PRACTICAL MAGIC

THE LEADERSHIP OF BLOCKBUSTER DRUG DEVELOPMENT

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RUMOR HAS IT THAT IN 1899 THE HEAD OF THE U.S. PATENT OFFICE, CHARLES DUELL, DECLARED THAT **"EVERYTHING THAT CAN BE INVENTED HAS BEEN INVENTED."** ALTHOUGH IT'S UNLIKELY THAT DUELL ACTUALLY SAID THIS, IT DID POP INTO MY MIND WHEN I READ *THE PHARMACEUTICAL JOURNAL* HEADLINE "GOODBYE BLOCKBUSTER MEDICINES."

This professional journal is not alone in this prediction. For a decade, the leading pharmaceutical headline has been "No New Blockbuster Drugs,"and it appears that these authors mean forever and ever.

A blockbuster drug is defined as a drug that earns at least $1 billion per year. Over the past twenty years, blockbuster drugs have been designed to meet chronic health care needs of large percentages of the population, improving the quantity and quality of millions of individual lives. Statins alone have lowered cholesterol of many millions of people.

Drugs have revolutionized the treatment of people with ulcers and allergies along with those in need of thinner blood. Cancer therapies have also had dramatic successes.

So, despite these successes, why do some experts think blockbuster drugs have passed their prime? There are three primary reasons.

The first is that big pharma has struggled to maintain top-notch Research and Development (R&D) shops and has instead invested in direct-to-patient marketing. Without investment in research, it is true that there will be fewer blockbuster drugs.[1]

The second reason is that the low-hanging fruit has been picked. Many chronic conditions shared by large populations have already been addressed. Bringing a new drug to market costs between $1billion and $2 billion. If a company is going to invest this type of money,[2] it needs some guarantee that it will turn a profit.

The third reason is the increasing threat of generics. Every new drug comes with a time bomb of its own demise. A drug company can plan on ten years of profits from its

invention, but then the formula of the drug can be duplicated by generic manufacturers and the original company can earn little money beyond that time period. Rather than focus on R&D for new health issues, big pharma focuses on extending the patent life of the original drug. They do this by changing some element of the formulation to achieve a process patent. The example of Claritin and Clarinex illustrates this strategy. Big Pharma also avoids the expense of R&D by buying out smaller companies that have promising drugs in their pipeline.

> *Despite these three challenges for blockbuster drugs, it is inaccurate to declare that they are dead. Afterall, there are still a number of pervasive diseases—Alzheimer's, Parkinson's, HIV and diabetes still impacting millions of people. Not to mention that there is still room to improve treatment for many chronic conditions from arthritis to brittle bones. Cardiovascular disease and cancer offer tremendous opportunities for better therapies.*

There are plenty of health issues that could be eradicated, or improved, by blockbuster drugs. But how can we change the market conditions so that pharmaceutical companies are more willing to invest the enormous sums of money required to do so? If we take a look at one of the earliest blockbuster drugs, Tagamet, we can uncover some valuable lessons.

The History of the First Blockbuster Drug

Blockbuster drugs are fairly new elements in the history of health care. The first was Tagamet, which was introduced to the market by Smith Kline in 1983 and exceeded $1 billion in sales in 1986.[3]

The history of Tagamet demonstrates the difficulty of research and development (R&D). It begins when Smith Kline French—an innovative company that discovered amphetamines, Thorazine, and the now-common practice of mailing samples of drugs to doctors--invested in Welwyn Research Institute in Britain. Here, James Black changed the R&D process from one of hunting to engineering. He called this process "rational drug design."His goal was to discover novel compounds not available in nature.[4]

After lengthy and extensive research into histamines, and the discovery of antihistamines, Black discovered that gastric acid production is stimulated by histamines. He then reasoned that an antagonist could reduce the acidity of gastric fluids as well as the volume of these fluids.[5]

Smith, Kline and French did not respond positively to this discovery and encouraged Black to stay on his original research mission involving beta-blockers. Black, however, persisted. Unfortunately, the antagonists were elusive and it took years and the efforts of many researchers and chemists to discover one. The antagonist was discovered in 1970, but it took the team many more years of testing to finally develop Tagamet, which came on the market in 1976. In 1977 Tagamet gained FDA approval and was sold in the US. In 1979 the drug was sold to over 100 countries and in 1986 it generated $1 billion for Smith, Kline and French. [6]

> *The discovery of this "wonder drug" elevated the small company into an investor's dream, and Smith, Kline and French became the 9th largest pharmaceutical company in the world.*[7]

Tagamet's patent expired in 1994 and Glaxo immediately introduced Zantac, which was more potent than Tagamet and only required dosing twice each day, half as frequently as Tagamet. Other companies also entered the rush for market share, bringing us Pepcid from the Japanese firm Yamanouchi, and Axid from Eli Lily. All four of these drugs have expired patents, and all are now available as OTC drugs. [8]

Lessons Learned

> What can we learn from the success of the first blockbuster drug?
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> *First, that persistence and tenacity are critical qualities for scientists and research teams, who will surely see frequent disappointments and few rewards. Resisting the temptation to cease the discovery process resulted in great success. The leadership at the top promoted environments that encouraged prudent risk-taking and did not unduly punish failure related to innovation and development of next-generation therapies.*

Second, communication between chemists, biologists, and third parties was critical to turning the laboratory success into a commercial success. Contrary to other researchers, Black shared every step of his discovery, which motivated scientists from academia and industry to join Black's search. Black literally gained nearly unlimited resources. Obviously, this would not occur today. Now the intellectual property of a company is carefully guarded, but this does not mean that there should not be some method of sharing scientific advances rather than hiding them.

Third, success is fleeting and a pipeline of innovations is essential for long-term success. Smith, Kline and French started research for Tagamet 1964, but two decades later they did not have a second-generation drug in the pipeline. The company's culture did not encourage innovation, and soon after Tagamet hit the market most of those responsible had left. Smith, Kline and French became a "one drug wonder."

The final lesson to be learned from the first blockbuster drug is the danger of a reputation for inept leadership or poor management. Smith, Kline and French avoided destruction by merging with Beecham Group in the UK. Beecham delivered Augmentin and Paxil to the combined sales force, along with Tagamet. This was not enough, and in 1995 Smith, Kline Beecham was subject to a hostile take-over by Sterling Winthrop. Although they retained a few employees, the majority of the scientists were let go. This was the first mass lay-off in the pharmaceutical business and it created great ill will.[9]

The new Smith, Kline Beecham and Sterling could not attract the gifted scientists it needed for another blockbuster drug. The layoffs caused such outrage in academic circles that professors refused to send their best students to the company. No young scientist wanted to start his career with a company notorious for poor management. Smith, Kline and Beecham could not possibly compete with more reputable companies for proven and gifted scientists. It took Smith, Kline and Beecham over a decade to overcome poor management decisions.[10]

THE FUTURE OF BLOCKBUSTER DRUGS:
THE HORIZON IS NOT EMPTY. THERE ARE A NUMBER OF PROMISING NEW DRUGS EITHER ENTERING THE MARKET OR PREPARING TO EMERGE:

- Gilead Sciences and Japan Tobacco have F/TAF, which treats HIV, waiting in the pipeline to replace expiring F/TDF.
- Merck will challenge Gilead's Hep C virus drugs, Sovaldi and Harvoni with MK - 5172A.
- Manufactured by Abbvie, Venetoclax is an oral medication for chronic lymphocytic leukemia that is resistant to traditional chemotherapy. The drug demonstrates nearly a 75% response rate.
- ACADIA Pharmaceuticals is introducing Nuplazid. This is the first and the only drug that is developed to treat Parkinson's Disease Psychosis.
- Introduced by Nippon Shinyaku and Actelion, Uptravi delays the progression of pulmonary arterial hypertension which affects the arteries in the lungs and heart.[11]

It is safe to say that blockbuster drugs will still come to market, but with less frequency. Nevertheless, the need for blockbuster drugs has not diminished. The mass killers of people, including cancer, heart disease, diabetes, and strokes are still with us.

Mankind still struggles with untreated symptoms, and the relief of chronic pain is the primary reason people visit a medical facility.

WHAT WE CAN DO TO MOTIVATE COMPANIES TO INVEST IN R&D **FOR BLOCKBUSTER DRUGS?**

Decrease the threat of generics to the original R&D investment

There's no question that the blockbuster drug is threatened by the generic pharmaceutical industry. Sometimes they are content to wait until a patent expires. Other times they challenge the patent in court. In 2005 there were 81 of these suits. By 2010 the number had grown to 230. In 70% of these cases the generic companies win. With that win is the right to take over as much as 65% of the branded market. In the hypertensive market alone, these lawsuits have resulted in losses of $14 billion to the companies that originated the drugs. As blockbuster drugs become more difficult to bring to market, the generic threat diminishes the risk a company is willing to take to achieve the next blockbuster.[12]

The risk can be spread if the original drug company also owns the generic company as Novartis owns the generic arm of Sandoz. This can also benefit the original brand by building awareness in high-growth market areas such as the emerging economies of the E7 countries (China, India, Brazil, Russia, Indonesia, Mexico and Turkey).

Recruit for business acumen in R&D roles

The new R&D leader must have both strong scientific and operational skills. In other words, he/she must have the ability to move the drug development cycle more quickly and efficiently. Big Pharma will have to develop and recruit for business acumen in R&D. That business acumen can drive efficiencies such as the development of fail-fast programs designed to identify drug failures early. Big pharma will also have the opportunity to recruit and develop next generation R&D leaders who will understand the value of and be able to leverage big data to increase speed to drug development.

Hire and Retain motivational executive leadership

Ultimately, the creation of a blockbuster drug likely depends to a great extent on the CEO and his/her team who provide guidance, leadership, motivation, energy, commitment and encouragement to the scientific team. A leader must motivate the scientists while planning for marketing. A leader must also anticipate challenges from generic firms and must realize that the blockbuster only buys ten years of economic success. Thus, a leader must be nimble in developing new drugs as well as creating a pipeline. This individual needs to have one eye on the lab, one eye on the future, and one eye on the stalkers lurking in the shadows.[13]

[1] Swanson. “Big pharmaceutical companies are spending far more on marketing than research,” *The Washington Post*, February 11, 2015

[2] DiMasi JA, Grabowski HG, Hansen RA. Innovation in the pharmaceutical industry: new estimates of R&D costs. Journal of Health Economics 2016; 47:20-33.

[3] Li, Jie Jack. *Blockbuster Drugs* (New York: Oxford Press, 2014), 27.

[4] Li,46.

[5] Li,14.

[6] Li, 5.

[7] Li, 26.

[8] Li, 35

[9] Li, 39

[10] Li, 39

[11] Lorenzetti. “7 Blockbuster Drugs to Watch in 2016,” *Fortune*, March 25, 2016

[12] Roane. “Generics’ new legal attack: Big Pharma’s aging drug patents,” *Fortune,* March 11, 2011

[13] Li, 13