BMJ

BMJ 2014;348:g2524 doi: 10.1136/bmj.g2524 (Published 9 April 2014)

FEATURE

ANTIVIRAL DRUGS

Tamiflu: "a nice little earner"

Is the story of oseltamivir, and similar antiviral drugs, a classic one of big pharma greed? **Andrew Jack** finds a more nuanced reality

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Viewed with hindsight, the story of flu antiviral drugs seems to be a classic story of "big pharma" greed. On the back of media hype and unfulfilled fears, a new medicine backed by only modest clinical data became a "blockbuster" generating billions of dollars for its producer. The reality is more nuanced, and the tale could easily instead have been a commercial and public health nightmare.

There is no doubt that Roche, the Swiss based pharmaceutical group, and its shareholders, have done very well from oseltamivir (Tamiflu). The drug became one of the most widely recognised medicines in the world as concern grew about a new flu pandemic in the middle of the previous decade.

As one City financial analyst puts it: "Tamiflu was a nice little earner. It reflected opportunistic action by a multinational corporation, which was able to be a little bit sharper in its marketing practices than you could now, given the debates over the disclosure of clinical data and how effective the drug was."

Yet other related antiviral drugs in the same class of neuraminidase inhibitors failed to take off; oseltamivir itself was nearly a flop; public health pressures capped its pricing; and policy makers and the drug company itself struggled with scant clinical information on efficacy. Its success was linked to the unprecedented purchase of such a large volume of drugs to prepare for a future pandemic threat from a still poorly understood infectious disease.

Unlikely success

Since its launch in 1999, oseltamivir has generated cumulative sales in excess of $18bn (£11bn; €13bn) for Roche. Half of the total expenditure was by governments and companies around the world for stockpiles for pandemic preparations. The US alone spent more than $1.3bn buying a strategic reserve of antivirals.[1] Most have never been used, and today the US stockpile consists of more than 65 million treatments. In the UK, the government spent £424m for a stockpile of about 40 million doses.[2]

Not all of Roche's sales were profits. In its peak year of 2009, Roche reported revenues from osteltamivir of $3.6bn. Like all drug companies, it does not disclose profits on individual products. Yet it paid out more than $50m in initial development costs to Gilead, the US biotech company that discovered the drug. In 2009 alone, it transferred royalties to the company of $393m. Since oseltamivir's launch, it has contributed royalties in excess of $2.2bn.

Oseltamivir is also relatively costly and complex to manufacture, with a multiple step synthesis that begins with extracting raw material from the star anise plant. Roche had to take account of direct marketing and storage costs, as well as a share of overheads across the business.

Under pressure to provide the drug to governments in large volumes as fear grew of a lethal pandemic, Roche sold oseltamivir for stockpiles at a discounted price of €15 per adult course in higher income countries and €12 in middle and lower income ones. Unusually, it also sold bulk pharmaceutical ingredients to governments at a discount to the price of the finished tablets in packets, as a way to prolong the shelf life.

Oseltamivir was never pivotal to Roche's overall commercial success, which over the past decade has been driven primarily by oncology products developed with its US biotech partner Genentech, which it fully acquired in 2009. In that year, which coincided with peak oseltamivir sales, the drug was still only its fourth largest product, accounting for just 8% of overall Roche revenues.

Pandemic sales patterns

Indeed, oseltamivir sits awkwardly in the company's portfolio, and in meetings with analysts and investors the company typically presented its past financial performance and future guidance excluding oseltamivir to avoid confusion. The drug offered lucrative but "lumpy" sales that rapidly surged—requiring a substantial investment in additional manufacturing capacity—and then fell again. That contrasts with the classic lifecycle of medicines, for which demand

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typically grows steadily until their patents expire while profits rise as their ongoing costs fall. While financial analysts' reports in the late 2000s referred to oseltamivir sales, few devoted much attention to the drug, and there is little evidence that the drug had a significant effect on Roche's share price.

Nevertheless, oseltamivir's margins were substantial by pharmaceutical industry—let alone broader corporate—benchmarks. Costs were kept low because there were relatively few expensive clinical trials. Marketing expenses were also limited because so many contracts were negotiated with a handful of decision makers in governments rather than the usual deployment of large numbers of sales representatives proposing medicines to a multitude of doctors and healthcare departments in each country.

By 2009—the last time of any substantial disclosure—96 countries had stockpiled enough oseltamivir to provide support for an estimated 350 million people around the world. Once pressure for orders from governments began to wane after the pandemic, the company sought to ramp up interest among individual patients, funding an extensive public relations campaign as flu cases rose.[3] It also targeted companies to buy pandemic stockpiles.

However, the pandemic was not a bonanza for all drugs in the neuraminidase inhibitor class, of which oseltamivir is the best known. GlaxoSmithKline's zanamivir (Relenza)—originally developed by Biota of Australia—was the first such drug. Yet its cumbersome inhaled formulation was less appealing than the oseltamivir pill, and it has generated cumulative sales over the past decade of less than $2.3bn.

BioCryst's attempt to commercialise a third related antiviral drug—peramivir, which is administered intravenously—have also been slow. It has so far sold $23m of the product, while receiving $235m from the US government for development funding and licensing payments from Shionogi of Japan and other pharmaceutical partners totalling about $35m.[4]

Pressure to be prepared

Even these rivals' sales—let alone most of those generated by Roche for oseltamivir—would not have taken place without rising concerns over a flu pandemic. The drugs were originally developed to treat seasonal flu, but there was little take-up other than in Japan. Health systems elsewhere were more sceptical about the drug's value long before the recent scrutiny of the Cochrane Collaboration questioning oseltamivir's clinical value.[5]

What changed, and drove sales, was a rising focus on the risks of emerging infectious diseases. At the start of the millennium, the outbreaks of severe acute respiratory syndrome (SARS) and then H5N1 "bird flu," triggered concern about the dangers of a new flu pandemic threatening humans. The scares coincided with growing pressure on policy makers to invest more in emergency planning, in the wake of a series of catastrophes including Hurricane Katrina in the US, a heatwave in France, and foot and mouth disease in the UK.

Until 2009, when H1N1 emerged in Mexico, neither public health officials nor Roche knew the characteristics of the next flu pandemic. It was impossible in advance to test oseltamivir's effectiveness on a still unknown virus, but a scientific consensus based on its use in seasonal flu suggested that the drug offered one of the few interventions with the potential both to reduce the severity of infection and mortality and to prevent disease.

It was seen as providing value in slowing the growth of infection around the world and flattening the surge in demand for treatment as a way to ease pressure on health systems and buy time to develop vaccines. Even after the outbreak began, it took many months to understand that H1N1 was relatively benign. In addition, testing oseltimivir in randomised trials was considered by many at the time to be ethically difficult. Given the high apparent demand at the time for oseltamivir, some campaigners argued that generic manufacturers should be allowed to produce it cheaply in larger quantities, with Roche paid a variable royalty if the drugs were ultimately used to treat patients.[6]

Looking back today, the strain of H1N1 identified in 2009 proved far less fatal than planners had feared, and much of the stockpile was never used. The Cochrane Collaboration has thrown doubts on the value of oseltamivir, based on a thorough review of the data from clinical studies of its use for seasonal flu.[5] There remains heated debate about what the observational data, gathered during the pandemic years, tell us.[7]

Jonathan Nguyen-Van-Tam, lead author of a Roche funded study that claimed oseltamivir significantly reduced mortality and morbidity in patients admitted to hospital with H1N1 influenza[8] and an adviser to the UK government in the build-up to the pandemic, says: "I continue to believe neuraminidase inhibitors are a useful drug for patients with severe flu who are hospitalised. Cochrane only accepted randomised control trials. If we had that sort of data we would give it primacy, but we don't live in that world. We needed to use observational data."

Since 2009, governments and public health bodies have paid little attention to revising guidelines on recommended coverage levels for future pandemics. Those that have been conducted tend to support coverage levels already agreed in the late 2000s. There have also been very few sales to governments since early 2010.

Ironically, oseltamivir has proved chemically extremely stable, with the result that many of the large remaining stockpiles around the world have had their original five year shelf life extended by at least two years.

New pandemic purchases on any significant scale are thus unlikely to take place before 2016, when oseltamivir's patents in most countries expire and the drug can be offered more cheaply by generic manufacturers. Roche undoubtedly did extremely well from oseltamivir, far beyond its initial expectations. In the absence of robust clinical data that did not and now cannot exist, taxpayers and public health specialists may long continue to debate whether the price paid was justified.

Competing interests: I have read and understood the BMJ Group policy on declaration of interests and have no relevant interests to declare.

This article is supported by a grant from the Open Society Foundations.

Provenance and peer review: Commissioned; not externally peer reviewed.

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Cite this as: *BMJ* 2014;348:g2524