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Outlook 2008

A series of legal, regulatory, and business developments affecting the life sciences industry occurred in 2007 that will continue to influence the industry in 2008, members of the *Life Sciences Law & Industry Report* editorial advisory board and other industry experts told BNA. Biologics, Patent and Trademark Office rules, and patent reform topped their lists of the most important life sciences issues for the coming year.

Following is a discussion of the experts' top 10 topics plus one.

Experts Predict Which Life Sciences Issues Will Predominate in 2008

Among the developments considered most important to the life sciences industry in 2007 was the U.S. Patent and Trademark Office (PTO) final rule to limit the number of patent continuation applications and patent application claims, scheduled to become effective Oct. 31, 2007, and which some considered to be adverse to biopharma companies (1 LSLR 526, 9/28/07). Lawsuits have been filed and the implementation of the rule enjoined by a district court.

In another significant development, Congress initiated patent reform only to have it momentarily or permanently stall at year's end (1 LSLR 639, 11/9/07). President Bush signed the Food and Drug Administration Amendments Act of 2007 (FDAA) Sept. 27, 2007, some provisions of which, taking effect in 2008, provide the agency with new authority to improve drug safety (1 LSLR 514, 9/28/07). The expected substantial growth of venture capital investing in biopharmaceutical and medical device companies in 2008 also may have a significant effect (1 LSLR 629, 11/6/07).

In addition to the FDAA, patent reform, and the PTO rules, board members and experts cited off-label use and pricing, generic biologics, and the effect of the Supreme Court's *KSR* decision and other litigation as issues to watch in 2008. Details follow.

1. Generic Biologics. A majority of the respondents said they expected various issues related to generic or follow-on biologic drugs to be of great importance for 2008. ''How science improves our ability to characterize proteins and how the Food and Drug Administration (FDA) further clarifies the regulatory requirements for follow-on biologics will have a major impact on the amount of investment put into antibody and protein therapeutics and what disease areas will be the focus of research,'' said Dr. Zachary R. Scott, a director with Burrill & Co., San Francisco.

Kevin E. Noonan of McDonald Boehnen Hulbert & Berghoff LLP, Chicago, noted the challenges of the issues concerning follow-on biologics. ''Generic competition, while desirable economically, threatens to create the situation where biologic drugs that patients need could be unavailable except from generic suppliers, and there is a different level of difficulty in producing these drugs equivalently (and more opportunity to 'cut corners' with unpredictable results). Also, the complexity of the products is accommodated by the innovator, who has moved the drug (typically) from the bench to the plant, with no incentive for helping the generic get up to speed on the technology,'' Noonan said.

Jill Uhl of Nixon Peabody LLP, Boston, said there are several generic biologics-related legislative initiatives. ''It isn't clear whether these will move forward in 2008, but if they do, they could have a dramatic impact on biologic companies and on patients,'' Uhl said.

Steve Barrett of Wilmer Hale, Boston, focused his comments on the FDA: ''The FDA's position on follow-on biologics is clearly evolving. The standards

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that will be imposed by the FDA on companies seeking to develop generic versions of complex biologics as well as potential legislation dealing with this issue will have a significant impact on the innovators of these biologics and on those seeking approval for 'generic' versions of these drugs.''

2. Effect of *KSR* Decision, Other Litigation. Maryland Attorney Jeff I. Auerbach said that the 2007 U.S. Supreme Court decision in *KSR International Co. v. Teleflex Inc.* (U.S., No. 04-1350, 4/30/07) ''will encumber efforts to patent modified biologicals and the use of biologicals for secondary indications.'' That decision rejected the Federal Circuit's long-applied requirement that the obviousness of an invention be proven by evidence of a teaching, suggestion, or motivation to modify the prior art and replaced it with a subjective, hindsight analysis of the predictability of the modification (See 1 LSLR 153, 5/11/07; 1 LSLR 559, 10/12/07). According to Auerbach, ''2008 will reveal the manner in which the PTO and the courts will apply the new test.''

Scott agreed: ''This is going to drastically alter what companies and universities file patents on and how they develop their patent portfolios. There is a significant risk that this could stifle innovation in the industry.''

Don Pelto of Sheppard Mullin Richter & Hampton LLP, Washington, suggested that a Supreme Court antitrust decision to be decided in 2008 also could affect the life sciences industries. ''In *Joblove v. Barr Laboratories Inc.* (U.S., No. 06-830), the Supreme Court will decide whether a settlement where an accused infringer receives substantial consideration and agrees not to market a generic version of the patented item violates federal antitrust laws.

''The plaintiff consumer and consumer organizations allege that a settlement between a pharmaceutical company and a generic dug manufacturer violates federal antitrust law,'' Pelto said. ''Pharmaceutical patent owners and generic makers have often been accused of cooperating in schemes to prop-up drug prices. In a number of cases, generic manufacturers have received payments from patent owners as incentive to drop patent challenges. So far the courts have approved the agreements, but the government is pushing its case for enforcement of antitrust laws,'' he said.

Auerbach also noted several patent-related cases for which decisions are anticipated in 2008: the Supreme Court's expected ruling in *Quanta Computer Inc. v. LG Electronics Inc.,* which concerns the ''exhaustion doctrine'' that limits the ability of a patentee to collect royalties from only the first (and not subsequent) sale of a product; the Federal Circuit's anticipated decision on the patentability of natural phenomena in *Classen Immunotherapies v. Biogen IDEC*, which concerns the patentability of a ''discovery'' that early immunization regimes against infectious disease protect against later development of chronic disease; and the Federal Circuit's long-awaited clarification in *Merck KGAA v. Integra Lifesciences* of how it will apply the law relating to research tools and infringement for drug development to determine the scope of protection to be accorded to research tool patents.

3. PTO Rules. Uhl, Auerbach, and Barrett all saw the outcome of the *Tafas v. Dudas* lawsuit, which challenged U.S. Patent Office regulations that would significantly change patent prosecution and led the court to enjoin the enforcement of the rules, as having a major effect on the life sciences industries (1 LSLR 619, 11/9/07). ''If the new rules as proposed by the PTO go into effect, life sciences companies will be impacted dramatically,'' Uhl said. ''The limitation on continuations and RCEs [requests for continuing examination] will force life sciences companies to change how they attempt to protect their patentable inventions. The limitation on the number of claims simultaneously pending is less draconian but still will force those companies to modify their behavior. Finally, the proposed rules as they relate to claiming in the alternative will disproportionately effect life sciences companies.''

Uhl added that the lawsuit ''is ongoing in the Eastern District of Virginia, a district known for its quick resolution of cases. It is likely to be resolved during 2008.''

4. Patent Reform. Congressional efforts at patent reform were cited as having a significant—and likely negative—effect on life sciences in 2008. Barrett said, ''In Congress, the most important provisions (passed by the House, not yet voted on in the Senate) are to change the United States from a 'first to invent' to a 'first to file' patent system. This is a huge change; besides eliminating interference practice, it changes the 'balance of power' between big and small companies and sole inventors (and universities), and arguably will make the next Bill Gates, Steve Jobs, Amgen, and Genentech a lot less likely to succeed.''

Barrett said the proposed provisions also include ''post-grant review'' that ''promises to increase the costs of patenting dramatically, since interferences are relatively rare, while challenges post-grant can be expected in any important case,'' and increased rulemaking authority for the PTO , which ''again shifts the balance of power against patenting, since there is no way to harmonize this new requirement with the traditional duty of disclosure.''

5. Off-Label Use and Pricing. Judith Hasko of Latham & Watkins LLP noted a situation related to off-label drug use concerning Genentech's products Avastin and Lucentis as having potential policy implications. ''Genentech first developed Avastin for treating cancer, then it took the same molecule, modified it a bit [to create Lucentis], and used it to treat macular degeneration (the leading cause of blindness in older adults). Genentech charges a lot more for Lucentis than Avastin, which led to widespread resentment by physicians and patients. Doctors began using Avastin to treat muscular dystrophy (MD), by taking small portions of the amount in an Avastin bottle and using it (by direct injection into the eye) to treat MD. This resulted in Genentech's seeking or imposing a limitation on Avastin use because such use is off-label and risky due to its unapproved nature. The government is now conducting head-to-head trials to explore relative safety and efficacy, I believe.''

Hasko continued, ''This situation is fascinating from several perspectives: the impact of negative public reaction to this pricing strategy by Genentech; exploration of related safety issues that could reveal important guidelines—we will see if Genentech's claims of increased safety by using Lucentis are supported by the trial; and how the experts weigh that against efficacy of the two products. Genentech appears to be internally conflicted about having two competing products, one of which cannibalizes sales of the other. From a public

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policy perspective this situation is a lightening rod for patients' rights advocates,'' Hasko said.

The controversy has drawn the attention of the head of the Senate Special Committee on Aging (1 LSLR 713, 12/7/07)

6. Effect of Doing Business With, In Other Countries. Respondents noted the benefits and concerns of the emerging trend of biopharmaceutical company globalization. Hasko said that conducting clinical trials outside of the United States clearly is growing because it is less expensive and because patients in other countries are less likely to have been treated with other drugs prior to participating. ''However, there are detriments: Clinical protocols may not be strictly followed; intellectual property rights and practices vary outside the United States, creating risks for biotech companies; and patients may not be as closely monitored and may not comply with treatment regimes well. I'm curious to see how this plays out,'' Hasko said.

Noonan said that China and India ''are also a major source of generic drugs, API [active pharmaceutical ingredients], and excipients, with little control or regulation from the FDA. Although there are moves to open up inspection of Chinese sources, these have not been fully implemented, and absent a thalidomide or ethylene glycol-type incident, there is little incentive for China to cooperate. Less-developed countries have taken advantage of 'loopholes' in international treaties to be able to obtain generic drugs even in the face of local national patents on the API or formulation. While this has occurred principally with anti-AIDS drugs, Thailand has extended its national law provisions to Plavix (hardly an epidemic-treating drug) [1 LSLR 256, 6/8/07]. How the international community deals with these developments, all sanctioned under GATT/TRIPs [General Agreement on Tariffs and Trade/Trade Related Aspects of Intellectual Property Rights] and the World Trade Organization but having the exact opposite effect as intended, is an ongoing saga,'' Noonan said

7. Overlap Between FDA, CMS Authority. Wendy Krasner of Manatt Phelps & Phillips LLP, Washington, said that there are increasing areas where both FDA and the Centers for Medicare & Medicaid Services (CMS) have roles, which can result in some confusion that may force some solution. ''This can be seen in the whole effort involving not only Congress but also FDA and CMS concerning erythropoietin (EPO) reimbursement. There is a blurry line between effectiveness, cost-effectiveness, and reimbursement and a continued lack of certainty concerning the legal, regulatory, administrative and policy issues raised by 'joint' jurisdiction over what is approvable and reimbursable, and not having those efforts be in separate buckets.''

Scott also noted the increasing use of pharmacoeconomics by CMS and private payers in making reimbursement decisions. ''As payers become more focused on how new treatments affect the overall cost of health care delivery, companies and investors will have to pay increasing attention to how their products 'perform' on an economic basis and not just a scientific one,'' Scott said.

8. FDA Amendments Act Implementation. Congress enacted wide-ranging FDA reforms under FDAA in 2007, and many of the provisions become effective in March. Barrett said, ''The way in which FDA implements these provisions could have a profound effect on the industry. At the very least, the new provisions will dramatically increase FDA's leverage over pharmaceutical and medical device companies.'' He added that the increased transparency mandated by the FDAA—the National Institutes of Health (NIH) is now required to expand its existing database of clinical trial information to include more information about more trials and must begin posting the results of completed trials in 2008—''could mean wide-ranging effects for pharmaceutical companies on issues such as the protection of competitively sensitive information and the post-market assessment of drug safety.''

9. Stem Cell Research. Pelto said that 2008 will see the effect of President Bush's 2007 executive order directing the Department of Health and Human Services and NIH to ensure that any human pluripotent stem cell lines produced in ways that do not create, destroy, or harm human embryos are eligible for federal funding (1 LSLR 282, 6/22/07). ''Specifically, the order expands the NIH Human Embryonic Stem Cell Registry to include all types of ethically-produced human pluripotent stem cells. The order invites scientists to work with the NIH to add new ethically-derived stem cell lines to the list of those eligible for federal funding,'' Pelto said.

10. Genetic-Based Profiles. Krasner said that a major issue for 2008 will be the continuing development of genetic-based profiles as an element of prescribing drugs and what that may lead to in terms of the need for genetic profiling of patients. These developments will create privacy issues, such as whether and how the patient-specific data are being captured in electronic medical records so that genetic profiling does not have to be repeated on the same patient, he said. Since the profile should not change over the years, it is more important that profiling not be duplicated than it is to repeat medical tests where the underlying medical condition may be changing/evolving, Kasner said. ''The most interesting thing to me is the issue of what genetic advances will mean to insurance and employer benefit plan coverage. For example, once we have gene therapy (or related applications) available, when will a genetic predisposition to a disease or condition rise to the level where it should be/must be covered?''

11. Life Sciences Company Consolidation. ''This doesn't require much explanation,'' Uhl said. '' The more consolidation that occurs, the greater the impact of each one.''

BY JOHN T. AQUINO