

Biotechnology: Hands-on Experiences

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Insights into the practical aspects of developing biotechnology licensing

To start with the basics, what is biotechnology? Biotechnology comprises all activities that involve biological systems or processing in the context of industrial production.

Thus, the term biotechnology can include anything from recombinant DNA-based pharmaceuticals, to plants with insect-killing proteins, to more traditional bacterial fermentation processes. Thousands stand among all of these in the presence or use of living and reproducing biological organisms somewhere along the process.

This is what makes biotechnology patenting and licensing so challenging. Naturally, the investment of living organisms and the rapid advances in science that are allowing us to manipulate and modify these organisms in previously undreamed-of ways only served to keep all of us licensors and licensees even more on our toes. Now, to get to some specific examples of how these factors can affect a license agreement:

Let's start with how we can define a licensed product in an agreement. Standard technologies may define a licensed product as "any product the manufacturer, use or sale of which would, but for the licenses granted herein, infringe a claim of U.S. Letters Patent 4, _____ and any foreign counterparts thereof, etc."

Here, we come across one of the first differences. In biotechnology, few of the relevant patents are issued at the time when it is desirable to lock up a license in an interesting regard. And if the patent is granted, the scope of claims

that the patent office is going to allow is extremely difficult to predict. The Patent Office began by allowing fairly broad claims in the "early" biotechnology applications filed in the late 1970s. The practice has then swung the other way to where it seemed the Patent Office was only allowing extremely narrow claims to one particular entry defined by a sample of the reagent that the inventor was required to put on deposit in a central distribution facility. Now it seems that the Patent Office may be creating a middle ground in the scope of claims they are willing to grant, but it is still very hard to tell what the range will hold and what will be included in your license if you define licensed product in such a way.

• Time Lag •

Another problem that I'm sure Patent Office-examiners will have a hard time addressing is remembering what the state of ordinary skill in the art was at the time of filing, as they finally get around to reviewing applications filed years earlier. The science is advancing so rapidly that it is mind boggling to realize what molecular biologists didn't know how to do just three years ago. As the Patent Office shifts up the biotechnology unit, some of these concerns may fade away but in the meantime this is a very real problem for those of us still pursuing cases that were filed three or more years ago.

Since I have hopefully now convinced you that having a licensed product definition on patent claims may be difficult in this industry, let's look at what might happen if you define it more on the nature of the reagent you are trying to obtain. Say you define licensed product as

"any product that utilizes a monoclonal antibody produced by the hybridoma designated as X." If molecular biologists weren't now as skilled as they are, this definition may be adequate but, depending on whether you are the licensor or the licensee, it may be too limited.

The licensor's situation may be able to make a better product candidate by pulling out the genes and making a more functional version of the antibody. Most antibodies are of human origin and are made by immunizing a mouse with a substance that you want it to raise anti bodies against, such as a tumor cell. When these mouse-derived antibodies are injected into man, they can trigger an allergic reaction so molecular biologists have learned how to make half humans, half mouse "chimeric" antibodies that may be safer to use. Now, the licensee may say that his new chimeric antibody falls outside the definition of licensed product, which, as I had stated, was simply any product using an antibody produced by hybridoma X and thus, does not owe the licensor a royalty. Obviously, this is not going to make you a great favorite of that licensor, so if you need to continue a relationship with the inventor you may not want to try this. Also, the licensor may try to return the favor by saying that, if it's not a licensed product it doesn't fall under your exclusive patent anymore, so he can in turn sell chimeric rights to someone else.

In my experience, it has never

*Dexter, Glynnos Technology, Miami, CENTOCOR, Malvern, Pennsylvania, paper presented at CLEO II, S.A. Grand Hyatt, Boston Regional Meeting, Tucson, Arizona, February 1988.

come to this type of a situation but, by playing devil's advocate, I hope to point out the full scope of the potential hazards that may be encountered here in those definitions. As biotechnology licenses or licenses, you should try to ensure that you have considered all possible outcomes over those early negotiations with the negotiators, and make sure that the scope of what you want to get of [pat] is carefully spelled out in the agreement. And, you may want to have a multiple-tier royalty structure to cover whether patents are pending, granted or abandoned and whether you are exactly those requests or one that either one of you invested a substantial amount in developing.

This reminds me of one final note on licensed product definitions in biotechnology agreements that some of you may not realize and that is that it is not uncommon to license totally unpatented subjects in this industry. Many biological entities are unique enough, like snowflakes, so that even if a competitor may be able to develop a similar subject, it won't have identical properties to yours. So, if you find one that is outstandingly good, it may be worth paying to license it exclusively even if there is no patent protection. This does, however, mean that a certain amount of effort must go into ensuring that others do not receive samples of the biological product of the subject from any source. This can be somewhat difficult to ensure in biotechnology because: 1) the source of many of the best subjects is from academia, and 2) the Patent Office often requires deposits in conjunction with biotechnology patents.

■Academic Involvement■

I will first address the issues related to academic involvement, since that leads to other considerations as to why biotechnology licensing may be different. Unlike a few industries that may have a large amount of licensing activity between companies, I would estimate that a majority of all licensing arrangements in the biotech industry are between a university and a company. And it is crucial to remember

that a university has a very different agenda than a for-profit company and a very different structure. Most universities are licensing as a way to raise extra money and to help bring advances to the public benefit. They want to do this as long as it does not interfere with the open pursuit of science. And, as long as it does not put the university at any kind of risk (from product liability suit, for example), I would expect a university to walk away from a fairly substantial monetary deal before it would share the risk burden of commercializing a new technology. Also, no matter how much you put on the table, you will not be able to persuade a university to interfere with a scientist's right to collaborate and interact with other scientists. This is as it should be and can be dealt with through reasonable compromises on the part of both sides.

My company currently has more than 25 university licensing arrangements in place and has obviously found them very valuable as a source of new biotechnology products. We have had to realize that there is a certain amount of risk in giving up the control that a company would otherwise have over internal research but the number and quality of the scientists we can work with on the outside is far greater than those we could attempt to support in house. And, even if we could get them there, they most likely wouldn't be as productive in an industrial environment.

So, how do you deal with university scientists? You educate them on why you need to see publications before they send them out, or why you need to review data before they give a presentation. It's not just to get in their way. Explain about the absolute novelty requirement in foreign countries. In spite of rumors you may have heard to the contrary, Ph.D.'s are pretty smart people, and they will probably understand the rudiments of patent law if anyone takes the time to explain it to them. If they know anything about patents it is probably limited to the fact that you have a job to file in the U.S. from the time of publication. This is just enough to get them in trouble with those of us

interested in global markets.

Also, if you need to limit their distribution of materials in collaboration, find a compromise. We let our collaborators supply others with antibody but not with the replicating hybridomas, which are the factory behind the whole thing. As for patents, offer to help decide what is patentable. Industrial lawyers often have a better idea of what is commercially valuable or feasible than a university lawyer.

The main thing to remember is that universities and scientists are generally not in this just for the money, so they will want clauses clearly addressing all of the above issues as well as more standard clauses concerning royalties, payments, etc. And, as I said before, don't expect them to budge on the indemnification clause. They are not going to put their researchers at risk.

As for the industrial lawyer, the more time you can take to explain exactly what it is going to take to get the licensed product to market, the more reasonable will be your agreement. Even experienced university lawyers may not understand that it will take \$100 million, many years, and a lot of regulatory uncertainty and unavoidable delays before a pharmaceutical product will come to market, which is something that all of you active in pharmaceutical licensing know and understand all too well. For biotechnology products, the timing is probably even harder to predict. The business of Biogen is still trying to define what is necessary to support the approval of a biopharmaceutical. As we've all heard many times, the more each side is educated in the needs of the other, the better chance there will be of negotiating a win-win situation.

Now, regarding distribution of subjects and deposits, it is obvious an exclusive license of a biological entity is not going to mean a biological factory capable of producing that entity is to be provided to others who may commercialize it. One of the problems in biotechnology is that others, the only way to ensure an ability to provide a viable sample of a subject is to send along an asexually reproducing cell that

will produce your reagent and its business. If you have licensed an unpatented reagent or the patent has not yet issued, you will want to try to keep some control over this.

If an academic inventor is involved, he or she must understand the risks to your license of making your reagent freely available. Educating the inventor on this is a job of the university licensing office and the industry licensee. In addition to a company possibly losing market share to a competitor who gets a free sample of the reagent, the licensee will lose royalties, since the new recipient will not be under any obligation to pay royalties to the licensor. Obviously, if the inventor receives a share of the royalty, it is easier for him to understand the impact of such a disclosure.

If the reagent is patented, there is still cause for concern. Universities often do not file foreign patents. Even if the domestic com-

position is protected, there is other countries that he set up in business if they can get a sample of the reagent from the inventor.

Unfortunately, there is an even easier way for a foreign company to get the reagent. That is through the Central Patent Depository, which makes deposited reagents freely available to anyone in the world once a U.S. patent issues. As I said before, many university inventions are only filed on in the U.S., thus making this a relatively common problem. The World Intellectual Property Organization has made some recommendations to change this situation, but unfortunately, nothing yet has happened.

Since this deposit issue is a fairly complicated topic, I will not dwell on it here. I want to alert you that, in biotechnology, there is a great need to keep track of who gets what from your inventor or the depository and to keep an eye on what

they're doing with it. This means determining before you sign a license agreement who has already received samples, whether patents are filed in the U.S. and abroad and whether deposits were made in connection with such filings. You obviously wouldn't want to pay a fee for a nonexclusive license and have a licensee or European company get the same reagent without cost.

A final issue I will mention relates a little bit back to the fact that the majority of the patents in biotechnology products are, as yet, unissued. Since they are for the most part unissued, they are also unlitigated. This means that there is very little case law to let us predict what claims will be defensible even once the patents issue. All claims relating to litigation obligations, costs of suits, etc. need to be drafted with this in mind. Also, interferences may become quite common.