

Mixed messages from Washington

With the economy sputtering toward recovery, federal outlays shriveling and the political scene in upheaval, the US biotech policy picture is more than a little blurred. Jeffrey L. Fox reports.

Midway through President Barack Obama's first term of office, uncertainty about patent reform (Box 1) and the regulatory pathway for follow-on biologics continues to loom over the industry. At the same time, the sector has been receiving mixed messages from the administration.

On the one hand, the White House continues to tout the value of innovation generally and biotech specifically. The updated *A Strategy for American Innovation*¹, which was released earlier this year, calls for accelerating the pace of biotech discovery with the aim of developing "new diagnostics, treatments, and cures." It also highlights the importance of doubling renewable energy supplies by the end of 2012. In Obama's February budget for fiscal year (FY) 2012, he backed this rhetoric with requests for increased funding for many federal R&D programs having biotech components (Table 1)—challenging, perhaps defying, the budget-cutting mind-set on Capitol Hill. Insiders also are hinting that the Obama administration is considering a radical overhaul of rules governing biotech crops to make it much easier to bring such products into commerce.

Meanwhile, the new budget proposes to boost the market for generics and follow-ons, shrinking exclusivity for biologics to 7 years from the 12 years previously agreed upon, potentially reducing the incentive for innovative R&D. Elsewhere in Washington, DC, officials at the US Department of Agriculture (USDA) are making statements that indicate a shift to accommodate the organic lobby, raising the possibility of the introduction of coexistence rules for genetically modified (GM) crops similar to those used in Europe.

Looking back to look ahead

The first years of the Obama administration include several noteworthy bright spots in terms of biotech policy, according to Thomas Murray, president of the Hastings Center, which focuses on bioethics, in Garrison, New York. For example, the synthetic biology report², which the Presidential Commission for the Study of Bioethical Issues completed last December, is "significant for the biotechnology industry," he says. "The report, which is sophisticated and thoughtful, gives an enthusiastic green light to R&D, and should give comfort to policy makers, the public and researchers in academia and



President Barack Obama greets small business owners after signing the Small Business Jobs Act in September 2010, one of his positive gestures toward industry.

industry." In a similar vein, efforts by the administration to foster human embryonic stem (ES) cell research remain encouraging, even though that research is faced with uncertainty because of pending lawsuits, he adds.

Also on the plus side, the healthcare reform debate and the worst fears roused by the global credit crisis have subsided, shifting concerns to more mundane matters, such as funding for the US Food and Drug Administration (FDA) and other federal programs affecting biotech, according to Jim Greenwood, president of the Biotechnology Industry Organization (BIO) in Washington, DC. "We're spending a lot of time trying to limit the damage done with proposals to cut spending," he says. Other major concerns include "risk aversion" at FDA, uncertainties about the agency's plans for the regulatory pathway for reviewing biosimilars, how comparative effectiveness research will play out with biotech therapeutics and ongoing Prescription Drug User Fee Act (PDUFA) 5 negotiations, due for reauthorization in 2012.

(PDUFA sets FDA user fees for industry and deadlines for agency reviews.)

"In the president's budget, the focus tends to be on the NIH budget, but how about the FDA?" says Michael Werner of Holland & Knight, a law firm in Washington, DC. The proposed NIH translational research initiative³ sidesteps the issue of "what budget FDA will get for regulatory-related research. People want agency officials to understand what they're regulating, but they won't do that research without resources, and that will put pressure on user fees," he says.

Indeed, says Peter Pitts, president of the Center for Medicine in the Public Interest in New York, "The new Congress wants to cut the FDA budget." But the "PDUFA 5 negotiations provide an opportunity to lay it on the line honestly and explain to Congress why FDA needs to be funded robustly." The first PDUFA of 1992 and subsequent iterations "gave industry better predictability and FDA more money," he adds. "But it swerved off that path, and promises were not kept. Industry now wants to get back to those promises."

However, new legislative responsibilities, particularly the Food Safety Modernization Act, which the Senate passed late in December and Obama signed early in January, complicate the picture for FDA. Although the FY 2012 budget request for FDA of \$4.3 billion calls for a steep increase in part to implement this new mandate, Republicans in both the Senate and House are threatening to cut, rather than expand, agency resources. "How can they not fund it?" Pitts asks. "That's empty rhetoric because people want safer foods and more drugs coming to market. That means FDA, which has always been underfunded, especially with respect to biotech, needs more funding. But FDA will need to spend its money more wisely."

Innovation bottleneck

Some observers are more pointed in their comments regarding FDA and its impact on drug development. "President Obama and Congress earn decidedly mixed grades," says Robert Nelsen, managing director of Arch Venture Partners in Seattle. "The administration's intent is good, and they understand what innovation is

Table 1 US science budget (\$ millions)

Agency	2012 request	2011 request	House plan for 2011	Senate plan for 2011	2010 enacted	Stimulus
NIH	31,829	32,090	31,090	31,003	31,084	10,400
NSF	7,767	7,424	6,567	6,800	6,926	2,401
NIST	1,004	919	733	754	856	610
USDA	23,879	28,642	23,275	NA	27,032	27,395
FDA	4,360	4,032	3,039	3,707	3,280	

NSF, National Science Foundation; NIST, National Institute of Standards and Technology.

Source: American Association for the Advancement of Science

and its importance.” For example, the NIH initiative to establish a center focused on translational research reflects that good intent, he says, even if “it’s a bit of a fantasy in terms of what the government can do to discover drugs.

“FDA is a well-meaning body that, ultimately, needs to balance risks, and it has good people working hard, who fear Congress beating them up over small issues of safety,” Nelsen continues. “I’m worried about both political parties in Congress and the administration, which has been passive but could take a leadership role to direct FDA to take more risks.” The federal government is “not intentionally suppressing innovation,” he adds. “But drugs are stuck in a giant bottleneck, and all this great research that’s being done won’t go anywhere with the bar being set too high. It’s as bad as it’s ever been.”

Devising ways to overcome “risk aversion at FDA is the highest priority for us,” says BIO’s Greenwood. The current round of PDUFA negotiations also takes aim at this deeply rooted issue, in part by addressing underlying uncertainties that go with product approval reviews, he says. That uncertainty is “one of the biggest impediments to innovation.”

One possibility is that the PDUFA negotiations could provide a “vehicle” to create a new office devoted to therapeutic product safety, according to Werner of Holland & Knight. However those initiatives turn out, the upcoming PDUFA legislation and the hearings surrounding it will “spur discussions” about FDA performance, while also evaluating specific programs such as the Risk Evaluation and Mitigation Strategy (REMS), which was established in 2007, and ongoing efforts to develop a working pathway for reviewing biosimilars, he says. “All will come up.”

The 2010 Patient Protection and Affordable Care Act—the healthcare reform act—permits licensure of follow-on therapeutic products and stipulates a 12-year period of data exclusivity for reference products. However, in the FY 2012 federal budget released this February, the administration proposes to reduce that exclusivity period to seven years along with its request for \$124-million with which to develop a specific pathway for approving follow-on biologics. Before the FY 2012 budget was even released, some members of Congress sought to clarify—or, perhaps, extend—exclusivity in a way that benefits developers of innovative biologics. Meanwhile, FDA Commissioner Margaret Hamburg says the agency plans soon to release its draft rules for overseeing that pathway.

“I’m a big supporter of the biosimilars [follow-on biologics] pathway, but FDA is moving at a snail’s pace to implement it,” says Greg Conko of the Competitive Enterprise Institute (CEI) in Washington, DC. “It’s going much quicker in

Europe. Although the [US] legislative framework is reasonably good, I’m disappointed that FDA is moving so slowly. Perhaps that is benefitting the biotech industry.” That pacing also might reflect recent changes in Congress, according to Conko. For instance, Representative Darrell Issa (R-CA), who now chairs the House Committee on Oversight and Government Reform, is a “strong advocate for lengthy data exclusivity,” Conko says. “It wouldn’t surprise me if Issa and [Rep. Anna] Eshoo [D-CA, who as a member of the House Committee on Energy and Commerce has weighed in on such issues] are urging FDA to go slowly.”

Gillian Woollett, chief scientist at Engel & Novitt, a law firm in Washington, DC, worries that some of the companies with brand products are marshaling “extreme arguments” to protect what is already licensed, while calling for follow-on biologics to meet standards that might prove difficult or even impossible for innovator products to overcome today. “Instead of using biosimilars [follow-on biologics] to identify the scientifically appropriate minimal standards needed to approve any biologic, a few powerful voices have gone to being more and more restrictive,” she says. “What are we regulating to prevent? FDA always needs to balance benefits versus risk, and safety is always a consideration at FDA. Let’s let the people at FDA make those decisions for all biologics.

“As an immunologist, I know of no evidence, nor even of a theoretical basis, whereby the switching of two biologics creates an immunogenicity problem that was not already present with one or the other product,” Woollett continues. “Switching studies, as a unique requirement for interchangeable biosimilars, [is] not scientifically justified, any more than [it] would be for the use of comparability in the support of manufacturing changes, where the pre- and post-change products are always interchangeable. To date, I am not aware of any sponsor of an originator product being required to do such studies prior to a manufacturing change.”

Thinking big, bypassing bottlenecks

“Much is said about the pace of drug discovery bogging down—that it’s too risky for venture capital and the regulatory pathway is a mess,” says Greenwood of BIO. In a quest for “bold ideas” to overcome this bottleneck, he brainstormed with CEOs and investors last year, and then commissioned the Zerhouni Group, a consulting group directed by former NIH director Elias Zerhouni, to develop recommendations for “changing the model,” he says. The idea was to “do big things to change the picture,” including building a vision of “an optimal policy environment for biotechnology to take off.”

Greenwood, who served 12 years in the House of Representatives, plans to use the Zerhouni report as a tool for persuading Congress to support biotech more fully and with greater consistency, he says. “We also need to change policies to induce investors, who continue to be skittish. That narrative was absent during the last [session of] Congress.” Other ideas include finding ways to make “NIH function better” and elevating FDA to be “a cabinet level agency.” The strategy is “first to create a vision” and then develop a “comprehensive bill that looks at the entire industry.” In the current political and economic climate, a five-year roll-out may be “realistic” for realizing these goals, he says.

Short of that comprehensive scheme, BIO continues to encourage patent reform—specifically, the Patent Reform Act of 2011, Senate Bill 23, introduced late in January (Box 1)—tax credits for R&D, measures to support development of biofuels through US DOE programs along with its joint programs with USDA. For instance, the DOE Office of Science is slated to receive more than a 9% increase in its 2012 budget to \$5.4 billion overall, and that request includes a 57% increase for renewable energy programs involving biomass. Although biotech-related programs are only a portion of these figures, these sought-after increases reflect Obama’s pledge to support federal R&D to accelerate biotech, nanotech and advanced biomanufacturing capacities, including through a requested 16% increase that will raise the National Institute of Standards and Technology budget to \$1 billion.

In addition to those programs, the administration also continues to support biodefense R&D and product procurement programs. For instance, the US Department of Defense (DoD) plans to build a facility at Fort Detrick, Maryland, to overcome bottlenecks in testing and evaluating vaccines and therapeutics to be used against biological threat agents according to George Ludwig of the US Army Medical Research and Materiel Command (AMRMC) at Fort Detrick. Containment laboratories in the facility will be available for industrial partners to use on a fee-for-service basis. “It’s designed for pilot and pivotal animal-rule studies, and to reduce the risk for small biotech firms working on countermeasures,” he says.

On the civilian side, the federal Biomedical Advanced Research and Development Authority (BARDA) also is funding development of biothreat countermeasures for their procurement under the BioShield program, according to Stephen Morris, chief of antitoxins and therapeutic countermeasures at BARDA in Washington, DC. “Product licensure is our goal,” he says. For example, recent and ongoing contracts and grants provide about \$700 million to support development and purchase of

anthrax countermeasures, including those being developed by several biotech companies.

“Most of the companies working in the bio-defense space are small biotechs, with little or no in-house access to high-containment labs,” says Phyllis Arthur, senior director for vaccines, immunotherapeutics and diagnostics policy at BIO. Although doing research at the anticipated DoD facility or others like it raises intellectual property issues, it may also “lower the risks of getting through the regulatory process,” she says, alluding to ambiguities surrounding FDA rules for evaluating countermeasures for which ordinary clinical trials would be unethical and impossible. “Clarifying the FDA regulatory process remains one of the most important hurdles.” Another big worry is the stability of funding for these programs, she adds.

Loosening the GM crop logjam

GM crops fall in an area where a regulatory logjam appears to be easing—amid careful hints from insiders that the regulatory apparatus itself is under review and could be radically upended. Early this year and in quick succession, USDA officials deregulated two GM plants: Roundup Ready (RR) alfalfa⁴, and corn to produce ethanol that carries a gene for a heat-tolerant amylase. They also partly deregulated RR sugar beets.

“I think we see some logs shifting, but no dynamite to break the logjam yet. There’s been no real movement in the right direction because politics has been injected into the decision-making process to a great degree,” says Val Giddings, a Washington, DC–based consultant on agricultural biotech and former BIO staffer and USDA official, referring to GM crop reviews by the USDA Agriculture and Plant Health Inspection Service (APHIS).

Researchers developing GM crops, particularly those outside major companies, admit to being frustrated with APHIS and other federal regulators who review GM crops. “Because of regulatory costs, we may never get our GM peanuts to market,” says plant pathologist Elizabeth Grabau of Virginia Tech in Blacksburg, referring to a peanut variety containing a barley gene that renders the plant resistant to fungal blight. “Public sector researchers simply can’t absorb those costs,” adds plant geneticist Nina Fedoroff of Pennsylvania State University in University Park. “Everything is reviewed on a case-by-case basis, and it takes years and millions of dollars.”

One component of this regulatory challenge is the “clash” between biotech and organic agriculture, according to USDA Secretary Tom Vilsack. Organic farming is playing an increasingly important role in US agriculture, but its farmers and customers insist on no cross-contamination with GM crops. “A conversation needs

Box 1 Patent reform...again

The US Patent Reform Act has had more variations than a bulldog has wrinkles—with versions introduced in 2006, 2007, 2008, 2009 and 2010. The bipartisan bill, now called the America Invents Act, which Senator Patrick Leahy introduced as the Patent Reform Act of 2011 at the end of January, passed the Senate by an overwhelming margin on March 8. The biotech industry has supported these efforts, and BIO specifically endorsed this bill, which awaits consideration in the House of Representatives. “Once enacted into law, it will strengthen and improve our nation’s patent system, spurring innovation and job creation,” says Greenwood of BIO. Its provisions will enhance “patent quality and the efficiency, objectivity, predictability and transparency of the patent system.”

The new legislation dispenses with many of the potentially damaging proposals in previous drafts and also goes some way to establishing a simpler, objectively based and internationally consistent US patent system⁵. Perhaps its most important component is to shift from a first-to-invent to a first-inventor-to-file system. This change puts US patents in line with those elsewhere and will eliminate arcane and costly litigation associated with the current system, whose unpredictability rises sharply whenever priority is contested. Although some universities expressed concern about this change, many academic scientists doing biotech are already accustomed to this practice because they want their patents to be accepted internationally, says patent attorney David Forman of the law firm Finnegan in Washington, DC.

The bill includes several provisions to shorten patent review times and to enable outside challenges. For instance, before a patent issues, third parties will be able to bring prior art to the attention of officials at US Patent and Trademark Office (USPTO). Further, for a limited time after a patent issues, third parties can challenge the validity of the patent in the USPTO on any grounds, supplementing existing mechanisms. Because these changes allow patents to be challenged at the USPTO before going to court, “this could reduce litigation costs,” Forman says. Such challenges will put more demands on the USPTO, but the new law begins to address those needs by ensuring that the agency retains user fees instead of those fees being diverted into the general federal funds, as they have been. “That’s very important” for the USPTO, Forman adds.

In addition, the legislation virtually eliminates the requirement for an inventor to disclose the ‘best mode’ for carrying out an invention (currently often used as a costly defensive argument by patent infringers), provides fee-setting authority to the USPTO, and opens the way for establishing regional branches of the USPTO. The bill also removes previously proposed damages provisions, recognizing that the courts have “cleaned up” this area that some people in the biotech industry said had threatened the sector’s “life blood,” Forman says.

to take place outside USDA between [biotech proponents] and those producing organic crops, who feel threatened,” he says. If this clash is not resolved, the biotech industry is likely to face more delays through lawsuits, he adds.

“I think there will be a continuing discussion on ‘coexistence,’” says Conko of CEI in Washington, referring to growing and potentially comingling organic and GM crops. “Because there’s a lot of money in organic farming, it’s a big business with a lot of political support for this discussion.”

Fedoroff, who was science advisor at the US State Department until last year, says that the President’s Office of Science and Technology Policy (OSTP) is trying to resolve this issue. She points out that as there have been no ill consequences from GM crops, the regulations that have been in place since the 1980s are unnecessary and ill-suited, even if they were a good idea when first implemented. “This is a clear-cut case

of regulations that don’t need to be there,” she says. “It’s the right moment, and [OSTP director John] Holdren says it’s progressing.” How such a regulatory overhaul would sit with organic farmers and other critics of GM crops is now a matter for conjecture, except to say that legal challenges seem a likely early response.

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Biotech patents: looking backward while moving forward

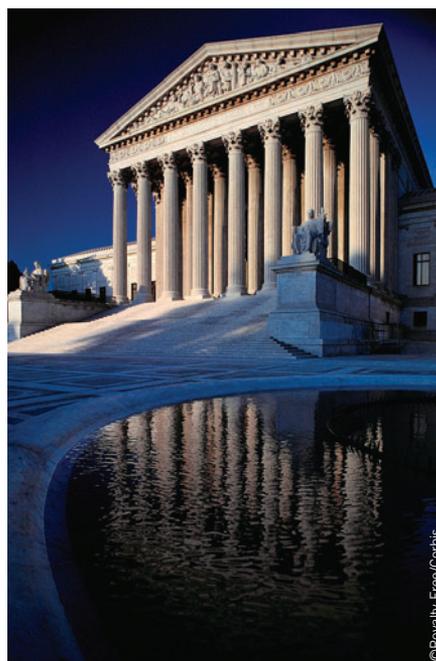
Rebecca S Eisenberg

Laboratory Corporation v. Metabolite Laboratories may signal renewed interest on the part of the US Supreme Court in what is, and what is not, patentable in biology.

Although the patent system is designed to promote the progress of science and the useful arts¹, it is slow to adapt to technological change. The statutory framework for US patent law, which has remained remarkably constant over the past two centuries, sets forth essentially the same rules for inventions in all fields of technology². Some observers have argued that the courts in fact apply these rules differently in different technological fields³, but US courts are bound to apply the rules laid down by US Congress and are therefore severely restricted in their ability to fine-tune the law as new technologies arise. Moreover, the common law method makes a discipline of looking backward to resolve new controversies in accordance with precedent, rather than forward in anticipation of change.

On the other hand, patent applicants have every reason to look forward. They stand to profit from drafting patent claims that cover their inventions in a durable way so that those who make incremental adaptations cannot easily get around their patents. Strategic claim drafting is itself an evolving art that advances in tandem with technology, subject to the constraints of patent law.

When patent claims on new technologies present unresolved legal issues, it typically takes years for these issues to reach the point of resolution in the courts. Only in the past year, for example, has the US Court of Appeals for the Federal Circuit had occasion to consider basic questions concerning the patentability of expressed sequence



Murky waters: The US Supreme Court recently granted a review of the case of *Laboratory Corporation v. Metabolite Laboratories*, ostensibly to examine the issue of patent eligibility.

tags (ESTs), a technology that is more than a decade old, and in deciding that case, the court relied on previous decisions involving technologies that are older still⁴. In theory, the focus on precedent in the legal system makes decisions more predictable, promising that future cases will be resolved consistently with past cases. But technological change often leads patent applicants to pursue novel patent claiming strategies that bring new questions into view, creating uncertainty as to the meaning of the applicable rules.

Diamond v. Chakrabarty

Consider, for example, a case that came before the US Supreme Court in the early years of the biotechnology era, *Diamond v. Chakrabarty*⁵. That case involved a patent claim on a genetically modified, oil-eating bacterium. The US Patent and Trademark Office (PTO) rejected the claim on the ground that the subject matter was “living,” setting the stage for lengthy appellate litigation. Previously, living organisms had generally been assumed to be ineligible for patent protection. In keeping with this understanding, pharmaceutical firms that used microbial strains to produce antibiotics had typically sought patent protection on methods of production, but not on the strains themselves⁶. But the basis for exclusion that had been articulated in judicial precedents was not that the organisms were “living,” but rather that they were “products of nature”⁷. The rhetoric of these cases presented nature as having done the heavy lifting, creating products and phenomena with awesome capabilities. The value added by human inventors, consisting primarily of figuring out what nature had done and then making minor adaptations, was relatively trivial.

In the anxious rhetoric surrounding genetic engineering in the 1970s, the relationship between nature and human inventors was pictured quite differently. Rather than merely copying from nature, humans seemed to be altering nature’s plans in unprecedented ways, making the concerns and intuitions that persuaded previous courts to leave natural products and natural phenomena outside the patent system seem inapposite in this context. By the time the issue was presented to the Supreme Court, the anxiety surrounding genetic engineering

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had begun to subside, and medically important genes had been cloned in microorganisms. The commercial potential of biotech had become manifest, and a host of *amicus curiae* briefs from the scientific community urged the court to uphold the patentability of genetically engineered microorganisms⁸.

Perhaps if the Supreme Court had considered the issue promptly after Chakrabarty's patent application was filed in 1972, it would have been more inclined to see the issuance of a patent on living subject matter as unprecedented. Ruling instead in 1980, it saw the exclusion of living subject matter as unprecedented, holding that Congress intended that patent protection be broadly available for "anything under the sun that is made by man."

In stark contrast to the public controversy surrounding the patentability of Chakrabarty's invention, the patenting of DNA sequences in the late 1970s and 1980s drew hardly any attention from the media. Following precedents upholding the patentability of purified versions of such naturally occurring products as adrenaline⁹ and vitamin B₁₂ (ref. 10), the PTO had no trouble allowing patents on "purified and isolated" DNA sequences and recombinant constructs incorporating such sequences. In the early days of the biotech industry, patenting the genes encoding therapeutic proteins looked like a high-tech variation on the familiar practice of patenting drugs. As a matter of legal doctrine, the courts and the PTO treated these inventions as chemicals¹¹. Although the analogy may never have been perfect, the characterization provided an extensive body of precedent to consult in establishing the patent ground rules for this emerging field, and doubtless reduced the considerable uncertainty confronting investors in new biotech firms. The scientific community did not register significant opposition to the patenting of DNA sequences until the early years of the Human Genome Project, when the US National Institutes of Health (NIH) began filing patent applications on ESTs¹². By this point, categorical objections to the patenting of DNA sequences seemed untimely and out of touch.

Anything under the sun?

Over the past quarter century, following the Supreme Court's broad directive in *Diamond v. Chakrabarty*, the Federal Circuit has gradually eviscerated what once appeared to be time-honored categorical exclusions from the patent system for such subject matter as "business methods"¹³ and "mathematical algorithms"¹⁴ in favor of a 'big tent'

approach to patent eligibility. Most of the cases that have raised issues of patent eligibility during this time period have involved information technology rather than biotech.

Since *Diamond v. Chakrabarty*, the Federal Circuit has gradually abdicated its authority to police these boundaries in favor of an approach that collapses the traditional restrictions on patent eligibility into a simple requirement that the invention be "useful".

More important than categorical exclusions in limiting the reach of the patent system for biotech have been the utility and disclosure standards for patent protection¹⁵.

Recently, however, the Supreme Court has signaled its interest in taking up the threshold issue of patent eligibility once again in a case called *Laboratory Corporation v. Metabolite Laboratories*¹⁶. This case involves a patent claim to a method of correlating elevated homocysteine levels in body fluids with cobalamin or folate deficiencies. The PTO issued the patent, and the patent holder successfully enforced it both at trial and before the Federal Circuit. The Supreme Court granted Metabolite Laboratories' request for review solely on the question of whether the patent "can validly claim a monopoly over a basic scientific relationship used in medical treatment."

The Supreme Court has been inundated with *amicus curiae* briefs in the *Laboratory Corporation* case, as it was 25 years ago in the *Chakrabarty* case. But whereas almost all of the *Chakrabarty amici* wrote in support of patent eligibility, the *Laboratory Corporation amici* are more sharply divided. Organizations that join Metabolite in urging the Court to rule against patent eligibility include the American Medical Association (Chicago), the American College of Medical Genetics (Bethesda, Maryland), the American College of Obstetricians and Gynecologists (Washington, DC), the Association for Molecular Pathology (Bethesda, Maryland), the Association of American Medical Colleges (Washington, DC), the College of American Pathologists (Northfield, Illinois), the American Heart Association (Dallas, Texas), the American Clinical Laboratory Association (Washington, DC), the American

Association of Retired People (Washington, DC), Computer and Communications Industry Association (Washington, DC), IBM (Armonk, New York), Bear Stearns (New York), Lehman Brothers (New York), and Affymetrix (Santa Clara, California). Several brief writers are urging the Court to refrain from addressing the issue of patent eligibility and to resolve the case on other grounds, including the Solicitor General and American Express Company (New York). Some are frankly more interested in the implications of the case for patents on other kinds of subject matter, including business method patents, than they are in its implications for biomedical subject matter.

Boundaries of eligibility

Inasmuch as the Federal Circuit did not consider the issue of patent eligibility in the facts of this case, it is highly unusual that the Supreme Court granted review on that issue, suggesting that the Court is going out of its way to find an opportunity to address the topic. The chorus of *amici* that have seized upon this opening to voice their competing views about the expanding reach of the patent system can only confirm the Court's suspicion that the issue is important and timely. But the failure of the Federal Circuit to address the issue of patent eligibility in this case leaves the Supreme Court with a poor record on which to consider the issue. This is particularly troubling because, if and when the Court takes up the topic of patent eligibility, it will be hard pressed to find any guidance on how to draw reasonable subject matter boundaries for the patent system in decisions of the past 25 years. Since *Diamond v. Chakrabarty*, the Federal Circuit has gradually abdicated its authority to police these boundaries in favor of an approach that collapses the traditional restrictions on patent eligibility into a simple requirement that the invention be "useful"¹⁷. The PTO has ultimately acquiesced in this liberal approach to the threshold requirement of patent eligibility¹⁸, diminishing the likelihood that the issue will come before the courts for review.

To find authority for limitations on patentable subject matter, the Court would have to go back to its own decisions from the 1970s and earlier. These decisions are riddled with contradictions and were hardly up to the task of guiding examination of the patent claims that were arriving at the PTO 30 years ago.

Yet the aspiration in these decisions to preserve an unpatented "storehouse of knowledge of mankind...free to all men and reserved exclusively to none"¹⁹ remains a worthy and inspiring goal, and one that is

fully consistent with the purpose of the patent system. That so many institutions with a stake in promoting innovation are urging the Supreme Court to return to the teachings of these decisions should be a wake-up call for the Federal Circuit and the PTO that the boundaries of the patent system are badly in need of fortification.

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2. US Patent Act, 35 US Code §§ 1 et seq.
3. Burk, D. & Lemley, M. Policy levers in patent law. 89 *Va. L. Rev.* 1575 (2003).
4. *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).
5. 444 US 1028 (1980).
6. See, e.g., *In re Mancy*, 499 F.2d 1289 (CCPA 1974).
7. See *Funk Bros. Seed v. Kalo Inoculant*, 333 US 127 (1948).
8. For a detailed review of the *Chakrabarty* case, see Eisenberg, R.S. The Story of *Diamond v. Chakrabarty*: Technological Change and the Subject Matter Boundaries of the Patent System. in *Intellectual Property Stories* (eds. Ginsburg, J.C. & Dreyfuss, R.C.) 327-357 (Foundation Press, New York, 2006).
9. *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F.95 (SDNY 1911), *aff'd*, 196 F.496 (2d Cir. 1912).
10. *Merck & Co. v. Olin Mathieson Chemical Corp.*, 253 F.2d 156 (4th Cir. 1958).
11. See, e.g., *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206 (Fed. Cir.), *cert. denied sub nom. Genetics Institute v. Amgen*, 502 US 856 (1991) ("A gene is a chemical compound, albeit a complex one....").
12. See Adler, R.G. Genome research: fulfilling the public's expectations for knowledge and commercialization. *Science* **257**, 908 (1992); Eisenberg, R.S. Genes, patents, and product development. *Science* **257**, 903 (1992); Healy, B. Special report on gene patenting. *N. Engl. J. Med.* **327**, 664 (1992); Kiley, T.D. Patents on random complementary DNA fragments? *Science* **257**, 915 (1992).
13. *State Street Bank & Trust v. Signature Financial Group*, 149 F.3d 1368 (Fed. Cir. 1998), *cert. denied*, 525 US 1093 (1999).
14. *AT&T v. Excel Communications*, 172 F.3d 1352 (Fed. Cir.), *cert. denied*, 528 US 946 (1999).
15. 35 US Code §§ 101, 112.
16. *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, 370 F.3d 1354 (Fed. Cir. 2004), *cert. granted*, 126 S. Ct. 543 (2005), *vacated, reconsidered, and cert. granted*, 126 S. Ct. 601 (2005); Supreme Court docket posted at <http://www.supremecourtus.gov/docket/04-607.htm>.
17. See, e.g., *State St. Bank & Trust v. Signature Financial Group*, 149 F.3d 1368, 1373 (Fed. Cir. 1999). ("Unpatentable mathematical algorithms are identifiable by showing they are merely abstract ideas constituting disembodied concepts or truths that are not 'useful.'...to be patentable an algorithm must be applied in a 'useful' way.")
18. *Ex parte Lundgren*, 76 USPQ (BNA) 1385 (Bd. Pat. App. & Interferences 2005); USPTO, Request for comments on interim guidelines for examination of patent applications for patent subject matter eligibility. 70 *Federal Register* 75451 (Dec. 20, 2005).
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Unsettled expectations: how recent patent decisions affect biotech

Brenda M Simon & Christopher T Scott

A look back shows that broad patents are a thing of the past and biotech inventors face heightened requirements for patentability.

There is perhaps no industry more dependent on the value of intellectual property than biotech. Yet obtaining and enforcing patents has become more difficult in this technological space over the last decade. Not only must biotech inventions be new, useful and nonobvious, but they also must meet heightened requirements for patentability. Here we review several recent patent decisions that can profoundly affect the biotech industry. In these cases, the courts ruled on essential questions to patentability, including whether inventions are even eligible for protection. We discuss how changes in the law can affect decisions of whether and when to seek patent protection, the expectations of investors, and most importantly, the validity and enforceability of entire classes of patents.

***Bilski*: a challenge for diagnostics**

Under US patent law, the first step for patent protection is showing eligibility. To determine whether the subject matter of an invention is eligible, the courts must ask whether the claims described in the patent preempt a fundamental principle, such as an abstract idea, natural phenomenon or law of nature (not eligible), or whether they apply a law or formula to a known structure or process (likely eligible). The ‘machine-or-transformation’ test is one way to determine eligibility. Under this test, the invention must be tied to a specific machine or transform an article. The machine or transformation must impose ‘meaningful limits’ on the

claims—not just adding a field-of-use restriction, or requiring insignificant extra-solution activity, such as data gathering.

The United States Supreme Court recently addressed the issue of eligibility in *Bilski v. Kappos*¹ in 2010. The question was whether a method of commodities hedging constitutes patentable subject matter—in the words of the Patent Act, is the method a “new and useful process, machine, manufacture, or composition of matter”²? The worry was that if method patents always had to be subjected to the machine-or-transformation test, it could significantly reshape the biotech landscape. Many patents that undergird corporate portfolios are based on method claims, such as advanced diagnostic medicine techniques. But the court held that the machine-or-transformation test is not the sole test for patent eligibility, but instead is an “important clue.”

In light of *Bilski*, are diagnostic methods patentable? The US Court of Appeals for the Federal Circuit tackled this question in *Prometheus v. Mayo*³ in 2010. The claims discussed a method of measuring a patient’s metabolism of a drug, and in response adjusting a drug dosage to treat gastrointestinal disorders. Because the claims covered the application of a natural phenomenon in a particular method of treatment, they did not preempt a fundamental principle. When a claim is directed to a method of treatment involving administration of a particular class of drugs, the court found it is transformative. Measuring drug metabolism in clinical tests was similarly transformative, as it requires extraction from the substances to be measured. This satisfied the machine-or-transformation test, and diagnostic claims tied to methods of treatment will be considered patent eligible. The Federal Circuit will shortly reconsider a similar case, *Classen v. Biogen*⁴, which concerns a method of optimizing vaccination schedules. The question

is whether the Federal Circuit will develop some other tool besides the machine-or-transformation test to assess preemption in these cases.

The Federal Circuit is also reviewing *BRCA* sequence patents in the *Myriad*⁵ litigation. Several of the method claims compare a given DNA sequence with normal and mutated *BRCA* sequences to determine susceptibility to cancer. Another claim describes a method of drug screening using recombinant cells that express a *BRCA* protein. Isolated DNA sequences and cDNA molecules comprise the composition-of-matter claims. Whether *Myriad*’s patents are eligible will likely depend on how broadly they are interpreted and whether the court applies the machine-or-transformation test. If practicing the method requires manipulation of the measured substances—as opposed to comparisons that can be performed mentally—the method would seem to satisfy the machine-or-transformation test articulated by the Federal Circuit.

The analysis of the composition claims will be more difficult. In general, products of nature are ineligible for patent protection. However, a product of nature that is altered, isolated or purified by an inventor has long been considered eligible for patent at the US Patent & Trademark Office (USPTO). Now, the determination of eligibility may depend on how broadly the term ‘isolated’ is defined. The *Myriad* decision has the potential to affect not only patents on isolated and purified genes, which are becoming less relevant as the discovery of single gene disorders slows down, but also those related to antibodies, proteins, cell lines and stem cells.

The case for usefulness

Even if an invention is eligible for a patent, the inventor must still show it is useful. Biotech inventions must show a higher degree of utility than many other types of inventions. Claims must show both specific and substantial utility.

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For specific utility, the inventor must indicate that the invention provides a particular public benefit. For substantial utility, the inventor must show the invention has “a significant and presently available benefit to the public”⁶.

In 2005, the Federal Circuit addressed the utility required for DNA fragments known as “expressed sequence tags” (ESTs) in *In re Fisher*⁶. An EST corresponds to a portion of a gene being expressed, which can be useful in identifying an unknown gene and its location. But, an EST does not explain the purpose and use of the gene. In *Fisher*, the court rejected an attempt to patent ESTs where the function of the genes represented by the ESTs was not yet identified. Awarding a patent in this case “would amount to a hunting license” for performing research that might not result in anything useful. In this way, the utility standard precludes patenting sequence information for genes of unknown function. This results in a heightened standard for biotech patents, which can delay filing until the required utility can be shown.

Are sequences and me-too drugs novel?

An invention must also be novel. Novelty is an increasingly difficult requirement for patents that claim genetic sequences and metabolites of previously patented drugs. Now that sequenced human genomes are accessible, the novelty of claims to genetic sequences is being called into question. In 2009, the Federal Circuit held in *In re Gleave*⁷ that a laundry list of nucleotide sequences renders claims to particular oligonucleotides not novel, even though there was no known use for the listed sequences. Although methods of use for such sequences are likely novel, new composition patents on them are not, and may soon become obsolete.

Until recently, drug manufacturers could obtain composition patents on metabolites formed after ingestion of their previously patented medications. This strategy would hinder market entry by generic manufacturers, even if the key patent on the drug had expired. But in 2003, the court in *Schering v. Geneva*⁸ invalidated a patent covering a metabolite of loratadine, the active ingredient in Claritin. It ruled that the parent patent on loratadine undercut the novelty of the later metabolite patent. Even though the patent holder did not recognize that the metabolite was formed until after filing the primary patent, the court held that the inventors did not have to know that the metabolite existed for it to invalidate the later patent. In view of this decision, patents claiming metabolites of previously patented medicines are called into question.

Beware the obvious

In addition to the utility, eligibility and novelty requirements, an invention must not be obvious.

To determine nonobviousness, the court asks whether one of ordinary skill in the art would have found the invention obvious in view of what is published in the literature, or is otherwise prior art. In 2007, the US Supreme Court provided for more flexibility in determining obviousness in *KSR v. Teleflex*⁹. The court held that the prior art does not have to provide some teaching, suggestion or motivation to make the claimed invention. Instead, courts can take into account predictability and what a person of ordinary skill, exercising creativity, would find obvious to try.

The Federal Circuit applied this reasoning to *In re Kubin*¹⁰ in 2009, which significantly changed the obviousness rule for biotech. This classic biotech invention at issue required isolating and sequencing a gene that encoded a known protein. Both the sequence and the protein were obtainable by known methods. The prior art both identified the protein and suggested its function. The court ruled the gene was obvious, as it was reasonably expected in view of the prior art, and obvious to sequence in view of the limited number of predictable solutions. Many gene patents still may be nonobvious despite *Kubin*, as the prior art in that case identified the protein, as well as suggested its purpose and use.

Obviousness was at the center of the controversial *inter partes* reexamination of three foundational embryonic stem cell patents held by the Wisconsin Alumni Research Foundation (WARF) and inventor James Thomson. The USPTO examiner first invalidated the claims for anticipation and obviousness, but later withdrew the rejections. The Foundation for Taxpayer and Consumer Rights appealed. In its 2010 decision¹¹, the Board of Patent Appeals and Interferences invoked rulings in *KSR* and *Kubin* and cited 12 instances of prior art in its rejection of the broadest of the three patents, which claimed rights to the lines themselves. Even if *Bilski* limits the patentability of genes, a higher bar for overcoming obviousness could have a greater impact on biotech patents.

Show possession

To obtain a patent, applicants must adequately describe and enable their inventions. Enablement requires the applicant to teach one of ordinary skill in the art how to make and use the invention without undue experimentation. The written description requirement generally calls for the applicant to demonstrate possession of the invention at the time of filing.

Compared to other fields, the courts ask for a rather stringent written description for biotech inventions. For genetic inventions, an applicant generally needs to provide the sequence of the claimed gene to satisfy the written description

requirement. Merely discussing how to obtain the sequence will not do the job.

The Federal Circuit recently clarified the scope of the written description requirement in *Ariad v. Lilly*¹², with all of the active judges rehearing the case in 2010. In *Ariad*, the court held that written description is a separate and distinct requirement from enablement. Ariad's claims recited methods of reducing the activity of a transcription regulator. For support, Ariad had discussed three classes of molecules that could potentially carry out this inhibition. The court invalidated the claims, holding Ariad's hypothetical description of the molecules was inadequate in view of the nascent state of the technology and the breadth of the claims.

In effect, the written description requirement hinders claims to a genus, as it has become difficult to describe a sufficient number of species for support. Inventors need to show they possess more than a couple of members of a large group and may need to show additional knowledge or functional relationship between them. This makes obtaining patents with genus claims more difficult, and easier to invalidate once they have been granted. A high threshold for written descriptions results in patents with narrower claims that can more easily be designed around.

Broad patents: a thing of the past?

The past decade has been a challenging one for biotech. Recent patent cases have made it difficult to obtain the broader protection to which the industry had become accustomed, while making challenges more likely. Considerable uncertainty exists in the areas of eligibility, obviousness and disclosure. How these emerging tests are applied has the potential to profoundly affect the biotech industry. In recognition of emerging developments in areas like personalized medicine, stem cells and synthetic biology, the courts seem reluctant to award broad patents that may tie up downstream innovation.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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2. 23 USC §101.
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4. *Classen Immunotherapies, Inc. v. Biogen IDEC, Nos. 2006-1634 and 2006-1649* (Fed. Cir. 2008).
5. *Association for Molecular Pathology v. USPTO and Myriad Genetics, Inc.*, No. 2010-1406 (Fed. Cir. 2010).
6. *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).
7. *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009).
8. *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373 (Fed. Cir. 2003).
9. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).
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