The return of Congress to Washington this month starts the clock ticking on a 10-month deadline (September 30, 2012) for updating the FDA’s authority on new drug approvals and post-marketing reports. Those guidelines were last tweaked in 2007, when Congress passed the FDA Amendments Act (FDAAA). The FDAAA is a melange of reforms wrapped around the fourth iteration of the Prescription Drug User Fee Act (PDUFA), which was passed in 1992. The PDUFA specifies the fees that drug companies must pay when they submit New Drug Applications (NDAs) to the FDA for approval of a medication or a biologic agent. The companies’ user fees supplement—in fact, exceed—annual congressional appropriations and help to underwrite the salaries of staff members, needed by the FDA, to comb through those applications, speed up approval times, and prevent backlogs.

Back in 2007, Democratic titans Representative Henry Waxman (D-Calif.) and the late Senator Edward Kennedy (D-Mass.) were ascendant, pushing a wheelbarrow of postmarketing safety reforms through Congress. Drug companies agreed to pay higher user fees for faster FDA approval times and agreed, for the first time, that these fees—to the tune of $225 million over a period of 5 years—could be directed toward the new safety programs.

What a difference these past 4 years have made. Republicans now essentially dictate congressional action. Well aware of the party’s antiregulatory bent, the FDA has produced a PDUFA V proposal heavily weighted toward “process” improvements in assessing NDAs and is cautiously considering commitments to tame some of the unruly aspects of some of the 2007 safety measures, such as Risk Evaluation and Mitigation Strategies (REMS). The 2007 law allowed the FDA to require REMS for new drugs if the risks were considered above the average. A REMS might require only the distribution of a patient medication guide (MedGuide), or it can be much more complicated, forcing physicians and pharmacists to follow numerous “Elements To Assure Safe Use” (ETASU).

The REMS produced by the drug companies have come in different shapes and sizes, making life difficult for pharmacists, because the FDA has so far not established a standard format. The companies haven’t been much happier with the FDA’s unfocused administration of its REMS authority, which the agency, in its PDUFA V proposal, admits needs to be clarified.

That will be the big issue for the pharmacy community as Congress begins to fashion the 2012 version of the FDAAA. The new version will be built around PDUFA V, which will specify higher fees for drug companies; however, revamping REMS won’t be the only issue. Pharmacists are concerned about another FDAAA provision: the FDA’s creation of an active Sentinel adverse reaction alert system, meant to supplement its existing passive MedWatch system, which has been roundly criticized for its shortcomings. In fact, both Democrats and Republicans, often at the behest of special interest groups, can be expected to toss all sorts of proposals into what will be a stew pot of FDA reform, simmering all year on the congressional front burner.

The FDA initiated the reform process in late August, when it published a draft commitment letter that outlined the kinds of process changes it wants to make to improve the current drug-approval and postmarketing programs. The agency aired those proposals at a public meeting at FDA headquarters on October 24.

The essence of that initial effort is an increase in drug companies’ user fees, to $712 million in fiscal year 2013, which starts on October 1, 2012. The fees amount to $672 million in fiscal year 2012. In exchange, the FDA essentially retains the PDUFA IV timeframes of approving 90% of priority applications for new drugs and biologic agents within six months and 90% of standard applications within 10 months. There is no proposed change here, which isn’t all that surprising; after it digested some of the FDAAA required reforms, the FDA did a good job of approving NDAs.

The core of this program focuses on additional meetings the FDA promises to hold with an applicant before the submission of an NDA and during the application process. With an eye toward helping drug companies speed up clinical trials, the FDA also plans to hire a staff dedicated to enhancing communication between the FDA and sponsors during drug development. There are also plans to add staff to review submissions that contain complex issues involving pharmacogenomics and biomarkers and to advance the creation of patient-reported outcomes and other endpoint assessment tools. In addition, the FDA made a vague commitment to hold workshops and listen to complaints concerning REMS and the Sentinel Initiative.

Starting in early 2010, the FDA put together its PDUFA proposal after hearing ideas from all interested parties. The agency winnowed that wish list down somewhat, dropping numerous proposals. Because the drug companies pay the user fees, the agency then submitted the ideas to the pharmaceutical industry, seeking its buy-in.

At the October 24 meeting, representatives of consumer and patient groups gave the PDUFA V proposals mostly lukewarm praise but highlighted ideas that had not been included; criticized the fuzziness of the REMS and Sentinel enhance-

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ments; and generally complained that the issue of drug safety was being made a handmaiden to the issue of easing the path to approval of new drugs.

Celia Wexler, representative of the Security Integrity Program at the Union of Concerned Scientists in Washington, D.C., says she was surprised by the tone of the FDA’s PDUFA V proposals: “I don’t have any problems with improving the FDA’s new drug review process, but this proposal is so wedded to timelines that it sends the message that promptness trumps all.”

Janet Woodcock, MD, Director of the FDA Center for Drug Evaluation and Research (CDER), says she hopes that “PDUFA can go through Congress cleanly.” By that, she means she hopes there are no policy initiatives tacked on to the process improvements that the FDA proposed in the draft commitment letter.

The FDA will deliver a formal PDUFA V proposal to Congress in January and may make changes to reflect some of the criticisms heard on October 24. Whatever final shape the proposal takes, members of Congress will probably try to graft on policy initiatives related to drug advertising, off-label use, conflicts of interest at FDA advisory committees, drug recall authority, inspection of foreign facilities, and much more.

There is a good reason why the FDA’s PDUFA V proposals for process improvement are so unambitious. Jeff Allen, PhD, Executive Director of Friends of Cancer Research, says that the FDA approval process is working fine as is. The FDA is approving new cancer drugs twice as fast as the European Union does. Of the 27 new cancer drugs that came on the market since 2003, all have been available in the U.S. before they were available in Europe.

Dr. Allen said that the “unsustainable crisis we are nearing” is the 15 years and $1 billion it takes to bring a new drug to market. He added:

The key objective for pharmacy groups, however, is a revision of the REMS provisions of the 2007 FDAAA. “That is our key priority,” says Marcie Bough, Senior Director of the American Pharmacists Association (APhA).

The good news is that almost all stakeholders, including the drug companies, think that the provisions of the 2007 REMS have been troublesome. The pharmaceutical companies complain that the FDA has no black-and-white criteria for determining when REMS are necessary and that the FDA requires them willy-nilly. Pharmacy groups complain that the REMS that the FDA has approved so far have been unwieldy in their provisions, complicating life for pharmacists in retail stores, hospitals, and nursing homes. Not only have REMS had workflow implications for pharmacists; they also, at least in hospitals, have added to existing confusion and opened the door to potential medical mistakes.

Kasey Thompson, Vice President of Office of Policy, Planning, and Communications at the American Society of Health-Systems Pharmacists, says, “It is not clear that REMS are being created for patient safety.” He said that some drug companies are creating REMS as marketing tools. REMS that include ETASU requirements have sometimes led to a problem the ASHP calls “brown-bagging,” a situation in which patients must obtain an injectable product from a specialty supplier and then bring that product with them for administration in the hospital.

The FDAAA essentially substituted REMS for the Risk Minimization Action Plans (RiskMAPs) that the FDA had been requiring of some new drugs since PDUFA III. After 2007, those RiskMAPs were automatically converted into REMS, and new first-time REMS were issued. Many of these essentially required only that pharmacists provide patients with a MedGuide when they picked prescriptions. In other instances, REMS include an ETASU, which the FDA, in a Federal Register notice previewing the October 24 public meeting, admitted “can be challenging to implement and evaluate.”

The agency acknowledged: “Our experience with REMS to date suggests that the development of multiple individual programs has the potential to create burdens on the health care system and, in some cases, could limit appropriate patient access to important therapies.”

REMS are designed from scratch by pharmaceutical manufacturers and are then subject to negotiations with the FDA during the new drug approval process. They can require such tools as prescriber or pharmacist training or certification; dispensing only in designated health care settings; documentation of safe-use conditions; patient monitoring; and patient registries.

Through March 2011, according to the APhA, the FDA had approved 177 drugs that included REMS, some of them converted from RiskMAPs. Most of these medications (123) had MedGuides only. Of the remaining 54 approvals, 37 included a Communications Plan and 17 included an ETASU; 12 drugs have been approved since passage of the FDAAA, and five drugs had RiskMAPs that were converted to REMS.

In terms of their impact on a pharmacy, REMS can involve restrictions on administration, training, education, registration, monitoring, and distribution. These restrictions can strain workloads and, consequently, may encourage prescribers and dispensers to seek alternative drug products that might not be as effective; that don’t require REMS; and that don’t limit patient access to a medication.

The FDAAA authorized the FDA to require REMS when they were necessary to ensure that the benefits of the drug outweighed the risks. In making that decision, the FDA must consider several factors:

- the approximate size of the patient population likely to use the drug
- the seriousness of the disease to be treated
- the expected drug benefit
- the expected or actual duration of treatment
- the seriousness of known or potential adverse events that might be related to the drug and the background incidence of such events in the patient population that is

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likely to use the drug
• whether the drug is a new molecular entity

The FDA has already taken a step toward standardizing REMS by seeking to develop industry-wide REMS with all brand-name and generic manufacturers of long-acting and extended-release opioids. In August 2011, an industry working group submitted proposed REMS for opioids to the FDA, although the agency has not approved it yet. The FDA originally proposed REMS for opioids in 2009, but the pharmaceutical industry balked, arguing it was too detailed, prescriptive, and onerous and would discourage physicians from prescribing the drugs. The FDA then loosened its terms, which led to the formation of the skeleton that the industry enhanced in its August 2011 submission.

The PDUF A V proposal does not mention all the spadework that was accomplished on the opioid REMS as a basis for standardizing REMS in the future. The draft commitment letter simply includes a pledge to develop and issue guidance by the end of fiscal year 2013 on how to apply the statutory criteria (i.e., in the FDAAA) to determine whether REMS are necessary to ensure that the benefits of a drug outweigh the risks. The FDA also promises to explore strategies to standardize REMS, when appropriate, to reduce the burden of implementing REMS on practitioners, patients, and others in various health care settings.

“There is almost nothing there on how the FDA plans to accomplish its goals,” commented Celia Wexler of the Union of Concerned Scientists.

Moreover, the intentions don’t go nearly far enough, given various criticisms, such as those voiced by the ASHP and the APhA. A workshop on REMS, sponsored by the APhA in July 2010 produced two detailed white papers, the most recent one in May 2011. The APhA would like to see an improved FDA Web site on REMS and, perhaps more important, a mechanism for reimbursing pharmacists for the time they spend implementing their part of REMS. The APhA’s Marcie Bough suggests, for example, that some part of the user-fee pool could be used to reimburse pharmacists.

Other than unspecified changes to REMS, the only other postmarketing safety change the FDA has talked about concerns its Sentinel Initiative, the supplemental adverse reaction system to MedWatch. Until now, the Sentinel system has been the data repository for admittedly incomplete and sometimes unclear reports from physicians, pharmacists, patients, and others on adverse reactions caused by drugs already on the market. The idea behind the Sentinel system is for the FDA, after receiving an inkling of problems with a newly approved drug (e.g., perhaps from the initial results of a postmarketing survey), to query a data bank containing health records of millions of Americans to learn whether the adverse reaction occurred often enough to take remedial action.

“It is very important to our membership,” explains Marissa Schlaifer, Director of Pharmacy Affairs at the Academy of Managed Care Pharmacy.

The FDA’s PDUF A V proposal on changes to the Sentinel Initiative, as is the case with its approach to REMS improvements, sticks to vague “clarifications” that would come out of public meetings in fiscal years 2013 to 2017. The draft commitment letter that was published in September 2011 says that the FDA will use user-fee funds to conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action.

The FDA is now using a pilot “mini-Sentinel” system with data from 17 data partners that control health information for more than 25 million individuals. The first real test was completed last July. Over a period of 2 days, the FDA queried mini-Sentinel on myocardial infarctions (MIs) experienced by individuals who were taking the smoking-cessation drugs varenicline (Chantix, Pfizer) and bupropion (Wellbutrin, GlaxoSmithKline). Varenicline was a relatively new drug at the time (approved in 2006), and the FDA wanted to see whether it was causing more MIs than the long-time drug used for smoking cessation, bupropion. It turned out that there was no difference between the two. However, one university researcher who worked on mini-Sentinel noted that the query was “quick and dirty” and not a full epidemiological study. Asked what the FDA was going to do next, he said he didn’t know.

Amy Allina, Program Director of the National Women’s Health Network, complained that the FDA has no specific plans for pushing Sentinel forward. She explained:

The agency has only vague statements in its PDUF A V plan. Sentinel has been tested, and it is working in a limited way. It is time to move forward. At some point, the rubber has to meet the road. If the FDA only uses Sentinel to find risks it expects to see, instead of broader data on unexpected adverse reactions, it will have missed a huge opportunity.

Talking about missed opportunities, every representative from every consumer and pharmacy group who spoke at the October 24 meeting advocated broader authority for the FDA so that it could review television, print, and Internet advertisements more thoroughly than it does now—that is, not thoroughly at all. The FDA draft commitment letter says nothing about drug advertising. Additional authority provided by Congress in 2012 would be the kind of policy initiative that Janet Woodcock opposes.

Sally Greenberg, Executive Director of the National Consumers League, says, “It is imperative that the FDA review ads for accuracy before they reach the consumer.”

Companies can now voluntarily submit their ads to the FDA for review. In some instances, they wait for a green light; sometimes, however, they air the ads before hearing from the FDA. Ms. Greenberg and others think that all ads should be reviewed before they are disseminated. She advocates a moratorium on ads for all new drugs if there are unanswered questions about safety or if there are questions that could be answered via postmarketing surveys.

She said, “User fees should be allocated for advertising reviews so that the FDA can hire additional staff.”

The FDA’s failure to include any requirements regarding proposed drug advertising changes and the general timidity of its PDUF A V proposal probably are no accident. No federal agency in its right mind would have the temerity, in this anti-regulatory political climate, to suggest expansion of its regulatory reach. Janet Woodcock and her FDA colleagues are not blind; they can read the “tea party” leaves.