In this white paper, Thomson Reuters provides a snapshot of the importance of patient-based drug sales forecasting in the current market conditions. This analysis looks at the role of forecasting and the factors to consider in developing a patient-based forecast.
INTRODUCTION

As the financial meltdown struck, a typically safe haven of the economy during a recession felt a panic. One of the more severe implications of this downward-spiraling economy was the loss of the traditional money-raising avenues of debt and equity issuance. Given the capital-intensive nature and high-risk component of drug development, biotechnology companies rely on new capital more than any other industry. With very tight credit markets, companies were unable to borrow or raise money, and prospective investors applied increased scrutiny to the potential value of companies’ assets, making the ability to construct a reliable forecast more important than ever.

The value of an asset is determined by analyzing the net present value (NPV) of its future cash flow. For drugs, this analysis begins with determining which patients will benefit, to arrive at the drug’s future sales potential. Understanding the current and potential market, the impact and timing of future events, and inherent risks are fundamental when developing product forecasts. Whether the purpose is to license a drug, raise capital, or purchase stock on the open market, developing a dynamic and reliable forecast is the analyst’s tool for determining the value drivers of a particular company.

THE IMPORTANCE OF FORECASTING: THREE PERSPECTIVES

1. BIG PHARMA

The success of blockbuster drugs has lead to impressive cash flow and high returns for pharmaceutical companies. However, with size also comes constant pressure to continue to innovate and grow. This is particularly acute now, as the industry faces a veritable cliff of impending patent expirations. There is a vital need for companies to fill their pipelines with new therapies to replace lost revenue. At the same time, developing and gaining approval for new drugs has become more difficult. These factors mean big pharma needs to employ new strategies to maintain and grow business. This is done through a better assessment of the risk/return profile of drugs in their pipelines and outsourcing risk by partnering with biotechnology companies in need of their financial, technical, and marketing resources. Forecasting plays an essential role in determining which drugs will lead to the best returns and which drugs should be dropped before they consume too many resources.

“Biotechnology companies are highly dependent on well functioning capital markets to finance their development projects since many will not see revenue for perhaps a decade. It generally takes approximately $1 billion, including the cost of failures, to get a new therapy to market. This financing generally comes in the form of equity investment. When credit markets seize up, as we’ve seen in the past 13 months, there is less capital available for investors to put at risk, and the capital that is put at risk is dedicated to shorter term, lower risk options. So while some areas of the economy have seen a slowdown, biotech has seen a near-freeze.”

Jim Greenwood President and CEO Biotechnology Industry Organization

“The cost of developing compounds has become so high and become so risky that we are looking to share the risks and opportunities and find more and more partnerships,” says William Weldon, Chief Executive Johnson & Johnson. “You’ll see more and more sharing of risks because the upside can be spectacular.”

2. SME INNOVATORS AND BIOTECHS

Smaller companies focused on innovating new therapies usually require outside financing to continue operations while they prove the value of their concept. Often they will seek to partner with a larger company that can offer greater development resources and market access. Whether their strategy is to secure financing, form a partnership, or both, it is necessary for smaller companies to develop forecasts that gauge the value of their pipeline and account for overall market conditions so they can properly negotiate agreements.

3. THE FINANCIAL COMMUNITY

For the investor, being able to accurately forecast the revenue of a product candidate, and hence the potential future value of a company is key to understanding investment risk and possible return.

Because most smaller companies have few drugs in their pipeline, each drug represents a great deal of exposure to the overall risk of the investment. Combine this with the unpredictable nature of drug development, and there is a high degree of volatility around important development events.

The value of the particular drug to an organization will determine the amount of volatility around the event. Depending on the type of company, an investor may look to capitalize off of the volatility or to avoid these risks altogether.
Patient-based forecasting is a reliable approach to use when analyzing a marketplace and the potential sales a therapy may have within it. “We don’t do patient-based forecasts because it’s fashionable,” says Thierry Boutin, head of forecasting for sanofi-aventis. “We need patient-based forecasts because a well-defined segmentation is needed to match the requirements of the payers.”

Understanding the primary drivers behind a forecast enables the analyst to create a dynamic therapeutic model, project the impact of future events, and quickly adjust the forecast as these events occur. We will now look at each of these drivers in turn.

THE PREVALENCE AND INCIDENCE OF THE DISEASE

The first step in patient based modeling is to identify the incidence and prevalence of disease within a select category. Typically, reliable data are available from government sources, prominent organizations and foundations. Examples are the Centers for Disease Control, American Cancer Society, World Health Organization, and the National Multiple Sclerosis Society. Beyond data from specific organizations, it is also important to review other sources to formulate the best estimate of a patient population. These may include estimates from:

- The respective disease foundations
- Medical literature
- Proprietary market research
- Companies developing drugs for the indication

Population estimates for different geographic locations such as the United States and Japan are available and can be used to adjust the rate of disease to the respective location. For example, the rate of obesity in Japan is much lower than in the United States, but the rate of osteoporosis in Japanese women is much higher than in Caucasian women.

There are then several ways to model future increases in the affected population. The estimated population growth of a specific demographic, past changes in rates, and estimates in the changing demographics of a country are all factors that will impact future disease rates. Perhaps the best example of this is the aging of the Baby Boomer generation in the United States and the upcoming increases in disease rates expected due to an older population.
THE NUMBER OF PATIENTS BEING TREATED OR DIAGNOSED

Once the overall affected population is determined, the next step is to eliminate those patients who will not be treated pharmacologically. At this stage, it is important to understand current and future trends in diagnoses and treatments so as not to eliminate patients who may benefit from future advancements in treatments.

Many times the sources used to measure prevalence/incidence can also be leveraged to determine the extent of diagnoses and treatment. Of course, not all diagnosed patients will go on to receive treatment. After determining the number of patients diagnosed, the percentage of patients treated is estimated from guidelines on current disease management.

THE NUMBER OF PATIENTS ELIGIBLE FOR TREATMENT BY THE SPECIFIC DRUG CANDIDATE

The forecast must identify the specific patient populations individual drugs will target. Once the number of addressable patients is determined, an analyst can narrow down eligible patients based on proposed therapy indication or clinical benefits. Typically, this is the patient population for which the drug is indicated, or for which it has shown clinical benefit. Many times this will be determined through the mechanism of action, an in-depth knowledge of the clinical trial populations, and the drug’s clinical profile. Increasingly, it may involve determining the proportion of patients who carry a specific biomarker. For example, an increasing number of biomarker-guided therapies are being developed such as HER-2 (Herceptin for breast cancer), K-Ras (Erbitux for colorectal cancer), and Apolipoprotein E4 (Bapineuzumab for Alzheimer’s disease). Only the proportion of the patient population that carries the relevant biomarker will be eligible for treatment.

In this segment of a model, it is also important to take into account potential indications beyond the primary indication that could expand the base market as the life cycle of the therapy progresses.
AVerAGE PRICE PEr PATIENT
For drugs still in development, the price of similar approved drugs can be used to determine if the drug should be priced at an equivalent value, at a premium, or at a discount. It is also important to take into account what the market will bear, especially when no drugs have been approved for an indication. By combining the price of the therapy and the proposed dosing regimen, one can develop pricing and revenue scenarios on a per-patient basis.

THE CANDIDATE’S MARKET SHARE
Estimating the peak market share a drug can achieve and the uptake of the drug into the marketplace involves numerous objective and subjective inputs. First, evaluators must quantify the use of drugs that are currently marketed. In addition, primary market research is essential. Explore the number and location of treatment centers, key thought leader discussions, and manufacturing capacity since, all play an important role in determining the potential market share available to new drugs.

ANALYZING MARKET SHARE ASSUMPTIONS
With the known inputs of patient population, drug price, and drug sales, an estimate for the number of patients treated can be obtained. Since analysts have identified the eligible patient population, the current market share of these drugs is determined by dividing the patients treated by the patients eligible. There are several ways to compare market share across drugs. The underlying estimate to use for this is the number of patients treated which can then be divided using different denominations of patient groups within:

1) total treated population;
2) eligible population;
3) drug class;
4) marketed products.

Dividing by the total patient population allows one to analyze the penetration of a drug or group of drugs relative to the total addressable market. This determines the current state of the market and the opportunity that exists for newer drugs to either grow the market or take share from current treatments.
COMPARING COMPETITIVE PROFILES

The primary driver for the use of a drug is the clinical data that has led to the drug’s label. It is fairly easy to compare major efficacy and safety findings between two drugs. In cases where the efficacy and safety are comparable, the route of administration, dose frequency, price, and ability of the corporate sales force also become important competitive factors. Often, the therapeutic areas are large enough to support multiple successes and adding new drugs to a market may not be a ‘zero-sum’ game.

APPROVAL AND LAUNCH TIMING

An estimate for when a drug will reach the market can be made using development catalysts such as trial data and regulatory events. Review periods vary depending on the nature of the application and the timing of each specific regulatory body.

PEAK MARKET SHARE AND SALES RAMP

Drug sales ramp up over time as doctors and patients become more informed and familiar with a product, sales organizations are built out, and additional clinical data are released. One can determine the appropriate growth curve for drugs by examining historical sales trajectories for similar drugs, although each drug needs to be evaluated individually in context with its competitors.
TYPE II DIABETES MARKET

The chart below illustrates Peak Market Share Forecasts for DPP-IV inhibitors, oral formulations, non-insulin type.

<table>
<thead>
<tr>
<th>PEAK SHARES-ACHIEVING</th>
<th>PEAK SALES YEAR</th>
<th>APPROVAL DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>JANUVIA/JANUMET</td>
<td>2013</td>
<td>15 Oct 2006</td>
</tr>
<tr>
<td>ALOGLIPTIN</td>
<td>2019</td>
<td>1 Apr 2012</td>
</tr>
<tr>
<td>ONGLYZA</td>
<td>2016</td>
<td>31 Jul 2009</td>
</tr>
<tr>
<td>ONGERO</td>
<td>2018</td>
<td>1 Oct 2011</td>
</tr>
<tr>
<td>DUTOGLIPTIN</td>
<td>2020</td>
<td>1 Apr 2014</td>
</tr>
<tr>
<td>AMG 222</td>
<td>2020</td>
<td>1 July 2013</td>
</tr>
<tr>
<td><strong>TOTAL DPP IV</strong></td>
<td><strong>26.00%</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Represents 26% of the total Type II Diabetes market in the US

UNDERSTANDING CURRENT AND POTENTIAL COMPETITION

Share assumptions will also be determined by looking at potential competitive therapies in development. Visibility to the pipeline for drugs within an indication and within a drug class or franchise helps determine the risk that more competition will emerge for a drug. Pipeline databases such as Thomson Reuters Pharma™ can provide a list of drugs in a therapy area and/or drug class, along with details on each. The clinical development timelines of possible competitors can also impact launch scheduling and ramp time.

TYPE II DIABETES: TOP TEN MECHANISMS OF ACTION WITH DEVELOPMENT STATUS

<table>
<thead>
<tr>
<th>ACTION</th>
<th>DISCOVERY</th>
<th>PHASE 1 CLINICAL</th>
<th>PHASE 2 CLINICAL</th>
<th>PHASE 3 CLINICAL</th>
<th>PRE-REGISTRATION</th>
<th>REGISTERED</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSULIN SENSITIZER</td>
<td>26</td>
<td>4</td>
<td>16</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>DPP IV INHIBITOR ANT</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dipeptidyl Peptidase</td>
<td>12</td>
<td>2</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Glucagon-Like Peptidase</td>
<td>10</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Insulin Release Stim</td>
<td>10</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Lipid Metabolism Mod</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
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<tr>
<td>PPAR Gamma Agonist</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-Protein Coupled Re</td>
<td>6</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemic Agent</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UNSPECIFIED DRUG TAR</td>
<td>5</td>
<td>6</td>
<td>1</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Data is taken from Thomson Reuters Pharma.
SENSITIVITIES AND SCENARIOS
Given the wide variety of inputs one must consider on even the most basic forecast, running different scenarios and looking at the sensitivities of different inputs becomes vitally important. For each input explored, an analyst can take a low, moderate, and high assumption to create a range of estimates for patients treated and drug sales. By estimating the future drivers behind each input, such as future clinical data results, one can quickly adjust the base case as events unfold and not be surprised by the outcomes if they fall within one of the scenarios projected.

APPLYING THERAPEUTIC MODELS TO OTHER DRUGS
Having well defined, transparent inputs within a therapeutic model allows an analyst to apply a comparable drug’s model to assumptions for a new drug, even those in early development that do not have a forecast.

Since a dynamic model of the therapeutic area has been created, the analyst can plug in assumptions for the different inputs for any drug and quickly obtain a new forecast. Determining assumptions for early stage drugs can be difficult as much less data have been released and the eligible populations and competitive profile are based more on future expectations for data rather than on a known clinical profile. For example, an early stage GLP-1 drug may show up in a company’s pipeline. Even though the dosing schedule may not be known for the new drug, an analyst can use different assumptions to create scenarios for dosing and efficacy. This will allow the estimation of peak share as compared to the current treatments and allow analysts to arrive at a range of future sales estimates.

REVENUE AND PROFIT SHARE SPLITS
Many times drug revenues will be shared via royalties or profit shares. For existing deals, one can use information provided by the companies involved, such as SEC documents or original press announcements, to evaluate the partnerships and the approximate split of revenue for each drug. Databases that contain pipeline and deals data, such as Thomson Reuters Pharma, contain deal terms linked to drugs.

If the information is not readily available, analysts can calculate the split by looking at comparable deals.

PATENT LIFE
When a drug goes off patent, typically many different versions of the drug flood the market at a much lower price point, causing revenue to plummet. This often results in it becoming unprofitable for a company to continue marketing the drug. A company can try to compete by lowering the price of the branded drug, or rely on the superiority of the brand name to retain what revenue it can. A forecast must take into consideration when the primary patent will eventually expire, if there is a possibility for extensions, and the effect the presence of a cheaper version of a drug will have on other drugs in the indication.
LIKELIHOOD OF APPROVAL (LOA)

The risk of a drug in Phase II development never reaching the market is much greater than for of a Phase III drug. It is possible to handicap a drug by the likelihood of the drug’s approval (LOA). Calculation of LOA starts with an objective Average Approval which represents the average probability of FDA approval for marketing in the United States for the specified indication, based on the historical performance of drugs in the same development phase. These are averages generally accepted by the pharmaceutical industry and research community. The Average Approval is a starting point for analyzing specific data about the drug to arrive at the LOA.

The average approval numbers are as follows:

- **Phase I**: 20%
- **Phase II**: 30%
- **Phase III**: 67%
- **NDA/BLA**: 81%

The probability of approval of a given drug for a particular indication is then subjectively moved up or down based on an analysis of each of the events relevant to the particular drug including:

- An examination of the clinical development program such as trial designs.
- The historical performance of similar drugs.

Events which may lead to an LOA adjustment include clinical trial data, regulatory events, partnership announcements, preclinical data, as well as events for competitive and related drugs.

CORPORATE FORECAST

If analysts are able to combine individual drug forecasts into a forecast for the corporation’s entire marketed and development portfolio, they can gain an in-depth understanding of the business drivers for a corporation. They can use the likelihood that a drug will come to market to weight the individual components of a revenue stream to reach a probability-adjusted revenue stream.

The analyst can then adjust the LOA-based future catalysts and predict how much a specific event will impact a company, either positively or negatively.
UNDERSTANDING TIMING AND IMPACT OF FUTURE EVENTS

There are several types of catalysts that can impact a forecast. As discussed above, clinical data determines how a drug will be used and in which patient population. Also, analysts must determine development timelines and regulatory events, which can take several months to years to resolve. They must build forecasts based on the different assumptions for the outcome of each of these events. Using a handicapping system such as LOA helps provide insight into the probability that one scenario will occur over another.

BENCHMARKING VERSUS OTHER ESTIMATES

Once analysts obtain a future sales estimate, it is important to crosscheck the outcome with other estimates. Research analysts working for investment banks publish reports in which they provide sales estimates for individual drugs. While just having the final sales number is useful, it is important to realize that in cases where sales estimates combine multiple indications, each therapeutic area needs to be included to reach comparable estimates.

A primary drawback to using consensus estimates is the lack of transparency into the many inputs involved. With patient-based forecasts analysts can use the sensitivity and scenario charts developed to gauge where the consensus estimates fall within their proprietary forecast.

CONCLUSION

Clearly, the business of forecasting a drug’s viability in the marketplace and as a financial investment is a complicated and multi-faceted process. It is an exercise made even more important by financial pressures impacting businesses of all kinds worldwide and making the need for sound financial decisions more important than ever.

In addition to the information provided in this discourse, readers will find resources to help in the development of more accurate and useful forecasts for pharmaceuticals by consulting Thomson Reuters Forecast. Information about this resource can be found at: go.thomsonreuters.com/forecast.
NOTES


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