of candidate genes,' comments Wood, 'and were rather surprised to find a kinase, a mitochondrially located one at that.'

Adding to the jigsaw

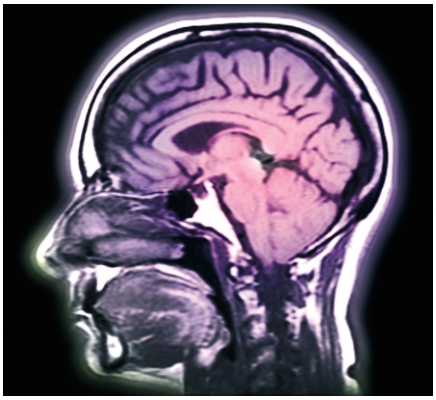
Other researchers, including Serge Przedborski, a professor at Columbia University's Center for Neurobiology and Behavior in New York (http://cumc.columbia.edu/dept/neurobeh), are excited by this discovery. 'We have done little but think about the implications of this result since it came out,' says Przedborski, who is particularly intrigued by results that indicate that loss of PINK1 activity might make neurons susceptible to cellular stress.

PD, explains Przedborski, 'seems to result from an interaction between a person's genetic makeup and some environmental toxin and these new results fit in with that idea.' In addition, mitochondrial defects have been implicated in PD since the 1980s, but although there are biochemical defects in mitochondrial complex 1 in PD, no mutations in the mitochondrially encoded genes for this complex have been found. 'The discovery of the *PINK1* mutation may mean that phosphorylation of complex 1 by PINK1 is essential for the mitochondria to work well under stress,' suggests Przedborski.

Wood agrees that the *PINK1* results put mitochondrial dysfunction right back on the agenda as far as understanding PD is concerned but, he cautions, 'there is a long way to go before it will be clear where PINK1 fits in the PD jigsaw. We don't even know the targets for PINK1.'

Therapeutic implications

For now, treatments for PD based on the discovery of *PINK1* mutations in hereditary PD are a distant hope. 'Until we know more about PINK1, it is difficult to envision any kind of therapeutic strategy,' says Przedborski.



Nevertheless, PINK1, like every piece in the PD jigsaw, is a potential drug target and perhaps more importantly, its identification could help researchers understand exactly how PD develops.

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Balancing US patent and FDA approval processes: strategically optimizing market exclusivity

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The patentability of products is essential in the biotechnology field, because limited market exclusivity compensates the investments of biotech companies' in R&D. The biotechnology field also uniquely faces Federal Drug Administration (FDA) approval, which includes considerable additional expense and time issues that a biotech company must address. Although balancing the patent and FDA approval processes might be complex, various strategies of patent extension, of accelerating approval processes, and of prolonging the market entry of generic drug companies can yield higher profit returns and maximize company value.

Biotechnology startups and their investors are primarily concerned with optimizing the value of the company, which can be measured by the quality and lifetime of its patents. Longer patent terms produce longer market exclusivity, which consequentially leads to increased profits and value. In the USA, patents are crucial to protect a company's ideas while FDA approval is necessary to legally market their products. Here, we address and outline strategies to extend patent terms and maximize market

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exclusivity while addressing FDA timing considerations in the USA.

Overview of patent and FDA approval periods

The average prosecution time for a US patent is 3.4 years and the average biotech patent is 4.4 years. Patents require novelty, utility, and the concept must not be obvious [1]. If the patent is granted by the United States Patent and Trademark Office (USPTO), then a 20-year monopoly is granted to the inventor in exchange for public disclosure of the invention [2].

Preclinical studies offer predictions and provide safety data for initial studies in humans. Researchers use *in vitro* studies and animals with analogous genetic structure, pharmacodynamic responses, metabolic profiles, cellular receptor interactions, and general physiology to humans. Preclinical studies vary depending on the complexity and success of initial research.

The United States Federal Drug Administration (FDA) approval usually requires 10–12 years of development and US$100–500 million in development costs [3]. The FDA approval period is split between the clinical trials and New Drug Application (NDA) approval. During the clinical trials, the applicant uses test populations to study safety, dosage, pharmacologic and metabolic effects, potential side effects, and effectiveness of the product. The NDA process then comprehensively analyzes the preclinical and clinical reports, applying a risk-benefit analysis to determine if the product will benefit the public at large [4].

Proper timing of USPTO and FDA filings to maximize market exclusivity

Large expenses accumulate throughout the research, development, and FDA approval of a particular biotech product. A longer patent term provides extended market exclusivity, which allows a company to recover its expenses and produce profits. Every day of market exclusivity is a potential profit for a pioneering company because generic drug companies capture 57.6% market share upon entering the market [2][a] Therefore, expedient and efficient USPTO and FDA approval is necessary to maximize company profits.

After the initial idea, preclinical studies should be the first step in the USPTO–FDA processes. Biotech patents regularly require experimental evidence to satisfy the utility requirement. Although researchers can concurrently conduct preclinical studies during patent approval process, basic *in vitro* and animal testing effectively support the patent claims. Regarding the FDA, preclinical studies are the rate-limiting step for later FDA clinical development because clinical trials cannot begin until there are sufficient extrapolation predictions for human testing. Therefore, preclinical studies should be performed as soon as possible to expedite the FDA and USPTO processes.

The utility requirement is a particular obstacle for patent applications. Occasionally an application's utility might not be clear enough without FDA approval. Therefore, it is good practice to emphasize practical functionality in the application, along with substantial preclinical evidence.

Nevertheless, strategically, patent approval should come before FDA trials in view of some considerations. If the innovating company begins FDA process before USPTO filing, then it runs the risk of another company patenting the invention before them. Consequently, the innovating company would have to license the biopharmaceutical, losing royalties, market exclusivity and company value; although they would have to abandon the FDA process and forfeit millions spent in R&D. Even if another company does not patent the biopharmaceutical, the innovating company must be careful not to disclose the invention, otherwise it has one year to file the patent before it becomes property of the public domain. Internationally, specifically in Europe, there is no 12-month grace period to file after disclosure. In Europe, once an invention is disclosed, it is public property and may not be patented.

Furthermore, issued patents drive FDA approval, speeding up the process [5]. Finally, filing patent applications and receiving approved patents will attract investors that will provide the necessary capital to fund the costly FDA clinical trials.

In addition to *in vitro* and animal data, safety measures and predicted dosage, the FDA requires demonstration of scientific review before FDA clinical trials can begin [6]. Due to the possibility of disclosure, scientific review should be conducted after the patent has been filed, or the company runs the risk of missing the one-year deadline for patentability.

It is advantageous to begin FDA clinical trials after patent prosecution with the USPTO and preclinical studies have commenced. However, a complex issue is to accurately time preclinical studies to end before, or at the same time as, the patent issuance. Each day that the preclinical studies extend past the issuance date, FDA approval is potentially delayed and the innovating company loses opportunity to exercise the market exclusivity.

Once the FDA has approved the biopharmaceutical for US consumers, the innovating company enjoys market exclusivity for the rest of its patent term.

[a] This statistic is based primarily on the market of low molecular weight organic generic drugs. However, given the complexity and difficulty of the reproduction of biopharmaceuticals and macromolecules, this percentage may differ significantly. Given their relatively new innovation, most complex bioproducts have not yet faced patent expiration. Although it is difficult to ascertain the ability for generic companies to reproduce more complex structures, the patent specifications will theoretically allow 'any person skilled in the art' to make the product after patent expiry. Thus the threat of generic companies may still be real.

Strategically written patents will effectively and efficiently protect against product infringement by other companies. In addition to ensuring market exclusivity for their product, the innovating company should develop strategies to retain market share following patent expiry.

Extending the patent term and market exclusivity after the patent term ends

Once the patent term ends, the innovating company loses its market exclusivity privilege as generic manufactures enter the market. There are, however, processes to extend the life of a patent term through 'patent term restoration'. Additionally, the innovating company still enjoys market exclusivity while generic manufactures undergo their required FDA approval process. Finally, there are strategies that can delay generic market entry. The methods to increase market exclusivity are crucial to maximizing overall profits.

The USPTO grants patent extensions to compensate for delays in USPTO examinations and prosecution that extend past three years. Thus, the average 1.4 years past the three year mark during prosecution may be tacked onto the 20 year patent term.

Another method of patent extension, due to the FDA approval process, is under the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. This act provides a maximum five-year extension, and is limited to a 14-year term from the time of FDA approval. The calculation of extension is complex and depends on patent prosecution and approval factors [7].

After the innovating company's patent term expires, generic companies can begin their FDA approval process on their generic drug equivalent. While the innovating company's FDA approval takes 10–12 years, the Hatch-Waxman Act allows generic companies to use the Abbreviated New Drug Approval (ANDA) process to gain approval within six months [7].

The requirements for a generic company to file an ANDA application are:

- The proposed generic drug must be the same as, or bioequivalent to, an FDA approved drug;
- The approved drug must be protected by a patent; and
- The applicant must not use a method of producing the proposed generic drug that is protected by a 'method of production' patent [8].

Because a 'production method' patent can be separate from a 'drug composition' patent, a tactful patent strategy is to file the production method patent a few years after filing the composition patent. Therefore, although the composition would be public domain, the term of the production method would still be running and would thus be protected. Put simply, a generic company has access to the product itself, but does not have rights to produce the product according to the patented method. This strategy is even more effective with biopharmaceuticals than with traditional chemical pharmaceuticals because of the complexity of macromolecules. Although there might be more than one method to synthesize a chemical compound, allowing competitors to design around the method of production patent, it is difficult to engineer around complex microbiological systems. Thus, a delayed production method patent can extend market exclusivity of a biopharmaceutical by protecting its production[b].

The 'metabolite defense' can be used to stall generic market entry. Metabolites are the metabolized derivatives of the original structure, formed after being introduced into, and processed by, the body. The strategy is to file patents for the metabolites in the years subsequent to the filing date of the main patent. Once the generic version is marketed, the innovating company holding the metabolite patent can bring a patent infringement claim against generic company because the generic company will be making products that inevitably become infringing products once digested by consumers. Although the metabolite defense has never actually prevailed in court, the litigated dispute can delay the generics' market entry for up to six months. This extended market exclusivity leads to increased profits by the innovating company[c].

Similar to raising the metabolite defense in court, an innovating company can file a 'citizen petition' with the FDA, which raises safety objections with the particular biopharmaceutical. Although the majority of petitions are rejected by the FDA or withdrawn by companies, the petition delays the FDA review staff from generic market entry for six months or more [9].

USPTO and FDA exceptions: avenues to accelerate the innovating company's market entry

One procedure to shorten the USPTO process is to make the application 'special,' in which the USPTO examiner will process the special patent application before all other categories of applications. The USPTO provides special provisions for biotech inventions that allow a biotech patent to have 'special' status. To qualify for a petition to be special, the company must be a 'small entity', which is a company with fewer than 501 employees, or a nonprofit

[b] The passage of Greater Access to Affordable Pharmaceuticals Act (GAAPA) is still pending, which would strike out the third requirement for ANDA filing and eliminate the use of the ANDA blocking strategy mentioned previously. Furthermore passage of this act would introduce a 30-day deadline to register patents with the FDA after approval, or be barred from civil actions for patent infringements.

[c] The metabolite defense can theoretically apply to both active and inactive metabolites. The metabolite defense has not actually proven valid in court, thus, using either type of metabolite will have a congruent result and purpose.

organization. The petition must also state that the patent applicant's technology will be significantly impaired if a patent examination is delayed. If the situation calls for special status, the FDA approval process can be started earlier and can result in extended market exclusivity.

The FDA can assign a biopharmaceutical as a 'well characterized' biotech product if its identity, purity, potency and quality can be determined and controlled substantially. This status allows a company to alter its manufacturing technologies as long as it can produce the same product. In the past, a company had to establish a fully developed process for the product before clinical trials could begin, and if it wanted to change its process it would have to repeat clinical trials again. However, with a 'well-characterized' biotech product, a company can immediately begin FDA clinical trials once it has the product and improve the manufacturing process at a later date [10].

Using treatment-IND and 'compassionate use' single-patient protocols, companies can market unapproved therapies that are undergoing clinical trials when no satisfactory alternatives are available. If the product is appropriate for the healthcare environment, marketing products concurrently with FDA clinical trials can significantly increase profits [11].

The 'accelerated approval' process allows products to be marketed to patients with serious or life-threatening conditions. The approval of a biopharmaceutical can be accelerated if there are adequate and well-controlled clinical trials that ascertain whether the biopharmaceutical's clinical outcome will provide a considerable therapeutic benefit over existing therapies [12].

Unique examples of how pharmagenomic inventions relate to USPTO and FDA timelines

Systems biology (SB) is currently in the initial stages of biotechnology and converging with IT software. The SB field primarily deals with programmable software for analyzing biological interactions and structures. The software processing does not directly affect the human body, therefore, SB inventions would not have to go through the FDA approval process. It would, however, have to go through the standard patent approval process.

As a concept, biosensors can be broadly defined as sensors that are capable of detecting biological activity at either the molecular or macroscopic levels. As technology advances, biosensors are being used in microarrays to monitor hybridization or can be implanted *in vivo*. FDA examination is only necessary if the biosensor is invasive or is a diagnostic. However, most diagnostics do not presently have to go through separate FDA approval. If a biosensor is used for *in vitro* research, it will most likely not have to undergo FDA approval.

Considering the potentially extensive benefits of pharmacogenomics, the FDA has already voiced its support for integrating pharmacogenomics in clinical trials for patient response and adverse events [13]. There have already been over 50 FDA submissions that incorporate pharmacogenomics associated with therapy [http://www.bio-itworld.com/archive/061202/horizons_lesko.html.]. The majority of pharamcogenomic-associated therapies involve screening for cytochrome P450 enzyme polymorphisms in clinical trials. Selection of a clinical trial participant is based on his/her cytochrome P450 genotype. The FDA anticipates that pharmacogenomic trials on NDEs in the near future. Although it has not been officially implemented yet, the FDA plans to develop a guidance for pharmacogenomics in 2004 [13].

In the near future, pharmacogenomics will efficiently speed up FDA clinical trials. Industry reports predict a reduction in the FDA approval process of about four years. Establishing an FDA bioinformatics infrastructure will potentially lead to many subtle implications, such as how the Hatch-Waxman's 14-year limit will adjust to the shorter FDA process. Nevertheless, the increased period of market exclusivity will be an incentive to develop new therapies [3].

Along with cutting approval time, discovery and development costs are predicted to decrease by US$137 million per drug [3]. This will similarly provide further incentives for drug companies to attempt to bring new therapies to the US marketplace.

Conclusion

There are multiple opportunities and strategies to increase market exclusivity for a patent's term. There are also many possible pitfalls in evaluating the USPTO and FDA timelines. Timing is crucial for the economic fate of small biotech companies developing novel therapies. A diligent and detailed patent prosecution team is necessary to balance the multiple USPTO and FDA concerns, while maximizing the opportunities to extend patent terms and market exclusivity.

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