FDA wants to make medical products more affordable by establishing a more-efficient regulatory process and by clarifying drug development requirements. At the beginning of 2003, FDA commissioner Mark McClellan unveiled a strategic plan that builds on FDA’s ongoing efforts to encourage the development of safer, more-effective and higher-value medical products. The initiative, which FDA has rolled out in recent months, incorporates the agency’s risk-based approach for regulating good manufacturing practices (GMPs). This new approach was launched in November 2002 and updated in February 2003 (1). The next progress report on GMP revisions was slated for this month (August 2003) and will be discussed in upcoming issues of Pharmaceutical Technology.

McClellan’s broader plan entitled “Improving Innovation in Medical Technology” aims to remove some of the roadblocks that may stymie development of new drugs and medical products (www.fda.gov/bbs/topics/news/2003/beyond2002/report.html). An immediate objective is to reverse the recent decline in market applications filed with FDA. The Center for Drug Evaluation and Research (CDER) approved only 17 new molecular entities (NMEs) in 2002 and relatively few priority therapies. In its annual report entitled Report to the Nation that was issued in May 2003, CDER director Janet Woodcock expressed concern that the agency approval rate for “truly new drugs” is “at the lowest level in a decade.”

In recent speeches to industry and interest groups, McClellan has blamed the situation partly on the rising cost and uncertainty associated with researching and testing medical products (see Sidebar, “No more easy targets”). Although FDA officials acknowledge that FDA alone cannot remedy this problem, they seek to identify the root causes of delays in new product approvals. McClellan maintains that making the R&D process more efficient and predictable will facilitate access to treatments, which is a very hot topic in Washington as efforts to craft a Medicare drug benefit are focused on pharmaceutical costs and availability (see Sidebar, “Medicare Rx benefit in the spotlight”). Although FDA officials acknowledge that FDA alone cannot remedy this problem, they seek to identify the root causes of delays in new product approvals. McClellan maintains that making the R&D process more efficient and predictable will facilitate access to treatments, which is a very hot topic in Washington as efforts to craft a Medicare drug benefit are focused on pharmaceutical costs and availability (see Sidebar, “Medicare Rx benefit in the spotlight”).

FDA aims to revise its regulatory operations by adopting a quality systems approach to the review process. This approach will involve informing companies early on of deficiencies in applications and providing clearer guidance for evaluating test products to treat critical diseases. The ultimate goal of these efforts is to reduce the need for multiple application review cycles of new drug applications (NDAs) and supplements. Too many submissions lack sufficient valid information about product safety, effectiveness, and manufacturing, and require the agency to seek more data from the company. To avoid such problems, FDA officials want to encourage more agency communication with manufacturers early in the development process to clarify data requirements and to identify deficiencies before an application appears in the review queue.

Manufacturing problems

This plan will involve working with manufacturers to ensure that they can fully demonstrate the ability to make a product according to current standards of acceptable quality and consistency. CDER’s Report to the Nation credits CDER’s initiative to gain insight into the problems manufacturers encountered at manufacturing facilities added to review times for both priority and standard NMEs. Similarly, an analysis by the Center for Biologics Evaluation and Review (CBER) found that the most frequent reason for delayed approvals of biologics license applications (BLAs) approved during 2001 was major changes in product manufacturing.

FDA is further examining past applications as part of its First Cycle Review initiative to gain insight into the problems that lead to poor quality applications, difficulties in manufacturing scale-up, and a lack of clinical data. The process aims to identify serious deficiencies during the initial review of an NDA to avoid multiple review cycles for clearly inadequate applications such as when a manufacturer cannot demonstrate that it can make a product according to current standards of acceptable quality and consistency. FDA acknowledges that such issues should be addressed at earlier development milestones such as before filing an IND or at the end of Phase I or Phase II studies.

A related initiative is to establish a continuous marketing application (CMA) process that will promote early guidance and feedback. The agency recently issued two guidances for implementing pilot programs that will provide more staff interaction with manufacturers during product development. This special attention is intended to help fast track drugs and biologics that show promise in treating serious diseases.

More guidance

Another FDA plan is to issue new guidelines to clarify filing requirements and use of clinical trial endpoints to spur development of treatments for cancer, diabetes, and obesity. These guidelines will be developed through workshops, advisory committee meetings, and other scientific gatherings. The guidance documents will address key clinical-trial design issues such as the selection of control groups and pharmacokinetic analysis. One topic on the list is whether manufacturing or formulation issues may raise questions about product consistency throughout a clinical trial, which could generate safety concerns.

FDA officials want to encourage more agency communication with manufacturers early in the development stage to clarify data requirements and identify application deficiencies.
No more easy targets

FDA’s plan for improving innovation in medical technology incorporates several factors that most likely have contributed to the decline in applications for new drugs and biologics. These factors include:

- a significant drop in R&D investment one decade ago
- a deluge of genetic, genomic, and proteomic data, which may hold promise for the future but reduce R&D productivity for the short run
- industry mergers that stop work and investment in candidate therapies within the same class
- the managed care environment and rise of generics, which decrease incentives for developing “me-too” drugs
- fewer easy targets for the development of treatments for acute conditions, requiring a shift to the more-costly and time-consuming task of studying chronic diseases
- increased FDA study requirements and conservation fostered by added safety concerns

related to new medicines, an attitude that FDA officials strongly dispute

- a continued rise in the cost of drug development because of increasingly large and expensive clinical trials and more postapproval requirements. The Tufts Center for the Study of Drug Development reported in May 2003 that the fully capitalized cost of developing a new drug now averages $897 million, including postapproval R&D costs such as studies to assess long-term safety and effectiveness issues, testing for new indications, and the development of new formulations. The new number is much higher than the $300-million figure that Tufts calculated in 1991 because drug development is “a time-consuming, risky, and expensive process,” said Tufts Center Director Kenneth Kaitin. Development failures add to total spending, as only about 20% of products that begin Phase I human trials are eventually approved for market.

Medicare Rx benefit in the spotlight

After years of debate, Washington policy-makers made remarkable progress in June 2003 to greatly expand Medicare by adding a $400-billion outpatient prescription (Rx) drug plan. Republicans had to sacrifice much of their plan for reshaping Medicare along more-competitive lines: the Bush administration initially wanted to allow HMOs and preferred provider organizations (PPOs) to offer more attractive pharmacy benefits than the traditional Medicare program would to encourage seniors to opt for more managed care. Democrats objected strenuously to any policy that would undermine the fee-for-service program and insisted that elderly patients who want to remain in the basic program have access to comparable Rx drug coverage.

The legislation began to move when the Senate Finance Committee approved the consensus Prescription Drug and Medicare Improvements Act of 2003 on 12 June 2003, setting the stage for adoption of the measure by the Senate. This approval stimulated movement in the House, where GOP leaders pressed for the approval of a bill that retained provisions that are designed to steer seniors into private plans, which is similar to a bill that had been adopted by the House in 2002.

The expected consensus package will allow Medicare beneficiaries to purchase stand-alone drug plans offered by insurers or pharmacy benefit managers (PBMs). Seniors who join managed care plans will receive pharmacy benefits equivalent to the basic plan. Elderly patients in Medicare FFS would pay monthly premiums ($35) and an annual deductible ($250–275) for stand-alone pharmacy coverage. The pharmacy plans then cover a share (50%–80%) of pharmacy costs up to $3500 and cover most of all costs after hitting a catastrophic level of $5000–6000. This arrangement leaves a hole in the program that forces patients to pay all of the costs between the coverage limit and the catastrophic threshold.

PBMs and health plans would negotiate lower prices with manufacturers and may control drug use through formularies and other pharmacy management tools such as tiered co-pays to encourage generic drug use. As the legislation moved forward, Democrats and patient-advocates decided that it was worth voting for a somewhat inadequate pharmacy benefit program with the idea of expanding it later. Republicans accepted a less-comprehensive reform to claim victory for enacting a bill that they believe will be a starting point for reshaping Medicare along more-competitive lines in the future.
WASHINGTON REPORT

Efforts to streamline new product development have led FDA to beef up its process for overseeing combination biotech–pharmaceutical–device products. Manufacturers are seeking approval of more combination products each year (33 in fiscal year 2002), which can raise controversial issues regarding which FDA center should have the lead responsibility for handling a review. To deal with this increasingly contentious process, FDA established an Office of Combination Products (OCP) in December 2002, as required by last year’s Medical Device User Fee & Modernization Act.

In addition to assigning oversight to specific centers, this larger and more powerful unit decides whether a manufacturer of a combination product has to file more than one application, how to assign user fees, and how well FDA centers oversee these products. OCP director Mark Kramer is developing mechanisms for tracking and reporting on combination products to ensure timely coordination of product reviews. Kramer plans to publish guidance documents to clarify procedures and to update intercenter agreements for determining assignments. One issue under review is which GMP standards and adverse-event reporting requirements will apply to a combo. A working group is examining when the agency should apply a mix of regulatory authority to a certain combination product or stick to the lead regulation. Policies in this area may change as more complex products emerge.

References