What New Cancer Pathway Programs Mean For The Drug Industry

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BY TOM SALEMI

Medical Devices

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BY DAVID CASSAK

THE NEW FACE OF BLOCKBUSTER DRUGS • J&J’S SYNTHES DEAL
THE NEW FACE OF BLOCKBUSTER DRUGS

Blockbuster drugs are not going away but as science and market conditions continue to evolve and unmet needs shift to new territories, their profile is likely to change again. Companies can use strategies to offset the potential shortcomings of the new blockbuster model and improve their chances of becoming the successful players of tomorrow.

BY PIERRE JACQUET, ELIZABETH SCHWARZBACH AND ILAN OREN

Blockbusters, defined as branded prescription drugs that generate more than $1 billion annually, have served as catalysts for driving value within the global drug market during the past 15 years. Top biopharmaceutical companies have been especially reliant on these blockbusters for their growth and shareholder value creation during this time period, as development of these drugs traditionally has delivered the highest returns on R&D investments.

In the early 2000s, reports began to emerge predicting the demise of the blockbuster model. Experts who held this belief cited the wave of blockbusters that were approaching the end of their patent lives and questioned pharma’s ability to replenish this gap. They predicted the future pharmaceutical winners would follow a strategy in which blockbusters play a much less important role. (See “Blockbusters To New-Engine Drugs: The Key Industry Shift,” IN VIVO, July 2003.)

To better understand whether or not these predictions hold true, L.E.K. analyzed data from two decades of biopharmaceutical sales to assess the recent contribution of blockbusters to biopharmaceutical growth and to identify key trends reshaping the formation of blockbusters. Supporting our findings is a proprietary database that tracks the commercial path of drugs that reached or will reach blockbuster status between 1995 and 2015, and captures detailed drug information such as product characteristics, disease indications, company type and revenue performance over time. (See sidebar, “Insight Into Market Analysis.”)

While dire predictions of the blockbuster’s demise have yet come to pass, the associated business model is evolving dramatically and may be at a pivot point.

According to L.E.K.’s analysis, the new generation of blockbusters will account for a smaller share of global biopharmaceutical revenues, with average size being steady or declining, and they will increasingly be aimed at specialty diseases in therapeutic areas beyond the traditional footprint of large pharma, as well as geographies outside the core US market.

Given that the blockbuster overall dollar value will be suffering shrinkage, growth prospects of large biopharmaceutical companies will be tested as revenue must be made up by having a greater number of blockbusters or relying on mid-size products.

Alternatively, companies will need to recalibrate their therapeutic focus into new blockbuster-rich disease areas and address the value leakage from externally sourced blockbusters by rethinking business development structure.
companies has continued to increase over the past decade, accounting for more than 60% of Top-10 pharma revenues today. (See Exhibit 2.)

Interestingly, this trend does not necessarily reflect an increase in R&D productivity from Big Pharma, but is a symptom of the recent extensive M&A wave in which Big Pharmas have acquired the parent companies of these blockbusters. Pfizer Inc. is a good illustration of the trend, deriving more than 70% of its current bio-pharmaceutical revenue from blockbusters, many of which were externally acquired. Among the Pfizer warhorses that came from elsewhere: Celebrex (celecoxib; from Pharmacia Corp.), Lipitor (atorvastatin; from Warner-Lambert Co.) and Premarin (conjugated estrogens; from Wyeth).

Regardless of how drugmakers acquired their top-selling products, the old vision that blockbusters would play a much less important role in the growth of leading pharmaceutical companies during the first decade of the new millennium appears to be wrong. Indeed, they have remained a major growth engine for these companies and have over-performed industry-wide growth for the past decade.

In addition to Big Pharma’s increasing reliance on blockbusters, the revenue profile of blockbusters has dramatically changed during the past 15 years. In 1995, the average blockbuster revenue was $1.6 billion, with the Top-10 selling blockbusters averaging $2 billion per drug. In 2010, the average blockbuster revenue grew to $2.5 billion, with the Top-10 best-selling blockbusters averaging an estimated $7.4 billion per drug. One of the main reasons behind this sharp increase has been the emergence of “mega-blockbusters” where select branded prescription drugs eclipse $5 billion each in annual global sales, skewing the average profile of the overall class.

The revenue contribution of these products to the blockbuster class has indeed increased fivefold since 2000, with mega-blockbusters accounting today for 28% of blockbuster revenues. Examples of blockbusters in this category include Lipitor, Humira (adalimumab) and Diovan (valsartan). The major drivers behind the emergence of these products have included the size of addressable markets, the ability to aggressively manage brand life cycles, and successful follow-on commercial strategies that use better efficacy, safety, and convenience to drive adoption in markets well characterized by early pioneers. In addition, few barriers to steady price increases have also played a role. To that point, the mega-blockbuster segment has been amenable to high price increases, with some of these drugs having increased their US price by more than 60% within the first 5 years after launch.

RESPONDING TO RECENT ENVIRONMENTAL CHANGES

Although our analysis suggests that blockbusters are not going away, the nature of blockbuster drugs has changed dramatically and is continuing to evolve. The first generation of blockbusters launched in the early 1990s tended to be small molecules addressing symptoms of primary care indications, with the commercial success of the drugs often anchored in the US. Most often, these blockbusters did not require major differentiation from standard of care; some level of improvement in efficacy, safety or convenience was often sufficient to grant blockbuster status. However, the recent generation of block-
Pharmaceuticals

Blockbusters has changed dramatically as many of the disease targets for primary care drugs had been discovered already by the time of their conception and development, often with multiple products (including generics) addressing these diseases.

In addition, most of the recent blockbusters were launched in a more cautious market environment, with increased regulatory scrutiny and rising threshold of innovation from regulatory agencies and health care payors. As a result, today’s blockbusters are reshaped along five attributes:

1. Increasing focus on specialty markets and biologics.

Two trends have contributed to the shift of blockbusters into specialty markets. First, marketing and sales spending in primary care markets has exploded in the past decade, mainly driven by a traditional commercial model where path to blockbuster status was achieved through the power of heavy share of voice and detailing force. Consider the evidence. More than two-thirds of the 42 primary care blockbusters in 2000 were promoted with sales forces of more than 1,000 reps in the US alone and accompanied by DTC campaigns. Marketing investment to launch these brands often ranged from $200 to $500 million during the first two years on the market.

Competitive intensity and generic erosion have also depleted easy-to-cure primary care markets of potential next-generation blockbusters. Of the 19 primary care-focused blockbusters in the market in 1995, more than three-quarters were concentrated around four disease markets: hypertension, gastroesophageal reflux/ ulcer, depression and bacterial infections. Within each of these primary care markets, it was not uncommon to see two to three direct competitors each having reached blockbuster status.

This rising cost of primary care promotion and the exhaustion of primary care market opportunities free of fierce competition have created a shift into chronic, more severe diseases where specialists write the majority of prescriptions. The expectation of these prescribers is to control the disease – and sometimes cure it. As reported by the World Health Organization, these chronic illnesses now account for 60% of deaths globally each year and represent an increasing economic burden on societies worldwide, with as much as 75% of health care resources of developed countries being consumed against the needs of those conditions. These markets are served today by specialty-focused brands that account for about 40% of blockbuster sales.

The therapeutic modalities behind blockbusters have also changed as biologics have increased their share, accounting for more than a third of blockbuster revenues. (See Exhibit 3.) In contrast, in the late 1990s Epogen/Procrit (epoetin alfa; from Amgen Inc./Johnson & Johnson) and Neupogen (filgrastim; from Amgen) were the only specialty, biologic blockbuster drugs. The encumbered route of administration, important side effects and disease modifying profile of these blockbusters have strengthened companies’ abilities to focus usage and prescription of those drugs within small specialty audiences, making their overall economic

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Exhibit 2
Pharma’s Increasing Reliance On Blockbusters

<table>
<thead>
<tr>
<th>Year</th>
<th>Top 10 Pharma Revenue</th>
<th>Revenues from Blockbusters</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>$898</td>
<td>$258</td>
</tr>
<tr>
<td>2000</td>
<td>$1508</td>
<td>$688</td>
</tr>
<tr>
<td>2005</td>
<td>$2558</td>
<td>$1568</td>
</tr>
<tr>
<td>2010</td>
<td>$3378</td>
<td>$2088</td>
</tr>
</tbody>
</table>

SOURCE: EvaluatePharma 2011; L.E.K. analysis

Exhibit 3
Changing Profile Of Blockbusters

SOURCE: L.E.K. analysis
profile and profitability very attractive. That has made the market for such medicines even more appealing to drugmakers, fueling the growth of such products. Within this group of specialty blockbusters, we are now noticing the emergence of blockbusters focused on more narrow markets, including orphan products such as Gleevec for chronic myeloid leukemia and Advate (octocog alfa) for hemophilia.

2. Value driven through disease modification or cure.

As a result of the previous trends, biopharmaceutical companies have also refocused their efforts on more complex targets, with mechanisms of action directly involved in the underlying cause of the disease. As anticipated a decade ago, innovation has reshaped the profile and attributes of the recent wave of blockbusters. (See “Rebuilding Big Pharma’s Business Model,” IN VIVO, November 2003.) Targeted therapies have enabled greater clinical impact on unmet medical needs, pushing the role of drugs in the treatment paradigm from symptomatic treatment to disease modification, or sometimes even cure. (See Exhibit 4.) For example, popular blockbuster drugs in the late 1990s included drugs that address symptoms or acute exacerbations of medical conditions, such as GERD, hypertension or inflammation. In contrast, many of today’s blockbusters have been approved on endpoints and health outcomes including reduction in death-related events, improvement of disability, reduced time to disease progression, increased progression-free survival or increased survival rate. This is demonstrated in oncology where in 1995 there was not a single blockbuster drug on the market, whereas today there are 19. Among the many: Avastin (bevacizumab), Erbitux (cetuximab), and Revlimid (lenalidomide), all of which impact disease progression and survival of cancer patients.

This is also true in other therapeutic areas where scientific breakthroughs led to the development of drugs with high clinical impact. HIV treatments in the 1990s included drugs that addressed symptoms such as wasting and emesis without directly impacting the cause of the disease. But the discovery of direct anti-virals – and the ability to package multiple active ingredients in a single pill – has helped drugs like Atripla (efavirenz/tenofovir/emtricitabine) or Isentress (raltegravir) reach blockbuster status. Because of their disease-modifying characteristics and the quality-of-life improvements they engender, these therapies command high prices even though they also require long duration of treatment. With the advent of newer agents to treat hepatitis C, that field is now undergoing a similar transformation.

Despite this migration into specialty disease modification, the primary care blockbuster model has not disappeared; high prevalent diseases managed by primary care physicians have remained an important source of blockbusters as illustrated by the class of recent entrants, including Advair (fluticasone propionate/salmeterol), Seroquel (quetiapine fumarate), Singular (montelukast), Nexium, and Celebrex among others. For some, the level of clinical differentiation has driven market leadership; for others, earning nominal market share through flawless commercial execution has been sufficient to reach blockbuster status given the large pool of addressable patients.

3. Declining role of core US market.

Geographically, increasing reliance on drug revenue from non-US territories has helped sustain the blockbuster drug model over the past 15 years. This growth is partly illustrated in the evolution of geographic distribution of biopharmaceutical revenues across the world. US revenue amounted close to two-thirds of total blockbuster revenue in 2000 and declined to less than half of total blockbuster revenue in 2010. In other words, the US revenue share of blockbusters has declined by more than 35% during the past decade. Novartis AG’s Gleevec, Sanofi division Genzyme Corp.’s Cerezyme (imiglucerase), AstraZeneca PLC’s Crestor (rosuvastatin calcium), and Pfizer’s Lyrica (pregabalin) are a few examples of blockbuster drugs that generate today more than 60% of their revenue outside of the US.

This new balance of biopharmaceutical value distribution across the globe has resulted from two external trends that have reshaped the industry over the past decade: an increasing contribution of non-US markets to the pool of addressable patients through improved health care infrastructure and the decline of the US dollar relative to foreign currency. Adding to that is the growing participation of emerging countries to the global pharmaceutical landscape. Although the US is still a necessary component for blockbuster success, focus on this region alone no longer will drive blockbuster status.

4. Fertile grounds beyond core therapeutic franchises.

Key ingredients for blockbuster status

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**Exhibit 4**

**Blockbusters Target Audience And Clinical Profile**

<table>
<thead>
<tr>
<th>Drug annual revenue:</th>
<th>&gt;$5B</th>
<th>$3-5B</th>
<th>$1-3B</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 Blockbuster drugs (n=47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 Blockbuster drugs (n=123)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Impact**

**Prescriber Base**

- Lifestyle
- Symptomatic
- Disease modifying
- Preventative/Curative

**Clinical Impact**

**SOURCE:** EvaluatePharma 2011; L.E.K. analysis
usually involve some combination of product differentiation, company promotional investments and a target disease environment with addressable unmet needs. (See “Blockbuster Ecosystems: Sustainable Development?,” IN VIVO, May 2003.) Of those three success factors, the one that has been the most challenged over the past decade relates to identifying fertile ground for blockbuster opportunities. In 1995, 90% of blockbusters were commercialized in disease areas where the company had a previous footprint, which suggests that the successful model at that time was to leverage knowledge, skills, network and scale in a narrow segment of the disease landscape to increase the odds of developing successful additional blockbusters. This concept of therapeutic franchise was built on the notion that knowing customers’ needs and owning the treatments for the disease in which it specializes gives a franchise holder the operational know-how to do more with any given product than another company. Bristol-Myers Squibb Co.’s oncology franchise, Merck & Co. Inc.’s cardiovascular franchise and Pfizer’s infectious disease franchise of the 1990s are good examples of successful blockbuster franchise models. (See “Drug Franchises,” IN VIVO, October 1998.)

L.E.K. analysis suggests that the current blockbuster generation grew up on different grounds. Of the 123 blockbusters in 2010, close to a third were generated in disease areas where the originator had limited clinical exposure and/or no commercial footprint prior to the launch of the product. This shift has happened either through the life cycle management of organic products into non-core disease indications, following the science into an adjacent therapeutic area, or through external business development transactions. Teva Pharmaceutical Industries Ltd.’s migration into MS with Copaxone (glatiramer acetate) and Roche’s Genentech Inc.’s expansion into ophthalmology with Lucentis (ranibizumab) (with all the intricacy of Avastin competition in this field) illustrate this blockbuster migration through lifecycle management. Examples of reliance on external sourcing include Eli Lilly & Co.’s expansion into male health through its joint venture turned acquisition of Icos Corp., Amgen’s entry in osteoporosis via its purchase of Abgenix, which it renamed Amgen Fremont Inc., and Sanofi’s recent jump into orphan diseases via its takeout of Genzyme. Interestingly, most of these successful therapeutic diversifications were completed through transforming M&A transactions rather than incremental product licensing deals.

5. External sourcing and increased shared ownership.

Big Pharmas are no strangers to outsourcing innovation. Indeed, the share of invented drugs from Big Pharmas continues to decline. Big Pharmas now originate barely a quarter of the overall industry pipeline, down from nearly 40% in early 2000. (See “Pharma R&D: Doing The Same Thing That Didn’t Work Before,” IN VIVO, April 2009.) The same trend applies to the origination of blockbusters. All except one of the blockbusters in 1995 were internally developed. By contrast, more than half of the leading blockbusters in 2010 have been generated from collaborations where the blockbuster originators retained regional rights and royalties for their products. This does not come without downsides. An analysis of the Top-10 pharmaceutical companies today reveals that there is significant blockbuster value given away to product originators (biotechs, specialty pharma, or academic centers). Of the 87 blockbusters commercialized by the Top-10 pharma in 2010, more than a third were under co-promotion agreement in some region of the world and most had royalty paybacks to third parties. Adding to that value leakage are clinical and commercial milestones paid to the originators. Overall, L.E.K. estimates that today a top pharmaceutical company captures less than 60% of the full life cycle value of some of its blockbusters originated externally.

THIRVING IN THE NEW BLOCKBUSTER ERA

As science and market conditions continue to evolve and unmet needs shift to new territories, the face of the new blockbuster is likely to change again. Although 48 new drugs are expected to join the blockbuster category by 2015, more than offsetting the number of blockbusters lost due to generic erosion during that time period, the amount of revenue they generate is expected to account for less than 30% of global pharmaceutical sales. (See Exhibit 5.)

The overall profile of these new blockbusters is also likely to depend more markedly on their performance in new territories. (See Exhibit 6.) Although $1 billion in global revenues will likely remain the threshold for the blockbuster title, the average size of these blockbusters is estimated by Wall Street to decrease slightly by 2015. Going forward, the mega-blockbuster category is one of the sub-sets at greatest risk due to the increasing pressure from payors and the evolving health care market in the era of reform. Despite the limitations of these predictions and the potential gaps between average forecasted drug performance by equity analyst firms and actual revenues, there is growing evidence that blockbusters will account for a smaller share of large pharma revenues, with average size being steady or declining over the next five years. (See “Mind the Gap: Different Views of Success May Drive Large Differences in Estimates of Pharma Value,” IN VIVO, April 2011.) If this scenario holds true, the industry may shift back its focus to mid-size products less exposed to the constraints of the new environment and
more profitable to the parent company. **A NEED TO RECALIBRATE**

In this environment, companies do need to make important changes to offset the potential shortcomings of the new blockbuster model. First, companies need to recalibrate their therapeutic focus into blockbuster-rich disease areas with high clinical unmet needs, potential for disease-modifying therapeutic intervention and significant product differentiation from standard of care and emerging competition. The boundaries for exploring these blockbuster-rich environments will need to be expanded well beyond the core therapeutic franchises of Big Pharma. The old paradigm of expanding only into disease adjacencies that provide synergies with the core therapeutic focus through similar pathophysiology, therapeutic modalities, targeted medical audience or commercial model will need to be revisited.

Opportunism will become more prevalent in this new model and R&D and business development functions will be more balanced between organic R&D groups that advance the company’s footprint in core biology pathways and scouting units exploring unknown territories where new blockbusters will likely emerge. In this context, portfolio prioritization will need to be redesigned to be more inclusive and less punitive on new disease opportunities, ensuring that the rigor and standards applied to in-house projects are similar to those for externally sourced candidates.

As companies may have to rely on a pool of smaller blockbusters to sustain their growth, flawless product launch, global commercialization and life cycle management will be required to maximize the value capture of each blockbuster. Our analysis indicates that while the 1995–1999 class of blockbusters took on average five to six years to reach blockbuster status (global revenues of at least $1 billion), the class of 2000–2004 took on average only four years to get to the same status. The evolving blockbuster marketplace will likely require new entrants to accelerate this ramp, increasing pressures on commercial organizations to dedicate resources and budgets to new product launches more early on in their life cycle and at unprecedented scale.

Finally, companies need to address the value leakage from externally sourced blockbusters by rethinking business development structures to emphasize those with higher retained ownership for partnered products. The goal is to form partnerships beyond licensing or co-promotion deals that avoid or shave off over time royalties and partial regional ownership structures. Specifically, companies need to look at designing deal structures where value capture for the pharma partner expands beyond sales milestones. These transactions should be designed to reward commercial effectiveness in an era of health care reforms and constraints. Moreover, internal processes and mechanisms that can identify earlier the blockbuster potential of partnered products are important as they can help reframe ongoing collaborations, driving actual acquisitions of licensing partners or alliance restructurings.

As illustrated previously, a significant portion of product originators ultimately get acquired by their pharma partners. (See “Biopharma: Beyond the First Product,” IN VIVO, June 2006.) However, most of these deals have happened after product launch, late in the commercial life cycle of the therapeutics. There is an undeniable logic to pharma’s desire to knock down all of a product’s commercial risks before inking a transaction with the compound originator’s company. However, there is now an impetus for pharma to execute even earlier transformative deals that provide full ownership for blockbusters, a scenario that allows drugmakers to increase their growth and address the value leakage caused by partial ownership. Understanding key trends in blockbuster formation and applying the knowledge from this analysis will enable biopharma executives to offset the potential shortcomings of the new blockbuster model and improve their chances of becoming the successful players of tomorrow.

**Exhibit 6**

**Today Vs. 2015 Blockbuster Profiles**

<table>
<thead>
<tr>
<th>Blockbuster Year</th>
<th>Specialty markets</th>
<th>Ex-US geographies</th>
<th>Biotech / mid-sized pharma</th>
<th>Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>41</td>
<td>52</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>2015 (incremental)</td>
<td>59</td>
<td>58</td>
<td>45</td>
<td>44</td>
</tr>
</tbody>
</table>

**SOURCE:** L.E.K. analysis

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