2010

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Abstract: The patent-eligibility doctrine serves a gatekeeper role in excluding from patent protection natural phenomena, principles of nature, abstract ideas, and mental processes. Beginning around 1980, the U.S. patent system embarked upon a pronounced expansion in its definition of patent-eligible subject matter, particularly with respect to software and business method inventions, but also in the life sciences. In recent years, however, we have seen a backlash, with many critics from the public and private sectors arguing that the threshold for patent-eligibility needs to be raised in order to ensure that patents fulfill their constitutional objective of encouraging innovation rather than impeding it. The courts and PTO appear to have heard these critics, and have begun to actively rein in the scope of patent-eligible subject matter. This shift in the swing of the patent-eligibility pendulum will likely have a profound impact on the patentability of innovations arising out of the pharmaceutical and biotechnology industries, particularly those relating to diagnostics and personalized medicine. In this article, I discuss the current status of the patent-eligibility doctrine, how it is that we got here, and what the future might hold, particularly for the life science industries.

Keywords: Chakrabarty, LabCorp, Metabolite, Prometheus, Classen, Ariad, thiopurine, fundamental principle, machine or transformation test, Patents, Bilski, patent eligibility, patentable subject matter, personalized medicine, diagnostics.

INTRODUCTION

It is generally acknowledged that patents play an important role in incentivizing the discovery and commercialization of important new technologies, and nowhere is this more evident than in the pharmaceutical and biotechnology industries. But increasingly the U.S. Patent and Trademark Office (PTO), the courts, and indeed the patent system itself, have come under criticism for issuing patents that seem at best inappropriate, if not just plain silly, or even detrimental to science and innovation [1]. Patents claiming peanut butter and jelly sandwiches [2], "combover" hairstyling techniques [3], and methods of exercising a cat with a laser pointer [4] have received a great deal of populist attention, but these patents are more cause for amusement than any real policy concern. Other questionable patents, however, particularly those relating to non-technological "business methods", such as strategies for investing money [5], conducting online commerce [6] and minimizing taxes [7], have become the source of widespread and legitimate concern, leading some to question whether the range of potentially patentable subject matter has come to encompass innovations and discoveries better left unpatented.

In the life sciences, patents broadly encompassing the practical application of fundamental biological discoveries, such as human genes and genetic mutations [8], regulatory pathways [9], and physiological correlations [10], has become quite controversial, not because these discoveries are mundane or lack a substantial technological aspect, but rather because of the fundamental nature of these discoveries. Many view these sorts of discoveries as the raw materials for future biomedical innovation, and argue that they should be made available to all, unencumbered by personal property rights. To a large extent these sorts of fundamental discoveries come out of university and publicly funded research, and some argue that these discoveries in most cases would be made, published and commercialized regardless of the availability of patent protection, so it is folly to unnecessarily tie these inventions up with patents. Because many of these discoveries were made under federally funded grants, critics argue that the taxpayer has already paid for the research, and that patents on these discoveries translate into higher prices for consumers, effectively making them pay for the discovery twice. As a result, many argue that patents on basic biological discoveries are prone to unnecessarily impede subsequent research and product development instead of encouraging it. Increasingly, these critics have come to question whether the scope of patentable subject matter has become too broad in the biological context, and whether future biomedical innovation might be better served by reining in the patent laws to exclude some of these discoveries from patent protection, or at least limit the scope of available patent protection.

There is a doctrine of U.S. patent law, the patent-eligibility doctrine, that is intended to serve a gatekeeper role in excluding from patent protection fundamental discoveries and other subject matter deemed better left unpatented [11]. The criterion for patent-eligibility is deceptively straightforward, at least when expressed in the abstract. Essentially, any man-made product or process, that is the result of active human intervention as opposed to a product or process of nature, is eligible for patent protection, so long as it satisfies the other requirements of patentability such as novelty,

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1568-0266/10 $55.00+.00

nonobvious and practical usefulness [12]. On the other hand, natural phenomena, principles of nature, abstract ideas, and mental processes, which U.S. courts have characterized as "fundamental principles," are patent-ineligible, even if newly discovered and satisfying all the other patentability requirements [13].

Although easy to state in the abstract, the test for patent-eligibility can be difficult to apply to specific discoveries and patent claims. The Supreme Court has pointed to the law of gravity and $E=mc^2$ as examples of patent-ineligible fundamental principles [14], but these examples provide little meaningful guidance. After all, these are merely observed physical relationships; neither is a product or process, so of course they are not eligible for patent protection. At times, the Court has stated that a patent claim is patent-ineligible if it "wholly preempts" all practical uses a fundamental principle [15], implying that the scope of a patent claim has some bearing on patent-eligibility, but providing little guidance as to what it means for a patent claim to wholly preempt a fundamental principle.

In practice, it is far from clear where to draw the line between fundamental principle and patentable invention, and the effective range of patent-eligible subject matter has expanded and contracted over the years as the courts and PTO have grappled with the issue. Historically, patents were granted primarily on traditional inventions arising out of the mechanical and chemical arts. But beginning around 1980, the U.S. patent system embarked upon a pronounced expansion in its definition of patent-eligible subject matter, prompted by some important Supreme Court decisions, as discussed in more detail below, and this trend accelerated rapidly around the turn of the 21st century. In recent years, however, we have seen a backlash, with many critics from the public and private sectors arguing that the threshold for patent-eligibility needs to be raised in order to ensure that patents fulfill their constitutional objective of encouraging innovation rather than impeding it. The courts and PTO appear to have heard these critics, and have begun to actively rein in the scope of patent-eligible subject matter. This reversal in the swing of the patent-eligiblity pendulum will likely have a profound impact on the patentability of innovations arising out of the pharmaceutical and biotechnology industries, particularly those relating to diagnostics and personalized medicine. In this article, I discuss the current status of the patent-eligibility doctrine, how we got here, and what the future might hold, particularly for the life science industries.

1980-2005: AN ERA OF EXPANDING PATENT-ELIGIBLITY

Prior to 1980, the range of subject matter generally regarded as patent-eligible was substantially more restricted to than it is today. Patents were generally limited to inventions arising out of conventional technologies, such as mechanics, electronics and chemistry. The nascent biotechnology and software industries were on the cusp of achieving substantial commercial significance, but it was uncertain to what extent patent law could be stretched to accommodate these new arenas of innovation. And without some assurance of the availability of patent protection, it was unclear how investments would be recouped, particularly in a field as capital-intensive and risky as biotechnology. At this point in time, the law regarding the patent-eligibility of inventions in these new fields of technology was not particularly encouraging.

For example, in the 1940 case of *Funk Bros. Seed Co. v. Kalo Innoculant Co.*, the Supreme Court invalidated a patent claiming an inoculant comprising a novel and useful combination of naturally-occurring bacteria [16]. Even though the patented combination of bacteria did not occur in nature, but was only obtained as a result of human intervention, and the combination produced synergistic benefits not found in nature, the Court nevertheless held that the discovery merely took advantage of "manifestations of the laws of nature," and thus constituted a patent-ineligible "natural phenomenon." Later, in *Benson v. Gottschalk* [17] and *Parker v. Flook* [18], two Supreme Court decisions from the 1970s, the Court upheld PTO rejections of software patents directed to computer programs for claiming patent-ineligible subject matter. In reaching this conclusion, the Court found that the patents amounted to an improper attempt to claim the algorithm underlying the program. According to the Court , these algorithms are mere abstract ideas, a type of fundamental principle, and the patent claims would have effectively preempted all practical uses of the ideas.

Interpreted broadly, *Funk Bros.* could have substantially limited the patentability of inventions arising out of biotechnology. However, in 1980 the Supreme Court charted a new course in *Diamond v. Chakrabarty*, a landmark case that opened the door to a more permissive interpretation of patent-eligibility, and at the same time set the stage for the growth of the biotechnology industry [19]. *Chakrabarty* was an appeal of a PTO decision to reject a patent claim directed towards bacteria genetically-engineered to degrade and metabolize hydrocarbons. The bacteria were purportedly useful for cleaning up oil spills. The PTO based its rejection on its determination that living organisms are not patent-eligible subject matter, a not unreasonable interpretation of decisions like *Funk Bros*. But in *Chakrabarty*, a slim 5-4 majority of the Supreme Court disagreed, and held that while a naturally occurring bacterium would be unpatentable, a genetically-engineered organism can be patentable because it is a man-made product of human intervention. In an oft-quoted passage, the Court stressed that Congress intended the realm of potentially patentable subject matter to encompass "anything under the sun that is made by man." Thus, the key distinction is human intervention; products and processes arising out of active human invention are patent-eligible, while "laws of nature, natural phenomena and abstract ideas" are patent-ineligible and free for all to use.

Chakrabarty has been widely credited for playing an important role in the development of the biotechnology industry, particularly in the United States, by reassuring investors in biotechnology that patent protection would be available for the innovations that would hopefully result from their investment. In view of the high costs and uncertainty associated with the development of biotechnology products, particularly in the early years of the industry, this reassurance was critical. Subsequent judicial and PTO decisions have expanded upon the principle set forth in *Chakrabarty*, establishing that genetically modified plants and non-human mammals are also eligible for patent protection, as are iso-

lated and recombinant genetic sequences and other biotechnology-based inventions [20]. In its 2001 *J.E.M.* decision, for example, the Supreme Court reaffirmed its stance encouraging the patenting of biological innovations, holding that utility patent protection is available for non-naturally occurring and genetically modified plants, and reiterating that the scope of patent-eligible subject matter is "extremely broad [21]." The court emphasized that the relevant distinction in determining the patent-eligibility of biological inventions is between products of nature and man-made inventions.

In *Diamond v. Diehr*, decided in 1981, the Supreme Court weighed in again on the question of patent-eligibility, this time with respect to a software invention. In *Diehr*, the Supreme Court reversed the PTO's rejection of the patent claiming a computer program to be used in the process of curing rubber. The Court distinguished *Benson* and *Flook*, noting that in those cases the computer program essentially did little more than implement an abstract mathematical algorithm, while the patent-eligible software in *Diehr* was directed to a more tangible process of producing rubber. The production of rubber looks more like traditionally patent-eligible subject matter than the more abstract algorithms for converting numbers embodied by the *Benson* claims. In any event, like *Chakrabarty*, *Diehr* was a landmark decision that represented a shift toward a more expansive view of patent-eligible subject matter. It also opened the door to the patenting of computer programs and other non-traditional technologies. Taking their orders from *Chakrabarty* and *Diehr*, the Federal Circuit Court of Appeals (the "Federal Circuit," is the highest patent specific court in the U.S. and bears primary responsibility for the interpretation and evolution of patent law in this country) and PTO embarked upon a course of pronounced and steady expansion of patent-eligible subject matter, particularly in the area of computer programs, so that by the late 1990s patent-eligibility no longer stood as a barrier to the protection of the vast majority of software applications of any commercial significance.

In 1998, the Federal Circuit decided *State Street Bank & Trust v. Signature Financial Group*, another landmark decision in the evolution of the patent-eligibility doctrine [22]. Prior to *State Street*, it was generally assumed that in order to be patent-eligible an invention must be technological in nature, and as a consequence methods of conducting business were generally treated as patent-ineligible. However, in *State Street* the Federal Circuit dispelled this notion, effectively announcing that there is no technological requirement to patent-eligibility, and that man-made innovations of all types are patent-eligible, including novel business methods. The years after *State Street* witnessed a progressive expansion of patent-eligible subject matter, resulting in patents on methods of conducting business over the Internet, financial schemes, tax planning strategies and the like, which in earlier times would have been treated as non-technological and thus ineligible for patent protection. The new phenomenon of widespread patenting of business methods was widely criticized, prompting the PTO and Congress to institute practices and enact laws specifically restricting business method patents. For example, the PTO applies a more rigorous examination process to patent applications directed towards what it deems to be methods of doing business [23]. Congress has limited the ability of the holders of business method patents to assert these patents against prior users of the patented method [24].

Although the bulk of the criticism against the expansion of patent-eligible subject matter post-*State Street* has focused upon business method, financial and Internet patents, the expansion has also been experienced in the life sciences, where it has generated its share of criticism and calls for reform that would raise the bar of patent-eligibility. One aspect of biotechnology patent practice that has caused an inordinate amount of controversy has been the patenting of inventions arising out of the discovery of naturally occurring genetic sequences [25]. These patents are often referred to as "gene patents," although this is something of a misnomer, since in fact the law is very clear that a gene as it exists in nature, e.g., a naturally occurring gene residing in a human body, is not patentable [26]. However, an isolated polynucleotide identical in sequence to a naturally occurring genomic sequence, or a cDNA corresponding in sequence to a naturally occurring mRNA, can be patented. Likewise, recombinant genetic constructs and genetically engineered biological organisms, as well as methods of using a recombinant polynucleotide corresponding sequence to naturally occurring gene, are routinely the subject of patent protection. Note that the line between naturally occurring genes, which are indisputably patent-ineligible, and patent-eligible isolated or synthetic polynucleotides and genetic constructs, is human intervention. This is precisely the distinction the Supreme Court made in concluding that the genetically engineered bacteria in *Chakrabarty* is patent-eligible, while the combination of naturally occurring bacteria in *Funk Brothers* was found to constitute a patent-ineligible natural phenomenon.

Although the patenting of isolated genes is a fairly recent phenomenon, U.S. patent law has a long tradition of permitting the patenting of naturally occurring biological molecules in an isolated state, purified from the biological context in which they naturally occur. For example, in the seminal decision of *Parke-Davis & Co. v. H.K. Mulford & Co.*, a court held that highly purified human adrenaline was patentable, because even though adrenaline is a natural product, in its natural state it only occurs in small quantities intermixed with the rest of the cellular milieu [27]. The court noted that by purifying the adrenaline the inventor had for all practical purposes created a chemical product that did not exist in nature, and which provided significant therapeutic benefits that cannot be obtained using naturally occurring adrenaline. This principle has been extended to isolated polynucleotides, proteins and other biomolecules, and is the doctrinal basis for many of the gene patents that have been issued over the last 30 years [28].

In the early days of gene patenting, many argued that genes are of such fundamental nature it would be a grave mistake to allow them to be patented. Some argued that gene patents would impede subsequent biomedical research, or restrict patient access to important gene-based treatments, while others simply found the concept of patenting the building blocks of life to be immoral. Nevertheless, the patenting of isolated or recombinant versions of naturally occurring genetic sequences has become common, first in the U.S., and eventually in other parts of the world such as Europe. For the

most part, the fears that have been expressed by critics of gene patents do not appear to have come to pass, although there are still many who would prefer to see the patenting of DNA abolished, or least the imposition of restraints on the ability of gene patent owners to enforce such patents [26]. Furthermore, with the rising importance of genetic diagnostic testing, particularly multiplex testing simultaneously checking for mutations in multiple genes, there is still substantial concern that gene patents might ultimately prove to be an impediment to the development of, and access to, sophisticated genetic testing procedures [29].

Aside from gene patents, there are a host of other patents relating to pharmaceuticals and biotechnology that some would argue overstep the boundary between patentable invention and unpatentable natural phenomena. For example, based on their discovery of the important transcription factor NF-κB and its role in regulating gene expression, researchers at Harvard, MIT, and the Whitehead Institute succeeded in broadly patenting methods of inhibiting NF-KB activity, and have proceeded to sue pharmaceutical companies for patent infringement, alleging that the mechanism of action of certain blockbuster drugs involves inhibition of this ubiquitous regulatory pathway [30]. As discussed below, to date the universities have not prevailed in these actions, but nevertheless they have compelled drug companies to expend considerable sums defending themselves. Similarly, researchers at the University of Wisconsin developed a methodology for maintaining primate embryonic stem cells in culture, and based on this discovery were able to obtain patents broadly claiming cultured primate embryonic stem cells [31]. The university then aggressively asserted the patent to restrict access to embryonic stem cells, although in response to widespread criticism they later announced the adoption of more liberal licensing policies with respect to the patented technology [32].

In another high-profile case, researchers at the University of Colorado discovered that an elevated level of total homocysteine is correlated with the presence of a vitamin B deficiency, and obtained a patent broadly claiming any method of diagnosing for vitamin B deficiency that involves assaying for total homocysteine. The patent was then successfully used to sue a diagnostic company for performing an independently developed total homocysteine assay as a service for doctors. The court accepted a rather convoluted argument that doctors infringed the patent by ordering a homocysteine test for a patient and, based on an observation of elevated total homocysteine, diagnosed a vitamin B deficiency, and that the diagnostic company performing the assay was liable for inducing the doctor's infringement [33].

In another example, a doctor discovered that by altering vaccination schedule the risk of developing an immune disorder could be reduced, and broadly patented methods of comparing alternate vaccine schedules to determine which one is least likely to lead to the disorder [34]. The doctor then proceeded to sue various manufacturers and distributors of vaccines, including major drug companies, whom he alleged infringe the patents by participating in post-approval vaccination safety studies [35]. As discussed below, the Federal Circuit recently invalidated these patents [36]. In another case, a doctor discovered an association between a woman's maternal serum level of free beta human chorionic gonadotropin (hCG) and gestational age and the woman's risk of carrying a fetus with Down syndrome, and obtained patents broadly claiming use of the method to screen for women at risk of carrying a fetus with Down syndrome [37]. The doctor then proceeded to sue a medical screening laboratory for performing prenatal screening that allegedly infringed his patents [38].

In yet another highly publicized case, University of Rochester researchers discovered the prostaglandin H synthase-2 (PGHS-2) (also referred to as COX-2) pathway, and obtained a patent broadly claiming methods of selectively inhibiting COX-2 by administration of a non-steroidal compound [39]. The patent failed to identify any non-steroidal compound that would function as an effective COX-2 specific inhibitor, but nonetheless effectively encompassed the use of any subsequently developed COX-2 specific non-steroidal anti-inflammatory drug. When Pfizer succeeded in bringing two COX-2 inhibitors to market, BEXTRA and CELEBREX, the university sued for patent infringement. The Federal Circuit ultimately invalidated the university's patent, but the case raised the issue of whether the university overstepped in attempting to broadly and preemptively patent the practical application of an important fundamental scientific discovery.

Other examples of issued U.S. patents that some would argue come close to crossing the line between patentable invention and patent ineligible fundamental principle include a patent that broadly claims the use of the three dimensional crystal structure of a fluorescent protein to rationally engineer a mutant with altered fluorescent properties [40], another that essentially claims computer readable data representing a naturally occurring genetic sequence [41], and a third that broadly claims methods for diagnosing the presence of a polymorphism in the human KCNE1 gene [8]. These sorts of patents can raise conflicting concerns for pharmaceutical companies. On one hand, they can be detrimental, particularly in cases where they are asserted against the drug company for selling a drug that was created with little or no input from the patent owner, or when a pharmaceutical company is sued for conducting post-approval studies of a vaccine, or for using a patented naturally occurring genetic sequence or protein as a research tool in early stage drug discovery. On the other hand, there is a trend towards increased integration of diagnostic testing and drugs, often referred to as personalized medicine, and a more stringent application of the patent-eligibility doctrine might effectively preclude patent protection these sorts of innovations. Clearly, a proper balance is necessary in order to optimize the role of patents in incentivizing the discovery, development and commercialization of new and innovative medicinal products.

LABCORP V. METABOLITE

In 2005, amidst a growing chorus of critics of the patent system who argued that the bounds of patent-eligible subject matter had grown far too expansive, resulting in a patent system that too often impedes rather than incentivizes innovation, the Supreme Court entered the debate by agreeing to hear *LabCorp v. Metabolite*, a case involving the patent-

eligibility of a diagnostic method [42]. Although the Court ultimately declined to decide the case, the mere fact that it took the case at all was significant, since it signaled that at least some of the Justices on the Supreme Court thought this was an issue meriting their consideration. The Supreme Court has the discretion to decide whether or not it wants to hear a case, and will only hear a case that it thinks is highly important, usually in an attempt to clarify a legal question of substantial policy significance. As a consequence, the Court only hears a small fraction of the cases referred to it, and years go by without the Court hearing a single patent case, although in the past few years the Court has become increasingly active in the area of patents. In retrospect, it is clear that *LabCorp* teed up the issue of patent-eligibility for serious reconsideration for the first time in many years. The repercussions have already been felt, and will continue to be felt for the foreseeable future.

LabCorp traces its origin to the discovery by doctors at University Colorado of a correlation between high levels of total homocysteine in the blood and a vitamin B deficiency. These researchers also developed an accurate method of assaying for free homocysteine, using gas chromatography and mass spectrometry. In combination, these two discoveries provided doctors with an improved method for diagnosing and treating patients suffering from a vitamin B deficiency. Not surprisingly, the researchers applied for and were issued a patent claiming their new method of assaying for total homocysteine, conventional process claims raising no issues of patent-eligibility [10]. But the patent they received also included a claim (referred to as "Claim 13") that purports to effectively encompass any use of the correlation to diagnose a vitamin B deficiency. In particular, Claim 13 appears on its face to be infringed by anyone (e.g., a doctor) that tests a patient's body fluid for total homocysteine, and then correlates the observation of elevated total homocysteine with a vitamin B deficiency. Significantly, Claim 13 is not limited to the specific homocysteine assay developed by these researchers, but can be infringed by the use of any total homocysteine assay, as long as the result of the assay is used to diagnose for a vitamin B deficiency.

Ultimately, the university's patent was licensed to Metabolite Laboratories, which in turn sublicensed it to LabCorp. LabCorp performed the patented homocysteine assay method as a commercial service for doctors, while paying royalties to Metabolite for the use of the assay. In 1998, however, LabCorp switched to a different homocysteine assay (the “Abbott test”), discontinued use of the Metabolite’s patented assay, and refused to make royalty payments to Metabolite for homocysteine assays performed using the Abbott test. In response, Metabolite sued LabCorp, arguing that regardless of what homocysteine test LabCorp performed, when a doctor used the results of the test to diagnose a vitamin B deficiency in a patient that doctor infringed Claim 13. Metabolite did not sue the doctors, but did hold LabCorp responsible for inducing the doctor’s infringement, and sued under a theory of indirect patent infringement. A jury agreed, deciding in favor of Metabolite, and on appeal the decision was affirmed by the Federal Circuit [43]. Significantly, during the course of the litigation, through the appeal to the Federal Circuit, LabCorp never raised the issue of patent-eligibility with respect to claim 13.

After losing at the Federal Circuit, LabCorp petitioned the U.S. Supreme Court to hear the case. In its petition, LabCorp raised a laundry list of objections to the Federal Circuit's decision, essentially arguing that doctors did not infringe Claim 13, or that if they did LabCorp was not responsible for the doctor's infringement, and that in any event Claim 13 was invalid for violating multiple rules of patentability, such as failure to enable the claims, inadequate written description of the invention, and indefinite claim language. But buried at the end of its petition, in what appears to almost be an afterthought, LabCorp pointed out that Claim 13 effectively covers the mental processes of a doctor who orders the test and recognizes the correlation between total homocysteine and vitamin B deficiency (a “scientific fact”), without requiring a doctor to physically do anything. While not explicitly invoking the patent-eligibility doctrine, these references to mental processes and scientific fact nonetheless clearly implicate patent-eligibility.

In retrospect, it might seem surprising that LabCorp did not focus more of its argument explicitly on the issue of patent-eligibility, and did not even bring the issue up in the lower courts. But at the time, after years of expansion in the scope of patent-eligible subject matter, the patent-eligibility doctrine had for the most part come to be viewed as imposing little meaningful limitation on patentability, and LabCorp's attorneys apparently did not view it as a viable basis for challenging Claim 13. Nonetheless, at least some of the Justices on the Supreme Court were troubled by Claim 13, and more generally claims like it, and saw patent-eligibility as an appropriate legal tool for excluding these sorts of fundamental discoveries from broad patent protection. These Justices voted to take the case, specifically to consider the patent-eligibility of Claim 13, a surprising move in view of the fact that the question of patent-eligibility had never been raised in the earlier proceedings - normally, the Supreme Court only reviews the decisions of lower courts, and does not address issues that were not previously raised in a lower court.

Ultimately, however, the fact that the lower courts had not addressed the issue of patent-eligibility appears to have been the appeal’s undoing. After the parties had fully briefed the issue for the Court, and orally argued the case before the Justices, the Court changed its mind, deciding that its earlier decision to hear the case had been "improvidently granted," and dismissed the appeal without deciding it [42]. Apparently, a majority of the Justices decided that it would be inappropriate to rule on the issue of patentable subject matter when the issue had not been directly addressed in the lower courts. This was probably a good decision. Any significant change in the doctrine of patent-eligibility could have had sweeping unintended consequences for other inventions, particularly in other areas of technology.

Nevertheless, a vocal minority comprising three of the Court's nine Justices dissented from the majority's decision not to decide the case. In a strongly worded dissenting opinion authored by Justice Breyer, these Justices voiced strong concerns regarding the policy implications of Claim 13, and appeared eager to decide the case regardless of whether the issue was argued in the lower courts [42]. These Justices argued that the case was not even close. In their view, Claim

13 clearly encompasses a natural phenomenon (the correlation between total homocysteine and vitamin B deficiency) and is thus patent-ineligible. Moreover, it was clear from the tenor of Justice Breyer's opinion that these Justices were generally concerned that the lower courts and PTO were applying an overly permissive interpretation of the patent-eligibility doctrine, which had resulted in a proliferation of too many patents broadly claiming fundamental principles and that threatened to impede science and innovation. While acknowledging that patents can encourage research by providing monetary incentives for innovation, he charged that patents can also "discourage research by impeding the free exchange of information and raising the cost of using patented information." He characterized the patent-eligibility doctrine, and particularly the prohibition against the patenting of natural phenomena and fundamental scientific principles, as an important tool for screening out discoveries better left unpatented. He also opined that there is currently much legal uncertainty with respect to patent-eligibility, and that the issue affects a "substantial number of patent claims."

LabCorp, even though never expressly decided by the Supreme Court, was to have a profound influence on patent law, revitalizing a legal doctrine that had become largely moribund in recent years. After *LabCorp* put the issue front and center, patent attorneys have became emboldened to raise the issue of patent-eligibility when challenging the validity of a patent. In particular, the issue of patent-eligibility has been raised by defendants accused of infringement in three cases involving pharmaceuticals and pharmaceutical research: *Ariad v. Eli Lilly* [44], *Classen v. Biogen* [45] and *Prometheus v. Mayo* [46]. A district court rejected the argument in *Ariad*, but in *Classen* and *Prometheus* the judge sided with the defendants and held that the patents were invalid for claiming patent ineligible natural phenomena or mental processes. The *Classen* decision was recently affirmed by the Federal Circuit on appeal. More recently, the *Ariad* was decided by the Federal Circuit in a manner that invalidated the claims on alternate grounds, thus avoiding addressing the issue of patent-eligibility [47]. The Prometheus appeal is probably the most important for biotechnology and pharmaceutical industry, but has not been decided as of the time this article was written. These cases provide a useful insight into how the patent-eligibility doctrine will play out in the pharmaceutical and biotechnology sector, and it is useful to consider the facts of these cases in more detail.

ARIAD V. ELI LILLY

The patent at issue in *Ariad v. Eli Lilly* arose out of the discovery of the transcription factor NF-κB by researchers at MIT, the Whitehead Institute, and Harvard University, and the critical role the NF-κB pathway plays in regulating gene expression in a variety of contexts. A patent application was filed on behalf of the researchers in the mid-1980s, and after a "16 year trek through the [PTO]," during which time the claims were repeatedly rejected for being overly broad, this fundamental discovery ultimately resulted in a patent with claims that appear on their face to be extremely broad, essentially claiming methods of inhibiting NF-κB-mediated intracellular signaling activity in eukaryotic cells [9]. The patent was assigned to Ariad, a private company, which joined with the universities in demanding licensing fees from pharmaceutical companies such as Eli Lilly and Amgen that sold drugs whose mechanism of action purportedly involves inhibition of NF-κB activity. Significantly, there is no indication that the discovery of the NF-κB pathway played any direct role in the development of the allegedly infringing drugs. In fact, Lilly applied for patents on its two allegedly infringing drugs, raloxifine (Evista) and drotrecogin alfa (Xigris), before the university researchers even discovered NF-κB. Eli Lilly refused to pay, and Ariad and the universities sued for patent infringement. In 2006 a jury found that Eli Lilly's sale of these drugs infringed the patent, and awarded Ariad and the universities $65 million in back royalties and 2.3 percent royalty on future U.S. sales [48].

Subsequent to the jury decision, and shortly after the U.S. Supreme Court agreed to hear *LabCorp*, Lilly went back to the district judge hearing the case and asked him to invalidate Ariad's patent for claiming patent ineligible subject matter. In particular, Lilly argued that Ariad's patent claims encompass NF-κB regulation that occurs naturally in cells, and thus impermissibly pre-empts all use of a natural phenomenon. As was the case with Metabolite's patent, Ariad's patent seems to broadly cover any practical application of a fundamental biological discovery. The NF-κB pathway is ubiquitous, and likely involved with the mechanisms of action of many drugs. From Lilly's perspective, the infringement is entirely inadvertent, since they began developing the allegedly infringing drugs without any knowledge of the discovery of NF-κB. Nevertheless, the judge rejected their patent-eligibility argument, finding that Lilly had failed to provide sufficient evidence to prove that NK-κB inhibition actually occurs naturally.

Part of Lilly's problem might have stemmed from its difficulty in overcoming a fairly strong presumption under U.S. law that an issued U.S. patent is valid. Lilly's case was also hindered by procedural issues; the judge refused to consider some of the evidence submitted by Lilly in support of its argument that the regulation of NF-κB occurs naturally in cells. Perhaps as a consequence of these procedural and evidentiary hurdles, Lilly failed to persuade the judge that NF-κB inhibition exists in living cells in a way that is encompassed by Ariad's claims. On appeal, the Federal Circuit invalidated Ariad's claims on alternate grounds, thereby avoiding the issue of patent-eligibility, as discussed in more detail below.

CLASSEN V. BIOGEN

Classen v. Biogen arose out of a doctor's discovery of a relationship between vaccination schedule (the timing of the administration of a series of vaccinations) and the likelihood that the vaccination would cause a chronic immune-mediated disorder. Based on his discovery, Dr. Classen obtained patents broadly claiming methods of comparing alternate vaccine schedules to determine which schedule minimizes the incidence or severity of a chronic immune-mediated disorder [35]. The doctor then proceeded to sue various manufacturers and distributors of vaccines, including Biogen, whom he alleged had infringed the patents by participating in post-approval vaccination safety studies. The district court held on a motion for summary judgment that the patents were invalid for claiming patent ineligible subject matter. The

judge's decision is not entirely clear as to the precise basis for his determination that the claims are patent-ineligible, at times asserting that the claims are invalid for claiming a mental process, while at other times complaining that that the claims encompass a natural phenomenon. The decision concludes by noting that "[c]learly, the correlation between vaccination schedules and the incidence of immune mediated disorders that Dr. Classen claims to have discovered is a natural phenomenon."

The court in *Classen* provided absolutely no reasoning to support its conclusion that a correlation involving a vaccination schedule is "natural." Clearly, immunization using human-generated vaccines is not something that occurs absent human intervention. One could argue that a biological phenomenon that exists only as a result of human intervention, such as vaccination, does not constitute a natural phenomenon, but the court chose not to address this issue. There would appear to be some tension between the conclusion in *Classen* that a vaccination schedule is a natural phenomenon, while the NF-KB pathway at issue in *Ariad* is not, but the different outcomes are probably best explained as the result of different evidence and arguments presented in the two different cases, or simply divergent applications of a very uncertain legal doctrine by two different judges.

PROMETHEUS V. MAYO

Prometheus v. Mayo involves patents directed towards a method of using diagnostic testing to individually tailor the dosage of a drug to the metabolism of a particular patient, and so is an example of a personalized medicine patent. It is widely believed that personalized medicine will play an increasingly important role in future drug treatment regimens, so this patent litigation could be of particular significance for the biotechnology and pharmaceutical industries. The patents at issue arose out of the discovery that, by monitoring the level of certain thiopurine drug metabolites in a particular patient (6-MMP and 6-TG, as shown in Fig. **1**), it is possible to adjust drug dosage to optimize safety and efficacy for that patient. The thiopurine drugs in question (AZA and 6-MP, as shown in Fig. **1**) were used to treat individuals with immune-

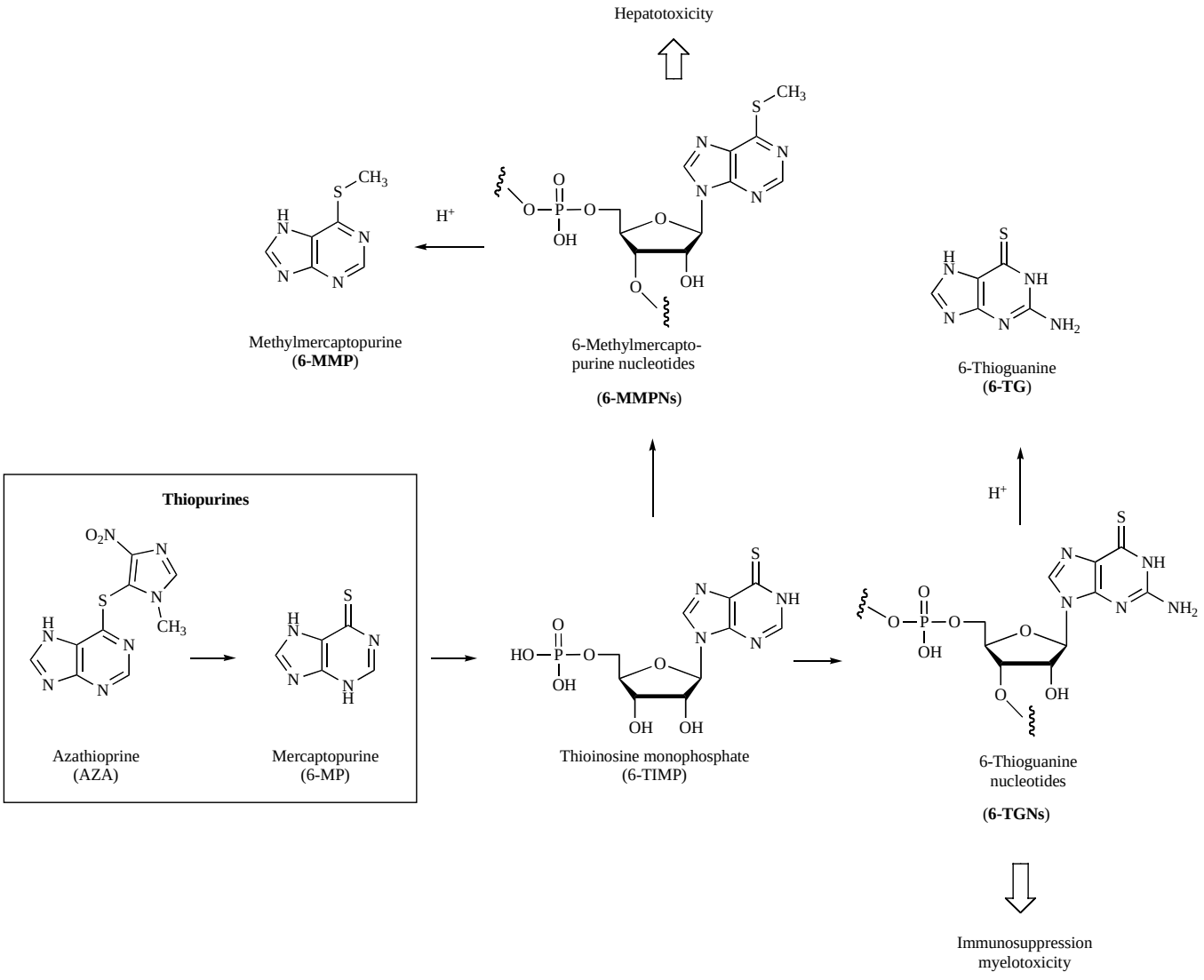

Fig. (1).

mediated gastrointestinal disorders such as Crohn's disease, but use of the drug was often accompanied by serious adverse side effects, including hepatotoxicity.

Because individuals metabolized the drug differently, it had been difficult for doctors to ascertain the proper dosage, and reportedly some doctors were even hesitant to prescribe the drugs for fear of toxic side effects. Based on the discovery of a correlation between drug metabolite levels and optimal dosage, Prometheus obtained patents claiming a method of treating individuals suffering from autoimmune disease that essentially entails administering a thiopurine drug to the patient, assaying for the level of certain drug metabolites (i.e., drug breakdown products), and recognizing that if the metabolite level exceeds an upper threshold the dosage should be decreased, while if the metabolite level is less than a lower threshold the dosage should be adjusted upward. Prometheus developed and marketed a diagnostic test for assaying for the level of these thiopurine drug metabolites in a patient, for use in determining optimal drug dosage for that individual, and licensed the technology to the Mayo Clinic. However, Mayo eventually developed its own thiopurine metabolite test, stopped paying licensing fees to Prometheus, and announced that it planned to compete with Prometheus by marketing its own test. Prometheus sued for patent infringement, and Mayo defended by challenging the patent-eligibility of Prometheus' patents, arguing that the relationship between thiopurine drug metabolite levels and optimal drug dosage is a natural phenomenon.

Prometheus argued that since the drug metabolites only exist in the human body as the result of human intervention (i.e., by administration of the thiopurine drugs), the correlation cannot be considered a natural phenomenon. However, the district court judge held that the correlation between the level of thiopurine drug metabolites in the human body and therapeutic efficacy and safety is a "natural phenomenon," and that Prometheus' asserted claim were invalid under Section 101 for "wholly preempting" this supposed natural phenomenon. Although some would argue that a correlation involving the interaction of a man-made drug with the human body cannot constitute a natural phenomenon, the judge found that since thiopurine drugs "are converted naturally by enzymes within the patient's body to form an agent that is therapeutically active, . . . the correlation results from a natural body process," and is thus is an unpatentable "work of nature."

In other words, the court in *Prometheus* found that the mere involvement of a natural process renders a correlation that exists only as the result of human intervention an unpatentable natural phenomenon. This rationale seems questionable, for if taken to its logical extreme, it would seem that any invention, in any area of technology, involves natural processes at some level, and would thus be unpatentable under this test. For example, any electronic invention relies on the fundamental nature of electrons and materials such as silicon. Mechanical inventions rely on the law of gravity and friction. And what biological invention does not involve natural biological processes? Drugs and methods of using drugs to treat illness are widely acknowledged to be patentable, but they typically interact with "natural body processes." As discussed below, it is hoped that the Federal Circuit will take up this issue and clarify the distinction between natural and non-natural phenomena, particularly in the biological and pharmaceutical context.

IN RE BILKSI

LabCorp not only opened the minds of lawyers to a new basis for challenging patent validity, it also put the PTO and the Federal Circuit on notice that the Supreme Court was receptive to the arguments made by those that complained that the patent-eligibility bar had been set too low, and if the PTO and Federal Circuit did not act to rein in the scope of patent-eligible subject matter soon it was likely the Supreme Court would choose to intervene in a future case. Historically, the Supreme Court has to a large degree given free rein to the Federal Circuit to oversee the evolution of patent law, but increasingly in recent years the Supreme Court has actively intervened, and at times rebuked the Federal Circuit when it felt that that the lower court's had gotten off track. Two recent examples include *KSR International v. Teleflex* [49], where the Supreme Court effectively reprimanded that the Federal Circuit for misapplying the standard for determining whether an invention is obvious (and thus unpatentable), and *eBay v. MercExchange* [50], where the Court held that the Federal Circuit had been wrong to automatically impose an injunction in nearly every instance where patent infringement was proven.

Apparently taking a cue from *LabCorp*, the PTO began to apply the patent-eligibility doctrine more stringently, and the Federal Circuit supported this move by affirming decisions from the PTO Board of Patent Appeals and Interferences ("the Board") of appeals rejecting claims for encompassing patent ineligible subject matter. For example, two important cases were *In re Nuijten* [51] and *In re Cominskey* [52], appeals of Board decisions that were decided on the same day. In both cases, the Federal Circuit affirmed the PTO's rejection of the claims as invalid for encompassing patent ineligible subject matter. *Nuijten* and *Cominskey* were both decided by three judge panels of the Federal Circuit, which is typical - most appeals are decided by three judge panels drawn from the twelve judges of the Federal Circuit. However, when the Federal Circuit wishes to make a more emphatic and binding statement of the law, particularly in an area of legal uncertainty with important public policy implications, all twelve judges will come together to decide the matter "*en banc*." Because it takes into account the views of all judges sitting on the court, an *en banc* decision carries more weight than the more typical panel decisions. An *en banc* decision can be viewed as a mechanism for the Federal Circuit to make a strong, authoritative statement of the law, and the decision must be followed by the lower courts and by subsequent panels of the Federal Circuit.

Therefore, not surprisingly, the Federal Circuit decided to hear a patent-eligibility case *en banc*, presumably to clarify the law in this area, and hopefully set their house in order before the Supreme Court stepped in and did it for them. The case they chose was *In re Bilski* [53], another appeal from the Board. Bilski had applied for a patent claiming, in essence, a method of hedging risk in the field of commodities trading, a business method patent of the type of that has been particularly targeted by critics of the expansion in patent-

eligible subject matter since *State Street*. The Board had affirmed the patent examiner's rejection of the claims, holding that what it characterized as a "transformation" of "non-physical financial risks and legal liabilities … is not patent-eligible subject matter," and that Bilski was impermissibly attempting to preempt any and every possible way of implementing an abstract idea.

The *en banc* Federal Circuit sided with the Board, affirming that Bilski's claims are indeed patent ineligible. The decision to affirm was not surprising; this is a classic "business method" claim, the type of claim that the public, and at least some members of the Supreme Court, would very likely object to, and eleven of the twelve Federal Circuit judges agreed on this point. What was surprising to many, however, was that a nine judge majority went much further than simply invalidating the claims at issue, and joined in pronouncing a single test for patent-eligibility that apparently will be applied from now on in assessing the patent-eligibility of all process claims. This test has come to be referred to as the "machine or transformation" test. Process claims are quite common in the life sciences, so this decision has profound implications for the pharmaceutical and biotechnology industries.

Before setting forth the machine or transformation test, the *Bilski* majority (referred to hereafter simply as *Bilski*) noted that, under binding Supreme Court precedent, the fundamental inquiry in assessing patent-eligibility is whether the patent "claim recites a ***fundamental principle*** and, if so, whether it would ***pre-empt*** substantially all uses of that fundamental principle." (emphasis added) *Bilski* uses the term "fundamental principle" as shorthand for "laws of nature, natural phenomena, [or] abstract ideas" and mental processes, categories of patent ineligible subject matter previously identified by the Supreme Court.

Note the court's emphasis on "preemption"; a claim limited to a particular "application" of a fundamental principle is patent-eligible, while a claim that "seek[s] to pre-empt the use of" that fundamental principle is not. In other words, an overly broad patent claim can be found patent ineligible if it substantially encompasses all practical uses of a fundamental principle. In a sense, *Bilski* treats patent-eligibility as a tool for limiting claim breadth, an objective traditionally accomplished by means of other patent law doctrines, particularly the enablement and written description requirements.

But after articulating the fundamental test as hinging on preemption, *Bilski* goes on to explain that in practice it is hardly straightforward for a court to determine whether a given claim would preempt all uses of the fundamental principle. So, in order to assist the courts and PTO in making this determination, *Bilski* articulates a more definitive test to determine whether a process claim is tailored narrowly enough to encompass only a particular application of a fundamental principle, rather than to preempt the principle itself. Under this "machine or transformation" test, a claimed process is patent-eligible only if it satisfies one of two criteria: (1) it is tied to a particular machine or apparatus, ***or*** (2) it transforms a particular article into a different state or thing. According to *Bilski*, this is the only applicable test and "must be applied . . . when evaluating the patent-eligibility of [any process claim]." In other words, the test appears to apply to process claims in the areas of biology and chemistry to the same extent as business methods. *Bilski* does not rule out the possibility that at some point in the future the Federal Circuit may refine or augment the test or its application, but the court did make clear that for the time being this is the sole governing test of patent-eligibility for process claims.

Furthermore, *Bilski* emphasizes that it is not enough that a patent claim merely involves the use of a particular machine, or the transformation of an article. The involvement of the machine or transformation must be central to the claimed process, constituting more than what the Court refers to as mere "insignificant extra solution activity." In other words, the machine or transformation must impose meaningful limits on the claim's scope. *Bilski* provides several examples of "insignificant extra solution activity." For example, the inclusion of a data-gathering step to a claim primarily directed towards a fundamental principle, such as a natural phenomenon or algorithm, will generally be insufficient to render the claim patent-eligible, even if the data-gathering step involves a machine or transformation. In effect, the data-gathering step will be disregarded in the analysis as "insignificant extra solution activity."

Bilski points with approval to an earlier judicial decision where a process of performing a clinical test and, based on the data from that test, determining if an abnormality existed, was held to be patent ineligible because, in essence, the claim was merely directed towards an algorithm combined with an insignificant data-gathering step. The court pointed out that every algorithm inherently requires the gathering of data inputs, and the mere inclusion of a general data-gathering step is insufficient to confer patentability on an otherwise unpatentable algorithm. At the same time, the court recognized that in some cases the recitation of a specific data-gathering process might be significant and sufficient to confer patent-eligibility on the claim. Again, it should be noted that the patent-eligibility doctrine is being used in *Bilski* as a mechanism to limit claim scope; a claim to an algorithm coupled with a general data-gathering step is generally unpatentable, but if the data-gathering step is limited to some specific methodology or reagents, the data-gathering step could be treated as substantial, and the claim treated as patent-eligible.

Bilski also provided some guidance with respect to what sorts of "transformations" would satisfy the test. For example, the court stated that a process for a chemical or physical transformation of physical objects or substances is clearly patent-eligible subject matter under the test. Furthermore, the transformation of data representing physical and tangible objects, such as "bones, organs and other body tissues" will also generally render a process patent-eligible. In contrast, a transformation of mere generalized data, not tied to any specific physical object, will generally not satisfy the test. In particular, transformations of "legal obligations or relationships, business risks, other such abstractions cannot meet the test because they're not physical objects or substances and they are not representative of physical objects or substances."

Three of the Federal Circuit judges disagreed strenuously with the majority's decision to establish the machine or transformation test as the sole governing test for patent-

eligibility of process claims. For example, Judge Newman pointed out that the test would exclude from patentability many of today's most important innovations, particularly in the growth industries of the U.S. economy, such as the computer and information service fields, which she saw as detrimental to U.S. competitiveness. Judge Mayer agreed that Bilski's claim was patent ineligible, but his approach would have been to simply classify all business method patents as patent ineligible. The machine or transformation test, he argued, will prove to be easily circumvented by clever drafting of patent claims, and in his view does too little to stem the growth of patents on non-technological methods and ideas. He also predicted that the machine or transformation test would prove exceedingly difficult to apply in practice, and will only lead to further uncertainty regarding the scope of patentable subject matter. Judge Mayer explicitly voiced his support for patents on pharmaceuticals, finding that the high cost of drug innovation justifies the award of a patent.

Finally, Judge Rader would have also found Bilski's claim to be patent ineligible for claiming what he characterized as an abstract idea, and challenged the wisdom of establishing the machine or transformation test as the sole means of assessing the patent-eligibility of all processes. He argued that the preferable and proper approach is to focus on whether the claim is directed towards a natural phenomenon, mental process or abstract idea. In particular, he argued that the patent claim at issue in *LabCorp*, Metabolite's Claim 13, is patent-eligible because the claimed process applies the relationship between high homocysteine levels and vitamin B deficiencies to achieve a useful, tangible, and concrete result - the diagnosis of a potentially serious condition in patients. He pointed out that the method of Claim 13 provides an elegant and simple way of testing for a vitamin deficiency, and argued that such life-saving innovations in the diagnostic field should be incentivized by the availability of patent protection. He goes on to predict that denying patent protection for this sort of innovation will undermine and discourage future research for diagnostic tools, and warns that the machine or transformation test "inadvertently advises investors that they should divert their unprotectable investments away from discovery of scientific relationships within the body to diagnose breast cancer or Lou Gehrig's disease or Parkinson's or whatever."

IMPLICATIONS OF BILSKI FOR THE LIFE SCIENCES

Will Judge Rader's dire prognosis of the impact of the *Bilski* machine or transformation test on certain types of biomedical research prove to be correct? It is much too early to say, but it is nonetheless prudent to consider some of the potential implications for the life sciences industry, particularly with respect to diagnostic testing and personalized medicine. First off, it is important to bear in mind that the *Bilski* machine or transformation test only applies to process claims, and so claims directed to products, such as drugs and drug formulations, polynucleotides, genetically engineered organisms, embryonic stems cells, diagnostic testing kits and the like should not be directly impacted by *Bilski*, although some of the principles articulated in *Bilski* might be applied by the courts when assessing the patent-eligibility of such product claims. Clearly, a product claim can be found patent ineligible, as illustrated by the decision in *Funk Brothers* invalidating claims to an inoculant (essentially a combination of bacteria), and claims directed towards naturally occurring molecules, such as genes or proteins in their native state, are beyond question patent ineligible subject matter.

With respect to process claims, *Bilski* appears quite emphatic that the machine or transformation test is, at least for the time being, the one and only general test for patentability of process claims, regardless of the nature of the process or the field of technology. But substantial uncertainty remains as to how the test will be applied, particularly outside the realm of business method patents from which the test arose. For example, the *Bilski* test requires the use of a "particular" machine or apparatus, or the transformation of a "particular" article. But how specific does the patent claim have to be with respect to a "particular" machine, apparatus, or article in order to satisfy the test? For example, will the use of a general computer be sufficient? Clearly, the machine or transformation test will function as a means for limiting the scope of patent protection, but the extent is unclear. For example, most diagnostic methods involve a gathering of data, which generally implies the use of some machine or apparatus and/or the transformation of some substance, e.g., a chemical transformation. Will that be sufficient to satisfy the test, or will the claim need to be limited with more particularly toward some specific machine, apparatus or transformation?

Perhaps the most significant issue implicated by the *Bilski* test, particularly with respect to diagnostic methods, will be the manner in which future courts decide whether a process step amounts to mere "insignificant extra-solution activity." In particular, the court was fairly explicit in its statement that, in general, a data-gathering step will generally not be sufficient to confer patent-eligibility, regardless of whether it involves a machine or transformation, if data gathering is inherent in carrying out a claimed algorithm, or for that matter any process that can be performed mentally (such as recognizing a biological correlation). *Bilski* strongly implies that the step of assaying for total homocysteine in Metabolite's Claim 13 constituted insignificant extra-solution activity, which would seem to render the claim patent ineligible. Once the assaying step is disregarded, the claim is merely directed towards the recognition of a correlation between total homocysteine and a vitamin B deficiency, which could be characterized as either an algorithm or mental process - in either event the result is apparently the same, patent ineligibility.

In fact, a Federal Circuit panel has already decided a case involving a data-gathering step coupled to what might be characterized as a biological correlation, *Classen v. Biogen* (discussed above), and implicitly seems to have treated the data-gathering step as insubstantial extra-solution activity. Shortly after *Bilski* was decided, the Federal Circuit affirmed the lower court's decision invalidating Dr. Classen's claims [54]. In a terse, unpublished opinion (and thus not binding on subsequent decisions of the Federal Circuit and lower courts), the Federal Circuit did not comment upon the district court's rationale for invalidating the patents, but simply concluded that the claims were patent ineligible for failure to satisfy the machine or transformation test, because the

claimed processes are neither "tied to a particular machine or apparatus" nor do they 'transform[] a particular article into a different state or thing.' In fact, the claims involve an immunization step, which clearly results in a transformation of the individual that was immunized. The Federal Circuit provides no explanation of the rationale it used as the basis for its decision, but it seems apparent that it must have concluded that the immunization step is merely a "data-gathering step," inherent to the practical implementation of an abstract idea or algorithm for optimizing an immunization schedule, and thus not central to the claim- in other words, mere "insubstantial extra-solution activity."

While the district court's decision in *Classen* was based, at least in part, upon its characterization of the relationship between immunization schedule and autoimmune disorder as a natural phenomenon, the Federal Circuit never addresses this issue in reaching its decision. As discussed below, the machine or transformation test seems better suited for dealing with claims that preempt abstract ideas, algorithms, or mental processes, the context from which the test arose, but largely inappropriate for cases where the fundamental problem with the patent claim is that it preempts a principle of nature or natural phenomenon. It is important to recognize that the machine or transformation test does not entail any inquiry into the specific nature of the fundamental principle, even though the test is meant to act as merely as a proxy for the ultimate determination of whether the claim preempts a fundamental principle.

Note that under the approach applied by the Federal Circuit in *Classen*, Metabolite's Claim 13 would likely also have been found invalid, since it appears to merely involve an algorithm or mental process (diagnosing a vitamin B deficiency based on elevated total homocysteine) coupled with a data-gathering step (assaying for total homocysteine) inherent to the algorithm. The *Bilski* majority also strongly suggested that under the machine or transformation test Claim 13 would be found patent ineligible. *Classen* does not bode well for a host of issued patents, particularly genetic diagnostic method claims which purport to broadly encompass any method of identifying a mutation, and could substantially limit the available patent protection for innovations in personalized medicine.

Prometheus might likewise not fare well in a post-*Bilski* world. Recall that the district court found the claims patent ineligible for wholly preempting a natural phenomenon. The logic supporting that conclusion seems doubtful at best, since the purported natural phenomenon is a correlation between the levels of a drug breakdown product in a patient's body and optimal dosage of the drug. This correlation arises solely as a consequence of the introduction of a non-naturally occurring, man-made drug into a patient's body, and it seems eminently wrong to classify this as a "natural phenomenon." To hold otherwise could establish dangerous precedent, because if followed to its logical conclusion it implies that any interaction of a drug with the human body is a natural phenomenon, which would presumably render broad claims directed to drugs and methods of drug treatment patent ineligible. But the Federal Circuit might very well never even address the "natural phenomenon" issue in future cases, if it proceeds to simply apply the *Bilski* machine or transformation test to *Prometheus* in the same reflexive manner employed in *Classen*.

Applying the machine or transformation test to the claims at issue in *Prometheus*, the Federal Circuit might have very well found the claims to be patent-ineligible. The claims recite the administration of the drug to a patient and determining the level of metabolite in the patient's body, but under *Bilski* these might well be treated as insignificant extra solution data-gathering steps. The only other steps in the claimed process are to gather data by observing the level of a drug metabolite in a patient, and based on that extra solution observation "be warned" that an adjustment in dosage may be required, neither of which appears to involve a machine or transformation sufficient to satisfy the *Bilski* test.

Prometheus and *Classen* illustrate an important point regarding the machine or transformation test; compliance with the test has little if anything to do with whether or not the claimed invention preempts a principle of nature or natural phenomenon, even though the Federal Circuit bases the test on its assertion that the involvement of the machine or transformation serves as a proxy for the ultimate question of whether a fundamental principle has been preempted. For example, while the district court in *Classen* based its decision at least in part on its conclusion that the claims preempt a natural phenomenon, the reason the claims failed the machine or transformation test on appeal to the Federal Circuit appears to have nothing to do with whether or not claims preempt a natural phenomenon.

Likewise, in *Prometheus* the district court's decision was based on preemption of a natural phenomenon, but if the Federal Circuit applies the *Bilski* machine or transformation test in deciding the case on appeal, the case will likely be decided based on whether the court finds the steps of administering a drug to a subject and determining the level of drug metabolite in the subject involve a "particular machine or apparatus," or a "transformation," that constitutes "significant extra-solution activity." The identification of a natural phenomenon, and the determination of whether that phenomenon has been wholly preempted, appears to play no role in the analysis under the *Bilski* test. In my opinion, the machine or transformation test seems designed to weed out patents that preempt abstract ideas, algorithms and mental processes, i.e., the types of subject matter claimed in business method patents; it seems ill-suited for analyzing whether or not a claim wholly preempts other categories of patent ineligible fundamental principles, particularly natural phenomena and principles in nature.

The inadequacy of the machine or transformation test in the context of a patent claim broadly encompassing a biological natural phenomenon is perhaps best exemplified by Ariad's NF-κB patent. One of Ariad's claims, for example, recites "[a] method for reducing, in eukaryotic cells, the level of expression of genes which are activated by extracellular influences which induce NF-κB -mediated intracellular signaling, the method comprising reducing NF-κB activity in the cells such that expression of said genes is reduced [55]." The claimed method seems clearly to involve a significant transformation, i.e., a reduction of NF-κB activity that results in reduced levels of gene expression will clearly transform the nature of the cell, as well as the organism. The whole

point of the claim is that a reduction of NF-κB activity will affect physiological transformations, which is why the NF-κB signaling pathway is involved in the mechanism of action of Lilly's drugs. *Bilski* explicitly states that a chemical transformation will render a claim patent-eligible under the test, and reduced NF-κB activity will clearly alter the biochemical makeup of the cell and organism. Furthermore, this transformation cannot be disregarded as "insignificant extra solution activity," because it constitutes the entire claimed process. The claim thus would appear to survive a literal application of the machine or transformation test, regardless of the extent to which it might preempt a natural phenomenon.

In my view, the machine or transformation test just does not work for claims, such as Ariad's, that at least implicate the preemption of a biological natural phenomenon. For example, a hypothetical patent claim broadly encompassing photosynthesis in a naturally-occurring plant involves a transformation of a particular article (i.e., carbon dioxide and water) into a different thing (sugar and oxygen), and thus appears on its face to satisfy the machine-or-transformation test as articulated in *Bilski*. But under binding Supreme Court precedent, acknowledged by the Federal Circuit in *Bilski*, the claim cannot be patentable if it wholly preempts photosynthesis, which is clearly a natural phenomenon. When the Federal Circuit decided *Ariad*, it had an opportunity to address the issue of whether the machine or transformation test truly is appropriate for all process claims, and particularly process claims relating to biological natural phenomena. Instead, the court ducked the issue by invalidating Ariad's claims on other grounds. But the issues raised by application of the *Bilski* test to patent claims of this type will need to be resolved at some point, and for the sake of the industry it would be better if the court provides guidance sooner rather than later.

Some of the most controversial biotechnology patents relate to genetic diagnostic testing. Some of these patents broadly claim methods of identifying mutations, with no explicit transformation of a particular article, and not tied to any particular machine or apparatus. For example, Myiad Genetics has sued competitors for infringing a patent which claims any "method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene . . . with germline sequences of wild-type BRCA1 gene . . ., wherein a difference in the sequence of the BRCA1 gene . . . of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject [56]." Similarly, DNA Sciences sued GeneDx for allegedly infringing a patent claiming any "method for diagnosing the presence of a polymorphism in human KCNE1 . . . wherein said method is performed by means which identify the presence of said polymorphism [57]." Arguably, these sorts of claims are merely directed to "comparing" naturally occurring genetic sequences, or "diagnosing" the presence of natural mutations, and lack the significant extra-solution step necessary for patent-eligibility under *Bilski*.

The PTO has indicated that it will find claims relating to diagnostics and personalized medicine patent ineligible if the claimed method is not limited to a particular machine, apparatus or transformation. For example, a PowerPoint slide presented by a representative of the PTO at the December 3, 2008 Biotechnology/Chemical/Pharmaceutical Customer Partnership Meeting concludes that a patent claim recite "[a] method for determining whether a human subject having breast cancer will be effectively treated with 'breast cancer drug X', said method comprising: a) considering data in a database comprising genetic patient information about the *ERBB2* gene at position 101 of SEQ ID NO:1; and b) correlating the presence of a cytosine at position 101 of SEQ ID NO:1 with effective treatment of the human subject with 'breast cancer drug X'" is patent ineligible [58]. This interpretation of *Bilski* could substantially allay much of the fears that have been expressed regarding gene patents blocking access to life-saving diagnostic testing, but at the same time raises concerns that future innovations in personalized medicine might not be amenable to effective patent protection.

As noted above, the patent-eligibility doctrine can be viewed as a tool for limiting claim scope; a patent limited to certain specified practical applications of a natural phenomenon is patent-eligible, while a broader claim wholly preempting essentially all practical uses of the phenomenon will be denied as patent ineligible. In particular, genetic diagnostic testing claims might be fine if limited to a specific test or tests, but patent ineligible if drafted so broadly as to effectively encompass any method for observing a genetic variation.

In summary, *Bilski* clearly signals a trend toward a more restrictive view of patent-eligible subject matter than we have seen in recent years, and will likely have a substantial impact on patent practice in the pharmaceutical and biotechnology industries, particularly with respect to diagnostics and personalized medicine. But at this point in time, it is still much too early to confidently predict where the courts and PTO will take the doctrine as it is applied to the life sciences. The Federal Circuit's recent decision in *Classen*, although non-precedential and thus in no way binding on subsequent courts, nonetheless suggests that patent-eligibility has become a significant issue for patentability in the life sciences. The Federal Circuit should decide *Prometheus* in the not too distant future, and hopefully will take the opportunity to clarify the patent-eligibility doctrine in a manner that promotes innovation in the pharmaceutical and life sciences.

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Received: April 7, 2009 Accepted: June 17, 2009