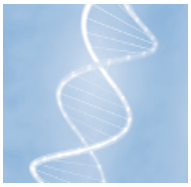

INTELLECTUAL PROPERTY

BIOTECH UPDATE

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Unanimous Supreme Court Vacates Federal Circuit and Extends Section 271(e)(1) Research Exemption

By: Christopher R. Liro*

The Supreme Court decided the case of *Merck KGaA v. Integra LifeSciences I, Ltd.* on June 13, 2005, unanimously vacating the decision of the Court of Appeals for the Federal Circuit.[1] At center stage was the scope of protection provided under 35 U.S.C. § 271(e)(1), the federal statute exempting from patent infringement liability certain infringing activities related to the development and submission of information under Federal law regulating drugs and medical devices.[2] Merck challenged the Federal Circuit's holding that Section 271(e)(1) did not protect Merck's experiments on Integra's patented compounds, which, as described by the Federal Circuit, "did not supply information for submission to the [FDA], but instead identified the best drug candidate to subject to future clinical testing under the FDA process."[3] The dispute involved primarily whether the protection of 271(e)(1) is limited to clinical investigations on humans to produce data for FDA submittal on a particular drug, or if the protection reaches further back through the research and development chain to apply to pre-clinical studies that may be used, for example, to identify and screen candidate drugs.

The Court first clarified that the exemption "extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the FDCA."[4] Thus, this "necessarily includes preclinical studies of patented compounds that are appropriate for submission to the FDA in the regulatory process."[5] Although Integra had conceded this point generally, it argued that the only such data of interest to the FDA were that pertaining to the *safety* of the drug in humans. The Court rejected this argument after examining the applicable FDA regulations, observing that the FDA requires that investigational new drug (IND) applications include preclinical data relevant not only to safety but also to the pharmacological, tocicological, pharmacokinetic, and biologic qualities of the drug in animals.[6]

The Court then turned to the issue of whether experiments to identify candidate drugs for further research and investigation could be covered by the exemption, or whether such experiments were merely basic scientific research that was not covered. The Court explained:

> Basic scientific research on a particular compound, performed without the intent to develop a particular drug or a reasonable belief that the compound will cause the sort of physiological effect the researcher intends to induce is surely not [within the exemption]. It does not follow from this, however, that § 271(e)(1)'s exemption from infringement categorically excludes either (1) experi-

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> mentation on drugs that are not ultimately the subject of an FDA submission or (2) use of patented compounds in experiments that are not ultimately submitted to the FDA. Under certain conditions, we think the exemption is sufficiently broad to protect the use of patented compounds in both situations.[7]

"use of patented compounds in preclinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to an IND or NDA."

The Court observed that scientific testing is a process of trial and error even at the late stages of product development, and that one can know at the outset that a particular compound will be the subject of an eventual application only if the active ingredient of the drug being tested is identical to that in a drug already approved, *i.e.*, when seeking approval of a generic drug. The Court held, however, that § 271(e)(1) did not provide a safe harbor only for generic drugs, but for "all drugs."[8] Accordingly, it ruled that experimentation was protected "at least where a drugmaker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA."[9] Similarly, recognizing that not all experimental data is necessarily included in the final FDA submissions, the Court concluded that "use of patented compounds in preclinical studies is protected under § 271(e)(1) as long as there is a reasonable basis for believing that the experiments will produce the types of information that are relevant to an IND or NDA."[10]

While the Court provided general guidelines, it remains to be seen how the Federal Circuit and district courts will determine the details—for example, when a drugmaker "has a reasonable basis" for believing that a patented compound may work "through a particular biological process, to produce a particular physiological effect." Indeed, here the Court declined to review the sufficiency of the evidence to determine if the jury's verdict that Merck's activities were not protected by 271(e)(1) should be sustained. Thus, Merck's victory may be hollow if the lower courts ultimately determine that a reasonable jury could have concluded that Merck's activities were not sufficiently focused to be covered by the § 271(e)(1) exemption.

Another issue that was left undecided, but which received significant attention in many of the 20 *amicus* briefs, is the effect of the statute on "research tools"—devices and processes that are themselves ***not*** the ***subject*** of the drug research but rather are used in the research process, *e.g.*, an assay kit, or a method such as PCR. The Federal Circuit panel majority concluded that its narrow interpretation of § 271(e)(1) was warranted because, among other reasons, to do otherwise would vitiate patent protection of this entire class of patents.[11] In dissent, Judge Newman argued that this was not a proper basis to reach a narrow construction because "use of an existing tool in one's research is quite different from study of the tool itself."[12] The Supreme Court, however, determined that the patented peptides at issue were not used as research tools and expressly declined to express a view on the issue.[13] The Court appeared, moreover, to word the opinion carefully to address the issue before it—whether studies of patented compounds were protected—leaving the issue of protection of patented tools used in the research and development process to be decided in another case at another time.

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Genomics Patents: Redefining the Scope of Utility?

By: Joseph A. Loy*

The Federal Circuit heard arguments on May 3, 2005 in *In re Fisher*,[1] presenting the Court with its first opportunity to comment on the USPTO's 2001 Revised Utility Examination Guidelines.[2] The Court's opinion may significantly affect genomics patenting because of its potential impact on the utility requirement of 35 U.S.C. § 101, and, more specifically, the scope of utility vis-à-vis nucleic acid patents. The CAFC's pronouncements may also appreciably influence the way in which biotechnology firms and other research entities structure their business models and appropriate their R&D resources.

The Fisher controversy is far from new. Its subject matter dates to over a decade ago when Dr. J. Craig Venter, then working at the National Institutes of Health, applied for several patents covering complimentary DNA (cDNA) segments. Dr. Venter described the claimed segments as "expressed sequence tags" (ESTs), and averred that the claimed ESTs were useful to map chromosomes, and to identify tissue types and particular gene regions.[3] Although the applications never issued as patents, the current controversy over the specificity with which an applicant must establish the usefulness of a discovered EST had begun.

Responding at least in part to the resulting brouhaha, the USPTO solicited comments and, eventually, issued guidelines to aid patent examiners faced with evaluating EST applications. Those guidelines notably left the door open for patenting ESTs, stating, "ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches those of skill in the art how to make and use the invention."[4]

The question now before the CAFC is whether Fisher's claimed ESTs meet the criteria for usefulness stipulated by § 101.

An invention must be "useful" to satisfy the § 101 utility requirement. What exactly constitutes a "useful" invention, however, is not always clear. Indeed, in its assessment of the term "useful" in the context of patentability, the Supreme Court recognized that "a simple, everyday word can be pregnant with ambiguity when applied to the facts of life."[5] The Court attempted to resolve the ambiguity by concluding that the utility requirement demands "an invention with substantial utility."[6] The Court seemed particularly concerned that without requiring applicants to outline specific and substantial utilities, patents that "block off whole areas of scientific development"[7] could unduly issue.

The '643 application contains only a single claim: "[a] substantially purified nucleic acid molecule that encodes a maize protein or fragment thereof comprising a nucleic acid sequence …." The patent examiner rejected Fisher's claim under § 101 as lacking utility and under § 112 as lacking enablement. Because the enablement rejection rests on the utility rejection, the real issue here is the utility requirement.

According to the examiner's assessment of the specification, the '643 application teaches that the ESTs are useful: (1) to produce a plant containing reduced levels of a protein, (2) to determine an association between a polymorphism and a plant trait, (3) to isolate a genetic region or nucleic acid, (4) to determine a level or pattern in a plant cell of a protein in a plant, (5) to determine a mutation in a plant whose presence is predictive of a mutation affecting a level or pattern of a protein, (6) as a molecular tags to isolate genetic regions, isolate genes, map genes, and determine gene functions, and (7) to identify tissues.

Nonetheless the examiner opined that these uses are non-specific and applicable generally to nucleic acids. Thus the uses failed to meet the specific utility requirement of § 101.

The Board of Patent Appeals and Interferences sustained the examiner's § 101 utility rejection. Before reaching its conclusion, however, the Board cited to *Brenner* and its progeny, stating those cases stand for the proposition that "not every 'use' that can be asserted will be sufficient to satisfy § 101."[8] By distinguishing between "useful" and "substantially useful," the Board equipped itself to challenge appellants' utility claims. One by one, the Board discredited appellants' utility arguments, rejecting each,

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with the exception of a market-based evidentiary argument, by characterizing appellants' purported use as not specific enough to constitute a substantial use, thereby affirming the examiner's § 101 rejection.

Monsanto, as assignee of the Fisher application, reiterates on appeal before the CAFC the same utility arguments it unsuccessfully presented to the Board. Monsanto also takes the position that, although the Board "conceded on appeal that the claimed ESTs can be used as probes in a variety of different scientific applications," the Board nonetheless erroneously rejected claim 1 and contemporaneously concocted a "new heightened standard of utility"[9] that speciously requires all EST applicants to provide "some undefined level of knowledge concerning the function of the corresponding gene."[10]

But Monsanto is not the only entity with stakes in this appeal. Supporting the USPTO as *amici curiae* are such power-houses as Eli Lilly, the Association of American Medical Colleges, Baxter Healthcare, the National Academy of Sciences, Dow AgroSciences, the American College of Medical Genetics, and, each filing separate *amicus* briefs, Affymetrix and Genentech. The grievances of several *amici* center around their common interest in fundamental research. These parties argue that extending patent protection to uncharacterized ESTs without disclosing the underlying biological significance of any associated protein will unjustifiably thwart advancements in science and biotechnology. Echoing the words of Justice Fortas in *Brenner*, *amici* characterize the applicants' claim as lacking utility because each articulated research purpose is merely potential and thus patent protection would constitute nothing more than "a hunting license."[11]

On May 3, 2005, the CAFC heard oral arguments. Monsanto maintained that the USPTO erroneously misconstrued the "specific utility" requirement of *Brenner* to mean "unique utility," thereby alleging that the USPTO heightened the legal standard as applied to Monsanto's EST application.[12] The USPTO, on the other hand, argued that the Board applied *Brenner* appropriately by requiring more than mere knowledge of an EST, and that the examiner correctly rejected the '643 application as lacking any specifically disclosed use or benefit.[13]

The question now for the judges to determine is to what extent Fisher has claimed in the '643 application a substantial use. The answer, of course, could profoundly influence the future of biotechnology patenting.

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1 *Integra LifeSciences I, Ltd. v. Merck KGaA*, 331 F.3d 860 (Fed. Cir. 2003), *vacated by* 545 U.S. __, No. 03-1237 (June 13, 2005).
2 For further background, see "Shielding Research Uses From Infringement Liability: The 'Experimental Use' and Section 271(e)(1) Defenses" in the Autumn 2002 issue of the Biotechnology Update.
3 *Integra*, 331 F.3d at 865.
4 *Merck*, slip op. at 8 (emphasis in original).
5 *Id.* at 9.
6 *Id.*
7 *Id*. at 12.
8 *Id*. at 13.
9 *Id.*
10 *Id*. at 14 (internal quotation omitted).
11 *Integra*, 331 F.3d at 867.
12 *Id*. at 878.
13 *Merck*, slip op. at 12 n.7.

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1 No. 04-1465 (Fed. Cir. filed May 27, 2004).
2 66 Fed. Reg. 1092-02 (Jan. 5, 2001).
3 Robert Patrick Merges & John Fitzgerald Duffy, Patent Law and Policy 250-51 (3d ed. 2002).
4 Utility Examination Guidelines, *supra* note 2.
5 Brenner v. Manson, 383 U.S. 519, 529 (1966).
6 *Id.* at 534.
7 *Id.*
8 *Ex parte* Fisher, B.P.A.I. 12 (2004).
9 Corrected Brief for Appellants at 22, *supra* note 1.
10 *Id.* at 25.
11 Brief of Eli Lily et al. as *amicus curiae* at 3, *supra* note 1.
12 AIPLA Reports, *Federal Circuit Oral Argument Addresses Utility for EST Patents* (May 12, 2005).
13 *Id.*