Not Yet: Patented Risk Evaluation and Mitigation Strategies May Delay (or Tax) Competitors

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INTRODUCTION

From Vioxx to heparin, high profile and well-publicized drug safety concerns have surfaced with increasing frequency, resulting in growing criticism by members of the media and public regarding how post-market safety risks are managed by the Food and Drug Administration (FDA). For its part, FDA has long bemoaned its lack of authority over drugs upon approval and has traditionally relied on voluntary efforts by industry to proactively manage post-market safety issues, as well as the Agency's own (reactive) authority to respond to safety issues when they arise. Congress addressed these issues in 2007, when it provided FDA with new tools and capabilities for post-market drug safety oversight. The Food and Drug Administration Amendments Act (FDAAA) gave the Agency authority to impose, as a condition of marketing approval for certain drugs, mandatory programs known as Risk Evaluation and Mitigation Strategies, or "REMS." REMS are programs implemented after a drug or biologic has been marketed to manage serious risks associated with the products.

FDAAA's provisions governing FDA's imposition of REMS on innovator companies account for the potential that such programs will be subject to patent protection when the innovator drug becomes subject to generic competition. This begs an important question: are REMs programs indeed patentable? Further, what benefit – if any – would accrue to an innovator company that expends the time and effort necessary to obtain a patent covering a REMS program? One potential implication, as seemingly recognized by Congress in enacting FDAAA, is that a patented REMS program will have an unavoidable impact on the approvability of follow-on generic versions of the innovator drug. Indeed, despite Congress's clear intent that FDA speed consumer access to lower-cost generic drugs, the imposition of REMS programs on innovator drugs, and the associated patentability of such programs, may have significant implications on the timing of generic competition. This article reviews FDAAA's new REMS provisions, and also assesses the patentability of such programs and the implication that patentability may have on generic competition.

LEGAL LANDSCAPE

Title IX of FDAAA, "Enhanced Authorities Regarding Postmarket Safety of Drugs," expands FDA's authority over post-marketing risk management activities. Section 901 allows the agency to require a REMS if FDA determines it is "necessary to ensure that the benefits of the drug outweigh the risks."[1] The statute includes a provision authorizing the agency to require a REMS for certain drugs that are already approved. Specifically, FDAAA states that a drug approved before the Act's effective date is deemed to have an approved REMS under FDAAA if the drug is otherwise subject to post-market restrictions designed to ensure safe use.[2] For such drugs, applicants were required to submit formal REMS to FDA by September 21, 2008.[3] Approximately sixteen drugs were identified by FDA as subject to this requirement in a Federal Register notice dated March 27, 2008.[4] In February 2009, FDA indicated that manufacturers of opioid pain killers may also be required to implement REMS.[5]

A REMS may include a variety of drug-specific elements.[6] FDA may, for example, require REMS to include elements of communication and may mandate the inclusion of "elements to assure safe use."[7] Such elements provide for restricted distribution of the drug by, for instance, requiring that providers have particular training or experience, limiting dispensing of the products to pharmacies or practitioners that have special certifications, or requiring the maintenance of a registry for persons prescribed the drug.[8]

The elements of a REMS may have significant impacts on the approvability of follow-on generic candidates, particularly if the elements are subject to patent protection. In particular, if a REMS includes elements to assure safe use, FDAAA provides that generics and innovators "shall use a single shared [REMS]," unless FDA waives the requirement because the innovator's REMS is covered by a patent, and the generic sponsor has sought a license but was unable to obtain one.[9] Thus, under FDAAA, a generic applicant must either duplicate the REMS of the innovator (a resource intensive and potentially cost-prohibitive exercise), or, if the REMS is protected by a U.S. patent, the generic applicant must negotiate a license with the innovator. In either case, these activities will cost the generic manufacturer time, effort, and money. Thus, although FDAAA explicitly states that innovators are prohibited from using a REMS to "block or delay approval of a [generic application] or to prevent application of [an element to assure safe use],"[10] the law nevertheless could result in a barrier to generic entry if an innovator develops and implements a patentable, complicated, and resource-intensive REMS. In addition, in light of FDAAA's mandate that follow-on applicants seek a license from the innovator to utilize a patented REMS in connection with a generic approval application, the statute provides innovators with a potential revenue source that may mitigate the costs of generic competition.

PATENTING A REMS

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[11] In other words, although certain exceptions and complications sometimes apply, the basic requirements for the patentability of a REMS essentially boil down to these: a REMS must be (1) new, (2) useful, and (3) non-obvious.[12]

To satisfy the novelty requirement, a REMS must be an original method to solve a problem, in this case the problem of the safe administration of a particular pharmaceutical. To determine novelty, both the U.S. Patent and Trademark Office ("PTO") and the patent applicant will search for prior descriptions of pharmaceutical risk evaluation and mitigation strategies that have been created, publicly used, or published prior to the filing date of the application. Such publicly known information is referred to as "prior art." If each and every element of the applied-for REMS is disclosed expressly or inherently by a single prior art reference, the REMS should not be considered novel and the PTO should not issue a patent.[13]

The corollary to this rule, however, is that the absence from a prior art reference of even a single step of an applied-for method will disqualify that reference as an obstacle to novelty. Because the REMS is fairly new and only recently mandated by FDA, there is unlikely to be substantial relevant prior art. Furthermore, because each REMS is pharmaceutical-specific, it is similarly unlikely that the prior art would disclose each and every element of the applied-for REMS. The novelty requirement of patentability is therefore unlikely to be a high hurdle for an innovator.

To satisfy the usefulness requirement, a REMS must have a specific and practical utility in the real world.[14] This threshold would also not likely present a substantial obstacle to patentability, as a REMS application directed to the safe administration of drugs and prevention of contraindicated uses would probably be deemed useful.

Finally, a REMS must be non-obvious to meet the standard for patentability. Specifically, "[a] patent may not be obtained though the invention is not identically disclosed or described" in the prior art "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains."[15] This "person having ordinary skill in the art" is a hypothetical person who is presumed to have known the relevant art at the time of the filing of the patent application.[16] Accordingly, to determine whether subject matter is patentable as non-obvious, the PTO will (1) assess the scope and content of the prior art, (2) ascertain the differences between the claimed invention and the prior art, and (3) resolve the level of ordinary skill in the pertinent art.[17] It is within this construct that the PTO will consider whether "[t]he combination of familiar elements according to known methods … does no more than yield predictable results."[18] If so, the patent will likely not issue because the subject matter is considered to be an obvious combination of prior art.[19]

The Supreme Court reaffirmed this framework as recently as 2007,[20] prompting the PTO to reissue guidelines for determining obviousness related to patentability.[21] For a REMS to be patentable as non-obvious, therefore, the innovator must ensure that – working within this context – the REMS is more than simply a predictable variation or combination of previously known methods for the safe administration of pharmaceuticals.

The benefits of a patented REMS are easy to recognize: the right to exclude others for 20 years from the date of filing from making, using, selling or offering for sale the patented method[22] – longer than the statutory exclusivity period for the drug itself.[23] The benefits of obtaining patent protection are accompanied, however, with associated risks and expenses. First, the application process can be costly: successfully prosecuting an application requires a search and review of the known prior art in the industry, and the additional personnel and resources devoted to the ongoing negotiation with the PTO regarding the patentability of the application, as well as regular maintenance after the patent issues. Second, the process can be time consuming: patent applications take on average approximately three years and four months to issue from the date of filing. Innovators who seek to have patent protection for their REMS concurrent with the launch of their

product require the foresight to begin the patent application process well before their product reaches the market. Third, there is no guarantee that the PTO will issue the patent. Appealing this adverse decision will divert personnel and resources from the innovator's business objective and likely will remain unresolved by the time the generic is ready to introduce its product into the marketplace. Fourth, patents have the potential of being designed-around and providing a roadmap for competitors to develop a non-infringing process. Thus, obtaining a patent on a REMS does not necessarily prevent a generic from designing and submitting its own REMS different from that of the innovator.

Notwithstanding the risks and costs, it appears that innovators have already concluded that the benefits of patenting a REMS far outweigh the risks. For instance, Celgene Corporation recently sought and received patent protection for the REMS designed to be used in conjunction with its marketing and distribution of thalidomide.[24] Celgene subsequently submitted a citizen petition[25] urging FDA not to approve generic versions of the drug, Thalomid. Celgene's rationale is that its patented risk management program was a key factor in gaining marketing approval and without the *identical* risk management program, the generic drug would not be equivalent. That citizen petition remains pending – over one and a half years since its filing date of September 20, 2007. Meanwhile, generic competition has been precluded from entering the market. The citizen petition process demonstrates that despite FDAAA's intentions to ramp up FDA's post-marketing efforts and to limit the use of those efforts as a barrier to generic entry, loopholes remain.

THE FUTURE OF REMS

FDAAA explicitly states that REMS may not be used to block generic competition. Nonetheless, the patentability (and related novelty) of a REMS program may have the practical effect of creating a generic approval condition that will be difficult and costly for a follow-on applicant to satisfy. Further, it is reasonable to assume that FDA will face difficulties implementing the new REMS requirements. Among other things, FDA may have trouble establishing criteria for determining whether a generic applicant's REMS adequately duplicates the REMS of the innovator. Multiple groups within FDA will likely be involved in these determinations, increasing the likelihood of bureaucratic inertia that may further delay generic approval decisions.

Although REMS are currently imposed on a relatively small class of products, the Obama administration's increased focus on public safety issues suggests that REMS could become more prevalent. Moreover, it seems reasonable to assume that many innovators will unilaterally seek to implement patented REMS programs as part of new drug approvals in order to delay generic competition. Thus, whether the increased use of REMS will ultimately benefit the public remains an open question. While the use of REMS will likely improve post-market surveillance and mitigate safety concerns, such programs may have the practical effect of delaying entry of lower-cost generic drugs, in contravention of FDAAA's express statutory language and the legislative intent underlying the Hatch-Waxman Act. Whether or how FDA responds to these issues remains to be seen, and both innovator and generic drug companies will need to remain attuned to the potential impact of a REMS on their products and potential products. IPT

ENDNOTES

1. FDAAA, Pub. L. 110-85, § 901, 121 Stat. 823, 926 (2007) (creating 21 U.S.C. § 355-1).
2. *Id.*
3. Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007, 73 Fed. Reg. 16,313 (Mar. 27, 2008).
4. *Id.*
5. U.S. Food & Drug Admin., Center for Drug Evaluation & Research, *FDA to Meet with Drug Companies about REMS for Certain Opioid Drugs* (updated Mar. 2009), *available at* http://www.fda.gov/cder/drug/infopage/opioids/default.htm.
6. 21 U.S.C. § 355-1(c)-(f).
7. *Id.* § 355-1(e), (f).
8. *Id.* § 355-1(f)(3).
9. *Id.* § 355-1(i)(1)(B).
10. *Id.* § 355-1(f)(8)
11. 35 U.S.C. § 101.
12. *Id.* § 101-103.
13. *Id.* § 102(a)-(e). This lack of novelty is also referred to as "anticipation."
14. *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005).
15. 35 U.S.C. § 103(a).
16. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986).
17. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).
18. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007).
19. Note that other secondary objective evidence of non-obviousness may be considered, as well, including evidence of commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *Graham*, 383 U.S. at 17-18.
20. *See KSR Int'l*, 550 U.S. at 398.
21. Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International v. Teleflex Inc.*, 72 Fed. Reg. 57,526 (Oct. 10, 2007). When applying for a patent, it is useful to read from the PTO's playbook and draft the application accordingly.
22. For patents filed after June 8, 1995. For patents filed prior to June 8, 1995, the expiration date of the patent is 17 years from the date of issue, or 20 years from the filing of the first patent in the family, whichever is later. Because the issue of patentability of REMS is only recently gaining attention, this provision is unlikely to affect the present analysis.
23. For example, FDA provides five years of exclusivity as an incentive to innovators to develop new chemical entities not previously approved by FDA. A three-year period of exclusivity is provided for a drug product that has an active moiety that has been previously approved. 21 U.S.C. § 355(c)(3)(E). In either case, this exclusivity period is shorter than the potential 20-year term for patent exclusivity associated with a patented REMS.
24. *See* U.S. Patent No. 7,141,018. Celgene's patented REMS includes the steps of (a) defining a plurality of patient risk groups based upon a predefined set of risk parameters for thalidomide; (b) defining a set of information to be obtained from the patient, said set of information comprising the result of a determination of the ability of the patient to become pregnant and optionally comprising a determination that the patient is either (1) not currently pregnant or (2) currently pregnant; (c) in response to said information set, assigning the patient to at least one of said risk groups and entering the patient, the information, and the patient's risk group assignment into the medium; (d) based upon the information and the risk group assignment, determining whether the risk that the adverse side effect is likely to occur is acceptable; and (e) upon a determination that the risk is acceptable, generating the prescription approval code before the prescription is filled.
25. Docket FDA-2007-P-0113-0002. Note that Celgene submitted its citizen petition prior to FDAAA's enactment. FDA has asserted in other cases that "the requirements, prohibitions and benefits described in [FDAAA's citizen petition provisions] do not apply to requests submitted before [FDAAA's date of enactment]." Docket FDA-2007-0170-0009 at n.1.