The campaign to establish an affordable Medicare prescription drug benefit is encouraging both the White House and Congress to explore ways to control drug spending. One strategy is to promote the increased use of less-expensive generic drugs by speeding regulatory approval of new generics and reducing protracted patent disputes between brand-name and generics manufacturers. Another initiative that reduces health plan and insurer coverage of pharmaceuticals is to spur manufacturers to switch more prescription drugs to over-the-counter (OTC) status (see Sidebar, “Pushing OTCs”). FDA’s Center for Drug Evaluation and Research (CDER) is responsible for implementing policy changes governing generic, OTC, and innovator drugs while also revising operations to accommodate the oversight of biotech therapies (see Sidebar, “CDER shifts personnel to oversee biotech therapies”).

In 2002, generic drugs accounted for 45% of all prescriptions in the United States, an increase of 5% from 2001, as generic versions of major antidepressants and medications for diabetes and heart disease became available. When speaking about FDA’s upcoming budget for fiscal year 2004 (beginning 1 October 2003), FDA Commissioner Mark McClellan cited research from the Congressional Budget Office (CBO) that estimated that generic drugs may save consumers $8–$10 billion a year at retail pharmacies. The commissioner acknowledged that brand-name manufacturers need adequate compensation provided by the patent system to encourage investment in pharmaceutical innovation, but he also voiced support for policies that will spur development of less costly therapies that are bioequivalent to brand-name products. Initiatives to implement this objective will affect the drug development procedures of innovator manufacturers as well as generics firms.

More FDA funding
Despite a tight FDA budget for fiscal year 2004, the Bush administration has requested a $13-million funding increase for FDA’s Office of Generic Drugs (OGD) to provide the office with a $60-million budget and 40 more staffers. The additional funding will allow OGD to establish a third division to review chemistry, manufacturing, and controls (CMC) data, which should help reduce review times for new generic products. FDA approved 384 generic drug applications in 2002, an increase from 242 in 1999. Approximately 80% of original abbreviated new drug applications (ANDAs) go through an initial review process within the desired 180 days, a large improvement from 1999 figures, but FDA continues to struggle to meet the larger goal of approving all ANDAs for market in six months.

To accomplish this task, FDA aims to reduce the multiple review cycles needed to approve most ANDAs. OGD often requires more than one year to fully approve new generic products because manufacturers frequently fail to meet FDA data requirements when they first file an application, causing them to correct the application’s deficiencies and to refile the document. The agency is moving to rectify these problems by encouraging earlier consultation with OGD reviewers and by examining how to improve guidance and communications with ANDA sponsors. FDA also has launched a major initiative to overhaul good manufacturing practices (GMPs) for the entire pharmaceutical industry to facilitate manufacturer demonstration of compliance with GMPs (1).

Some of OGD’s additional funding will support research to assist manufacturers in developing generic versions of more-complex drug dosage forms. FDA is planning studies to establish standards for products that have been difficult to test for bioequivalence such as topical creams, nasal sprays, injectibles, controlled-release capsules, and metered-dose inhalers.

Regulation versus legislation
One reason manufacturers submit inadequate ANDAs is because the rules governing generic drug approvals influence firms to rush to file an application with the agency. The current system for listing and challenging innovator drug patents was established by the Hatch–Waxman Act of 1984, which greatly simplified data filing requirements for generic products to gain FDA market approval. However, the complex statute also has led to
legal battles concerning when an innovator patent expires and a generic competitor can come to market. In 2002, Congress almost approved legislation backed by generics manufacturers that would have made significant changes in Hatch–Waxman policies, but opposition from brand-name firms blocked final enactment. The Bush administration agreed that the reform legislation went too far in diminishing innovator patent protections and has tried to address some generic industry concerns by revising FDA regulations.

In an unusual move, President Bush personally unveiled a new FDA proposed rule in October 2002 to signal strong White House interest in the issue (2). The rule aims to prevent excessive delays in FDA approval of new generics by

- permitting only one 30-month stay to prevent FDA approval of an ANDA on the basis of innovator patent infringement claims
- clarifying that certain types of patents (for packaging, metabolites, or intermediates) may not be listed in FDA’s Orange Book and that other patents (claiming drug substance, drug product, method of use, and product by process) may be submitted to FDA
- requiring a top executive of the firm that holds a new drug application (NDA) to sign a more detailed declaration accompanying patent submissions to reduce the filing of inappropriate or frivolous patents.

CDER shifts personnel to oversee biotech therapies

CDER has established a new Office of Biotech Products (OBP) in its Office of Pharmaceutical Science (OPS) to conduct product quality reviews of therapies transferred from CBER to CDER. Yuan-yuan Chiu, formerly head of OPS’s Office of New Drug Chemistry (ONDC), is the acting head of the new office, which will house most of the 200-plus CBER staffers moving to CDER. In OBP, staffers will continue to conduct research and review the manufacturing sections of biologics licensing applications for new biotech therapies. A smaller group of former CBER staffers will review clinical data as part of CDER’s Office of New Drugs, and several CBER compliance officials will join CDER’s Office of Compliance.

Chiu began her new task of overseeing the transition process in May 2003, setting the stage for the reorganization to occur 1 July 2003. The consolidation becomes official on 1 October 2003, the beginning of the federal government’s 2004 fiscal year.

Moheb Nasr, director of the Division of Drug Analysis in CDER’s Office of Testing and Research, has moved to head ONDC temporarily; one of his main tasks will be to help implement a quality systems approach to chemistry reviews.

Seeking compromise

FDA finalized its generic drug rule as Congress moved to enact generic drug reform legislation. In June 2003, a bipartisan group of Senate leaders announced that they agreed on a new bill to resolve some generic drug issues that generate costly patent disputes. Senators Judd Gregg (R-NH), chairman of the Senate Health, Education, Labor, and Pensions Committee,
and Charles Schumer (R-NY) led the effort to seek speedy Senate approval of reform legislation (S.1225) that contains

- new language that allows an innovator firm one 30-month stay on an FDA approval of a generic product that challenges its patent. The revision aims to clarify which listed patents could trigger a stay and sets time limits on the stay process.

- a new enforcement mechanism that permits a generics company to file counterclaims if a brand-name firm sues for violation of a patent. The provision replaces a measure in last year’s bill that allowed generics firms to sue innovators outright for listing “frivolous” patents, which was strongly opposed by pharma companies. Generics firms cannot collect monetary damages but may seek delisting or correction of patent information in the Orange Book.

- a requirement that generics firms must bring newly approved products to market in a timely manner or forfeit the right to the 180-day exclusivity granted to the first applicant to gain FDA approval of its ANDA. The legislation clarifies when the 180-day exclusivity clock starts and other related provisions.

- a clarification that FDA may use other scientifically valid methods to ensure bioequivalency of innovative dosage forms such as topicals and inhalants. The legislation allows FDA to revise criteria for Orange Book listings and to require stronger declarations from patent filers, as specified in its new regulation. The difference in setting limits on 30-month stays may warrant revision to avoid confusion between FDA regulation and the new legislation. In unveiling the generic reform bill on 5 June 2003, its sponsors promised to seek speedy Senate approval for the measure. One strategy may be to add the legislation to separate Senate Medicare reform legislation that aims to establish a Medicare prescription drug benefit. Senator Gregg and his colleagues predicted that the measure could save Medicare about $20 billion throughout 10 years in drug expenditures. Action in the Senate would set the stage for House consideration of the measure.

**Battle over biologics**

Innovator firms may prefer that Congress drop the generic reform bill, but firms should be relieved that the measure specifically avoids FDA approval of generic or follow-on versions of biotech therapies. The Generic Pharmaceutical Association (GPhA) has been lobbying for such a change as the biologics market continues to mature.

Without specific legislative authority, it is not clear how FDA can regulate new ver-
sions of biotech therapies made by another manufacturer. Most biologics are governed by the Public Health Service Act and thus do not fall under Hatch–Waxman. This situation raises questions about FDA’s authority to approve equivalent biologics on the basis of clinical and preclinical data from the innovator firm. Biotech companies maintain that interferons, growth hormones, and proteins do not lend themselves to generic production because living cell cultures yield considerable variation among batches. Consequently, these products require much more testing than conventional drugs to ensure uniformity, potency, and purity.

Generics makers acknowledge that biologics are more complex products but believe that more-sophisticated production and testing methods will address concerns about product quality. New technology may facilitate the development of therapeutically equivalent or interchangeable versions of

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### Pushing OTCs

Another Bush-administration strategy for controlling pharmacy benefit expenditures is to encourage many widely used drugs with good safety profiles to switch to over-the-counter status. Such changes could save millions of dollars for healthcare payers and insurers because most OTC products are not covered by public or private health plans. The effect on consumers, however, is mixed. Although patients with limited or no drug benefits would gain access to less costly OTCs, individuals that do have pharmacy benefits would pay more out of pocket for medicines that make the switch.

FDA Commissioner Mark McClellan seeks to encourage more switches as FDA tries to resolve OTC regulatory issues raised by insurers five years ago. Wellpoint Health Networks filed a citizens petition in 1998 calling for FDA to switch leading prescription allergy medications to OTC status to make them more accessible for patients. Schering-Plough voluntarily switched Claritin in 2002, largely because its patent was running out anyway, but Pfizer (Zyrtec) and Aventis (Allegra) still had plenty of patent life and refused to follow suit.

FDA lawyers believe the agency has legal authority to determine that a prescription (Rx) drug meets OTC safety standards, but forcing a switch is difficult. FDA will have trouble obtaining label comprehension data and other information to support such a change without manufacturer cooperation, and the legal process for orchestrating a forced switch could take years. FDA may hold a public meeting similar to an important session in June 2000 that discussed the Wellpoint petition, to discuss Rx-to-OTC switches. Meanwhile, FDA’s OTC drug review division stands to gain an additional $1 million in funding under the agency’s 2004 budget request, an increase designed to enable FDA to boost switches by 50%.

McClellan told industry analysts in May 2003 that FDA won’t force any manufacturer to sell products OTC. However, the agency could encourage such action by declaring a product suitable for nonprescription use. FDA could support such findings through review of side effects and optimal dosing information in published studies and in data from foreign markets where a product is available OTC. In addition to second-generation antihistamines, other OTC switch targets include statin drugs, emergency contraceptives, and microbicides.

If the manufacturer of the brand-name Rx drug opposes a switch, one possibility is that another pharma company or generics maker could seek FDA approval of an OTC version of an Rx drug under the 505(b)(2) policy. This could allow the follow-on manufacturer to rely on safety and efficacy data submitted under the original NDA to support market approval of a different version of that innovator product.
biologics in the future, particularly for growth hormones, insulin, and monoclonal antibodies that can be fairly well characterized.

One controversial issue is whether the 505(b)(2) provision in Hatch–Waxman provides a viable route for a manufacturer to produce a biotech therapy that is different from the innovator product yet relies in part on innovator data. The 505(b)(2) process is considered a hybrid between a regular NDA with full clinical data and an ANDA, but has been used only on occasion during the past 15 years to approve new products. Currently, more mature generics companies and some biotech firms want to use this policy to develop equivalent versions of more-complex products, according to attorney William Schultz of Zuckerman, Spaeder, who played a central role in crafting Hatch–Waxman in the 1980s.

FDA issued a draft guidance for implementing the 505(b)(2) process in 1999, but innovator manufacturers strongly oppose increased FDA reliance on this procedure to bring therapeutically equivalent or follow-on products to market (www.fda.gov/cder/guidance/2853.dft.htm). In April 2003, the Biotechnology Industry Organization (BIO) filed a citizens petition with FDA that calls for the agency to withdraw the draft guidance and begin public hearings on the issue (www.bio.org). BIO argues that complex biotechnology products should be approved only if a manufacturer meets the same research and data requirements imposed on pioneer firms. Differences in product composition and manufacturing procedures at various companies can result in “significant safety or efficacy differences,” BIO states.

As an alternative approach, generics firms and policy makers are exploring whether FDA may allow development of follow-on biologics by manufacturers that establish comparability protocols similar to those developed by innovator firms to manage postapproval manufacturing changes. Biotech companies have filed more than 100 comparability protocols with FDA since 1997. These protocols define how the company can document that subsequent changes in manufacturing processes, facilities, quality controls, or formulations do not adversely affect the identity, strength, quality, purity, or potency of the product. The key question is whether procedures designed to help the innovator firm manage manufacturing changes can be used by another manufacturer to document that its product meets similar quality standards.

**Evolving Policy**

For now, FDA says it will consider these issues on a case-by-case basis. FDA has approved comparable versions of some biologics such as human growth hormone on the basis of data that document pharmaceutical equivalence. The agency recently proposed new policies to extend the comparability protocol approach to a broader range of conventional drugs.

CDER director Janet Woodcock says that FDA will begin examining data requirements for generic biologics in coming months. She has indicated that the evaluation of equivalence for biotech products requires full CMC information, including comparative characterization data for the listed drug and the follow-on product. The information is essential to determine the need for preclinical safety tests, comparative pharmacokinetic studies, and possibly full comparative clinical studies.

Experts on both sides agree that considerable analytical testing and probably some preclinical and clinical studies are needed to document the comparability of biotech products made by different manufacturers, but also point to advances in bioinformatics, microarray, and pharmacogenomics technologies to yield more-reliable testing of comparable therapies. Woodcock notes that FDA policy on biotechnology equivalence is evolving and that the consolidation of oversight for CBER therapeutics in CDER provides an opportunity for coherent policy development. Eventually, legislation may be needed to establish an approval process for follow-on biotech therapies as for generic drugs.

**References**