After months of debate, legislation to reform federal policy governing generic drug exclusivity and patent protections stalled on Capitol Hill in October. In July 2002, the Senate approved bill S. 812, which is designed to curb brand-name manufacturers from delaying market approval of new generic products. Despite strong pressure from both those who provide and those who pay for healthcare, the Republican-controlled House blocked action on the measure. Opponents regarded the bill as too complex and objected particularly to providing new legal authority for generic-drug manufacturers to file suits against patent holders.

As Congress adjourned for the November elections, the White House picked up the gauntlet. On 21 October 2002, President Bush announced that FDA would alter its rules to accomplish many of the objectives of the generic reform legislation and to help consumers gain access to low-cost generic medicines. Coming just two weeks before election day, the move aimed to appeal to voters, but even skeptical generic-drug makers and consumer groups acknowledged that the proposed policy offered changes that could reduce costly legal disputes. Some pharmaceutical manufacturers backed the proposal as a way to clarify patent exclusivity periods—and to avoid the more restrictive Senate bill.

On 25 October, FDA published a proposed rule in the Federal Register to implement the its proposal. The rule primarily makes two significant changes:

- it reduces opportunities for brand-name companies to obtain multiple 30-month stays on FDA approval of a new generic competitor. The Hatch–Waxman Act of 1984 permits patent holders to delay marketing a new generic product for 30 months pending the resolution of a patent infringement case brought by the innovator against a generic challenger. In the past, only a handful of products were involved in such patent disputes, but in recent years the number has increased noticeably. As more blockbuster drugs come off their original patents, these cases are expected to proliferate.

The Bush proposal would limit brand-name manufacturers to one 30-month stay for patents filed before an abbreviated new drug application (ANDA) is filed. This is similar to a recommendation from the Federal Trade Commission (FTC) and is more generous to innovator firms than the Senate legislation, which permits a single stay for only those patents filed before approval of the original NDA.

- it clarifies requirements for listing patents in the FDA’s Orange Book. The goal is to prevent innovator companies from delaying generic competition by filing later-issued and frivolous patents. The new rule specifies that manufacturers must list patents for drug substances (i.e., active ingredients), drug products (i.e., formulation and composition), and methods of use. It also states that manufacturers cannot list process patents and patents claiming packaging, metabolites, or intermediate forms of a drug. The rule requires company executives to sign a more detailed attestation to the validity of a patent submission and sets severe penalties for anyone submitting false statements.

Although these provisions would limit innovator patent claims, the proposed rule also permits listing “products by process” patents, by which the manufacturer claims the product. The rule seeks to distinguish these claims from process patents, which are not allowed to be listed. Even more controversial is the proposal to expand accepted patents to include polymorphs, a move FDA has opposed in the past. This new policy reflects FDA’s recognition that a generic drug’s active ingredient is not required to have the same physical form as the reference listed drug. FDA reasons that if a generics maker can gain product approval with a different form of active ingredi-
An important Office of Generic Drugs initiative seeks using added revenues to launch new research programs to develop and test generic versions of more-complex pharmaceuticals.

Although these provisions may benefit the generic-drug approval process, the proposed regulatory change is much more limited than the Senate reform bill. The FDA rule does not require brand-name and generics companies to meet the FTC recommendation for filing copies of joint marketing agreements with that agency. It also makes no changes in the current 180-day exclusivity period that FDA grants to the first generics applicant that challenges an innovator patent. However, limiting innovator firms to one 30-month stay is significant and offsets the proposed expansion in Orange Book patent listings.

FDA is soliciting comments about the proposed rule through 25 December 2002 and likely will be inundated with suggestions. The White House estimates that the new rule will save consumers $3.2 billion in the first year and nearly $35 billion during the next 10 years, which is not quite one-half the savings predicted by the Senate bill. Conversely, the rule is projected to reduce revenues for innovator firms by more than $50 billion during a 10-year period.

As a result, brand-name manufacturers are expected to challenge the FDA proposal in court. The argument at hand is whether the agency has authority under the Hatch–Waxman Act to alter the policies for listing and challenging patents. Federal judges have ruled in several recent cases that FDA has gone too far in its attempts to regulate medical products. The agency’s authority to impose a single 30-month stay remains unclear.

Meanwhile, patent disputes continue to escalate. Just days after the White House announced the FDA rule change, Pfizer filed suit to block competitors from marketing their drugs that compete with Pfizer’s Viagra. In what is considered an innovative legal tactic, Pfizer claimed that its newly approved use patent covers all drugs that treat erectile dysfunction by inhibiting a specific enzyme. Sorting out

ent, the innovator should be able to list patents for those different forms (see sidebar “Addressing polymorphism in drug development”). FDA acknowledges that this change could delay ANDA submissions and expects considerable comment on the proposal.

Less restrictive

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all the legal issues certainly will take months, during which time the pending regulatory proposal will undergo significant change and ultimately may never be finalized.

\textbf{Addressing polymorphisms in drug development}

An increasingly volatile issue for FDA and drug manufacturers—particularly for generics firms—is dealing with different crystalline arrangements or conformations of a drug substance. The heightened importance of this topic is seen in the provision in the FDA proposed rule about generic drugs that permits brand-name firms to file patents for polymorphisms in the \textit{Orange Book}.

Because polymorphisms often appear during the latter stages of drug development, they can complicate the production and regulatory process. Scientists in FDA, academia, and industry are grappling with questions about whether differing forms of an ingredient may be considered therapeutically equivalent. They are exploring whether polymorphism may affect the rate of bioavailability and absorption or whether polymorphisms are bioequivalent and have the same dissolution rate. A key issue for OGD officials is when and how polymorphisms of drug substances in generic drugs should be monitored and controlled during manufacturing.

The \textit{FDA Advisory Committee for Pharmaceutical Science} examined these issues at its meeting in October 2002 and reviewed an effort by the agency to develop a guidance document about polymorphism. The guidance proposal features a series of “decision trees” to determine whether a need exists to establish polymorph acceptance criteria for solid oral dosage forms and liquids containing undissolved drug substances. FDA aims to refine this document and issue it for public comment.

\textbf{The Office of Generic Drugs (OGD) revs up}

While lawyers and manufacturers argue the merits of the administration’s reform plan, FDA officials are taking steps internally to spur the development, testing, and approval of new generic products. The OGD in FDA’s Center for Drug Evaluation and Research (CDER) is beefing up its staff to further reduce logjams in the application review process. It also is investing added resources to research methods of streamlining generic product testing and evaluation. At the October 2002 conference of the Generic Pharmaceutical Association, OGD director Gary Buhler told manufacturers that he expects his office to receive a $5 million budget increase to support these and other initiatives such as:

- accelerating the application review process.
- overhauling the \textit{Orange Book} listing operation.

CDER recently transferred this program to OGD, and Buhler is reviewing its operation and looking for ways to speed up the revision process. One
FDA struggles with new aseptic processing guidance

At the October 2002 meeting of FDA's Advisory Committee on Pharmaceutical Science, FDA compliance and review officials opened a much-anticipated discussion about a proposal to revise the agency's outdated policy for ensuring sterility in aseptic manufacturing operations. Manufacturers are upset that agency field inspectors are citing them for violations in this area on the basis of new FDA policies that differ from established practices. The current FDA guidance on this topic dates from 1987 and provides fairly minimal GMP standards for preventing contamination of sterile drugs. The guidance also reflects 1980s technology, and FDA recognizes the need for additional clarity and guidance to facilitate current industry compliance.

The agency began an effort to revise the guidance five years ago but has been slowed by controversy within the process. To move forward, FDA now has prepared a background “concept paper” that describes its current thinking on the issue. The plan is to revise the paper and issue a proposed guidance to generate broad-based public comment. A formal draft guidance may not appear until next year because of manufacturers' objections to the initial paper.

Joseph Famulare, director of CDER's Division of Manufacturing and Product Quality in the Office of Compliance, outlined the concept paper at the advisory committee meeting. He noted that improving manufacturers' ability to ensure product sterility is a top priority for FDA's risk-based approach to regulation, as embodied in the agency's new GMP revision initiative. Contaminated therapies pose an unacceptable risk to patients, and supply shortages of these important therapies as a result of manufacturing difficulties may raise national security concerns.

The concept paper thus emphasizes a risk-based approach to aseptic processing that encourages adoption of new manufacturing technologies. The proposal encourages manufacturers to focus on critical control points in the production process and to address key sources of contamination, namely personnel practices, facility design, and environmental monitoring. A related goal is to improve consistency in FDA inspection and review processes. To this end, the paper includes an appendix addressing aseptic processing topics related to biologics.

Manufacturers object to the paper's scope and specific provisions, as seen in a critique offered by Russell Madsen of the Parenteral Drug Association (PDA). He describes technical inaccuracies related to air filtration and integrity testing. PDA finds FDA's concept paper too vague regarding procedures for conducting medical fills and that it fails to provide a “rational approach to aseptic process control and risk estimation,” according to Madsen. The apparent lack of harmonization with international standards also is a concern.

A theme in industry comments is that it may be time to seek alternatives to massive media fills to validate a sterile processing system. Madsen encourages FDA to “break the mold” in relying on media fills, noting that these test procedures cannot directly ensure sterility in production lots and that alternative process simulation tests now may be in order. Manufacturers also support broader consideration of terminal sterilization instead of aseptic processing as another means to reduce contamination problems.

FDA's call for using new technologies to further reduce human involvement in the production of sterile products emerged as a common goal. Increased adoption of isolators would further reduce human involvement with sterile product lines, but according to Madsen, a lack of guidance for using isolation technology has delayed industry implementation.
goal is to use new electronic information systems to establish a daily update capability. Another objective is to find a way to retain “no-longer-listed” patents in the Orange Book as a reference.

● clarifying the drug development process. OGD is finalizing a guidance for using a biopharmaceutics classification system to clarify bioequivalence testing requirements. Other pending guidances may address federal bioequivalence and bioavailability/bioequivalence as well as assist development of generic nasal products and topical antifungals. Generics firms also want OGD’s Division of Bioequivalence to accept the use of sequential designs and other innovative biostudy methods to accelerate the review of bioequivalence data and to reduce the number of failed studies.

● expanding the generic drug education program. FDA spent $400,000 this year to develop an educational program on the quality and safety of generic drugs. The initial effort produced public service ads designed to reduce consumer fears about generics, and a future campaign also will target physicians and healthcare providers.

● revising the inactive ingredient list. FDA has been struggling to update its 1996 version. OGD had hoped to post a new version a year ago, but now expects that a list more helpful to manufacturers will appear soon.

● encouraging more electronic submissions. A key strategy for accelerating reviews of ANDAs and supplements is to develop an electronic filing format for these applications. In June 2002, OGD issued a guidance for submitting electronic ANDAs to further this effort.

New era
The coming year marks a new era for OGD, Bauer comments. The office no longer is on a shoestring budget and will be able to initiate new policies and programs. A main goal is to enhance its science base to reduce challenges to policy decisions.

An important OGD initiative seeks using some of the added revenues to launch new research programs to develop and test generic versions of more complex pharmaceuticals. This will involve developing new bioequivalence methods for testing products such as topicals, injectable suspensions, metered dose inhalers, and liposomes. This activity will be overseen by the Research Initiative Committee, lead by Lawrence Yu, OGD director for science; Rabi Patnaik, associate director for bioequivalence; and Frank Holcombe, associate director for chemistry. OGD officials plan to consult with manufacturers about the research that the industry is conducting to avoid duplication. In addition to expanded in-house efforts, FDA hopes to develop partnerships with outside organizations to pursue this undertaking.

In the same spirit, FDA–industry partnerships also will be involved in further development of the proposed guidance for aseptic processing (see sidebar “FDA struggles with new aseptic processing guidance”).