

The Big Shift

FDA explains its plan for moving most biologics under the authority of CDER. But a big question remains: What will the change do to approval times?

A new era in the regulation of biotech therapies is being launched as oversight of these products moves from FDA's Center for Biologics Evaluation and Research (CBER) to the Center for Drug Evaluation and Research (CDER). At the same time, FDA is examining how its policies may have contributed to an overall decline in development of new drugs and biologics. The agency has received fewer applications for new therapies in recent years, yet has been slow to review and approve them. FDA commissioner Mark McClellan recently unveiled an initiative for improving the review process that aims to reduce product development time and costs and could help CDER establish more effective review policies for biotech therapies as well as conventional drugs.

Stage Set for Transfer

The CBER-CDER product consolidation process entered its final phase in January when FDA announced which biotech products would shift to CDER and how the transfers would be funded (1). FDA officials gave CDER oversight of:

- monoclonal antibodies;

- cytokines, growth factors, enzymes, and interferons; and
- proteins extracted from animals and microorganisms.

In a key decision, CBER retained lead responsibility for therapeutic vaccines, which, in the view of agency officials, fit well with CBER units conducting research and review on vaccines and cellular products. But officials stipulated that application reviews will be "fully coordinated" with CDER.

FDA will transfer about \$33 million in budget funds and more than 200 staffers from CBER to CDER. Most personnel will come from CBER's therapeutics office, a few will transfer from epidemiology and management staffs for biologics, and five positions will be taken from agency field operations. Decisions on specific staff transfers will be made later this year. CDER director Janet Woodcock is weighing whether to create a new office to keep biologics reviewers together, or to disperse them.

CBER will continue to regulate blood and blood components, plasma products, allergen patch tests, allergenics, antitoxins, in vitro diagnostics, vaccines, toxoids intended for immunization, and gene therapy. The biologics center also will retain oversight of monoclonal antibodies, cytokines, growth factors, and other proteins when used solely as an ex vivo constituent in a manufacturing process or as a reagent in production of a CBER-regulated product.

One concern is whether this considerable shift of resources will hamper establishment of CBER's Office of Cellular, Tissue, and Gene Therapy Products, which was elevated from a division to an office just last fall. Phil

Noguchi heads the new office, which remains embroiled in challenging issues such as tissue contamination and gene therapy research. CBER stands to lose many research programs and support services important for its oversight of those cutting-edge products.

Leadership Continuity

The decision to leave therapeutic vaccines with CBER may reflect successful politicking by the Center's new director, Jesse Goodman, who was appointed in December, soon after the resignation of long-time CBER director Kathryn Zoon. Goodman's surprisingly quick promotion avoided a lengthy candidate search and provides continuity and reassurance for CBER staffers.

Goodman, previously CBER deputy director for medicine, will serve as FDA's point man for countering bioterrorism, developing new vaccines, and ensuring a safe blood supply. A virologist with expertise in infectious disease, he led a task force on antimicrobial resistance when he first came to FDA in 1998 and recently headed the agency's response to West Nile virus. He will be involved in the Bush administration's new Project BioShield that aims to protect against a bioterrorist attack with new vaccines and therapies. The White House also wants to expand public stockpiles of pediatric vaccines and increase free vaccinations for children (2).

CBER's loss of a significant portion of its portfolio was reflected last month when the Bush administration released its budget plan for fiscal year 2004 (which begins 1 October 2003). The budget requests \$170 million for CBER, down from almost \$200 million this



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year. CDER's allotment jumps from \$426 million to \$485 million to support 3,200 staffers, compared to CBER's 1,100.

No Slowdown

A prime concern of FDA officials and industry is to avoid disruptions in application reviews and other operations during the CBER-CDER transfer. There has been considerable debate over an apparent slowdown in application review times for drugs and biologics. CDER reports that it speeded its average approval time for new molecular entities (NMEs) last year to an average of 15.2 months, but that's still slower than the 12.5-month NME review time in 1999. Moreover, the agency approved only 17 NMEs last year, down from 24 in 2001 and 27 in 2000. CBER approved nine biologics in 2002, up slightly from previous years. But the average review time for therapeutics was 22 months, and even longer if the count includes two long-pending vaccines.

FDA analyzed these activities to support its new initiative to speed up review processes and improve the quality of submissions for new medical products (3). The goal is to accelerate development of truly innovative therapies by reducing the cost of new product testing and regulatory compliance.

To do this, FDA is focusing on curbing multiple review cycles of market applications for new drugs and biologics. (The program will eventually be extended to medical devices and animal drugs.) FDA officials believe that they will be able to review more applications in the first cycle by helping sponsors submit all the data needed to document product safety, efficacy, and quality in the initial application. They acknowledge that they can't do much about many problems after an application is filed, but want to encourage more agency communication with manufacturers to clarify data requirements and identify deficiencies early on. The agency also plans to adopt a "quality systems approach" to the application review process.

Manufacturing Issues

More than half of priority NMEs filed in 2000 and 2001 took more than the desired six months to approve; a significant cause of delay was problems with chemistry, manufacturing, and controls (CMC) documentation. A review of biologics

No More Easy Targets

Why so few applications for new drugs and biologics? FDA's plan for improving innovation in medical technology lists several contributing factors:

- A significant decline in R&D investment in the 1990s
- The deluge of genetic, genomic, and proteomic data, which may cause short-term declines in R&D productivity
- Elimination of candidate therapies by industry mergers
- Managed-care curbs on incentives for developing "me-too" drugs
- Fewer "easy targets" for development, requiring a shift to the more costly task of studying chronic diseases
- Increased FDA study requirements and "conservatism" fostered by safety concerns over new medicines.

license applications (BLAs) approved by CBER during 2001 showed that the most frequent reason for delayed approvals was major changes in product manufacturing. Standard NME reviews were held up most often by safety and efficacy issues, but manufacturing concerns and CMC difficulties also raised problems.

To encourage innovation, FDA will issue new guidances on clinical trial endpoints and on reduced filing requirements for cancer therapies. Another goal is to improve agency guidance on how manufacturers can navigate the regulatory process for emerging technologies such as cell and gene therapies, tissue-engineered products, therapeutic vaccines, regenerative medicine, and novel drug delivery systems. FDA plans to reduce regulatory uncertainty and to help industry improve product manufacturing and quality assessments by:

- sponsoring conferences and workshops to develop standards for human study and for manufacturing of gene therapies
- issuing guidance on submitting pharmacogenomic information to FDA
- analyzing FDA review issues involving novel drug delivery systems including infusion pumps and drug-eluting stents.

More Combos

One benefit of the CBER-CDER consolidation may be to simplify FDA's process for deciding how to regulate combination biotech-pharmaceutical-device products. FDA is being asked to review more combos each year (33 in fiscal year 2002), which requires agency staffers to select one center to take lead responsibility for handling application review. To deal with this increasingly contentious process,

FDA established an Office of Combination Products in December 2002, as required by last year's Medical Device User Fee & Modernization Act.

This new office will decide whether a manufacturer of a combo product has to file more than one application, how to assign user fees, and how well FDA Centers oversee these products. Medical device makers have complained about CBER regulation of certain diagnostics and often lobby to have these products assessed by FDA's device center (CDRH). The combination products office plans to publish guidances to clarify its procedures for assigning and regulating products and to hold workshops on important issues.

Manufacturers will be watching FDA closely in coming months to assess the impact of review consolidation. Critics of the change have predicted problems in processing applications efficiently, particularly in dealing with manufacturing and product quality issues, which are very different from chemistry reviews for drugs. To help biotech companies adjust to the new regulatory scheme, the Biotechnology Industry Organization (BIO) recently brought in Gillian Woollett from Pharmaceutical Research and Manufacturers of America (PhRMA) as vice president for science and regulatory affairs. Her familiarity with drug and biotech regulation should help to bridge the gap. *BPI*

References

- (1) FDA talk paper, 8 January 2003, www.fda.gov/bbs/topics/ANSWERS/2003/ANS01188.html.
- (2) HHS press release, 25 January 2003.
- (3) "Improving Innovation in Medical Technology: Beyond 2002," FDA, 31 January 2003.