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SYMPOSIUM

Follow-on Biologics: A New Play for Big Pharma

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The U.S. pharmaceutical industry plays a vital role in shaping the face of American healthcare. As an industry rooted in innovation, its continued evolution is inherent. With major patent expirations looming and thin product pipelines, the industry now must consider new directions to maintain growth and stability. Follow-on biologics, derived from living organisms and marketed after the patent expiration of similar therapies, represent a growing opportunity for big pharmaceutical firms, as discussed during Yale's Healthcare 2010 conference in April. Key characteristics of follow-on biologics make them a worthwhile investment for big pharma companies: They command high prices, will likely have fewer entrants than generics due to high barriers to entry, and play to the existing strengths of big pharma firms. With the recent healthcare legislation providing the way for consistent Food and Drug Administration (FDA†) regulation, the timing seems right to continue the push into this new and growing market.

At a time when healthcare issues are on the mind of every American, it would serve us well to consider the future of one of the most influential players in the sector: pharmaceutical companies. National health expenditures for pharmaceutical products are hovering around 10 percent, meaning that one out of every 10 dollars that we, as a nation, spend on healthcare goes toward drugs. These drugs regulate our cholesterol levels, promote the growth of white blood cells in cancer patients, manage our restless leg syndrome, help us sleep better at night, and provide myriad other benefits to our health and well-being. Yet, for all the benefits that the pharmaceutical industry provides, it is also criticized by many for the expense of its products and the high profit margins that these products command. The growing popularity of biologics — treatments derived from living organisms, such as antibodies and interleukins — has particularly increased the price of drugs in the United States. The current price of the average biologic is more than 20 times that of a traditional, chemically synthesized small-molecule drug. There is a trade-off between high prices and innovative new therapies. Moreover, pharmaceutical companies themselves argue justifiably that prices ac-

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†Abbreviations: FDA, Food and Drug Administration; R&D, research and development; TNF, tumor necrosis factor; EU, European Union, PPACA, Patient Protection and Affordable Care Act.

count not only for the price of production, but also for the research and development (R&D) for that therapy as well as numerous others that did not make it all the way through the regulatory process and to the clinic.

In recent years, we have witnessed the breakdown of the well-oiled innovation machinery of the traditional big pharma company. While R&D departments spent more and more (well over $1B per drug), they did not see promising results in the form of late-stage drug candidates [1]. Over time, this led to a strategic shift in portfolio management within big pharma companies toward an acquisition-heavy plan to build up their pipeline of drugs. In-house R&D projects were cut, and layoffs of scientific staff were rampant. This phenomenon continues, with 2009 bearing witness to the most mergers and acquisitions in the pharmaceutical industry to date. Industry-wide consolidation aimed to find complementary development projects and synergies in manufacturing and emerging markets. What has been the effect of all of this? The answer is not as hopeful as the pharmaceutical industry would have liked. A giant "patent cliff" still persists, referring to a number of blockbuster drugs that will go off patent over the next two years and cause a dramatic decrease in sales for big pharma firms. Without a strong pipeline to fill in the valley with new product sales, big pharma companies have begun scrambling to find new ways to generate revenue.

Meanwhile, the biotech industry's foray into therapeutics has been a wild success story. From the 1980s to the present, biologics have reshaped the face of medicine in many disease areas. The spawn of highly innovative, nimble biotech firms, biologic drugs are large, complex molecules grown in living cells rather than synthesized chemically like small molecules. For example, Enbrel is a fusion protein that acts as a tumor necrosis factor (TNF) inhibitor to stop inflammation. This drug is being widely prescribed for rheumatoid arthritis as well as psoriasis, among other indications, with sales last year reaching $5.9 billion, up 9.3 percent from 2008 [2]. Enbrel was first developed by Immunex and released in 1998. Immunex was acquired by a rival biotech firm, Amgen, in 2001 [3], and subsequent marketing of the drug in the United States was jointly undertaken by Amgen and Wyeth (now taken over by Pfizer in the mega-merger of 2009). Enbrel's is the classic story of the modern biologic: a novel therapy developed at a small biotech firm and acquired or licensed up the food chain to feed bigger firms' appetites for late-stage assets.

Enbrel is by no means unique; there are many blockbuster biologics on the market. Like Enbrel, many of them will reach the end of their patent life soon. Enbrel's patent expiration is set for 2012, at which time it will be exposed to potential competition from generic versions. Therefore, though there are many novel biologics therapies that can provide new ways of treating patients, there is also a huge opportunity for generic versions of biologics that did not exist even one decade ago. This opportunity is hard to quantify, but one recent estimate shows that biologics responsible for $20B in annual sales will go off patent by 2015 [4]. Unsurprisingly, small-molecule generics firms are flocking to this space. Teva, the world's largest generics manufacturer, has partnered with the Lonza Group to make and sell so-called follow-on biologics. These treatments are similar, but not identical, to preceding biologics whose patents expired. Meanwhile, Novartis's generics arm, Sandoz, has increased capacity in biomanufacturing to ramp up its efforts. Big pharma itself has made motions of interest in the business of follow-on biologics, as witnessed by the dedicated division of Merck, BioVentures, established in late 2008 for the development of follow-on biologics. Interestingly, even Pfizer is testing a follow-on version of Enbrel, now in phase 2 clinical trials [5]. With a big market opportunity and a number of firms interested, follow-on biologics will surely play an important role in shaping the future of the pharma industry.

For large pharmaceutical firms, what is needed is a way to diversify and mitigate risk, a way to supplement their rollercoaster

sales figures year after year. Follow-on biologics may be a smart play for big pharma companies. Like their generic cousins, biologics manufacturing has strong economies of scale that big pharma firms can leverage. But unlike generics, there are higher barriers to entry because of the technical challenges of manufacturing biologics and the necessary clinical proofs of equivalency. Pharmaceutical companies already are practiced at navigating the global clinical-trials arena and should be able to exercise a significant competitive advantage in this area, especially over the existing generics manufacturers attempting a play in the follow-on biologics market. It has been estimated that the investment necessary to bring a follow-on biologic to market is eight to 10 years and will cost $100-$200M [6]. This investment of time and capital is substantial and tends to favor larger firms with significant R&D budgets. However, to put the investment into perspective, this is only one-tenth of the cost of developing a full-scale innovative pharmaceutical product and has less associated risk of failure — a proposition that the big pharma industry should find appealing. Additionally, the trend for current follow-on biologics on the market in the European Union (EU) and United States has been to use traditional detailing and marketing practices to compete with branded products. This, too, puts big pharma at a competitive advantage over other players lacking an army of detailing pharmaceutical reps, who can use their established relationships with doctors and medical personnel to promote new follow-on biologics.

One counter-argument to the case for a move into follow-on biologics is that the new healthcare reform, the Patient Protection and Affordable Care Act (PPACA), passed in March of this year will harm any would-be generic biologics makers with its 12-year exclusivity for branded biologics. However, while this length of time is significantly longer than the proposed five years that generics proponents pushed for, the surety of a secure path forward through the FDA for follow-on biologics outweighs the downside of lengthy biologics exclusivity. It is reasonable to hope that within two to three years, the FDA will have functional guidelines for the regulation of this nascent market. Now more than at any other time in the past, the ambiguity associated with government regulation is manageable. And if big pharma becomes more intentional about entering the follow-on biologics market, its powerful lobby, PhRMA, could influence the way that the details of the FDA regulations are written.

If the pharma industry does find the follow-on biologics market appealing and makes a bet on it for supplementary revenue, what can we expect from the patient perspective? It could mean greater access at cheaper prices, but the dynamics are much more nuanced. The economics of the small-molecule generics market likely will not be transferrable to the follow-on biologics market. High barriers to entry, high fixed costs of manufacturing, and marketing expenses will more likely manifest themselves in a market that has a small number of firms with relatively small price drops upon introduction of follow-on therapies. In small-molecule generics, the price typically decreases by about 80 percent from the original branded drug price after one year of generic competition. However, in current follow-on markets in the EU, this has not been the case. Since its introduction of biosimilars regulation in 2004, the EU has successfully introduced numerous follow-on biologics for three classes of branded drugs. The results hint at what might be expected for U.S. firms: By 2008 in Germany, biosimilars had captured an estimated 14 percent to 30 percent market share and discounted prices by 25 percent [7]. The U.S. story of follow-on biologics will likely mirror that of EU biosimilars rather than that of small-molecule generics.

With healthcare legislation passed and the inevitable refocusing on bending the cost curve in healthcare expenditures, big pharma firms may be able to boost their reputation with the public as well as their bottom line with a continued push into follow-on biologics. The decreased risk of approval and steady returns will help diver-

sify pharmaceutical companies' volatile revenue streams, while concurrently winning favorable public opinion by promoting price reductions for some of the most expensive drugs available. The cost savings to consumers will increase access for patients as FDA regulation is finalized and more and more follow-on biologics enter the market. This could be a win-win scenario for big pharma and for patients.

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