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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Appendix 1

Estimated costs of developing ivacaftor and lumacaftor

Considering only the average costs of drug development may fail to reflect Vertex's experience. This supplementary analysis thus examines Vertex's expenditures on R&D. This exercise is challenging, as expenditures specifically related to Kalydeco and Orkambi are not available.

The substantial costs for R&D in Vertex's annual 10-K reports are shown in Supplementary Table 1.

SUPPLEMENTARY TABLE 1. Vertex's annual reported R&D expenditures ('000)

	Research ($)	Development ($)	Total ($)
2002	120,406	77,932	198,338
2003	113,435	86,201	199,636
2004	113,276	78,886	192,162
2005	120,779	127,761	248,540
2006	142,647	229,066	371,713
2007	164,402	348,652	513,054
2008	165,381	351,531	516,912
2009	174,267	376,007	550,274
2010	189,273	448,143	637,416
2011	216,903	490,803	707,706
2012	213,550	552,355	765,905
2013	233,651	648,446	882,097
2014	257,483	598,023	855,506

Source: Vertex 10-K reports, various years. Numbers are in thousands of dollars.

Development typically involves clinical trials, whereas research tends to be focused on bench science. The "research" on ivacaftor was conducted in the period up to 2005, with clinical trials from 2006 to 2010. According to various sources, most of the basic research on ivacaftor and lumacaftor was funded directly by CFFT (Werth 2014). Once Vertex had developed a viable molecule, it was the expectation that Vertex would fund clinical trials and bring the product to market. As it happened, Vertex went

back to CFFT to provide partial funding ($13.3 million) to accelerate the Phase 1 clinical trials of ivacaftor in 2006 and 2007 (Werth 2014). The proposed total budget for developing ivacaftor was $27 million in 2006 and $41 million in 2007.

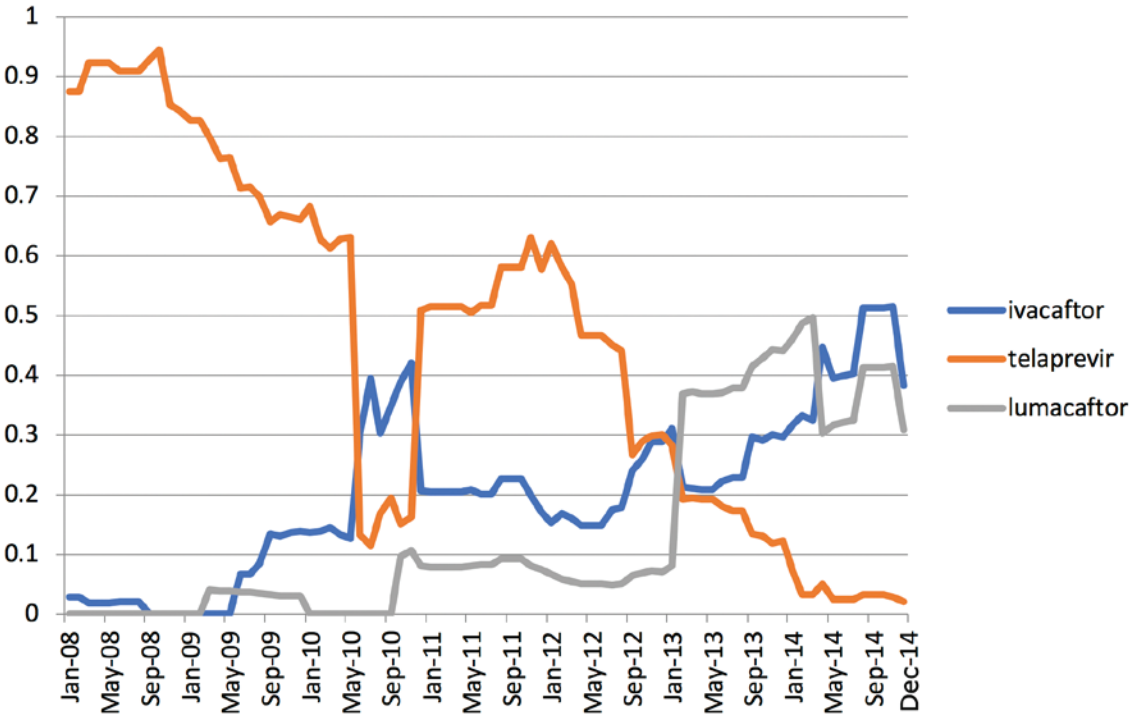
Ivacaftor was not a significant component of Vertex's R&D budget in 2006–2007, representing approximately 8% of its R&D budget during those years. Assuming that clinical trial costs represented at least 50% of the R&D costs associated with ivacaftor at that time, the credit would be worth roughly $7 million in 2006 and $10 million in 2007. This leaves Vertex with a net cost during 2006 and 2007 totalling $38 million for its share of drug development costs during that period for ivacaftor.

To estimate ivacaftor's share of R&D costs after 2007, one can use the number of patients in clinical trials. Ivacaftor was approved for the gating mutation at the end of January 2012, so the trials before that date are the ones relevant for getting approval.

Vertex's financial reports show the total cost of clinical trials during the relevant years; these can be allocated between drugs according to the extent of clinical trials for each drug. The allocation is the difficult part of this. Using clinicaltrials.gov, the website maintained by the US federal government, I obtained data on all Vertex's clinical trials in 2008–2014. Each trial lists a start date and end date, as well as the number of patients included in the trials.

Assuming that all patients listed were present in the trial from the start until the end, I calculated the total number of patients in clinical trials sponsored by Vertex for each month from January 2008 until December 2014. The share of patients in trials related to ivacaftor and lumacaftor in each month is shown by the blue and grey lines in Supplementary Figure 1.

SUPPLEMENTARY FIGURE 1. Share of patients in trials of Vertex drugs, by month



Source: author's calculations, based on data from clinicaltrials.gov.

Until mid-2012, Vertex appears to have allocated most of its clinical trial spending to telaprevir, a treatment for hepatitis C. Assuming that the cost of clinical trials was proportional to the number of patient-months, then we can infer the share of the total development expenditure related to ivacaftor and lumacaftor during the years 2008–2014. This calculation is shown in Supplementary Table 2.

SUPPLEMENTARY TABLE 2. Estimated clinical costs for ivacaftor and lumacaftor

Year	Total clinical costs ($)	Share of patient-months for ivacaftor and lumacaftor (%)	Clinical costs for ivacaftor and lumacaftor ($)
2008	351,531	22	77,674
2009	376,007	18	67,734
2010	448,143	21	95,036
2011	490,803	28	136,035
2012	552,355	43	239,555
2013	648,446	63	410,899
2014	598,023	80	478,592
Total	3,465,308		1,505,526

This approach yields an estimate of roughly $1.5 billion in clinical trial costs for ivacaftor and lumacaftor, most of which is in Phase 3 clinical trials.

On average, there is a 55% rate of approval for drugs that enter Phase 3 trials (DiMasi et al. 2010); adjusting for this risk, we obtain an estimate of risk-adjusted clinical trial expenditures that is roughly $3 billion combined for ivacaftor and lumacaftor. After again adjusting for the US orphan drug tax credit, we obtain a net cost of roughly $2.25 billion for both drugs together, or $1.1 billion per drug. Thus, Vertex's risk-adjusted expenditures on ivacaftor and lumacaftor appear to be in line with the estimates of DiMassi et al. (2016) (Tufts Center 2014).

References

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Appendix 2

The correspondence below between Michael Siauw, Country Manager – Canada, Vertex Pharmaceuticals, and Dr. Aidan Hollis, the author of "Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi," occurred after the decision to accept this paper for publication was made public.

For transparency purposes, the editors of the journal have agreed to share the correspondence from Vertex Pharmaceuticals and Dr. Hollis's response.

Vertex Pharmaceuticals' comment:

"The article inaccurately reports Vertex's investment contribution to bringing our drugs to market:

- It was the commitment of hundreds of Vertex scientists and billions of dollars invested over 20 years that brought these medicines to people living with cystic fibrosis (CF). Every molecule was discovered, developed and commercialized by Vertex scientists in a Vertex lab. Vertex has invested over $11.8B USD in R&D just since 2000, the majority in CF.
- While the Cystic Fibrosis Foundation (CFF) provided an important initial investment in the early stages of Vertex's CF research, it was only a small fraction of the billions Vertex has invested. It is also worth noting that the CFF sold its royalty rights in 2014 for $3.3B USD."

Author's response:

"The article reports that Vertex invested heavily in developing and bringing to market both ivacaftor and lumacaftor:ivacaftor. The total investment of Vertex in all drug R&D is of course much larger, since it includes development expenses for numerous other drugs."

Vertex Pharmaceuticals' comment:

"The article relies solely on HTA (NICE and CADTH) of medicines to characterize the clinical benefit and cost effectiveness, without recognizing the limitations of these assessments:

- Medicines for rare diseases are assessed by the 'Standard Assessment' criteria designed for mass diseases. We do not agree with many of the clinical criteria and the cost effectiveness modeling used as they do not adequately reflect the benefits patients, their families and society stand to gain by having access to these important medicines.
- We have successfully engaged with many HTAs around the world on their criteria and have reimbursement agreements in place in [17] countries for our medicines. We continue to engage in a dialogue with CADTH and other health authorities on these topics.
- We are committed to working with all stakeholders to secure access to our innovative medicines for all eligible patients as soon as possible and continue to engage at all levels of government in many countries."

Author's response:

"I do not express an opinion on whether the assessments of health technology assessment (HTA) agencies are valid, and I wholly support Vertex's efforts to make its products accessible to patients in need."

Vertex Pharmaceuticals' comment:

"Your article has inaccurate information about the tax structure in the US and inaccurately reflects tax impact on our R&D costs:

- You inaccurately state: "The net expense to Vertex is, however, substantially reduced because of a US tax credit for clinical trial expenses for orphan drugs. This tax credit was worth 50% of qualifying costs. Clinical trials are not the only cost of development: also included are costs related to chemicals, production process development, and regulatory submissions. If the tax credit amounted to 25% of Vertex's clinical expenditures, then Vertex's development costs were approximately $2.5B on a risk-adjusted basis. In effect, if the quasi-rents from Kalydeco and Orkambi were $2.5B, Vertex would be fully compensated.")
- Since 2000, Vertex has invested over $11.8B in R&D and accumulated $488M in federal and state tax credits as of the end of 2018, which represents less than 5% of our cumulative R&D spend.
- In 2018 alone, our 2018 US federal and state tax credits were $52.6M which represents less than 4% of our $1.4B R&D spend."

Author's response:

"There is no inaccuracy in the quoted statement. However, I would like to respond to Vertex's claim that it has received, in total, only $488M in tax credits. My paper implies that orphan drug tax credits for ivacaftor and lumacaftor:ivacaftor alone could have been about $900M, which is more than Vertex's claimed total tax credits. One reason for the difference is that in calculating Vertex's clinical trial expenditures, I used the risk-adjusted, capitalized cost of clinical trials, following DiMasi et al. (2016). The tax credits referred to by Vertex's representative reflect cash values only, and do not account for the cost of capital or the risk of failure."

Vertex Pharmaceuticals' comment:

"The article significantly overstates Vertex profits, inaccurately suggesting the company earned $21.1B:

- We are one of five companies in the history of the biotech industry that have internally discovered and developed four drugs. Since the company's inception, it has only had three years of profitability (2011, 2017 and 2018) and has incurred ~ $3B in cumulative losses. Despite this, we have continued to invest consistently in R&D, investing more than $11 billion in R&D since 2000. Additionally, over the last five years, our aggregate R&D costs represented over 70% of our total operating expenses."

Author's response:

"I applaud Vertex's success in developing new drugs. And I recognize that the company's accounts show cumulative losses. Why is it, if the company is so spectacularly unsuccessful, that its share price has climbed so high, or that this perennially loss-making company pays its executives so well? Vertex has made losses because it has spent even more than the profits earned Kalydeco and Lumacaftor on development of new drugs, in effect because it is trying to grow. This shows as an accounting loss, but if the new drugs are successful, then Vertex will earn even more profits, which is what has started in 2017 and 2018."