

POLICY

Use Patents Can Be Useful: The Case of Rescued Drugs

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Contrary to conventional wisdom, use patents can have both commercial and therapeutic value.

Pharmaceutical firms regard strong patent protection as critical to drug development and thus may forego development of small molecules for which they cannot secure strong “product” or “composition-of-matter” patents (1). During the time these composition-of-matter patents remain in force, they not only give the patentee the right to exclude others from making and selling the drug for the same purpose as the patentee but also block the marketing of any new use that another party discovers.

In contrast, so-called “use” patents, which protect a selected therapeutic use for a small molecule or biologic, can often be evaded. For example, a generic drug-development firm might obtain approval for marketing of a known drug by arguing that the composition-of-matter patent has expired and that the generic version is intended only for a nonpatented use (a phenomenon sometimes called “skinny labeling”). The U.S. Food and Drug Administration (FDA) does not prohibit physicians from prescribing the generic drug (or any other drug, for that matter) off-label for other uses, including patented uses. Moreover, the high standards for proving patent infringement make it difficult to bring a legal claim that generic firms are inducing physicians and patients to infringe use patents (2). Still, despite the apparently limited commercial power of use patents, pharmaceutical firms do seek them, even on relatively small improvements. Consequently, use patents as a category are frequently viewed as covering innovation of only “secondary” therapeutic value (3).

Here, we discuss an important context, relevant to new trends in small-molecule development, in which use patents can have substantial commercial and therapeutic value.

CURRENT SKEPTICISM

In recent years, skinny labeling has played a prominent role in facilitating market entry for generics. For example, in fiscal year 2010, FDA approved 11 generic drugs with skinny labeling. Indeed, three of the five top-selling brand-name drugs that “went generic” that year did so as a consequence of skinny labeling (2). Despite this reality, firms that seek patents on uses that represent a fairly small improvement on prior uses are vulnerable to the charge of attempting to unduly extend patent life. Thus, all types of use patents get caught up in debates over patent “evergreening.”

Although some criticize use patents as evergreening, industry often points to their limitations, including in burgeoning efforts to address currently untreatable diseases through new uses for old molecules. As traditional methods of drug discovery fail to produce safe and efficacious first-in-class small molecules for addressing these diseases, the notion of finding new uses for old molecules has become quite popular (4). But when the new use involves repurposing—that is, finding a different use for a drug that has already been approved for one use—a use patent may not provide much protection from generic competition: The use-patent holder may undertake costly clinical trials in order to secure from FDA the ability to market the new application “on-label” only to have physicians prescribe cheaper generic competitors off-label for that very application.

However, both proponents and critics of the pharmaceutical industry have largely overlooked contexts in which use patents offer protection nearly identical to that of a composition-of-matter patent without raising any prospect of evergreening. One increasingly important context involves drug candidates that are known to be safe for use in human subjects but failed clinical trials because of a lack of efficacy with respect to their original indication (or indications).

Use patents on these so-called “rescued” drugs should serve as financial incentives for companies to reintroduce countless numbers of small molecules into the pool of potential drug candidates.

USE PATENTS TO THE RESCUE

For drug rescue, a use patent can offer relatively robust financial incentives. If the new use proves to be therapeutically successful, FDA will approve the molecule only for that use. Moreover, because skinny labeling by a generic competitor is possible only in the context of an FDA-approved use that is no longer under patent protection, a use patent precludes skinny labeling and protects the developer of the original patent from generic entry. In fact, a competitor that wishes to enter the market with the same molecule will have to conduct independent clinical trials—which require substantial resources—to show efficacy for an entirely different use. Moreover, those with the resources to carry out such trials will likely be deterred by the fact that they would be direct competitors with the developer of the original FDA-approved use—whose drug can be prescribed off-label for precisely that entirely different use.

In many respects, the developer of the entirely different use will be in a position similar to that of a “me-too” drug developer—that is, the developer of a molecule that has the same mechanism of action and use as the originator molecule but manages to avoid the originator’s patent. The availability of me-too competition has not prevented firms from engaging in more pioneering discovery. To the contrary, the incidence of me-too drugs appears to have declined in recent years, perhaps because of price constraints that insurance firms can impose when they are able to choose between multiple competing drugs in the same class (5).

Thus, a use patent for a rescued drug functions like a product patent (6). Indeed, even if use patents do not prove as valuable as product patents, they are likely to be sufficient to drive development of rescued drugs, which have already been derisked to some extent in early-phase clinical trials for safety. Critics of evergreening should also have no cause for complaint. Because no medical use was established for the molecule, it is logically impossible for the new, patented use to be a trivial extension of a prior use. Although this strategy for use patenting appears to have been relatively rare in the past—according to one analysis, only 12 out

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Table 1. Patent information on selected NCATS molecules.

Molecule code	Patent no.	Patent name	Priority date*	Inventors	Notes
LY50030307	7,354,951	Substituted benzopyrans as selective estrogen receptor- β agonists	5 October 2005	Bryan Hurst Norman; Timothy Ivo Richardson	
	7,442,812	Substituted benzopyrans as selective estrogen receptor- β agonists	8 April 2004	Gregory Lee Durst; Bryan Hurst Norman; Timothy Ivo Richardson	
	7,585,985	Substituted benzopyrans as selective estrogen receptor- β agonists	8 April 2004	Bryan Hurst Norman; Lance Allen Pfeifer; Timothy Ivo Richardson	Divisional of '812 patent†
	7,842,822	Substituted benzopyrans as selective estrogen receptor- β agonists	8 April 2004	Gregory Lee Durst; Bryan Hurst Norman; Timothy Ivo Richardson	Divisional of '812 patent†
AZF0530(2 projects)	8,304,417	Crystalline forms of 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline	14 December 2005	James Gair Ford <i>et al.</i>	
ZD4054	5,866,568	Heterocyclic compounds	4 June 1996	Robert Hugh Bradbury <i>et al.</i>	
	6,060,475	Substituted pyrazin-2-yl-sulphonamide-(3-pyridyl) compounds and uses thereof	4 June 1996	Robert Hugh Bradbury <i>et al.</i>	Divisional of '568 patent†
	6,258,817	Substituted pyrazin-2-yl-sulphonamide (-3-pyridyl) compounds and uses thereof	4 June 1996	Robert Hugh Bradbury <i>et al.</i>	Divisional of '568 patent†
PF-03463275	8,124,639	Bicyclic [3.1.0] heteroaryl amides as type 1 glycine transport inhibitors	6 April 2006	Stanton F. McHardy; John A. Lowe III	

*The priority date is the date from which the 20-year patent term begins. †A divisional is a patent that is a subset of, and thus has the same priority date as, a prior patent.

of 170 molecules approved by FDA between 1996 and 2004 relied solely on use patents (7)—the current interest in finding new uses for old molecules provides a prime opportunity for embracing the strategy.

As with composition-of-matter patents, use patents will have some limitations. For example, patent law may preclude patentability in cases in which public domain information suggests a use. Moreover, if the rescued molecule for which a new use is found was originally developed as a me-too drug, other drugs in the original class might be prescribed off-label for that new use.

DERISKING

The most appealing candidates for use patents are those that have failed FDA efficacy trials (phase 2 and 3) after passing the safety trial (phase 1). With only ~10% of compounds that enter phase 2 testing currently passing phase 3, many candidate molecules are added to the pool every year. For these molecules, the risk of phase 1 failure, which currently stands at ~46%, is eliminated (8). In addition, with preclinical development and early-stage clinical testing no longer necessary, out-of-pocket development costs may be reduced by as much as 50%. Moreover, when developers use drugs that have already been through preclinical trials,

phase 1 trials, and failed efficacy trials, they might be able to rely on these prior data to better tailor future research endeavors. Specifically, although the issue is ultimately an empirical one, the wealth of trial data might help to decrease future failures in phases 2 and 3, an arena in which failure rates are currently increasing (8). Last, one prime fear that developers face when they test an already marketed drug for a new use is that FDA trials for the potential new use will reveal negative side effects that either scare patients away from the original, blockbuster use or even force the company to pull the drug from the market entirely (9). Focusing on molecules that never made it to market obviously avoids this risk.

PROTECTING USE-PATENT POTENTIAL

Although use patents for rescued drugs have much potential, maintaining the ability to be granted a patent on a new use may not be easy. If any information about the new use is in the public domain, potential patent applicants may fail to meet the novelty requirement for patentability. Even speculation that has not been validated experimentally could create novelty hurdles. At the same time, successful new drug development may depend on having a large number of researchers contributing ideas

for rescue; this makes data sharing necessary—and thus increases the risk of novelty-compromising activities.

For the purpose of striking a balance between sharing information on potential new uses and maintaining the possibility of use-patent protection, NIH's NCATS (National Center for Advancing Translational Sciences) Discovering New Therapeutic Uses for Existing Molecules program is instructive (www.ncats.nih.gov). Eight pharmaceutical companies provided NCATS with 58 molecules that had passed phase 1 trials, and NCATS has made information regarding the molecules' mechanisms of action, original development indications, and routes of administration available to the scientific community. This data-sharing effort has driven "crowdsourcing" of ideas for new biomedical uses for these derisked molecules. However, the Confidential Disclosure and Collaborative Research Agreements template developed by NCATS for the participants ensures that specific information regarding potential new uses remains confidential, preserving the ability of participants to seek use patents. The template contracts capitalize on the role NCATS can play as a trusted intermediary (10). At the same time, because the contracts are publicly available, they could be used as a starting point for

crowdsourced private-sector rescue efforts in which NCATS is not involved.

NCATS has now selected and funded nine academic centers to work on eight different molecules. Although NCATS has not revealed the chemical structures, we were able to use publicly available information to “reverse engineer” the identity of four of these eight molecules. According to our analysis of the four molecules under investigation by five of the nine centers, all will have product patent protection for years to come (Table 1). A preference for product protection may have influenced not only decisions about which molecules pharmaceutical firms chose to put into the NCATS program but also NCATS’s decisions about which molecules to choose.

Efforts to maintain some composition-of-matter patent protection are certainly

rational. However, as rescue efforts prove successful, the risk-reward calculus should shift drug development toward drugs based on small molecules that are not covered by composition-of-matter patents. In the case of rescued drugs, developers may finally recognize that use patents are indeed useful.

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