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GEARING UP FOR THE BIG BATTLE

The Politics and Policy of PDUFA

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Many in the pharmaceutical industry have assumed that the user fee framework for drug reviews is now an immutable fact of life. Surely everyone remembers the controversy over the "drug lag" we faced before the Prescription Drug User Fee Act (PDUFA) was first enacted in 1992, when over 70 percent of all new drugs were first marketed overseas, and almost 60 percent were on the market abroad for more than one year before being approved in the United States. In fact, although the user fee construct will undoubtedly be reauthorized before PDUFA III sunsets at the end of September, 2007, basic questions are still being asked on Capitol Hill about the user fee approach, and highly influential Members of Congress are probing whether PDUFA has distorted the culture and drug review process of the Food and Drug Administration (FDA).

Some of these questions grow out of legitimate drug safety policy objectives, as well as a limited knowledge of PDUFA history and operations among new Members and staff. However, in many respects this reevaluation is being driven by agendas far afield from the drug review process, including the economics of pharmaceutical coverage, concerns about the impact of pharmaceutical marketing, the competitive goals of generic or "follow-on" companies, and—last but not least—partisan politics going into an election season.

Although the data suggests that the original PDUFA goal of "safe drugs faster" has been achieved, this reauthorization is a tightrope walk for all stakeholders. For FDA, the challenge is securing adequate and stable funding for human drug reviews, and expanding related funding for activities such as postmarket risk management and guidance development, while fending off destructive changes to the agency. Patient advocates must balance the desire to have new therapies as soon as possible with the need to ensure FDA independence and enhance risk management requirements. The pharmaceutical industry wants reasonable fees tied to meaningful review and risk management goals, clarity in agency review policies, and improvements in FDA drug review infrastructure. Members of Congress are balancing the fiscal realities of paying for a world-class, efficient drug review and safety system with concerns about drug safety, conflicts of interest, marketing and advertising, and drug costs. Some critics of FDA and industry simply want the unachievable: no risks, all benefit, a completely unfettered agency, low cost drugs, and no surprises.

What is PDUFA?

PDUFA was first enacted in 1992 in response to public and Congressional concerns about delays in drug approvals and the constraints on congressional appropriations to improve drug review timelines. PDUFA allows the FDA to collect a fee per New Drug Application (NDA),

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Biologic License Application (BLA), supplemental application, establishment, and listed drug. The funds allow FDA to hire additional staff and meet specific performance goals for reviewing applications. Fees do not guarantee approval; rather they establish a timeline that FDA must adhere to for review cycles so that applicants and patients are assured that resources are allocated properly and drug approval will not be delayed because of administrative issues.

Over the program's 15 year history, PDUFA has successfully reduced drug review times, albeit with fluctuations. The median approval time for standard NDAs and BLAs has decreased from 22.1 months in FY 1993 to 16.2 months in FY 2006. The decrease for priority applications has been even more dramatic: the median approval time for priority NDA and BLA applications, was 6 months in FY 2006 compared to 13.2 months in FY 1993. In addition, under PDUFA the number of full-time equivalent FDA staff (FTEs) devoted to the new drug review process nearly doubled between 1992 and 2004, increasing from 1,277 FTEs in 1992 to 2,503. More efficient review and more staff have led to approval of 1,220 new drugs and biologics since PDUFA was first enacted.

Although not completely without debate, these positive outcomes overwhelmingly supported the rapid reauthorizations of PDUFA in 1997 and 2002. With each reauthorization, the fees have increased and the program has evolved: in PDUFA II, Congress expanded the performance goals to include activities related to the investigational phases of a new drug's development, and in PDUFA III, Congress improved the financial footing for the program, authorized the use of funds for postmarket safety surveillance for the 3-year period after approval, and funded the development of important risk management guidance documents.

As required by PDUFA III, over the last year FDA and industry, with input from other stakeholders, have negotiated an agreement on the user fee amounts, performance goals, and additional aspects of PDUFA IV. The agreement was published in the January 11, 2007 *Federal Register* and FDA held a public meeting on February 16, 2007, to present the recommendations and hear comments from the public. For PDUFA IV, FDA proposes that annual user fee collections be increased to $392.8 million for FY 2008, which is an increase of $87.4 million over the current baseline. For FY 2008, 25 million dollars of new user fee funding would be dedicated to new postmarket safety activities, including hiring 82 new staff to perform postmarket safety work, validating risk management tools, and improving FDA's scientific and informatics capabilities. More than $4 million of new user fees will enhance the process for premarket review of human drug applications and support the hiring of 20 new staff. FDA proposes to establish a separate user fee program for fully funding a voluntary review process for drug television advertising. Four million dollars will be dedicated to improving information technology infrastructure for premarket drug review. In addition, FDA plans to adopt new scientific approaches, develop critical guidances, evaluate improvements to the adverse event reporting system, and enhance communication between pre- and postmarket staff.

Facing Budgetary Constraints

The overwhelming factor in PDUFA reauthorization is fiscal reality. While consistently burdened with new statutory mandates and other sources of increased costs, FDA has historically not received significant annual budget increases from Congress, and therefore is operating with a paucity of funding for almost all of its programs. User fees from all programs account for approximately 27 percent of FDA's annual budget, and such fees account for over 50 percent of all resources devoted to the review of human drugs.

The current fiscal climate makes it difficult, if not impossible, to replace such fees with annual appropriations. For example, in order to avoid sacrificing drug review goals, for FY 2008 Congress would need to provide $400 million to replace industry user fees, resulting in a total annual agency budget of $2 billion. Furthermore, industry's willingness to pay user fees—as long as such funds are dedicated to the drug review process and related activities, rather than consisting of merely a tax on drug development—eliminates significant pressure on Congress to act.

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amendment to add $40 million for the FDA in the FY 2008 Budget was significant, as a practical matter, under prevailing congressional "PAYGO" rules, any new funding for FDA will need to come from other governmental programs, which is an exceedingly difficult in the current political environment. Nor would full federal funding of drug reviews necessarily make sense in light of the many other under-resourced FDA core functions that cannot be funded by user fees.

PDUFA IV Complexities

Despite what would normally be a general consensus on the success of the PDUFA framework, various factors are complicating reauthorization. Beyond the budget reality, by far the biggest factor is public and Congressional concern about the U.S. drug safety system. A handful of high profile drug withdrawals and controversies, usually associated with extensive product liability litigation, have fed the debate on drug safety and drawn Congress's attention to the issue. Questions have been raised about FDA's internal drug safety culture, and its ability to appropriately monitor drugs postmarket without additional authorities. In particular, FDA's drug safety surveillance system has been described by the agency, the Institute of Medicine (IOM), and government "watchdogs" as inadequate and archaic, built upon outmoded databases and epidemiological surveillance tools, and supported by voluntary reporting system.

Some believe the drug safety problem lies in having those at FDA who initially reviewed drug products involved in postmarket safety evaluations and surveillance, alleging that such reviewers have an undue interest in preserving their original review decisions. However, the danger in a compartmentalized approach is clear to industry, patients, and many in Congress—the risks of drugs are inextricably related to the benefits, and marketed drugs cannot be rationally evaluated with solely a safety orientation.

In reality, the current PDUFA IV recommendations and other FDA reforms would go a long way toward addressing many of the drug safety concerns that have been raised. The key issues are not necessarily vested interests and lack of authorities, but management and appropriations—giving FDA the resources it needs to use existing science and regulatory tools to address drug risks in the context of benefits, including greater involvement of postmarket drug safety experts throughout the process.

Another critical factor is public and Congressional concern about industry influence on FDA and the drug approval process. The much-heard allegation of a "cozy" relationship between FDA and industry often strikes those in industry who actually deal with FDA as an absurdity. Nonetheless, many on Capitol Hill are convinced that such a relationship is a fact, and believe that it has been fostered by PDUFA. Moreover, reports of alleged conflicts of interest in advisory committees have resulted in less confidence in the review and approval process and great concern about FDA's independence and judgment. In response to these concerns, FDA recently published draft guidance which in most cases will prohibit an expert's participation on an Advisory Committee if he or she has a financial conflict of interest valued over $50,000 either currently or in the prior year. While some would like to go further and bar all industry consultants from FDA panels, influential Members of Congress have applauded the guidance, which may decrease the likelihood of drastic legislative changes.

Another PDUFA reauthorization complication is the perception that FDA is an agency in a cultural crisis. The September 2006 IOM report, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," examined, among other things, the culture of the Center for Drug Evaluation and Research (CDER). Interviews with staff and leadership found that "the organizational culture in CDER confirms some of the adverse perceptions conveyed in the mass media, and that the center is an organization in urgent need of great change."

The IOM report cited, "a work environment that is not sufficiently supportive of staff (as evident in problems with morale and attrition), polarization between the premarketing and postmarketing review staff, and evidence suggesting insufficient management attention to scientific disagreement and differences

of opinion" as key challenges FDA needs to address to improve the drug safety system. Members of Congress have repeatedly expressed concern about such cultural issues, both in hearings and in letters to FDA. Others are willing to give Commissioner von Eschenbach time to implement efforts to "fix" the agency drug regulatory cultural and management concerns.

Drug Safety Legislation

Although PDUFA has been touted by some as a potential "must pass" vehicle for a broad array of programs and reforms—most notably a follow-on biologics framework—drug safety legislation is acknowledged to be the most likely add-on to PDUFA. The central legislative proposal is the Enhancing Drug Safety and Innovation Act (S.484) introduced by the Senate Health, Education, Labor, and Pensions Committee Chairman Edward Kennedy and Ranking Member Michael Enzi (R-WY), which is similar to, but in certain respects more limited than, H.R. 1561, introduced by Oversight and Government Reform Committee Chairman Henry Waxman (D-CA) and Representative Edward Markey (D-MA). S. 484 and H.R. 1561 would establish a Risk Evaluation and Management Strategy (REMS) for all newly approved drugs and certain existing products, in order to improve risk communication, increase surveillance of adverse events. Under certain circumstances, limits could be imposed on drug distribution and direct-to-consumer advertising. Other provisions include instituting civil penalties for violations of REMS, and reform of the advisory committee conflicts waiver system. The legislation would also mandate postings on a clinical trial registry and results database for all Phase 2, 3 and 4 studies, and set up the "Reagan-Udall Institute," a public-private partnership to advance FDA's Critical Path Initiative.

In contrast, the FDA Safety Act introduced by Senators Charles Grassley (R-IA) and Christopher Dodd (D-CT) and Representatives John Tierney (D-MA) and Jim Ramstad (R-MN) (S. 468 and H.R. 788) would go beyond risk management to change CDER structurally by establishing an independent Center for Postmarket Evaluation and Research for Drugs and Biologics (CPER) to take over the functions and duties of the current Office of Surveillance and Epidemiology (OSE).

The drug safety reform debate in the Senate is an ongoing battle of media positioning, hearings, investigations, and pointed letters to FDA. Nonetheless, many believe the debate will ultimately coalesce around some form of the bipartisan Kennedy-Enzi approach. The scope of the REMS proposal remains a matter of some debate, with considerable concern around issues such as the potential impact of REMS restrictions on the practice of medicine and patient access to treatment, the scope of any restraints on direct-to-consumer marketing, and the process for negotiating disputes over REMS issues between FDA and applicants. A critical question will be whether such legislation will slow the PDUFA IV reauthorization process by requiring renegotiation of aspects of FDA's PDUFA IV recommendations on funding and performance goals.

The situation is potentially more complex on the House side. Chairman Dingell of the Energy & Commerce Committee, which has primary FDA authorizing authority in the House, stated his reservations at a March 22, 2007 Oversight and Investigations Subcommittee hearing: "I, for one, do not see anything in the new FDA proposal that effectively responds to the many problems identified by this Committee over the last few years. None of these 'reforms' impose structural guarantees to stop the cultural bias that has skewed the Agency's judgment … Drug safety continues to be the central concern of this committee as the reauthorization of the [PDUFA] goes forward."

In the end, Congressional debate about PDUFA IV will center on constituents. Widely reported issues of drug safety concerns, thousands of websites and blogs, and an aggressive media looking for dramatic stories, have ramped up public interest, while grossly oversimplifying these issues. Ultimately, the politics of PDUFA in an election season will involve balancing public perceptions with the fiscal and policy realities of drug development and healthcare. Although the process has been and will continue to be difficult, the 110th Congress will likely be critical for the future of the FDA drug regulatory framework. ∆

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