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Personalized Medicine

Observations on Recent Developments in Patent Law: Is the Generic Claim Turning Into an Endangered Species?

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Patents promote innovation by providing inventors with a time-limited right to exclude others from practicing their inventions.[1] Patents may be obtained for ideas that are new, useful, and non-obvious.[2] To secure patent protection, an inventor must provide a patent specification that describes the invention, enables a person of ordinary skill in the art to make and use the invention, and sets forth the best way the inventor knows for practicing the invention.[3]

This bargain between the government and the inventor grants exclusionary rights in exchange for disclosure and promotes innovation in several ways. First, the inventor's disclosure teaches the public how to make and use the described technology, which becomes freely available once the patent expires. In addition, the patent system promotes further innovation by creating incentives for others to design around patented technologies so as to avoid liability for patent infringement. And of course, patents also promote innovation by providing economic incentives for investment in new technologies. The exclusive rights patents provide allow investors to recoup a fair rate of return by preventing others from free riding on their investments.

On the other hand, patents arguably impede innovation. A dense patent landscape can make it difficult to bring new technologies to market because royalty burdens reduce profit margins to unattractive levels, or because a required license may be unavailable. The patent system promotes innovation when an appropriate balance is struck between the scope of available patent protection and the degree to which the invention advances the art.

We are currently in the midst of a rebalancing of these competing interests in the Courts, the legislature, and the U.S. Patent and Trademark Office ("PTO") that is shifting towards a diminished scope of available protection and hence could hurt innovation. This article summarizes some of the recent changes in patent law and considers how they affect the ability of personalized medicine companies to capture value from the diagnostic products they create.

Patent Actions on All Fronts—Judicial, Legislative, Executive

The Supreme Court has recently issued an unprecedented number of decisions that affect the rights of patent owners. In *KSR v. Teleflex*[4] the Court found that a patent claim may be more easily invalidated for obviousness. The decision also makes it easier for a patent examiner to reject a patent claim as obvious over the prior art. The *eBay v. Merc Exchange* decision[5] reduces a patent owner's ability to obtain an injunction against an adjudicated infringer at the conclusion of a lawsuit. Furthermore *MedImmune v. Genentech*[6] provides standing, and a judicial forum, for a patent licensee to challenge the validity of the licensed patent without first having to breach the license agreement, thus making it easier for a licensee to challenge a patent. *Merck v. Integra*[7] also diminishes the usefulness of a patent by expanding the range of activities shielded from infringement so that many aspects of the drug screening process are, arguably, exempt from infringement under the safe harbor exemption provided for activities related to regulatory filings.[8] Finally, in *LabCorp. v. Metabolite*[9] the Court raised but did not resolve the question of whether a claim to a diagnostic method reciting generic " assaying" and "correlating

steps" was so broad as to be an improper attempt to claim a law of nature.[10] Although the majority of the Court agreed to dismiss the case, a vigorous dissent by Justice Breyer expressed concern that overbroad patents are unduly burdening the healthcare system and contributing to rising healthcare costs.[11]

The U.S. Congress has also been acting to weaken patent protection. Patent reform legislation[12] recently passed the House and includes provisions that modify the ways that patent litigation damages are calculated by requiring an analysis of a patent's specific contribution over the prior art, and make it harder to obtain enhanced damages for willful infringement.

The same can be said about some recent rule changes passed by the PTO. One of these limits the number of patent applications that can be filed in a patent family.[13] If a patent examiner determines that a single application includes claims directed to multiple inventions, the examiner can "restrict" the application to one of the inventions. Claims restricted from that original application can be pursued in "divisional" applications. Divisionals form new patent families under the new rules and so provide a way for an applicant to increase the number of applications that can be filed to mine patent claims from a patent specification.[14] If an application includes more than five independent and 25 total claims, the new rules require an applicant to search for prior art and prepare an examination support document that provides a patentability analysis of the pending claims in view of the identified prior art.[15] This shifts the initial burden for examining patent claims from the patent examiner to the applicant. The new rules also include provisions designed to prevent applicants from gaming the system by filing multiple applications directed to similar subject matter in order to avoid the new limits on the number of applications and the number of claims they contain.[16] One of these provisions requires an applicant to prepare a report for the PTO listing all applications filed within a four-month window that include at least one common inventor. Complying with these self-reporting provisions can be burdensome and costly to an applicant.

The patent office currently is also considering adopting new rules to govern examination of claims that use alternative language. See Fed. Reg. Vol. 72 No. 154, August 10, 2007.[17] These types of claims, "linking claims," have for years provided a way to link together multiple variants, or species, in a broad, single claim as encompassed within the scope of the alternative language claim. The use of a linking claim traditionally prevented the examiner from restricting into separate applications narrower claims directed to individual species that fall within the generic linking claim.[18] The proposed rule change makes it easier for a patent examiner to require restriction among the recited alternatives if the alternatives can be considered to cover independent and distinct inventions. Restriction among alternatives would not be proper under the proposed rules if the alternatives share a substantial feature essential for a common utility, or they are obvious over each other.[19] These changes are geared toward the practical problems of managing examiner caseloads.[20]

From a patent examiner's perspective, alternative language claims can pose difficulties for conducting a thorough prior art search as the claims can potentially cover an enormous number of species. From the applicant's perspective, alternative claims provide a compact and economical way to achieve adequate claim scope for protecting inventions that can be practiced using a large number of different variations. If restriction is required between alternatives, the practical result is that the cost of covering each alternative in a separate patent application can rise to the point of unaffordability, which denies to the applicant the benefit of the claim scope to which he or she is entitled.

Patent Reforms Pose Risks for Personalized Medicine

The combined effect of the court decisions, pending patent legislation reform, and the adopted and proposed PTO rule changes increases the risk that personalized medicine companies will be unable to adequately protect innovation. This can dry up investment and slow innovation. Personalized medicine companies must be able to effectively exclude others so as to make their investments in innovative diagnostic technologies worthwhile. A personalized medicine diagnostic can employ at least one variable in an interpretive function

to yield a single, patient-specific result (such as a "classification," 'score," "index," and so on), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.[21] These diagnostics can be used to score or classify patient samples based upon quantitative predictive modeling using expression values for single or multiple biomarkers, such as genes, proteins, or protein/protein interactions, as inputs.

Personalized medicine diagnostics are being developed that provide rich predictive information for diagnosing or prognosing heart disease, inflammatory conditions such as rheumatoid arthritis, or for predicting whether a cancer patient will respond to treatment with a particular drug. The information they provide has the potential to generate enormous savings to the cost of medical care by bringing to patients more effective, individualized therapies.

Companies developing personalized medicine diagnostics face several challenges in obtaining effective patent protection for their inventions. The prior art often includes reports of studies that correlate the expression of individual or multiple markers with particular disease conditions. Claims to methods for scoring a sample using expression values for a set of markers based on a quantitative predictive model can be challenged by an examiner as obvious in view of this prior art. Under the new KSR standard, these rejections can be countered using arguments highlighting the unexpected ability of the predictive models to accurately prognose, classify, or diagnose a particular condition.

Because expression values of multiple biomarkers may be highly correlated to disease or drug response, it is possible to construct predictive models using any one of a number of these correlated values. Claims directed to these models may recite as alternate input choices a number of these correlated biomarkers that can be used in the method. Under the existing rules governing alternate language claims, a patent examiner usually will request the applicant to elect one of the alternates (or one set of alternates) as a species on which the examiner would search. If no art is found, the examiner should continue to search on remaining species until either the list is exhausted (in which case the broad alternate language claim should be allowed) or prior art is found that reads on one of the species.

Working With the New Rules

The proposed new rules could make it easier for an examiner to require restriction instead of species election. Pursuing each alternate in a separate application can be a costly option; if alternatives are not pursued, an applicant may be left in the difficult position of having disclosed subject matter yet being unable to afford to pursue claims directed to each alternative because disclosed but unclaimed subject matter is presumably dedicated to and freely available for use by the public.[22] An argument can be made that the proposed rules should not change examination of claims that enumerate highly correlated biomarkers as alternatives. Each alternative shares a substantial feature essential for a common utility—that is, each alternative provides the same effect as an input for the predictive model.[23]

In some cases, the cost of additional applications, such as divisionals, may be worth the investment. Predictive models can derive their power from a small number of powerful predictive components, or from a larger number of less informative components. Attaining effective coverage for these alternatives requires an applicant to anticipate a competitor's ability to use the second type of model to design around the first type. To effectively cover both types requires the patent applicant to describe multiple models and prepare claim sets that are directed to each one. Applicants should consider suggesting restrictions among these alternative models as a tool for increasing the total number of claims that can be obtained under the new rules to the number needed to prevent competitors from designing around the diagnostic product.

The balance between the cost of divisional applications and the benefits of divisional applications is influenced by the presence of nucleic acid and amino acid sequences in the claims and specification. Currently, the PTO requires applicants to submit sequence listings that provide exemplary protein or nucleic acid sequences corresponding to the proteins or genes whose expression values are determined by the personalized medicine diagnostic. The sequence

listings are used by the PTO to search for prior art, and to reduce uncertainty as to the identity of the expressed product. The use of sequence listings can adversely impact applicants in a number of ways. First, there is the risk that the issued claims are limited to models based on expression of the specific sequences disclosed in the application. This leaves open the possibility that the claims will not cover informative markers that have slightly different sequences such as alternative splice variants or naturally occurring polymorphisms. Second, substantial attorney costs can be incurred for preparing sequence listings that include a large number of markers.

The personalized medicine industry should consider working together with the PTO to eliminate the requirement for sequence listings in patent applications directed to personalized medicine diagnostics. This is appropriate because patents directed to personalized medicine diagnostics do not seek to obtain exclusive rights on biomarker sequence information, but rather on the results obtained using biomarkers. Effective searching could be accomplished by substituting the sequence information with existing standardized nomenclature to identify biomarkers whose expression values are used to construct a predictive model.

Undoubtedly, more sophisticated search methods need to be developed before the PTO would consider adopting the use of standardized nomenclature in lieu of sequence listings. These methods will need to provide cross-referenced lists of common synonyms used for standard nomenclature and be able to correlate this with sequence information to allow effective searching of prior art that might not be captured using standard nomenclature or synonyms.[24] Industry should consider developing these tools and promoting their use for patent examination searching to reduce the search burden. Presumably, if examiners are provided with better tools for efficient prior art searching, they should be well equipped to properly analyze even those alternative language claims that cover numerous species and to issue patent claims having sufficiently broad scope to assure appropriate protection for personalized medicine diagnostics.

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Before becoming an attorney, Dr. Shuster's career experience included graduate research in the laboratory of Professor Eric Kandel at Columbia University as part of a team focused on discovery of mechanisms by which short-term memories are stored, research for which Professor Kandel was awarded the 2000 Nobel Prize in Medicine. Dr. Shuster then moved to the Department of Biochemistry and Biophysics at the University of California, San Francisco, where he pursued his interests in ion channel biophysics and protein structure. Dr. Shuster received his B.A. from Brandeis University in 1981, magna cum laude, and his Ph.D. from Columbia University in 1986. He received his J.D. cum laude from the University of San Francisco School of Law in 1997.

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Observations on Recent Developments in Patent Law (continued)

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FOOTNOTES

1 U.S. Const. art. I, § 8.

2 35 U.S.C. §§ 101, 102, and 103.

3 35 U.S.C. § 112.

4 *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007).

5 *eBay Inc. v. MercExchange, L.L.C.*, 126 S. Ct. 1837 (2006).

6 *MedImmune, Inc. v. Genentech, Inc.*, 127 S. Ct. 764 (2007).

7 *Merck KgaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 125 S. Ct. 2372 (2005).

8 35 U.S.C. § 271(e)(1).

9 *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 126 S. Ct. 2921 (2006).

10 *See* Shuster M.J., and Anderton H.T., Jr., "Planning for the other shoe to drop – Future echoes of LabCorp v. Metabolite," *Burrill Report Personalized Medicine, November 2006.*

11 *Lab. Corp.* at 2928-2929.

12 Patent Reform Act of 2006 (H.R. 1908, S. 1145).

13 37 C.F.R. 1.78(d)(1)(i - iii), (d)(3); 37 C.F.R. 1.114(f, g).

14 37 C.F.R. 1.78 (d)(1)(ii-iii).

15 37 C.F.R. 1.75(b).

16 37 C.F.R. 1.78(f).

17 Such claims are commonly referred to as "Markush Group" claims and list alternatives using language such as: "wherein the widget is selected from the group consisting of A, B, and C," or "wherein the fastener is a nail, a screw, or an adhesive."

18 Manual of Patent Examining Procedure (MPEP), 8th edition (rev. August 2006) § 809.

19 *See* 37 CFR 1.75(a) and 1.140(a).

20 *In re Weber*, 580 F.2d 455, 198 USPQ 328, 331-332 (CCPA 1978).

21 At some point, certain personalized medicine diagnostics that includes more than one analyte ("In Vitro Diagnostic Multivariate Index Assays, or "IVDMIAs") may be regulated by the FDA as Class II devices. FDA draft guidance defines an IVDMIA as "a device that: 1) Combines the values of multiple variables using an interpretation function to yield a single, patient-specific result (e.g., a classification, score, index, etc.), that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, and 2) Provides a result whose derivation is non-transparent and cannot be independently derived or verified by the end user." FDA Draft Guidance For Industry, Clinical Laboratories, and FDA Staff – In Vitro Diagnostic Multivariate Index Assays, July 24, 2007. Available at www.fda.gov/cdrh/oivd/guidance/1610.pdf.

22 *Johnson & Johnston Assocs. Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002).

23 See MPEP § 803.02.

24 In fact, any nomenclature that defines the biomarkers with reasonable clarity, deliberateness, and precision should be acceptable. See MPEP § 2111.01 and *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 19994).