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Protecting innovation in biotechnology startups

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A solid understanding of the myriad IP issues faced by biotech startups is essential to the long-term viability of these companies.

Because most biotechnology startups lack products and derive their value from innovative technology instead, properly protecting their technology via patents and establishing their freedom to develop and commercialize that technology without infringing competitor patents is of paramount importance. Indeed, a strong patent position is a crucial ingredient for successfully raising venture capital and leveraging alliances with other companies. Here, we provide an overview of some of the intellectual property (IP) issues facing new companies, together with a few recommendations.

Why strong IP is important

Committing the resources necessary to build a strong patent portfolio is important to the viability of virtually every biotechnology company. Very few biotechnology startups actually have products to sell; their primary assets are usually proprietary technologies. The value of the company then is often tied to the ability to safeguard proprietary technologies with strong patent protection. For example, before investing in a new company, venture capitalists often hire patent counsel to perform a due diligence analysis, which involves, among other things, studying the company's pending patent applications and issued patents to determine whether core technology has been properly protected. In our experience, significant investments often turn on a report from counsel that a company has a strong (or weak) patent position.

A strong patent portfolio can also create business opportunities in other ways, through licensing and as a tool to leverage alliances with other companies. For example, assume that a company is formed around the discovery that a DNA vector expressing 'Antigen A' raises neutralizing antibodies against 'Pathogen X' in an animal model. As a result, the company's primary research focus is on exploiting this discovery to develop a DNA vaccine against Pathogen X. At this stage, company management must decide whether to view the IP arising out of this technology as a mere commodity or as an integral component of business strategy. If viewed as a commodity, the company may, for example, decide to save money up front by negotiating with their patent attorney a cap on the cost of preparing patent applications. Unfortunately, this may result in a narrow or poorly drafted patent document that is relatively easy for competitors to design around (see Box 1). On the other hand, certain companies have successfully raised significant venture capital by quickly procuring a large number of very narrowly drafted patents that, in reality, have only a limited chance of ever dominating a competitor.

When viewed as an integral component of the company's overall development strategy, patents can also create significant business opportunities. Using the hypothetical example above, assume that the company's scientists can reasonably envision, but have not yet confirmed experimentally, that the method would work equally well with other antigens and pathogens. The patent attorney then duly recommends that management invest the resources necessary to fully describe these other prophetic embodiments (see Box 1) in the patent document. Assuming that an adequate written description has been included, it is indeed possible that patent protection could be obtained for a reasonable number of variations in the company's core technology.

Since the company's own commercialization interests are limited to Antigen A and Pathogen X, broad patent protection may make it possible to offer field-of-use licenses to others interested in developing DNA vaccines with

other antigens and/or pathogens, while the company maintains exclusive rights in its primary field of interest. Alternatively, if the commercialization interests of the company and a competitor overlap, broader patent protection could more effectively force alliances to share research and development costs. Finally, as others will invariably make improvements on the company's core technology, having broader IP protection increases the likelihood of cross-licensing opportunities with respect to improvements.

In many countries, a last issue to bear in mind is that an initial patent application often forms the basis for an entire series of continuing applications (see Box 1). Thus, even if the company first seeks only narrow protection to expedite issuance of a patent (narrow patents tend to be easier and more rapid to obtain than broad ones), broader protection can be pursued later in continuing applications, provided that the necessary resources are initially committed to fully describe the later claimed prophetic embodiments (see Box 1) when the original patent document is drafted. Continuing applications may also be useful for claiming inventions not originally covered by the claims of the initial patent—an important benefit as disclosure of an invention in the text of an initial patent (omitted from the claims) dedicates the invention to the public.

Commercial breathing room

Assume that your company is prudent and files well-drafted patent applications that will eventually issue as patents with claims that properly protect the technology. Now that the company has patents, it may assume that it can commercialize without worrying about infringing the patents of others. This assumption, which is sometimes made by new companies, is wrong.

The patent grant is the right to exclude others from practicing a claimed invention. Importantly, a patent does not confer the right to commercialize. To use another hypothetical example, consider the scenario of multiple patent domination. In this scenario, 'Inventor A' engineers a specific fluorescent detection label for use in enzyme-linked immunosorbent assay (ELISA) arrays and obtains a patent. Inventor A wants to sell his fluorescent-labeled monoclonal antibody targeted against human papilloma virus. But 'Inventor B' owns a patent that covers fluorescent ELISA labels generally, 'Inventor C' owns a patent covering ELISAs and 'Inventor D' owns a patent to monoclonal antibodies against human papilloma virus. It is clear from this example that Inventor A may obtain his/her own patent (provided it meets the standards of patentability including being novel and nonobvious), but nonetheless cannot commercialize without infringing the patents of others unless he/she obtains permission (that is, licenses) from Inventors B, C and D.

With rare exceptions (*e.g.*, under certain circumstances, the federal government can force patentees to license patents arising out of inventions made with government funds), there is no compulsory licensing in the United States. Thus, a patentee may exercise his/her right to exclude and choose not to license a patented invention to competitors. Moreover, as the above example illustrates, even if patentees are willing to grant licenses, multiple licenses may be required, leading to potentially burdensome 'stacking royalties' (see Box 1). To some extent, creative licensing arrangements, which include a total royalty cap beyond which the licensee does not have to pay, can be used to alleviate this problem. But it remains important for a company to have freedom-to-operate studies (also called collection searches) performed at an early stage to guide commercialization strategies and research plans. Otherwise, the company runs the risk of investing millions to develop technology along certain lines, only to learn later that it is blocked from commercializing by dominating patents owned by others.

A freedom-to-operate study involves searching patent databases to identify issued patents and published patent applications that could potentially pose an obstacle to current and future commercialization efforts. For example, assume Inventor A finds that Inventors B and C are willing to license their patents under reasonable terms. However, Inventor D refuses to license because he/she is already selling monoclonal antibodies against human papilloma virus and would lose market share. Had Inventor A known about these patents earlier, he/she may have been able to avoid wasting valuable resources by refocusing the company's efforts on developing a different monoclonal antibody that was not the subject of patent protection. Thus, freedom-to-operate studies provide a road map for companies attempting to determine which patents can be licensed and which must be invented around.

Most patents screened during a freedom-to-operate study will be neither relevant nor require further analysis. However, a few may be found that do require further study. The terms appearing in patent claims must be interpreted in light of the text (referred to as the specification) as well as the prosecution history (the documented negotiation that occurred between the patent applicant and the examiner that led to issuance of the patent). On the basis of this review, a determination may be made that the claims in a competitor's patent cannot be interpreted in a way that dominates your company's activities and thus there is no chance of infringement. Alternatively, the claims may encompass your company's activities, but may have been drafted so broadly that they capture subject matter that is already in the public domain and thus are invalid. In such circumstances, your company's patent attorney would probably recommend preparing a formal non-infringement and/or invalidity opinion, which, if deemed well reasoned by a court of law, would provide the company protection against a charge of willful infringement (see Box 1) if sued by the patentee (indeed, established biotechnology companies often seek formal noninfringement/invalidity opinions from outside counsel as

insurance policies against potential allegations of willful infringement by patentees). If willful infringement is found, the patentee can be awarded enhanced damages, up to three times the amount of actual damages found at trial.

The clinical research exemption

In the United States, the clinical research exemption from patent infringement[1] permits experimentation with certain patented inventions by exempting from infringement activities that are reasonably related to seeking regulatory approval from a federal agency, such as the US Food and Drug Administration (FDA; Rockville, MD). The intent of the exemption is to facilitate competitor development of patented products that can enter the market immediately upon expiration of a patent. However, the exemption only applies during the clinical trial process (that is, only until a product is approved). Thus, companies in clinical trials ignore the existence of third-party patents at their own peril.

We recommend having freedom-to-operate studies performed early on in the research process and updated periodically to determine if additional patents have issued during the interim. Of course, patents set to expire before the expected FDA approval date of a new product are not a concern. However, it may make sense during the clinical trials process to start negotiations with owners of patents that do not expire until beyond the projected FDA approval date to avoid being 'held hostage' by onerous licensing terms later.

The extent to which the clinical research exemption reaches back into pre-clinical research activities is presently an unsettled legal issue, and is currently before the US Court of Appeals for the Federal Circuit in *Integra LifeSciences I, Ltd. vs. Merck KgAA*[2] (see Box 2).

Enforcement

In the absence of a well-funded, litigious industrial partner, new companies typically avoid patent litigation (a rule of thumb is that patent litigation costs at least $1,000,000 per patent per year). Most potential defendants are also litigation-adverse and therefore entertain reasonable licensing inquiries from patentees rather than face the possibility of being held liable for willful infringement. However, there are situations where new companies find that others are infringing their patents with impunity.

We recommend that new companies seeking to enforce their patents keep the following general considerations in mind. First, potential licensees should be identified and categorized. For example, competitors who already have a product (*e.g.*, a service provider or reagent manufacturer) are attractive licensing targets as are competitors undergoing a round of financing (companies undergoing a round of financing may be motivated to take a license to avoid disclosing a threatened or pending litigation to potential investors). Less attractive are those in the initial stages of clinical trials as their activities likely qualify for the exemption from patent infringement. Even so, the possibility that commercialization rights might be blocked upon receiving FDA approval can motivate such competitors to negotiate licenses while still in early clinical trial stages.

Second, cease-and-desist letters (see Box 1) should not be sent to potential licensees, unless the patent holder is prepared to litigate. This is because cease-and-desist letters are generally deemed sufficient by courts to confer to the recipient standing to sue for a declaratory judgment that the patent at issue is invalid and/or not infringed. Thus, rather than cease-and-desist letters, most patentees initially send patent-notice letters or invitations-to-license, which are carefully worded to avoid elevating the recipient to the status of plaintiff. Although not as strongly worded, such letters must nonetheless be taken very seriously by the recipient as they document the date the recipient has actual notice of the patent. If the recipient refuses to take a license and continues infringing, litigation may lead to a court ruling willful infringement.

Finally, the company should be aware of the strength and scope of its own patents in the event that litigation is later necessary. It is, of course, preferable to assert strong patents with claims that literally cover a competitor's activities.

Last thoughts

In sum, building a strong patent position to facilitate attracting venture capital and leveraging alliances with other companies can be a daunting task for startup biotech companies with limited resources. Given that proprietary technology is often their only asset, it is important that company executives gain a clear appreciation of the IP issues facing their company and implement a sound strategic plan.

Box 1: Glossary

Cease and desist letter. A letter sent by a patentee to a competitor demanding that the competitor stop all infringing activities.

Claims. A series of tersely worded statements at the end of the patent document that precisely defines the scope of exclusive rights attached to the patent grant.

Continuing application. A patent application that claims benefit of the filing date of an earlier filed patent application.

Design around. The practice of purposefully designing competing products to avoid patent claims covering patented product.

Embodiment. A 'nuts and bolts' detailed description of an example of the invention. A 'preferred embodiment' is the inventor's best-guess description of the product at the time the patent application is written.

Prosecution history. The documented negotiation that occurred between the patent applicant and the patent office examiner that led to issuance of the patent.

Stacking royalties. Royalties arising from multiple patents each dominating a company's product development effort; for example, producing a monoclonal antibody may require licenses to different patents covering the antigen, the vector, the purification method, etc.

Specification. A patent specification provides a clear and complete disclosure of the invention and a way of performing it, comprising a description, the claims, a summary and illustrations.

Willful infringement. Knowingly infringing a patent without a good-faith belief that the patent is either invalid and/or not infringed.

Box 2: Discovery tool patents under threat

In *Integra LifeSciences I, Ltd. vs. Merck KgAA*[2], Merck has alleged that certain drug-discovery experiments are exempt from infringement under the clinical research exemption. Integra, however, contends that Merck's interpretation would expand the scope of the exemption to such an extent that any and all research in the chain of events that could ultimately lead to development of a drug requiring FDA approval would be exempted from infringement. There is concern in the biotechnology industry that such a broad reading of the exemption could render patents covering drug discovery tools essentially useless, a development that could prove harmful to the numerous small companies having a drug discovery platform as their core technology. A decision on this issue is expected from the Federal Circuit in the near future.

EKS and TJS

References

- 35 USC 271(e)(1).
- *Integra LifeSciences I, Ltd. vs. Merck KgAA*, Nos. 02-1052 and 02-1065 (Fed. Cir. Nov. 21, 2001).