

Biotechnology in the Limelight: the Year Ahead

Continued concerns about bioterrorism will shape legislative and regulatory initiatives affecting biotech manufacturers

The September terrorist attack, along with an economic downturn, has altered our political landscape. Only a few months ago, the main policy issue for biotech companies was how to address public concerns about pricing and access to new therapies. A wave of anthrax contamination, though, heightened fears that terrorists could unleash lethal viruses and infections on an unsuspecting nation. That has policymakers concerned about ensuring supplies of critical medicines that can save lives. The focus now is on devising policies to encourage development of new vaccines and other preventive treatments to defend us against dangerous pathogens.

Circumstances have created new opportunities and challenges for manufacturers and government agencies. Industry leaders have met with officials at the Department of Health and Human Services (HHS) and the Department of Defense (DOD) to discuss what manufacturers can and are doing in areas related to germ warfare and combat readiness. Pentagon officials are interested in what products (such as new wound-healing treatments) have been developed for

the commercial market that could be important to the military. DOD and manufacturers will continue to discuss military needs for biomedical therapies, vaccines, antidotes, and other treatments.

Government officials also are concerned about ensuring the security of pathogens in agency laboratories and those maintained by industry. HHS has asked pharmaceutical and biotech companies to examine what reagents and products they use that might interest terrorists, as well as what technologies could be used to defend against biological or chemical attack.

The shift in political priorities will affect policy developments on Capitol Hill, at the White House, and at FDA. Manufacturers will face a number of issues and challenges this year that will affect their resources, their operations, and the markets they serve.

Reinvigorating Vaccines

Vaccine production has emerged as a critical component of antibioterrorism strategies. Congress and HHS are continuing to evaluate proposals to encourage new vaccine development and ensure reliable supplies of existing products. Although major expansion of government vaccine stockpiles may revive this shrinking industry, such efforts will put considerable pressure on FDA to ensure that safe and effective products get to market (as detailed in the "Ensuring Product Safety and Purity" box).

After weeks of anticipation, HHS signed a contract in November worth more than \$400 million with Baxter International

(www.baxter.com) and Acambis plc (www.acambis.com) for 155 million doses of smallpox vaccine in addition to 54 million already on order. HHS chose a relatively small, British-based biotech company over more established manufacturers because it offered the lowest price and promised speedy delivery. Acambis is preparing pilot lots for FDA review. Baxter plans to produce the vaccine at a plant in Austria and ship it to an Acambis facility in Massachusetts for refinement and packaging. Other U.S. companies will be involved in product testing and development.

The purchase decision by HHS raises questions about the wisdom of relying on one company for the nation's entire smallpox vaccine supply, and all parties will be watching to see how well Acambis meets its promise for delivery by the end of next year. Meanwhile, vaccine production will remain in the limelight as federal agencies expand support for research and production of vaccines for anthrax, AIDS, and infectious diseases.

Perennial shortages of vaccines for influenza and other infections (as well as continual difficulties in developing a reliable process for making a new anthrax vaccine) are prompting congressional leaders and government watchdogs to call for new approaches. Carl Feldbaum, Biotechnology Industry Organization president, has suggested that vaccine development needs both public funding of R&D and an FDA fast-track review process with liability relief for manufacturers. Several expert groups



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have called for the government to get into the vaccine manufacturing business by building its own facilities.

Those developments present a major challenge for FDA to oversee clinical research and manufacturing of smallpox and other new vaccines. In the past two years, it has received about \$10 million for bioterrorism activities, mostly (\$7 million) to help the Center for Biologics Evaluation and Research (CBER) expand its capacity to evaluate new vaccines. Now the agency is slated for a significant boost in funding to support antibiterrorism programs. Those developments will increase pressure on FDA to help the industry expand its capacity to produce new vaccines rather than present a roadblock to the development of needed treatments. At the same time, "The last thing we want to do is approve a vaccine from a new source that is not safe or effective," commented FDA's top deputy commissioner Bernard Schwetz at a meeting of the agency's science board in November.

Fees and FDAMA

As policymakers debate reauthorization of the Prescription Drug User Fee Act (PDUFA), which expires in September 2002, they will be closely examining FDA's ability to evaluate new technologies and efficiently approve applications for new drugs and biologics. There is broad interest in continuing the user fee program, but FDA and manufacturers have different proposals for changes.

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Ensuring Product Safety and Purity

A key issue for manufacturers of vaccines and other biotech therapies is developing procedures that ensure the removal of adventitious agents in production processes. Such efforts were accelerating before 11 September, but have assumed increased importance as the bioterrorism scare illustrates a need for more efficient and effective manufacturing processes. The challenge is to develop new methods to validate the ability of manufacturing procedures to inactivate or remove adventitious viruses from biotechnology products derived from human and animal cell lines. Key issues are how to design small-scale validation studies, selection and testing of source material to ensure the absence of undesirable viruses, protein characterization strategies, and adoption of new analytical methods. Efforts to improve how manufacturers demonstrate that an established commercial-scale clearance process meets critical performance parameters will be of interest to FDA in the coming months.

The agency sought comment on these issues beginning at a PDUFA public meeting in December. FDA officials acknowledge that the agency has been taking longer to fully review and approve new drug applications and issuing more "approvable" letters to buy time to resolve difficult issues. However, they blame the problem on burdensome tracking requirements in PDUFA 2. The agency wants to boost current user fees, which officials say are too low to cover all the tracking and performance requirements in the current program. And they want additional revenues to cover the review of investigational therapies, of fast track programs, and of postapproval monitoring.

Pharmaceutical and biotech companies, however, want to retain performance standards that make FDA accountable for meeting certain time frames during the product development and application review process. The debate promises to be heated, but the general success of the program during the past 10 years makes compromise before the renewal deadline likely.

The Prion Problem

A related concern is to ensure that FDA-licensed products are free from contamination by any materials that could be infected by bovine spongiform encephalopathy (BSE). The discovery of BSE-infected cattle in Japan a few months ago revived fears about the possible spread of the disease to the United States. U.S. officials are most concerned about animal feeds and food imports, but FDA also is monitoring the use of bovine-derived raw materials in medical products and in the production of biologics and vaccines. Over the past decade, CBER has advised manufacturers to avoid the use of bovine-derived materials from countries with documented cases of BSE, which have been only in Europe up until now. The agency continues to weigh evidence of the need for more stringent controls while it learns about more advanced inactivation techniques and alternatives to animal-derived raw materials.

FDAMA and other reforms. The need to reauthorize PDUFA may provide an opportunity to review and revise a number of FDA policies, such as occurred five years ago when Congress enacted the FDA Modernization Act (FDAMA). Any FDAMA revision this year is expected to be more modest than the 1997 bill, although some "modernization" initiatives are likely to surface. Those may address international standards, postapproval safety monitoring, and clinical research safeguards. FDA is looking to expand and upgrade postmarketing adverse event reporting systems for drugs and medical products. That initiative would support administration plans to build a better national health data network as part of antibiterrorism defenses. Such a network would link the Centers for Disease Control and Prevention (CDC) and other federal agencies with state and local health officials to disseminate information quickly about infectious disease outbreaks and biological attacks.

Continued on page 57

The FDAMA legislation also may seek to enhance FDA management of additional counter-bioterrorism programs. One question is how FDA policy should indicate whether and when it is appropriate to use investigational drugs or biologics to respond to a bioterrorist attack. Related to that is the need to clarify procedures for conducting clinical trials on therapies that animal study

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models have shown treat exposure to toxic substances.

Another topic on the legislative reform list is revision of the Hatch-Waxman Act of 1984, clarifying a number of controversial issues that affect generic and brand-name drugs. Increasingly intense competition between innovators and generics makers has imposed a heavy burden on FDA and generated costly legal battles among various parties. The key issue for biotech companies is a push by generics makers to open the door to FDA approval of generic biologics. Debate is intensifying over whether concepts such as “therapeutic equivalence” and “comparability” provide a basis for developing generic or “equivalent” versions of some biotech therapies.

Going Global

Patent policy will continue to generate considerable debate as generic-innovator battles at home raise questions about U.S. protection of intellectual property rights around the world. Pharmaceutical manufacturers got a black eye last year when they tried to enforce patents for AIDS therapies in South Africa. Even though the companies dropped the lawsuit and offered their HIV therapies at cut-rate prices, the initial legal action encouraged developing nations to push through an anti-patent declaration at the World Trade Organization (WTO) negotiations in Doha, Qatar in November.

Manufacturers avoided a total rewrite of the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, but poor nations gained an extra decade (until 2016) to come into full compliance with TRIPS and the right to grant compulsory licenses for patented drugs to deal with public health crises such as AIDS. Although the declaration still recognizes WTO’s commitment to intellectual property protection for the development of new medicines, its new language is expected to encourage poor nations to press manufacturers for cut-rate prices on needed medicines.

Harmonization. Third-world nations will be encouraged to establish regulatory systems to register and regulate drugs and biologics through the efforts of the International Conference on Harmonisation (ICH). ICH participants will continue to implement the Common Technical Document (CTD) for submitting registration information on drugs and biologics to regulatory authorities in the United States, Europe, and Japan. At the same time, those parties will encourage broader use of the CTD in other nations along with development of uniform electronic data transmission systems. ICH also will continue to develop and refine international standards that ensure the quality and safety of biotech products and drugs, with added attention to postmarketing drug safety and gene therapy research.

Supporting Good Science

A major concern for biotech manufacturers is whether government policies will encourage or stymie efforts in biomedical discovery. Publication of the human genome more than a year ago is providing new

Correction

A mathematical error appeared on page 46 of J.M. Przechocki’s “Simplifying Pharmacological Analysis with Programmable Scientific Software” (November 2001). The last sentence of the fourth paragraph should read, *The EC₅₀ value can be easily calculated from the log(EC₅₀) by raising 10 to this value.*

opportunities for scientists to expand their understanding of the causes of human disease in ways that could lead to many therapeutic innovations. At the same time, policymakers are concerned with how individual genomic information may be used to violate personal privacy standards. Heated debate continues over the ethical implications of research using embryo stem cells as likely to lead to cloning of a human being.

Last summer, the Bush administration sought to resolve the stem cell controversy by adopting a compromise. It permits some government funding of stem cell research, with limits to appease those who consider the destruction of human embryos unethical under any circumstances. The policy allows the federal government to support R&D using existing embryo banks, but not to create embryos solely for research purposes. In response, Congress dropped efforts to regulate this area. However, since researchers announced in November that they had succeeded in creating human embryos through cloning, Congress has revived its call for a complete ban on cloning research.

Those issues will be examined further by a new White House Council on Bioethics that will advise President Bush on policies related to biomedical science and technology. The panel also may review ways to protect human research subjects and the consequences of limiting scientific investigation. Biotech manufacturers will be interested in how such deliberations shape the ethical guidelines governing new scientific investigation and discovery. **BP**