Guardians at the gate
Patent protection of therapeutic monoclonal antibodies through product life cycle management—Part 3

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Product life cycle management, which necessarily utilizes a multidisciplinary approach, is an essential tool for companies that develop or market therapeutic monoclonal antibodies (mAbs). Too little attention to such a plan, or use of the wrong resources, could substantially curtail a product's life span. The most difficult part of the therapeutic antibody business is the development of high-quality, safe and effective products. Great care should thus be taken to ensure that products with these characteristics are positioned in a marketplace that is competition-free for as long as possible. In an era of mAbs with billion dollar markets, the loss of even a single day of sales could cost companies millions of dollars in lost revenue.

Introduction

As stated in the first of this three-part series, “[w]herever big business exists, especially in high margin products such as therapeutic monoclonal antibodies (mAbs), competition is inevitable.” Understanding that eventuality, companies developing mAbs can best position themselves for competition with a well-executed product life cycle management (PLM) plan. To date, eight therapeutic mAbs approved in the US and other countries have annual global sales over $1 billion. Therefore, the loss of even a single day of sales could cost companies millions of dollars in lost revenue. A PLM plan is specifically designed and implemented to ensure that such sales are not lost prematurely. Although these plans are most effective if implemented well before regulatory approval, at least some benefit can be derived from PLM regardless of when the plan is initiated.

A critical part of most successful PLM plans is a clear understanding of the regulatory laws that govern the product. For example, as discussed in Part 2 of this series, the biosimilar product legislation that is pending in the US Congress will impact the therapeutic mAb business. The extent of the effects will not be known until legislation is finalized, so, at the moment, both innovator and biosimilar companies have the opportunity to influence the language of the legislation to benefit their particular interests. Such actions could be considered PLM for mAbs at any stage of development, or those already in the market.

Thus, to ensure that the greatest amount of rights, and therefore revenue, are retained for a given product, a constant dialog between various groups must occur. Early integration of key decision-makers from areas such as intellectual property (IP), discovery and regulatory affairs into a PLM team aids in development of a successful management plan.

Key Plan Attributes

The goals of PLM plans can be achieved in several ways. The integrated team approach discussed here is more expensive and cumbersome to implement than an approach devised by a PLM manager; however, the results delivered by a team approach may be greater due to the increased level of participation. Whether implemented as a team or a PLM manager, the point of a
PLM plan is to take into account as much information about the product and its particular position in the market, so that a complete PLM plan can be designed and implemented. Successful PLM plans generally have five characteristics in common. They (1) start early, (2) are based on a firm understanding of the product, (3) involve the right parties in the plan, (4) collect and analyze a broad spectrum of information, and (5) are ongoing, reiterative plans that evolve over time.3

Start Early

Although it is never too late to initiate a PLM plan, an early start may be the most common, and important, feature of successful plans. The optimal time to start a plan is while the product is in clinical, or even preclinical, development. The key to success is the timely identification of critical information about the product (e.g., properties, formulation, manufacturing) that the company can exploit as part of life cycle management.

In fact, PLM plans can actually guide the development of products. Problems of various sorts invariably arise during the process of product development and regulatory approval. Such problems may also be opportunities to secure additional patent protection for the product because most inventions are essentially solutions to problems. However, if the knowledge gained by solving a problem is not properly capitalized in a timely fashion, then it invariably becomes known in the prior art and, in that case, potential patents may be lost.

Understand the Product

Successful PLM plans are based upon a firm understanding of product attributes, how that product fits within the company’s portfolio, and the overall competitive landscape in which the product is, or will be, marketed. Although an early start is the foremost indicator of success, having a complete picture of all relevant information is key to making the right decisions. This picture necessarily dictates what life cycle management strategies can be implemented.

Unique scientific discoveries may be made during every product’s development and provide further opportunities for product life cycle enhancements. For example, perhaps a mAb undergoes aggregation when formulated, and significant steps are undertaken to avoid aggregation of the final product. Or, perhaps a novel strategy for producing or purifying a mAb is developed. In these cases, a detailed analysis should be performed to see if the formulation or purification steps necessary to obtain the final end product could be exploited to extend the time of protection. In addition, numerous regulatory strategies should be considered for therapeutic products such as mAbs. Regulatory strategies can be triggered in a wide variety of areas, including dealings with suppliers, marketing and the quality control that ensures minimal batch to batch variation.

A wide variety of data about the product and the competitive environment such as IP (e.g., patents, trademarks, trade secrets); product attributes and potential benefits to patients; knowledge of product manufacturing and sales or distribution capabilities; regulatory issues; and information about competitors and their product offerings can factor into a PLM plan. Obtaining this in-depth understanding often requires a multidisciplinary team with expertise in these areas. A PLM plan that utilizes the collective knowledge of such a team can allow the company to identify, and then prioritize, the opportunities for each product or product line in order to maximize revenue. For instance, Genentech Inc., filed its first patent on monoclonal antibodies directed to the HER2 receptor on March 17, 1998.4 As of May 2005, 77 patents have issued in the United States directed to trastuzumab (Herceptin®).5

However, an essential component to every PLM plan also includes the proper application of trade secret protection. Indeed, in the pending era of biosimilars, the risks presented by disclosure of information such as product characteristics and production processes through patent application filings must be weighed against the benefit a patent would accord the product, and further against the company’s other alternatives, including trade secret protection. A trade secret can be generally defined as a formula, process or design that is not generally known or reasonably ascertainable by which a company can obtain an economic advantage over a competitor. Unlike a patent, trade secret protection is not limited by a set period. Some trade secrets, such as the formula to Coke®, have been protected IP for over a century.

Trade secret protection should have particular advantages with regard to manufacturing and purification processes for mAbs. It is not uncommon that special know-how is required to arrive at a stable, pure formulation. If this process cannot be easily reverse engineered, then a biosimilar applicant may not be able recreate the process. Indeed, the European Medicines Agency guidelines that were recently published highlight many factors that the innovator and biosimilar applicant would need to consider in either developing a PLM plan, in the case of the innovator, or a biosimilar approval package by the biosimilar applicant.6 Thus, understanding trade secrets, and when and how to rely upon such protection, is an equally vital component to any PLM plan.

Build the Right Team

Successful PLM plans require the involvement of the right stakeholders and decision-makers. The exact composition of the team is necessarily influenced by the unique composition of both internal and external resources the company has available to it, but will generally includes experts in IP, discovery, preclinical and clinical research, regulatory affairs, marketing, manufacturing, finance and corporate strategic planning.

The team must define the strategic goals of the PLM plan, and outline how these will be achieved by setting up deliverables and timelines from the various functional groups within the corporation. Strategic opportunities to improve the product life cycle should be identified and prioritized by the team through creative thinking about the company’s strategic plan, capabilities, and short- and long-term goals. The team should also develop a comprehensive long-term strategic plan for the product, but that plan should be constantly reassessed as information is learned about the product, and changes to any factor incorporated in the plan are discovered.
For example, information from regulatory affairs was a major factor in extending protection for Accutane® (isotretinoin). When Accutane® was approved for severe acne in 1982, no specific age group was detailed in the labeling, but, in 2001, Accutane® became the first drug with a dermatologic indication to be granted pediatric exclusivity. The pediatric exclusivity extended patent protection by six months, which translated into millions of dollars in revenue for Hoffmann-La Roche.

The term of regulatory exclusivity currently being negotiated for biosimilars is an example of a factor that could have effects in the future. The length of term obviously has the potential to greatly impact a company’s PLM plan. However, as each plan is unique, the impact of the term of exclusivity on any given product will need to be evaluated and managed by the PML team.

**Use of Market and Competitive Intelligence**

PLM plans are also implemented to ensure that the company has freedom to manufacture and sell the product. As explained in Part 1 of this series, patents only provide a right to exclude. Having a patent provides no guarantee that a company can manufacture and sell the product covered by that patent. Thus, it is critically important to identify potential dominant patent rights during the development of a product. Knowing of the existence of such patents early in the product cycle provides a company with the ability to navigate around the patent, either through a product design change or by licensing the patent. Given that therapeutic mAbs are regulated products, a product change once the approval process is underway is usually not an option. Similarly, license terms may be far more reasonable early in the development process compared to when a product is on the cusp of regulatory approval.

Therefore, a critical piece of any successful PLM plan involves obtaining market and competitive intelligence. The company must understand the market and constantly assess its competitors. This process typically involves traditional market research and analysis of what consumer wants and how the corporation might fill that need. Such traditional market research and analysis can also uncover what competitors are doing in the same space, and provide valuable insight into anticipated changes in the marketplace over the lifespan of the strategic plan.

However, a complete picture of the marketing and competitive situation for a given product or product line also involves surveying and mapping the IP landscape. This assessment can identify opportunities for product innovation that could result in new IP protection, thereby extending the life cycle of the product by obtaining and leveraging the exclusivity that IP provides. For example, using appropriate competitive intelligence, companies can proactively mine existing IP to obtain patent protection over candidates that may be in development by competitors. Thus, rather than being on the defensive, a company could offensively use IP to keep the competition from entering desired market space.

**Evolution of Life Cycle Management Plans**

Properly done, product life cycle management is recursive, dynamic and constantly evolving. The information that constituted the basis for the plan is constantly in flux. As a consequence, plans must be constantly reassessed and adjusted as required over time to take into account changes that may occur in the competitive and legal environment. Competitors invariably will seek to enter space defined by marketed products, e.g., by seeking to market biosimilar mAb products or develop competing products. In addition, more information is gleaned about a product every day that it is studied, marketed and used by patients. For example, physicians may develop treatment regimens for marketed products that were not studied in the clinical development program. Collecting and using that information is critical to the continued success of a product life cycle plan.

The legal framework that formed the underpinnings of a PLM plan can also change. The most significant recent change was the decision by the United States Supreme Court in *KSR v. Teleflex*. It is well-recognized that the Supreme Court’s decision in *KSR* substantially lowered the threshold for finding patents obvious in the US, and so this decision significantly impacts life cycle management strategies.

The Supreme Court’s *KSR* decision emphasized the use of common sense, ordinary creativity and ordinary skill to determine obviousness. In the context of PLM, there are usually a finite number of identified, predictable solutions that will improve a product, and have the potential to extend its life cycle. This decision therefore necessarily materially affects many strategic life cycle plans by reducing the number of solutions that might constitute inventions. If a company seeks long term success, then such changes to the law must be taken into account, and new strategies to maintain the necessary exclusivities to bar competition from its market space must be devised.

An illustration of how *KSR* has affected the patent landscape is provided by the litigation over Pepcid Complete. During the course of the development of that product, Ortho-McNeill’s scientists observed that the active agent in Pepcid had a bitter taste. They sought to mask the bitter taste of the product with an enteric coat, but apparently used a pre-existing formulation rather than a novel coating. The company subsequently patented the combination of active agent and coating. The court later found that such a combination was obvious, despite arguments by Ortho-McNeill that the product actually had unexpected properties relating to degradation of the product.

The role of a good product life cycle management team is to ask strategic, long-term questions about how decisions might potentially impact the life cycle of a product. It is thus interesting to speculate as to whether such a team might have directed the Ortho-McNeill scientists to develop a novel solution to mask the taste of the product. In that case, the litigation results could have been quite different.

Of course, the composition of a PLM team should change over time. At the outset of a PLM plan, for example when the product is still in the preclinical phase, the composition of the team would be very different than the composition of the team during the clinical development or
post-approval period. It is also commonplace that the size of the team changes with the changing requirements of a PLM plan. Thus, for example at the earliest stages of the PLM plan, the team could consist of only one person, typically the IP lawyer for the company. However, during later phases of the product, such as clinical testing, the team size grows to integrate the clinical findings into the PLM plan.

Too much is at stake for a company to squander product market exclusivity through poor planning. This is especially true near the end of the life cycle because companies are generally reaping the highest historical margins on products at that time. At any stage of product life cycles, companies should have management teams in place and plan for competition.

Note

The views expressed herein are the views of the authors and should not be attributed to Sterne, Kessler, Goldstein & Fox, P.L.L.C. or any of its current, former or future clients.

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