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The Right Path

The patent cliff is leading many companies to explore alternative revenue sources. As a result, some firms are readdressing the 505(b)(2) pathway, which can provide a quicker and less costly route to drug development, but is not without its complexities

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According to IMS Health, in the four years leading up to the patent cliff in 2012, the value of the generics market was about $94 billion, or $23.5 billion annually. In the seven years between 2013 and 2019, it will equal $96.1 billion, with an annual average of $13.1 billion. This dramatic fall-off in available revenue is driving pharmaceutical companies – specifically those that could previously rely solely on the success of a few major patented drugs to generate the bulk of their revenue – to adjust their business strategy in new ways to address this loss.

One way pharma companies are doing this is by looking more closely at Section 505(b)(2) of the Federal Food, Drug and Cosmetic (FD&C) Act to obtain drug approval in the US. This regulatory strategy can offer a faster and less costly drug development route, with lower risk and potential marketing advantages. At a recent pharma industry meeting with investors, chief executive officers of generic companies reported that the 505(b)(2) pathway will have a significant role in their business strategy in the years ahead – and this will likely be true for the rest of the industry as well (1).

Regulatory Appeal

In 1984, the Hatch-Waxman Amendments to the FD&C Act provided an alternative pathway under Section 505(b)(2) for approval of a new drug application. Under this provision, some or all of the safety and efficacy data required for approval can be extracted from existing studies for approved drugs that were not necessarily conducted for or by the applicant.

What is particularly appealing about the regulation is that the 505(b)(2) process encourages innovation in drug development without requiring studies to prove what is already known. Without time-consuming and expensive repetition in research studies, a drug can gain faster access to the market, and thus a faster return on investment. As a result, even small companies with

limited resources for R&D have incentives to make innovative changes to existing drugs. In addition, the process offers market protection: three years, five years and, in some cases, seven years of market exclusivity may be possible, depending on the number and complexity of new studies required.

Global Perspective

As developers are turning to Section 505(b)(2) to save development expense, they are also seeking to cut the time and cost of clinical trials by conducting them outside the US. Due to more rapid approvals, lower costs and faster patient recruiting, the use of sites in developing regions is becoming increasingly common. More than three-quarters of applications to the FDA contain data from patients or trials beyond US shores.

The Asian market, in particular, is emerging as a particularly dynamic region –for both sponsors seeking clinical trial data from this region and companies seeking to enter these markets. The growth of businesses in the Asian pharma sector and the large Asian population, especially in China, suggest huge potential in the coming years. According to IMS Health, China had the seventh-largest pharma market in the world in 2009; reached third with revenues of $67 billion in 2011; and will have the largest pharma market by 2020.

However, regardless of whether pharma and biotechnology companies want to bring a drug to market in an emerging region, or are just seeking the clinical data that will lead to US approval, if the strategy involves 505(b)(2), it is vitally important to seek professional help from partners experienced in the regulation and the region. Regulatory environments are incredibly complex, and companies cannot take advantage unless they have market familiarity. For example, an Israeli developer was preparing to conduct a 1,000-patient trial, until advisors demonstrated that a 250-patient study would be adequate, saving $6.7 million in the process.

Emerging Market Data

The benefits of holding trials outside the US and EU include:

- Larger numbers of patients enrol in clinical trials to gain access to drugs that otherwise might not be available to them
- The talent needed to conduct clinical studies is expanding as the workforce becomes more educated and obtains more experience
- A new influx of scientists is creating a medical community engaged in modernising medicine to Western standards of care
- The pure ethnic strains available in some populations may be more conducive for drug dosing, safety, metabolism and effectiveness studies than the diverse ethnicity in developed markets
- Trials can be conducted at a fraction of the cost compared to the US, due to large local labour pools, lower overheads and lower cost of living

The benefits, however, are accompanied by a number of complications. For example, intrinsic ethnic factors may influence the ability to extrapolate clinical data between regions. Researchers must also consider factors such as gender predominance, genetic differences in receptor sensitivity, genetic polymorphism of drug metabolism, and racial differences in disease manifestation.

Similarly, researchers should consider extrinsic ethnic factors in a population, which are not so much a result of genetics, but of culture or behaviour. These include climate, diet, exposure to pollution and sunshine, socioeconomic status, and use of tobacco and alcohol.

When developing the study protocol, researchers account for prevailing medical factors, including diagnostic criteria or social acceptance of the disease, the population's compliance with prescribed medications, or non-medicinal therapies that may contribute to differences in trial results.

Managing the Risks

As a result of both the intrinsic and extrinsic considerations, as well as other factors – for example, determinations assessing a drug's potential for drug-drug and drug-diet interactions, or a drug's potential for protein binding – the FDA may or may not determine that a compound is ethnically sensitive. If it is, the FDA could require controlled clinical trials to confirm the findings in an ethnically relevant group of patients before the data can be used; if ethnicity is not a factor, pharmacologic studies may suffice.

Finally, there is a multiplicity of other challenges facing trials in emerging regions – starting with a potential lack of manpower. The staffing levels in regulatory agencies will vary, but none approach the level of staffing found within the EMA or FDA. Logistics – always a concern in the US and EU – may become overwhelming in a developing country. Because heat and humidity can destroy many medications, the availability of refrigeration equipment or the development of heat-stable forms of medication must be considered.

According to the FDA's Center for Drug Evaluation and Research, complaints pertaining to foreign research sites include informed consent issues, failure to follow protocol, inadequate records, unqualified personnel, failure to get review board approval, drug accountability, recruitment practices, patent regulations in countries that have no 505(b)(2) regulation or similar process, and many more. All are challenges that will need to be overcome to manage risk in large global projects.

Viable Candidates

While there are both unique benefits and challenges to be had with studies outside the US, the basic route that drug developers must follow to reach FDA approval along the 505(b)(2) pathway is similar, regardless of where the data is obtained. And although what this pathway offers in terms of speed to market, cost savings and market

exclusivity is substantial, following it is by no means simple.

To minimise financial risk, multiple considerations must be carefully assessed long before any trial data is sought, starting with a determination of the candidate's viability. A drug candidate has to meet certain prerequisites in order to ensure its scientific, medical, regulatory and commercial viability. Developers certainly want to demonstrate that the science is sound, but they should also ensure the active pharmaceutical ingredients are available and affordable, and the formulation is achievable and scalable.

Such an assessment will not only determine viability, but will also provide critical information that developers will need further down the line. For example, assessing whether a product can be marketed at a profit, or verifying market requirements before development begins, will help inform the design of studies to meet various objectives, such as to gain essential labelling language.

Sponsor Assessment

Besides viability, it is important to have an assessment of the sponsor's assets, specific goals and business needs. Identifying viable candidates is essential, but deciding whether and how a company should pursue development is also critical. To move forward, developers should:

- Assess criteria selection, looking at everything from preferred dosage form to a sponsor's exclusivity requirements
- Evaluate potential candidates against that criteria
- Narrow the potential candidates by choosing the most important criteria and investigating in sufficient detail to clearly identify the most attractive options
- Select the candidate. In this final stage, detailed research is undertaken on a number of fronts. Considerations include a broad range of research concerning the market, the product, manufacturing and regulatory affairs, as well as an understanding of the marketing and investor strategy

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Assessing viability and ensuring a candidate fulfils the sponsor's needs are the first steps toward a comprehensive drug development plan that includes testing, formulation and manufacturing plans, and a process for conducting any needed preclinical and clinical studies. It is this that developers will need in order to gain the FDA's concurrence, usually by requesting a pre-investigational new drug meeting.

Knowledgeable Approach

Developing alternative revenue sources and reducing costs will continue to be integral goals for the pharma industry in the upcoming years. Increasingly, companies are turning to the 505(b)(2) pathway to help them reach these targets and obtain FDA approval for their products. In addition, China, the EU and many other countries have adopted pharma development pathways that are similar to 505(b)(2) – some based on the US model – making these regions attractive places to enter the market or hold trials.

Yet, Section 505(b)(2) is not a panacea, regardless of where the data is obtained. For trials outside the US or EU, companies face a tug of war as they weigh the benefits with the hurdles that accompany these trials. The management of quality data, local regulatory environments, access to necessary patient populations and availability of highly trained healthcare professionals will continue to challenge sponsors as they manage risk in large global projects.

Clearly, the pathway offers benefits; the reduced cost, speed to market and potential for market exclusivity make it attractive for a variety of projects. Generic companies, as well as developers, are interested in a myriad of other opportunities – new indications of an approved drug, orphan drugs, prodrugs, and drugs with new active ingredients or changes in dosage form or strength – all stand to realise the benefits possible with the 505(b)(2) pathway.

However, developers must approach 505(b)(2) with an appreciation of the complexities involved, partnering with companies proficient in this regulatory pathway and familiar with the market opportunities, to pursue viable candidates and maximise their return on investment.

Reference

1. Ken Phelps, Generic company CEOs: 505(b)(2) development strategy to drive growth, *Contract Pharma*, 2014. Visit: www.contractpharma.com/issues/2014-04-01/view_back-page/generic-company-ceos-505b2/

About the author

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