

From the Boardroom

Valuation of early-stage companies in the biotechnology industry

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ABSTRACT

The prospect of government regulation, product liability lawsuits, and customer reliance on third-party payers contribute to the complexity of valuing biotech start-ups. In addition, the inherent complexity of biologic drug manufacturing and storage creates secondary risks that must be considered in a valuation.

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INTRODUCTION

THE BIOTECHNOLOGY (“BIOTECH”) industry consists of companies using living organisms or molecular and cellular techniques to provide chemicals, food and services that meet human needs. As part of

the biotechnology industry, biopharmaceutical companies (“biopharmas”) engage in manufacturing and developing large molecules medicines that are similar or identical to bodily proteins. The biopharma industry comprises thousands of small firms, whose identities change as new start-ups are formed and established firms grow, merge, or are acquired by other established companies. Mergers or acquisitions are used as an exit strategy for smaller biotech firms who often have financial difficulties, such as few or no marketable products and low cash-to-sales ratios. Partnerships and acquisitions of pharmaceutical start-ups, including biopharma start-ups, account for between one-quarter and one-third of most large firms’ pipelines. The number of large

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pharmaceutical companies seeking to bolster a lagging product line by finding late-stage drug development projects that could be launched quickly is decreasing and valuing start-ups with early-stage projects is becoming increasingly common.

There are three well accepted valuation methods that should be considered when valuing early-stage biotech companies:

- **Asset Approach** – used to calculate a business’s value as the fair market value of a company’s assets less the fair market value of its liabilities;
- **Income Approach** – used to calculate a business’s value based on the present value of expected future cash flows; and
- **Market Approach** – used to calculate a business’s value based on metrics from guideline publically traded pharmaceutical companies and privately held businesses.

Of the three valuation methods identified above, the most commonly used method for valuing early-stage biotech companies is the income (or Net Present Value “NPV”) approach. The NPV approach involves the quantification of expected revenues, costs, and potential risk parameters.

Revenues are forecasted by considering market size, market share, and market growth opportunities for the biotech company’s potential drug or drugs. The number of patients receiving treatment, the price of treatment per patient, and existing sales data of products in the same therapeutic class as the drug candidate of interest are considered in determining the market size. Market share is determined by analyzing competition from other available treatments and whether other companies have similar products in their development pipeline. Pricing, the relative advantages of the subject drug compared with current treatments, clinical evidence of efficacy, and patient and physician product loyalty to pre-existing treatment options will influence market penetration. Market growth is generally affected by changes in the patient population, spread of illness, frequency of occurrence, frequency of diagnosis, and treatment practice. Rates of product ramp-up, historical peak sales, and rates of market erosion are often analyzed. If patent technology relating to the subject drug is present then it is important to understand if and when patent protection will expire and also whether critical generic competition may occur.

Development costs are broadly grouped into four categories as follows: (1) *Discovery and pre-clinical development costs* related to the discovery of the chemical compound or the biological agent; (2) *Clinical*

development costs including trial design, patient recruitment, clinician, monitoring, and close-out and reporting costs; (3) *Regulatory review costs* required to gain regulatory approval; and (4) *Launch, manufacturing and marketing costs*.

Although historical data for products in the same therapeutic class as the drug candidate of interest can be valuable resources for forecasting, significant uncertainty exists around forecasting revenue potential, development cost, and risk. Values derived from quantitative modeling are sensitive to changes in revenue and risk parameters, which explain why it is important to understand the challenges and risks involved in valuing early-stage biotech companies. This article is intended to address both common challenges in forecasting revenues, costs, and risk, and to highlight specific risk factors related to early-stage biopharma companies.

CHALLENGES AND RISKS TO CONSIDER

Incorrect assumptions involving drug development costs, anticipated revenues, or risk can have a significant impact on any valuation. Early-stage companies in the biopharma industry face market and scientific challenges that valuation professionals must understand. These risks depend not only on the stage of development and the experience of the company, but also the types of drugs being developed.

The biopharma industry encompasses various risk factors and hurdles that must be overcome prior to attaining a commercially successful drug. Start-up biopharmas face a highly regulated global industry, increasing research and development (“R&D”) costs, escalating costs of litigation, reimbursement risk, growing threats to patent life, and the rise of generic competition. In a 2013 study DiMasi, et. al. reported that only 32 percent of biologics that entered Phase I trials were approved. The same study found that the approval rate was even lower for oncology biologics at just 12 percent. Notably, as of 2012, only 15.4% of all orphan designated drugs in the U.S. were approved.

Increasingly, new drug ideas originate in small companies, which often then license-out their drug compounds to more experienced firms for later-stage drug development, regulatory review, and commercialization. While these start-ups may focus on traditional chemical compounds, many develop biological drugs, otherwise known as “biologics,” which are complex substances derived from living sources. Start-ups also often focus on orphan drugs, which are either classified as traditional chemical compounds or as biologics, and are defined in

the U.S. as treatments for diseases affecting 200,000 or fewer people.

Many start-ups will never reach the stage of pursuing an initial public offering (“IPO”) or being acquired and many drugs being developed by small cap companies will never see the light of day. Understanding not only the risks that face all pharmaceutical companies, but additional challenges faced by biotech start-ups in particular, is important to conducting a valuation. An overview of the complexity of the drug development process as well as sources of costs and risk inherent to the pharmaceutical industry follows.

UNDERESTIMATING COST AND RISK IN THE DRUG DEVELOPMENT PROCESSES

In the U.S., a newly discovered chemical or biological entity must overcome numerous regulatory hurdles: pre-clinical development is followed by application for permission to proceed, three phases of drug approvals in the U.S., final Federal Drug Administration (“FDA”) approval, and at times, additional Phase IV studies. The entire development process takes on average 12 years for traditional drugs and between 10 and 15 years for biologics, which includes initial basic research and frequent delays in the approval process. The percentage of drugs that fail during the various clinical stages is approximately 90 percent (and can be as high as 95 percent for biologics).

Orphan drugs and biologics frequently experience difficulty in recruiting patients, due to the rarity and severity of diseases the drugs are intended to treat. Center Watch, a source of information regarding clinical trials, estimated that difficulties in recruiting patients can delay 81 percent of drug trials related specifically to biopharmaceuticals for up to six months. Furthermore, additional costs may be incurred if regulators demand post-marketing studies and the establishment of patient registries, which is frequent for orphan drugs. The development of orphan drugs is further complicated by a lack of data on the natural course of the disease, poor or late diagnosis, limited expertise in the medical community, and major logistical difficulties in the organization of clinical trials. Moreover, once clinical proof of principle is established for an orphan drug for which there is no alternative, the manufacturer may be under enormous pressure from patients, physicians, and/or politicians to provide the therapy in development to patients, especially to children, under a compassionate use program. Thus, apart from any financial aspects, this pressure may undermine the ability of a company to perform controlled clinical trials.

Biopharma start-ups often focus on novel drugs, banking on a greater return on investment upon drug approval. Thus, regulators may require larger numbers of patients and longer durations of exposure for truly novel agents to assure that a rare serious adverse event will not be missed. The sponsor of the first product in a drug category to reach regulators will have to negotiate all the criteria for approval and the size of safety database with the regulators. Regardless of the novelty of the drug candidate in question, there is evidence that success depends not only on the potency of the subject biologic, but also on knowledge of the regulatory approval process. Pharmaceutical companies, including biopharma firms, which received prior regulatory approval have a 51 percent chance of receiving approval on the first submission, as opposed to a 30 percent approval rate for companies which had received prior New Drug Application approval. As a result, companies that do not have a strong relationship with the FDA are likely to experience costly delays in obtaining regulatory approval.

As of 2010, the average pharmaceutical industry return on R&D was less than nine percent. Smaller pharmaceutical companies, despite their smaller size and inherent efficiencies, generally are no more productive at R&D than are large pharmaceutical companies. Many drugs will fail in the last two clinical stages of drug development, clinical trial Phases II & III, which are the largest, most expensive, and most lengthy clinical trials in the drug development process. Only 84 percent of biologics transition from Phase I to Phase II, only 53 percent transition from Phase II to Phase III, and only 74 percent transition from Phase III to regulatory approval. Despite the high rates of failure in later stages, Phase III clinical trials cost approximately 18 times more than does basic research, and approximately 11 times more than the cost of the initial discovery and the costs of preclinical trials. For orphan drugs, Phase III clinical trials represent over 90 percent of development costs. Underestimating the cost of drug development or the risk of late-stage failure can have a significant impact on the valuation of a startup or early-stage biopharma company.

RISK OF OVERESTIMATING PATIENT POPULATION

Another risk facing biotech companies, namely those targeting rare diseases, is the potential to overestimate the patient population. The actual number of patients that need to be treated, as compared to an extrapolated estimated prevalence, is often uncertain. Overestimation of the prevalence rate of many rare diseases is most probably related to the fact that prevalence studies are usually done in regions of higher prevalence and usually based on hospital data. Even if a drug

candidate receives regulatory approval, overestimation of the patient population can have a significant effect on forecasted revenues, and as a consequence, the value of the startup.

REIMBURSEMENT RISK

An important consideration when valuing early-stage biopharma companies is the insurance status of target patients – notably whether they are covered at all as well as the scope of coverage and the limits placed on coverage. It is essential that a specific drug be included on preferred drug lists, especially on the list of Medicare and Medicaid reimbursable drugs. Preferred status translates into lower patient cost, which decreases the impact of the price variable. Features of the Medicare Part D plan could significantly affect beneficiary access and costs, including “tiered” cost sharing, requirements for prior authorization or coverage and step therapy, and quantity limits.

In the case of specialty drugs, such as many biologics and orphan drugs, rather than paying a fixed copayment per prescription as is typical for less expensive drugs, beneficiaries must typically pay a percentage of the cost of medication in the specialty tier as coinsurance. For the 2010 plan year, the median coinsurance rate for medications in the specialty tier across plan was 30 percent. As of 2010, 46 percent of orphan drugs were included in specialty tiers by 50 percent or more of stand-alone Part D plans. One-third of orphan drugs were subject to prior authorization requirements before coverage was granted by 50 percent or more of stand-alone plans.

In the case of biologics, the expense of these drugs, as well as increased budget constraints, has already led to risk sharing, which includes performance-based contracts, efficiency stipulation schemes or effectiveness guarantee schemes. In other words, risk sharing allows payers such as private or public insurers to pay only if the treatment is effective. Just as in the case of overall lower prices in Europe, their single payer system enhances their ability to obtain such risk-sharing concessions. Moreover, regulatory authorities in countries such as the U.K. are beginning to impose “fourth hurdle” requirements that drugs must demonstrate cost effectiveness, not just safety and efficacy.

In an environment of intense pricing pressure, new drugs that treat unmet medical needs stand the best chance of commanding higher prices. However, there is a risk that patients will most likely not be able to afford to pay for these higher priced drugs (e.g., orphan drugs) directly and payment to the pharmaceutical company will be through a third-party payer. Therefore,

pharmaceutical companies, including biopharma companies, anticipating the high prices commanded by drugs for rare diseases have to deal with the risk that their revenues will be severely harmed if drugs fail to receive reimbursement approval through Medicare, Medicaid, or private insurance.

RISK OF LITIGATION

Litigation risk is another area for consideration when valuing early-stage biotech companies. In spite of extensive risk management efforts and input to board committees of pharmaceutical companies, there has been a rise in the number of settlements for violations of a variety of laws in the last two decades. Between 1991 and 2011, more than 165 cases of civil and criminal actions by federal and state governments were settled in the U.S. by pharmaceutical companies, with total criminal penalties of approximately \$19.8 billion. Awards of damages or settlements involving 73 percent of these cases occurred between 2006 and 2010.

In April 2010, the U.S. government amended the Fraud Enforcement and Recovery Act of 2009 to narrow down its public disclosure provision, making it easier for whistleblowers to bring lawsuits; which has resulted in massive recoveries in subsequent years. Additionally, in July 2010, the U.S. government passed the Dodd-Frank Act, which increased the authority of the U.S. Securities and Exchange Commission (“SEC”) to reward whistleblowers with a newly established, \$451 million fund and provided them with enhanced protection against retaliation.

Settlements and financial penalties stem from various types of violations, but drug safety issues accounted for over 50 percent of major lawsuits. Therefore, it is important to note that the complexity of biologics and many orphan drugs, precisely the drugs produced by biotech companies, may increase product safety risk. Large-molecule drugs are sensitive to even minor changes in the manufacturing process, and subtle changes can significantly affect the safety and efficacy of these products. For instance, during clinical testing, 31 percent of orphan drugs had more pronounced side effects than did non-orphan drugs and 13 percent of FDA approved orphan products provoked more side effects than were anticipated.

In addition, because biologic products are defined by a manufacturing process, biotech companies may be at greater risk of design defect claims. Since design defect claims apply to every product sold, they therefore pose a greater threat of litigation damages as opposed to standard manufacturing claims which only apply to individual products or lots.

Increased liability due to adverse drug effects could pose significant risks to the financial stability of a biopharma company and its ability to fund R&D for future revenue growth. Public litigation could also have detrimental consequences for the reputation of a new drug. Despite this growing risk, the threat of adverse drug effects on the pharmaceutical industry can never be eliminated, only managed; and therefore, should be considered in any valuation.

HUMAN RESOURCES RISK

A study of U.S. biotechnology companies also shows that the lack of human capital is a barrier to growth prospects of a biotech company. Human capital problems facing firms are often a result of an inability to find experienced managers and regulatory personnel. There is an intensifying global “war” for talent in the pharmaceutical industry. There is a risk of shortages of highly skilled personnel in developed industrial economies due to two principle factors: (1) an increased demand and higher wages for personnel in their foreign countries of origin; and (2) international agreements that limit “brain drain”, the large-scale emigration of large groups of technically-skilled individuals, which could increase the cost of hiring highly skilled migrants.

Thus, locating and retaining highly competent and experienced staff, who also know how to navigate the FDA approval process, is a growing concern to biopharma companies. Not only could a lack of appropriate talent potentially hinder the FDA approval process and cause additional delays, it could also drive wages upwards. Human resources risk could significantly impact estimated future profits, and therefore, the accuracy of any valuation.

RISK OF OUTSOURCING

Due to slow revenue growth in the pharmaceutical industry, pharmaceutical companies including biopharma firms, are tempted by the short-term cost savings that outsourcing can provide. Contract research organizations (“CROs”) are increasingly able to offer specialized services and capacity at lower costs. However, many CROs have been hurt by increasing competition, resulting in the pressure to hire less qualified staff. Failure to complete work on time or on budget is a risk, as is the potential for low-quality work. Because the pharmaceutical industry is so highly regulated, there exists more opportunity for CROs to violate rules concerning clinical trials, manufacturing, and/or distribution. Furthermore, a biotech company’s reputation can be placed in jeopardy

if the third party contractor engages in unethical or inappropriate activities, even during drug development before a start-up company partners or is acquired. As a result, outsourcing risks should be considered when valuing early-stage biotech companies.

RISK OF COUNTERFEIT DRUGS

Similar to increased litigation and outsourcing, the augmented quantity of counterfeit drugs worldwide poses significant reputational risk to biotech companies. Ernst & Young observed that as of 2008, counterfeit drugs accounted for approximately 10 percent of the world’s pharmaceutical product supply. However, according to the Counterfeit Incident System managed by the Pharmaceutical Security Institute found that only 1.23 percent of counterfeits are biologics. Nevertheless, counterfeit biologics pose an exceptional risk greater than its statistical representation. The probability of a counterfeiter successfully creating a biologic with any therapeutic value is miniscule. Biologics require continuous testing and validation to prevent even slight variations. Despite the difficulty in manufacture, counterfeit biologics are extremely challenging to detect, and they are extremely vulnerable to environmental degradation, more so than other drugs. Moreover, biologics, especially vaccinations, are frequently administered to a large number of persons at one time, increasing the potential for a catastrophic event.

At present, of the 191 WHO member states, only about 20 percent are known to have well developed drug regulation. Of the remaining member states, about 50 percent implement drug regulation at varying levels of development and operational capacity. The remaining 30 percent of member states either have no drug regulation or have very limited capacity to do so. Inadequate, ineffective, or weak drug regulatory control could promote unregulated importation, manufacture, and distribution of biologics. Counterfeit biologics thus pose a significant risk to a pharmaceutical company’s reputation if the drugs are ineffective or unsafe.

RISK OF PARALLEL TRADE

Parallel imports, or gray-market imports, are drugs that are legally produced under patent protection, placed into circulation in one market, and then imported by an intermediary into a second market without the authorization of the local owner of the intellectual property. Parallel trade thrives when there are significant price disparities between countries, and it is legalized in many countries, including those in the European Union. As a result, the

ability of pharmaceutical companies to price discriminate is diminishing as more countries adopt national price regulatory policies that reference prices in other countries and/or legalize parallel trade. Pharmaceutical companies are thus encouraged to delay or not launch new drugs in low price markets. This launch delay or the decision not to launch new drugs, in turn, would shrink the potential market size and projected revenues for biotech companies. Moreover, parallel trade could reduce safety and potentially harm a company's reputation due to the circumvention of domestic inspections.

SUPPLY CHAIN AND DISTRIBUTION RISKS

Potential risks related to a biotech company's supply chain and distribution network occur prior to commercial manufacturing and also during clinical trials. In many cases, clinical trials are conducted globally, and protecting intellectual property rights throughout the supply chain can be a serious concern. Furthermore, the consequences of producing suboptimal quality or quantity on a commercial scale can be detrimental because of the amount of material consumed and also the scope of those receiving the drugs is potentially wide and much more difficult to contain. One lost shipment of a critical compound, due to improper storage, transport, or administration, can lead to an entire phase of a clinical trial being delayed or aborted. For a small cash-constrained start-up, this could have major business implications if replenishment supply involves cost and time lines that it can ill afford.

RISK OF BIOSIMILARS

The risk of generic "biosimilars" entrants is an important risk factor that should be considered. The introduction of generic alternatives that are less expensive, effectively truncates the life of a patent. In 2010, the Biological Price Competition and Innovation Act was passed that provided 12 years of market exclusivity for biologics, but opened the door for biosimilars. This means that after 12 years, generic companies can start marketing cheaper biosimilars. Prior to this legislation, there was no regulatory pathway to approve biosimilar products and therefore, most biologics were afforded the benefit of never having to compete with generic products.

In addition, the 12 year exclusivity afforded to biologics under this act may not provide the expected protection. Exclusivity does not necessarily prevent a "non-similar" product (e.g., a small molecule versus a biologic) from receiving orphan drug designation for the same therapeutic indication as an existing

product or prevent that product from reaching the market. Furthermore, as stipulated in the orphan drug regulations of the U.S. and the European Union, a clinically superior product, even if similar, can break the market exclusivity of a marketed orphan drug.

In international markets, the introduction of generics can precipitate even greater impacts on branded drugs. For instance, several world markets including Germany, the Netherlands, and New Zealand, have established reference pricing. In reference pricing, products are often clustered by therapeutic group. Consequently, if the reference price is based on the least expensive drug in the cluster, once generic entry occurs, all products in a reference group drop to that price, effectively truncating patent life for the newest drugs in a reference category. Reduction in patent life due to reference pricing, as well as the limits to market exclusivity of biologics, ultimately translates into lost revenues for a biotech company.

CONCLUSION

Various risks are present throughout the drug development process, from the discovery of biologics to final FDA approval, to market introduction, and day-to-day sales. While the development of traditional drugs involves risks, orphan drugs and biologics commonly produced by biotechs present additional complexity with accompanying increased risks. The risk is further compounded when the developing company is small with insufficient resources and little experience with the regulatory approval process in the U.S. or abroad.

Early-stage biotech companies often lack the resources to tackle risks such as parallel trade, counterfeiting, global supply chain disruptions, and potential theft of intellectual property. Likewise, these small biotech companies may have no choice but to outsource, opening the door to drug safety concerns. They may face the risk of exclusion from preferred drug lists and other cost containment hurdles that reduce revenues. These early-stage biotech companies operate in an industry with substantial rates of litigation that could bankrupt an otherwise promising company while producing biological products with an elevated risk of safety concerns.

Whether these small firms, often with a single drug, remain independent, are acquired, or enter in partnership arrangements ultimately depends on their perceived value. Understanding the challenges and risks that face start-up and early-stage companies in the biotech industry is important to forecasting revenues and costs; and therefore, must be considered in any valuation. In this article we discussed various factors that should be evaluated and analyzed with respect to early-stage biotech companies, specifically biopharma firms. Each valuation

must be based on the facts and circumstances specifically relating to the subject company as of the valuation date. Accordingly, the factors discussed above may or may not be pertinent in every given valuation.

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