The Secret of Success

The growth of biosimilars is leading many biopharma firms to seek second-generation patents, particularly for antibody production – prompting legal moves to help protect trade secrets and give more freedom to operate

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While the adage 'the product is the process' may overly stress the influence of production processes on a biologic's attributes, there is clearly a strong relationship between the manufacturing process for making an antibody and the antibody's final characteristics. This is because, as opposed to small molecules, there are many steps to produce an antibody – from cell line development, through cell culture and purification, to final formulation and finishing.

Traditional small molecule pharmaceutical companies have historically exploited all areas of development for subject matter that goes beyond the usual coverage provided by patents for a composition and its methods of use. These so-called 'second-generation' patents have been directed to subject matter such as combination therapies, dosing regimens and pharmacokinetic/pharmacodynamic data.

Although biopharma firms have in the past been slow to identify equivalent opportunities, they are now identifying many prospects to obtain their own second-generation patents – not the least of which involve bioproduction processes.

Patent Hurdles

The number of patents covering antibody production processes has been steadily increasing with the realisation that upstream/downstream processing events provide a potentially abundant source of second-generation patent protection. However, the major obstacle to obtaining patent protection for bioproduction processes is to show that the process is novel, and not obvious in view of the state of the prior art.

Some groups are prolific patent filers, claiming a wide variety of processes – from methods of culturing cells with a particular chemically-defined media, to methods for regenerating a chromatography matrix. Others choose to keep their manufacturing products and processes secret.

The difficulty in obtaining these second-generation patents generally results from disclosure of processes for producing the original antibody composition in the 'first-generation' patents. For example, the disclosure of the original antibody may contain background information about how the genetic construct was made, the type of host cell used, the cell culture conditions, and the chromatographic steps to purify the product, as well as generic disclosure relating to the type of formulation and finishing of the antibody.

Production processes typically change during scale-up from the initial studies to manufacture of the clinical material. As such, novelty is less likely to be an issue for the later-filed patents, but demonstrating that the new processes are not obvious over the first disclosures or existing practices can be a difficult hurdle.

Prior User Defence

Until the recent US patent reforms introduced by the Leahy-Smith America Invents Act (AIA) became law in 2011, many groups which kept their processes secret ran the risk of being sued for patent infringement, even if they were using a patented process prior to the filing date of the third-party's patent. However, the AIA ushered in a defence for patent infringement for these companies – the prior user rights defence – together with a new avenue to challenge bioproduction patents through *inter partes* review (IPR).

Prior user defence covers "subject matter consisting of a process, or consisting of a machine, manufacture, or composition of matter used in a manufacturing or other commercial process". It is important to note that the prior user defence is simply that: a defence. In other words, it is a safe harbour that protects a company wishing to use the invention or process in private. It is not a means for invalidating or challenging a patent.

The hope behind the defence was that it would help protect trade secret owners and other alleged infringers, by providing a defence to a claim of patent infringement. Trade secrets are very important in the arena of bioproduction because many companies keep their production processes secret, or at least do not make them readily known.

Trade Secrets

The topic of trade secrets and whether or not to file patents is becoming increasingly popular in the antibody field as biosimilars look set to become a reality in the US. By 2020, the 12 most commercially successful biologics will be coming off patent protection; these represent about $67 billion in US sales.

With respect to biosimilars, the reason for increased interest in keeping information secret is the sense that many originator companies will bypass filing for patent protection – and the disclosure of their process of manufacture to the public that comes with a patent filing – in favour of keeping some of their critical processes secret. However, since the grant of a patent provides an enforceable right to exclude others from copying your process, the identification of a process through which many competitors must pass can also serve as the basis for generating a vast licensing revenue stream for the company. The most famous examples of a significant revenue-generating technology are the Genentech Cabilly patents – directed at methods of producing recombinant antibodies.

Business Flexibility

The prior user defence offers a number of advantages for companies developing antibodies. In particular, it provides a company with greater flexibility to determine how best to protect its technology, because the defence can be applied to any subject matter. As a result, a company is still able to patent an invention and place the world on notice that it has the rights to exclude others from using its technology. Alternatively, a company can choose to keep its invention or process secret, and now has the added prior user defence as a benefit.

Unfortunately, there is never a one-size-fits-all approach that will suffice in every case, or even for the same technology. Therefore, the benefits and risks for patenting or maintaining technologies' secrets will need to be weighed on a project-by-project basis.

In addition, some argue that the prior user defence provides flexibility for companies with respect to cost. The argument follows that the cost for a patent filing is much greater than that associated with keeping a technology secret. However, the cost for systems that must be in place to ensure secrecy in today's digital world cannot be minimised.

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Thus, meticulous documentation and preservation showing prior commercial use through laboratory notebooks and chemistry, manufacturing and control documents is of paramount importance.

One question that remains is what the effect will be on the ability to raise the prior user defence, should even minor changes be made to, for example, the chemically-defined cell culture medium in the case above, or the method to regenerate the chromatography matrix. Will even a minor change nullify the ability to raise the defence, or will minor variations be allowed as long as they fall within the scope of what is considered to be routine optimisation? While there are no easy answers, it is clear that to best position themselves to take advantage of all available avenues, antibody companies will need to preserve dated and witnessed documents that establish the earliest dates of use and details of all relevant processes.

***Inter Partes* Review**

AIA also ushered in an abbreviated pathway to challenge the validity of patents outside of the US court system. IPR was created to reduce the volume of court-based litigation using a streamlined process to challenge patent validity on the basis of prior art. The rapid adoption of IPR suggests the new procedure may achieve this goal. As of 16 January 2014, some 827 petitions for IPR had been filed, including around 50 in the bio/pharma sector. Only two final decisions have been issued so far but, in both cases, all reviewed claims were found to be obvious.

IPRs challenge the validity of a patent only on the basis of anticipation (novelty) or obviousness (inventive step) over patents and printed publications. There is no time limit to when a petition for IPR may be filed. A review consists of two stages: a petition to institute a trial in front of the newly created US Patent Trial and Appeal Board (PTAB), and the trial itself. The petition must show there is reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged. So far, 80-90% of the petitions met this standard for at least one challenged claim.

Time and Cost Benefits

The two major benefits of IPR are the time to a decision and reduced cost. A decision on instituting a trial is promised within six months of the filing of a petition for IPR; and a final decision on validity is promised within 12 months from initiating the trial. The PTAB has so far met these deadlines.

This timeframe is generally less than half the amount of time seen in court-based litigation. Furthermore, the PTAB has been establishing procedural rules that facilitate speedy conclusion of a trial – for example, by limiting the number of claims reviewed in a single IPR, the possibility

of discovery and the scope of claim amendments. Due to the limited discovery and rapid conclusion of a trial, the cost of IPRs is significantly reduced compared to court-based litigation.

IPR also provides many advantages over court-based litigation for challenging patent validity, including:

- It can be used to attack a patent before the patent owner asserts it
- The challenged patent is not presumed valid
- Invalidity is adjudicated using a lower evidentiary standard (preponderance of evidence) than that in court-based litigation (clear and convincing evidence)
- The PTAB is composed of patent law specialists with strong technological backgrounds who are receptive to complex technical arguments

Thus, IPR represents a unique avenue to challenge blocking patents outside the US court system and promises prompt, cost-effective resolution.

Bioproduction processes represent fertile ground for exploiting new patentable subject matter than can be used to extend the patent life of an antibody. However, these patents are not bulletproof, as competitors may be able to avoid them if they can establish they were using the identical process or can challenge their validity in an abbreviated forum.

Note

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