drugs, and using DiMasi's estimates, Vertex's share of costs for two drugs is approximately $3.4 billion.

The net expense to Vertex is, however, substantially reduced because of a US tax credit for clinical trial expenses for orphan drugs (Seoane-Vazquez et al. 2008). This tax credit was worth 50% of qualifying costs. Clinical trials are not the only cost of development; costs

related to chemicals, production process development and regulatory submissions are also included. If the tax credit amounted to 25% of Vertex's clinical expenditures, then Vertex's development costs would be approximately $2.5 billion on a risk-adjusted basis. In effect, if the quasi-rents from Kalydeco and Orkambi were $2.5 billion, Vertex would be fully compensated. Supplementary Appendix 1 provides an estimate of the R&D costs for these products specifically using Vertex's public financial records; this places Vertex's risk-adjusted R&D expenditures in the same range. The upper and lower boundaries in Table 1 assume Vertex to have spent 50% less or 50% more than the estimated middle R&D cost.

Discussion

Vertex is expected to earn substantial profits on its investment, as Table 1 shows. These large profits are only obtained thanks to the high prices charged. This makes it important to address the question of whether payers should support these substantial profits. Four justifications are commonly presented for high orphan drug prices.

Benefits to patients

First, it is asserted that these medicines provide "significant" clinical benefits to patients (Taylor-Cousar et al. 2016). For most patients, the benefits of these medicines are considerably limited, whereas many lower-priced medicines in other disease areas also provide similar or greater benefits. For example, Sovaldi, which is itself famously high-priced, provides a high cure rate of hepatitis C virus for a one-time cost of about $80,000, which compares favourably to the $250,000 annual cost of Kalydeco or Orkambi, and its cost per QALY has been estimated at being in the range of $50,000 (CADTH 2014). Given the limited budgets, spending on high-cost drugs squeezes out other treatments.

Every funding decision has an opportunity cost, and if payers are looking to maximize health benefits from their limited budgets, then they should not insure drugs with a low benefit/cost ratio. If the cost of a product per QALY exceeds that of displaced interventions, insuring that product will *decrease* population health (McCabe et al. 2008).

Support for continuing investment

The second justification is that high prices support investment in innovation. Vertex's CEO stated that "the company was relying on the income from Kalydeco to finance its goal of curing cystic fibrosis by 2020 (Werth 2013)." Indeed, Vertex recorded losses in 2015 and 2016, even though its revenues far exceeded its costs of production, royalties, SGA and interest, because of a substantial investment in R&D.

From an economic perspective, this justification is counterintuitive, and wrong. Patents create an incentive to invest in developing products valued by the market. The investment comes first, and the reward of monopoly over invention follows. Shareholders can choose to take profits as dividends or re-invest the profits. The decision to invest in new drug R&D

is driven by the hope of a high return from that investment. It seems improbable that if the products Vertex is currently developing are approved, Vertex will discount them because their costs had been covered through profits earned on Kalydeco and Orkambi.

Expected prices need to be high enough to stimulate R&D investments; similarly, current prices should fairly compensate investments made in the past. However, we should not justify high prices today by the prospect of future medicines that will also be high-priced. The society needs a sustainable system of pricing in which investments made today can be appropriately compensated when they turn into valuable products.

Fewer patients

The third rationale explaining the high prices for Kalydeco and Orkambi is fewer patients, which means high R&D costs per patient. On this basis, Vertex executives have made a case for the high price of the drugs (Nocera 2014; Verstraten 2014). The same theme is restated in general about drugs for rare diseases: "Pricing of orphan drugs is unique because R&D costs need to be recouped from a small number of patients." (Picavet et al. 2014).

The claim that prices should reflect the number of patients seems reasonable but does not justify *any* price no matter how high. If a company claims that a high price is needed because of high costs per patient, the price should be no higher than those risk-adjusted costs including the cost of capital (Berdud et al. 2018; Fellows and Hollis 2013). Although insurers may find that they cannot apply a standard cost-effectiveness threshold to orphan drugs such as Orkambi, there is a reasonable argument that prices far above this threshold should not simply be enabling excessive profits. For Vertex, the claim that prices must be high because of fewer patients is inconsistent with the enormous profits that the company is making from the sale of its drugs; a much lower price would still be enough to compensate the company.

Profits are an incentive mechanism

Another common argument is that the prospect of large profits stimulates firms to address the problems that are of greatest importance. However, in a healthcare system with a limited medicines budget, if one firm gets more, others must get less. Thus, if one company captures unexpectedly high profits, the incentives to create new drugs are not increased: revenues are simply spread among companies in a different, less predictable, way.

Controlling orphan drug prices

As the example of Kalydeco and Orkambi shows, pharmaceutical companies do not set prices based on the cost of production or development but on the price that will be profit-maximizing, given the policies in place. Patients could not normally afford extremely high prices, and it is only because of insurance that high prices can be profitable for such companies. Insurers, in this context, have a critical role in deciding what to insure. This decision

should arise from carefully considered policies. The use of a cost-effectiveness threshold may not suffice in all situations, and it will often fail to apply well to drugs for rare diseases, as they are frequently priced far above the normal threshold. In many cases, pharmaceutical companies can take advantage of poorly designed policies to raise prices indiscriminately. For example, Turing Pharmaceuticals purchased the rights to an older drug, pyrimethamine, and then attempted to raise its price in the US by 5,000% (Ghinea et al. 2016).

We should distinguish Vertex from a company like Turing. Vertex helped bring new, valuable drugs to market, as opposed to increasing generic drug prices rapaciously. But the policy framework that allowed Turing to increase prices is the same one that allows Vertex to charge a price that is far above its costs, while "justifying" its pricing based on high costs per patient. Insurers have no easy solution to high prices: Should they pay whatever the company asks, or hold the line and watch patients suffer and die? Turing's strategy, being transparently abusive, elicited outrage; Vertex's strategy has elicited concern about how patients can access needed medicines.

Vertex's financials show that high prices are not justified by costs or the need to support innovation. Instead, the prices seem more designed to reward shareholders: Vertex's previous CEO has been selling stock options in Vertex according to an approved trading plan, with a net profit of approximately $1 million per week, or approximately $50 million for 2015 (Vertex Pharmaceuticals Incorporated 2017). Without Vertex's aggressive pricing, shareholders and the executive team would have to do with less. Would the high-price strategy be acceptable to payers if they fully understood why the prices for these drugs are so high? There are approximately 180 patients in Canada who are eligible for Kalydeco under provincial insurance plans (Cystic Fibrosis Canada Kalydeco 2017). At $225,000 per patient, they will generate approximately $41 million in revenues per year, or a little less than the former CEO has been earning.

Insurers should critically analyze the prices that they pay and the claims made about costs. There may be a role for greater transparency to inform insurers about what are the true average costs of developing drugs, as has been proposed most recently by the Italian Government (Ministero della Salute of Italy 2019). Such data would help establish maximum prices when insurers feel compelled to provide access to drugs but not to provide excessive returns to shareholders.

Conclusions

This study has shown that the pricing of Kalydeco and Orkambi is far higher than is needed to recover the costs of development, even assuming that such costs are as high as the most generous estimates. That is, a large fraction of the price represents excess returns for shareholders of Vertex, rather than a reasonable payment for its investment. The situation calls for payers to explore new strategies for addressing the challenges created by high-priced drugs.

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Note

Following the acceptance of this manuscript, Vertex Pharmaceuticals contacted the author and requested to clarify several issues that were – in their opinion – inaccurate. The author had responded to the queries. For the purpose of transparency, the editors of the journal have decided to include the correspondence from Vertex Pharmaceuticals and Dr. Hollis' response as part of the manuscript as an online Appendix, available at longwoods.com/content/25937.

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