

THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT AND THE FOOD AND DRUG ADMINISTRATION: METAMORPHOSIS OR MAKEOVER?

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The Food and Drug Administration Modernization Act of 1997 (FDAMA) is the first legislation to bring about significant and widespread modifications to the regulatory environment for drugs and biologicals in more than 35 years. The expectations of what FDAMA is to accomplish are high. This article reviews the results from the first two years of implementation of the major FDAMA provisions for drugs and biologicals. First, however, the elements of the adversarial culture that brought about the impetus to modernize FDA are discussed. Next the article focuses on FDA's more "modernized" approach to the process of governing, through the use of such mechanisms as governance by guidance, direct final rules, national videoconferences, and stakeholders meetings. In addition, the process for implementing FDAMA and what the products of that process have been, both the rules themselves and the outcomes for the regulated community, are discussed. Lastly, the article considers whether FDA is capable of change and what the real message of FDAMA is.

Key Words: FDA Modernization Act; FDAMA; Food and Drug Administration; Rule making

INTRODUCTION

THE FDA MODERNIZATION Act of 1997, which includes the reauthorization of the Prescription Drug User Fee Act (PDUFA), is the first major reshaping of the regulatory landscape for pharmaceuticals since the 1962 amendments to the Food, Drug, & Cosmetic Act. Prior to FDAMA, FDA never had a formal mission statement. In FDAMA, Congress provided one, which focused on three main objectives for drug development:

1. Protecting the public health by ensuring that the products FDA regulates meet the appropriate agency regulatory standards,
2. Promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a manner which does not unduly impede innovation or product availability, and
3. Participating with other countries to reduce regulatory burdens, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements (1).

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The expectations for what FDAMA will accomplish are very high. Industry anticipated that FDAMA enhancements to FDA's

regulatory procedures along with the PDUFA-mandated dedication of resources to drug approval would shorten drug development time by about a year (2,3). Moreover, passage of FDA reform would finally bring predictability to the drug development process (4). The compromise reached in the passage of FDAMA was to be the beginning of an “era of good feelings” between industry and FDA (5). FDAMA was to move FDA from an “adversarial culture” to a “collaborative culture” (1).

CULTURE SHOCK

Where did the adversarial culture come from? Where has it gone? Part of the problem, according to Dr. Janet Woodcock, Director of FDA’s Center for Drug Evaluation & Research (CDER), is that “Typically, CDER personnel do not understand drug developers’ environments, requirements, and costs . . .” (6). More significantly, she admits that FDA, by tradition, was not focused on economic concerns, even when it did consider drug development at all. Yet, she notes that FDA has a profound impact not only on the drug approval process, but on clinical development as well, through its standards requirements, sequencing of trials, “process costs” such as clinical holds and protocol reviews, trial audits, and FDA-sponsor interaction. Finally, Woodcock acknowledges that FDA has only recently come to the recognition that facilitating drug development is part of its mission.

In addition to often overlooking industry needs, FDA, in the opinion of some, was also blinded by adherence to ritual, defined as “. . . an activity that is undertaken on a routine basis regardless of whether it is necessary or makes sense in a specific situation” (7). There were four basic sources of these rituals: laws, tradition, scientific curiosity, and fear (7). Statutes, regulations, and guidelines form the framework of FDA’s routine activities. Tradition comes into play when the regulatory framework fails to supply the appropriate ritual for a particular situation, that is, we do it this way because “we have

always done it that way” (7). As for scientific curiosity, drug development, in general, is the purview of scientists both in industry and government. It is the nature of scientists to be curious and to seek more and more information until everything has been explained, sometimes regardless of its actual impact on safety and efficacy (7). In some ways, perhaps unconsciously, scientific curiosity is also linked to the last source of ritual—fear of making a mistake or being criticized (7). This is an especially negative motivator for regulators whose mission is to protect the public. In the face of anything not fully accounted for, the response was to require more and more information.

So how has FDA begun to rid itself of the rituals and traditions which have hampered its progress towards modernization? It started with FDA recognizing that it needed to understand more about the process of drug development (6). Then, FDA’s new leadership voiced its dedication to the spirit and letter of FDAMA. As early as her Senate confirmation hearings, Commissioner Henney emphasized that she was committed to breaking down barriers that have kept the agency from being as effective and productive as it could be and to building bridges of communication (8). Lastly, there was a willingness to make the workings of FDA more transparent, to start an ongoing dialogue with its constituency, and to experiment with the actual process by which it governed.

ADVENTURES IN GOVERNING

On the same day that FDAMA was signed into law, a policy on direct final rules was published in the *Federal Register*. Basically, direct final rules are used to streamline the rule promulgation process when the action is believed to be noncontroversial and consists of publishing the proposed rule and final rule at the same time. If significant and timely negative comments are received, then FDA can withdraw the final rule, but use the proposed rule to fix a new final rule without having to start the process all over again.

Alternatively, it may adopt as final any parts of the rule that do not draw significant adverse comments (9).

As FDA was to be reminded very quickly, nothing the agency does is “noncontroversial.” Less than a year after the policy was published, FDA had to withdraw one of its first attempts at a direct final rule designed to implement a major FDAMA provision—dispute resolution. Two years into FDAMA, dispute resolution is still unresolved. The Pharmaceutical Researchers and Manufacturers of America (PhRMA), an industry trade association, has called for clarification of a number of issues related to the threshold for access to the process and the time frames for carrying it out (10).

Another early experiment was the so-called “governance by guidance” approach taken by FDA to nudge the regulated community in the direction of the agency’s current thinking on an issue without bringing to bear the force of law (ie, an alternative approach may be used as long as it complies with applicable regulations or statutes). Roger Williams, then deputy director for Pharmaceutical Sciences at FDA, noted that FDA was converting to “regulation by guidance,” a collaborative and resource-intensive process driven by the demands of PDUFA, FDAMA, and the International Conference on Harmonization (ICH) process (11). From the industry perspective, this proliferation of guidances was considered an indication of the cooperative era ushered in by the passage of FDAMA (5).

Even governance by guidance is no longer viewed through rose-colored glasses. In addition to early concern that this tactic flouts the Administrative Procedures Act (5), there is growing awareness that guidances are not cure-alls. After little more than a year, FDA had to issue a new guidance (12) on FDAMA’s pediatric studies exclusivity provision to clarify the first guidance (13). Moreover, the process has drawn attention to the fact that the era of good feelings still has a lot of chipped shoulders to deal with. A former FDA official who now works for industry, Dr. Bruce Burlington, recently pointed out

that industry has trouble presenting a united front in response to a draft guidance and that persistent distrust of both the FDA and advocacy groups prevent it from interacting with them to further its own interests (14).

The most visible and ambitious of FDA’s new look to governing was its initiative to create open and transparent processes and encourage collaboration. This initiative was carried out by stakeholders meetings, national videoconferences open to all interested parties, numerous public meetings on specific provisions of FDAMA, and FDA-sponsor conferences (15), in addition to increased public access to FDA information on the Internet. The more novel and publicized elements of this initiative—national videoconferences and stakeholders meetings—involved thousands of attendees, dozens of speakers representing every conceivable health care special interest group, and hundreds of sites throughout the country.

These efforts have drawn praise, both general and specific. With regard to the transparency of public participation processes, the FDA Office of Special Health Initiatives and the Office of Women’s Health were highlighted as having model approaches for promoting education and interaction with their constituents (16). Industry and advocates have also praised CBER’s “open door” policy and use of the Internet to make information publicly available (17). Senator Kennedy generally lauded FDA’s increased efforts to maintain a dialogue with the industry, the health care community, and consumers. He further noted that all of the agency’s major divisions have significantly increased these contacts, and their actions represent a positive change in the agency’s operations (18).

While welcoming the opportunity to hear stakeholders voicing their concerns, Commissioner Henney acknowledges that “all these voices can sometimes create a cacophony” (15). In an attempt to gain direction from the voluminous input, FDA is systematically evaluating the information by using a process called influence structuring, which identifies the importance of a single issue in

relation to its effect or influence on all other issues. So far, 26 cross-cutting issues have been identified (19). Nevertheless, making sense of the diverse and often discrepant public input has been a resource-intensive and painstaking process. Perhaps, FDA hinted at this when it noted that it would be taking a six-month hiatus after its first round of stakeholder outreach to review each and every comment received (19).

All in all, FDA has received high marks for the process of implementing FDAMA. As detailed by Senator Kennedy at the second FDAMA implementation hearing, every statutory deadline has been met so far, and FDA has issued 20 final rules, 16 proposed rules, 42 guidance documents, 14 notices, and 7 reports (18). There is no question that FDAMA's call to remake the process has engendered a flurry of new activities at FDA; but what has been produced by all that process?

MAKING FDAMA WORK AND THE MAKINGS OF A WORKABLE RULE

Simply enacting a new law does not automatically ensure that the changes embodied in the law will be implemented. It is the statutory duty of the Secretary of Health and Human Services and the Commissioner of FDA to implement the law in the way Congress intended (8). To assist FDA on its path to modernization, FDAMA was to provide "clear statutory guidance" (1).

As with all major legislation, however, the devil is in the details. The actual implementation of a public law passed by Congress, later codified as a statute, is left to the discretion of the executive agencies through a process of rule making. The end products of this process are rules "... designed to implement, interpret, or prescribe law or policy ... or practices" (20), which can remain nonbinding statements of the agency's current thinking or subsequently become codified as binding regulations.

What makes a workable rule? The formulas run from the classical to the clinical. The classical ones are derived from the manual of rule making, the Administrative Procedures

Act (APA), and the bible of our American democracy—the Constitution. The APA's definition of rule states that it "means the whole or a part of an agency statement of general or particular applicability and future effect . . ." (20). The purpose of rule making is a basic lesson in every introductory course on Administrative Law—to put affected parties on notice of impending changes in regulatory policy and to give them an opportunity to be heard before the agency's position has crystallized (21). The use of rule making provides the regulated with more precise notice of what conduct will be sanctioned and promotes equality of treatment among similarly situated persons (22). While the APA is the letter of the law on the process of rule making, the spirit comes down from the Constitution. As interpreted by the United States Supreme Court, the constitutional premise of rule making is to maintain the system of separated powers and checks and balances, which safeguard "the separateness but interdependence, autonomy but reciprocity" necessary for a democratic but workable government (21). It thus becomes axiomatic that an administrative agency's power to promulgate legislative regulations is limited to the authority delegated by Congress (21).

The clinical *raison d'être* of a rule is derived from its functions: to put the regulated on notice of what will be expected before it is expected, to encourage consistency and fairness in the application of laws by the regulators, to convey a sense of predictability of the law for the regulated, and to implement the intent of Congress (and, at least arguably, the will of the people) within the limits of authority delineated by the Constitution and the APA. Rule making can encompass a continuum of regulatory decision making from a guidance document without the force of law to a regulation later determined to exceed the agency's constitutional authority. It involves both process—how the rule is developed, and product—the rule (or guidance, policy, etc.) itself. Under FDAMA, these processes are to be open and collaborative (15), and the products are to be limited to FDA's specific statutory obligations (8,16).

FDAMA AND FDA: A MIXED REACTION

FDA's regulatory decisions in response to FDAMA's major drug development provisions at the two-year mark seem to fit into four categories:

1. *Minimal process*—FDA's response to health care economic information (ie, pharmacoeconomics), the single controlled trial efficacy standard, and the review of efficacy supplements,
2. *Bad process*—as occurred with the dissemination of off-label information,
3. *Mixed process*—as happened with the implementation of scientific advisory panels (SAPs), dispute resolution, and pediatric studies, and,
4. *Good process*—characterizing FDA's approach to a number of FDAMA provisions, such as PDUFA, abbreviated study reports, expanded access, stakeholder input, and most notably, fast track.

Minimal Process: Is Less Process Always Good Process?

When FDA responds with a minimal process approach, it seems to be the result of one of three rationales:

1. The provision is self-executing,
2. The provision calls for a wait-and-see stance, or
3. The provision is a codification of existing policy.

The reaction of FDA to the pharmacoeconomics provision of FDAMA is considered, by contrasting viewpoints, to exemplify both of the first two rationales for minimal process—self-executing language and wait-and-see. Whereas, the codification of existing policy rationale may explain the agency's minimal process response to both the single controlled trial efficacy standard and the approval of efficacy supplements.

Deciding when a statutory provision is self-executing is the premier regulatory fi-

nesse move and one which FDA is still perfecting. Consider, for example, the response to the pharmacoeconomics provision, which allows drug companies to supply information on the cost-effectiveness of drugs to health care providers if the information meets the competent and reliable standard and restricts its claims to approved indications. FDA has not published any guidance on providing pharmacoeconomic information two years into FDAMA (and for two years before that despite expectations to the contrary). Perhaps, FDA thought none was needed as PhRMA described the statutory language of the provision as self-executing in the first FDAMA implementation hearing (3). A year later, however, the biotechnology industry criticized this approach as leaving it in limbo. According to the biotechnology industry's spokesperson at the second FDAMA implementation hearing, Ms. Janice Bourque, biotechnology companies are increasingly asked to provide pharmacoeconomic data to managed care and health insurance companies. Since there are many different strategies for doing pharmacoeconomic studies and FDA has not issued any guidance documents, however, they do not really know how to respond to those requests (23).

By contrast, FDA's approach to pharmacoeconomic information has also been characterized not as inaction, but as a purposeful delay of action. According to this view, FDAMA's authorization of cost-effectiveness claims for approved drugs was deliberately couched in vague language, the claims contingent upon prior scrutiny by FDA, and the whole program subject to a study by the Comptroller General with a report to Congress, because it is something of a trial run (24). In this view, then, FDA's minimal process is an intelligence-gathering exercise because that was what was intended all along—wait-and-see.

FDA's third line of reasoning for utilizing minimal process is that the provision is a codification of a pre-FDAMA policy. FDA's response to the related FDAMA issues of the single controlled trial efficacy standard and the requirements for efficacy supplements

are examples of this. These two issues were the subject of a guidance that existed in draft form for months before FDAMA was passed (25). This draft guidance was then republished as a final guidance after FDAMA became law (26). While industry often welcomes such minimal process, this time it may represent something of a disconnect, either between FDA and industry, or between FDA and Congress, as to what was needed for efficacy supplements. Congress called for “new policy” in this area of regulation (27). The only new policy provided by FDA (at least for drugs and biologicals), however, was a guidance document in which the title (*Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements*) is almost as long and as informative as the document itself (28). Yet, industry appears to need new direction in this area. A number of FDAMA provisions were designed to encourage the submission of efficacy supplements (eg, pharmacoeconomics, pediatric studies, dissemination of new uses, exemption from user fees for certain categories of supplements, etc.). Increased numbers of efficacy supplements should have resulted. It may be too early to tell, but so far that is not happening. Instead, in fiscal year 1998, there were fewer efficacy supplement submissions for drugs and biologicals than the year before, by almost 20% (29), and, in calendar year 1999, efficacy supplement approvals by CDER declined by over 20% from the previous year (30,31).

Bad Process Leads to Bad Product

The Dissemination of Information on New Uses provision of FDAMA was an attempt to reconcile a long-standing and refractory dispute between industry and FDA (5). It was also considered by some to be unquestionably the most controversial reform and one of the few genuine innovations made by FDAMA (24). The off-label use of drugs is the uneasy trade-off between the dictates of the Federal Food, Drug & Cosmetic Act that all uses of a drug must be approved by FDA, and the agency’s longstanding practice of

medicine policy that it should not restrict the actual prescribing decisions of medical professionals. Because of this tension, there is the need for both timely dissemination of accurate information on new unapproved uses of drugs as well as the need to protect the public from unproven treatments, which could potentially cause harm. FDAMA authorized drug, biologic, and device manufacturers to distribute certain written information on a use of a product, which is not described in the product’s approved labeling, to health care practitioners and insurance providers, but not to consumers. The manufacturers, however, must meet certain conditions related to the source and quality of the information as well as pursue labeling for the unapproved use.

The process of implementing what appeared to be a legislative compromise went bad when FDA overlooked the need to temper some potentially restrictive statutory language. Instead, in somewhat of a ritual response, it merely retrofitted the existing FDA policy, which was unworkable and unenforceable, to create a regulatory framework that became unworkable, unenforceable, and, perhaps ultimately, unconstitutional. It was no surprise that it suffered the fate of many bad products upon reaching the marketplace. It was rejected by consumers (ie, the pharmaceutical firms) from day one for being unusable, and subsequently recalled by the government (ie, a Federal District Court) for being constitutionally defective. The District Court’s pending decision hung like a pall over the FDAMA provision right from the start, and the regulated community anticipated its death knell with inaction.

FDA estimated that FDAMA would result in over 300 submissions each year from manufacturers to disseminate new use information (32); instead it received only 17 submissions almost two years into the statutory period (33). The legal authority cited in the District Court’s Order to set aside “the policies, rules, and regulations” generated by this provision of FDAMA was the Administrative Procedures Act, which proscribes agency actions contrary to constitutional rights and

privileges (34). Now even Senator Frist, who was one of the authors of the provision, believes the statute was unconstitutional and that the process may have been flawed because it was premised on a basic distrust of the capacity of physicians as sophisticated listeners (35). Bad process makes for bad product. Even if the provision is salvaged by some legal legerdemain, two to three years will have been wasted.

Mixed Process: A Product of Regulatory Paternalism?

FDA's final pediatric rule, which in its proposed form predated the FDAMA pediatric studies provision, is the most typical example of mixed process. Mixed process occurs when FDA is unable to let go of its pre-FDAMA, often paternalistic (ie, well-intentioned goal but heavy-handed means) approach to an issue while attempting to implement a FDAMA compromise.

The final pediatric rule, mandating sponsors to conduct pediatric studies on new and marketed drugs of potential benefit to the pediatric population for which adequate safety and effectiveness information does not exist for claimed indications, was issued by FDA on December 2, 1998. This was just one year after the enactment of FDAMA's pediatric studies provision, which allowed an additional six months of market exclusivity as a reward for the voluntary performance of pediatric studies. FDAMA had harmonized FDA's proposed pediatric rule by stating that any pediatric studies required by the rule might also serve to fulfill the requirements for FDAMA as well. Despite the regulatory amenity implied by this harmonization clause and Commissioner Henney's assurance that they would be "complementary and mutually reinforcing" (36), FDA's promulgation of the final pediatric rule so early in the FDAMA implementation period seemed to signal a return to the premodernization tactics of carrot-and-stick.

The carrot-and-stick approach raises the concern that FDA's final pediatric rule may interfere with the implementation of FDAMA

instead of complementing it. FDA predicted that approximately 80 drug studies per year would result from the rule, with only about half of these studies likely to be conducted voluntarily for the FDAMA reward (37). FDA already appears to have its hands full keeping pace with the pediatric studies requests generated by FDAMA. Approximately 184 study proposals have been submitted to the agency as of December 1, 1999 (just 17 months since the first guidance document was issued), with 119 official go-aheads coming back out, but only 9 approved drugs actually awarded market exclusivity (38).

Since the bulk of the pediatric studies engendered by FDAMA are likely to balloon into the latter part of the year 2000 and all of 2001, industry's momentum will crash headlong into the deadline for compliance with FDA's final rule at the end of the year 2000. Will demand exceed supply? There are serious questions as to whether there are enough pediatric patients, researchers, and appropriate facilities to handle what could be a two- or even three-fold surge in pediatric studies (39). And what about FDA overload? According to Dr. Murray Lumpkin, CDER deputy director for Review Management, one of the causes of a downturn in first cycle approvals of standard NDAs from fiscal year 1997 to fiscal year 1998 may have been the demands of the pediatric studies program (40).

Despite two years of the pediatric program having already elapsed, Commissioner Henney noted that it was too early to comment on the "track record" of the effects of the program, but that it was true that studies had been completed for only a handful of products, resulting in a few label changes (35). Yet, little time remains. Even without formulation development, it can take up to 15 months just for protocol development of a pediatric study (37) (a proposal for a pediatric study would include this level of information at a minimum) (13), and then FDA has four months to review the proposal and issue a written request (12). The entire process could take about 1.5 years. The actual opportunity window, then, for initiating a pediatric

study request under FDAMA was from June 1998 (when the first guidance came out) until June 2000 (1.5 years from program sunset on January 1, 2002). Except for the drugs that can withstand the gauntlet of conditions for surviving sunset, the voluntary FDAMA program is functionally a two-year program, not a five-year program. This is in stark contrast to the mandatory obligation under the pediatric rule that will run in perpetuity. That makes for a very short carrot and a very long stick.

There is no question that FDA wants the pediatric studies initiative to achieve all that has been hoped for. In the long term, perhaps, FDA's mandatory approach may be one way to fill the gaps left by FDAMA for no-incentive drugs and biologicals lacking market exclusivity life, and for low-incentive, newly developed drugs. In the short term, however, the rule detracts from the voluntary and incentivizing character of the FDAMA pediatric studies program that Congress intended, and may divert industry and FDA resources away from its implementation. Whether mixed process, involving a pre-FDAMA holdover to a FDAMA done deal, will bear mixed results—only time will tell.

Formula for Regulatory Success: Good Process + Good Product = Good Result

The last rule making approach to be considered is exemplified by FDAMA's Fast Track Products provision that codified an existing panoply of programs within FDA to expedite the development of drugs which are intended to treat serious or life-threatening illnesses and have the potential to address unmet medical needs. Prior to FDAMA, fast track was a conglomeration of regulations and policies that lacked cohesion and comprehensibility, leading to underutilization by industry. Some parts of fast track, however, such as accelerated approval (41) and FDA-sponsor conferences (42), demonstrated positive effects on expediting development for eligible drugs. Since regulations already by-and-large existed, FDA implemented the FDAMA provision through a guidance document, which

essentially made the program more user-friendly by gift-wrapping it under one designation, incorporating existing regulations, clarifying policies, and expanding the scope of eligibility.

Industry has responded enthusiastically to this FDA overture. FDA anticipated 60 applications a year for fast track designation, yet in the first six months since the guidance document came out, there have been 55 applications (43). This is not only double FDA's projection, but is close to the total of all the approvals granted under the entire previous 10 years of the "old" fast track programs (ie, subpart E designation and accelerated approval). Fast track designation has been granted for a wide range of therapies, not just AIDS and cancer, but also atherosclerotic vascular disease, acute stroke, diabetes, adult respiratory distress syndrome, pancreatitis, and rheumatoid arthritis. Two drugs, Herceptin and Enbrel, which were the beneficiaries of the "rolling review" program offered under fast track, had approval times of 4.7 months and 5.8 months, respectively. Even the FDA's guidance document on the program has received compliments as being an excellent resource for sponsors (15). Essentially, fast track was a good product that needed some good process to make it a more attractive package to industry.

IS FDA CAPABLE OF CHANGE?

It is a pivotal time for FDA to reconsider this most fundamental question. The aptly titled FDA Modernization Act has launched the agency on a reform initiative, which could complete FDA's passage from its obscure, 19th century origin in the Department of Agriculture's Bureau of Chemistry to renaissance as a showcase administrative agency for the 21st century. FDA shows every sign of trying to remake itself into a more modern and model agency. In so doing, it is natural for the agency to experiment with the process by which it regulates. Stakeholders meetings, videoconferences, Internet access to FDA documents and reports, governance by guidance, and the direct final rule are all novel

and notable efforts to remake the process. One of the best modern generals of organization, Mahatma Gandhi, noted the importance of process when he said that the means are the goal in the making. While process is important, it is not all-important. It is still only the means to the goal. In a period of intense agency ferment, an emphasis on process is both natural and desirable. Yet, FDA's modernization efforts must not become overly focused on the process, and short-sighted on the final product: fair, workable rules.

FDA knows that change is needed—not just change in process, but change in attitudes and culture, as well (19). Earlier, the question was posed: Where has the adversarial culture gone? Vestiges of the traditions and rituals of the adversarial culture still plague FDA. When Commissioner Henney was questioned by Senator Reed in the second FDAMA implementation hearing on whether she thought the FDAMA approach to dissemination of off-label information was reasonable, she said she thought it was and that FDA would appeal the decision. Only on further questioning by Senator Frist did she concede that if the Court of Appeals did not support FDA, it would work with Congress to determine the right approach (35).

FDA's lack of attention to industry's real-world concerns was highlighted by a biotechnology spokesperson's complaint concerning scientific advisory panels. The spokesperson noted that when the SAPs meet in public and make recommendations on the approvability of a drug or biologic, regardless of the nature of those comments, great fluctuations in the stock of the sponsor company result (23). Yet, in FDA's view nothing undermines the working relationship and trust between industry and the agency as any suggestion that the agency should avoid or delay actions due to concerns that it may influence shareholders or other financial decision makers (44).

More ironic, perhaps, is the fact that FDA acknowledges that sometimes even when things work, the agency is not sure why. For example, Dr. Woodcock admits the agency does not know why more intense FDA-sponsor interaction during drug development

expedites the process (6). Similarly, Dr. Raymond Lipicky, director of CDER's Cardio-Renal Drugs Review Division, seems bemused as to what it is about fast track that appeals to industry, since he believes that it does not make any difference in the way his division handles things (45).

Another obstacle to constructive change is that FDA is often distracted because it works amid a "number of tensions" (6). Even as FDA has primary influence over the industry, what FDA does is influenced by many groups such as the academic community, special interest groups, consumer protection advocates, and patients, in addition to industry, Congress, and the Executive Office. FDA is also conflicted by resource constraints. After subtracting the allotment for priority programs (PDUFA, mammography standards, the tobacco rule, and food safety), what is left in FDA's fiscal year 2000 budget for everything else is \$119 million less than in 1993 (38). FDA is expected not only to do more with less, but to do for more. CDER staffers complain that newcomers to the industry—be they venture capitalists, solo investigators, or start-up companies—look to FDA as a de facto, free-of-charge "consulting service" (44). Dr. Woodcock notes, moreover, that increasing FDA's role as industry consultant may require diverting resources away from core activities such as NDA review (6). Thus, the industry must address its own tensions and conflicts in order to present FDA with a uniform agenda and a focused strategy for how FDA and industry can meet each other's needs. Industry must first look inward before it looks outward.

Even though FDA rituals are giving way to a more collaborative process and attitudes are changing, the agency's learning curve will continue to be steep because the drug development process has been "shrouded in a kind of secrecy" (6). Lowering the shroud is an act of trust that the industry may not be ready for quite yet, given the premium on competitive intelligence and senior staff turnover at the agency. In the meantime, Dr. Woodcock laments that strategies, problems, and failures are not discussed with FDA for

competitive reasons, thus sacrificing collective valuable learning tools (6). Transparency in government needs to be a two-way process between the regulators and the regulated: those inside need to see out and those outside need to see in. Industry must help FDA in order to help itself.

FDAMA: HOW GREAT A CHANGE?

One view of FDAMA is that it was going to make FDA all things to all people. FDAMA was to streamline the regulatory system, countervail the adversarial relationship between FDA and the regulated industry, limit the FDA's agenda with a clear-cut mission and sphere of responsibility, foster innovation, and ensure timely public access to beneficial new medicines without sacrificing safety (1). These expectations for what FDAMA can achieve belie the reality of today's health care environment. Medicine advances too fast for any politician to keep up, and any reform will only cast in stone a set of standards that will be out of date before they are even passed into law (46). But it is not only medical science that is advancing too fast, the world is changing too fast. Not only can Congress and FDA ill afford to take several decades before the next overhaul of medical products regulation, they may already be playing catch-up after just the several dozen months that have passed since FDAMA was written.

At the time of the original FDAMA hearings, the impetus for passing the act was the existence of an adverse environment for medical products in the United States, consisting of: the time, complexity, and cost of bringing new products to market; delayed access to life-saving medical therapies and higher costs; the growing disincentive to research here with an incentive to move it overseas, especially as the European Union was adopting a uniform system; and, changes to the product market and revenues of the industry due to the evolution of a managed care health system in the United States (1).

How much force remains in these influences and in what direction are they impact-

ing drug development? PDUFA by itself may be responsible for as much improvement in drug approval times as was practical to expect from the system, whereas other provisions of FDAMA may even be counterproductive to expediting drug development in the short term. Faster access to new medicines is being villainized in the media as also increasing health risks, while the availability of new "lifestyle drugs" is portrayed as contributing to increases in the cost of health care. The European regulatory system no longer seems any more efficient than the United States (47), which is still the number one launch market for drugs. The pharmaceutical industry's real competition is no longer from outside our borders but from other industries (eg, Internet and telecommunications) within the United States for investment capital (48). Lastly, managed care may be as much a boon as a bane to industry revenues, since managed care prefers pharmaceuticals as a treatment modality (49).

The other view of FDAMA is more prosaic. Many of FDAMA's "reforms" simply codified existing FDA policies and programs. FDAMA was really a Congressional "fine-tuning" of the agency's process, expanding its mission and authority while narrowing its discretion with detailed instructions for carrying out its charter. FDAMA largely accepts the basic framework and seeks to improve agency implementation (24). In this view, FDAMA is designed to effectuate more of a renovation than a structural change, a sign that FDA is doing something right. It does not need a metamorphosis, just a make-over.

CONCLUSION

Both these views see the future role of FDAMA as a force for change. Only the magnitude is in dispute. Yet, the real import of FDAMA may not be to bring about change in the regulatory environment as much as it is to react to change in the environment of the regulated. FDAMA provisions reflect the new realities of this environment. PDUFA is a harbinger of the necessity of private-public

partnership. The advent of pharmacoeconomics indicates the strengthening influence of managed care in determining access to new medicines. The pediatric studies program signals the growing fragmentation of the health care market into submarkets of special populations. FDA and industry have entered not so much an era of good feelings as a period of heightened evolutionary pressure compelling an ineluctable awareness of their mutual dependency. FDA and industry need to modernize together, symbiotically and continuously. Perhaps the real message of FDAMA, for both industry and FDA, is not to change the institution, but to institutionalize change.

REFERENCES

1. *Food and Drug Administration Modernization and Accountability Act of 1997*. Senate Report 105-43, to accompany S 830, Committee on Labor and Human Resources, 105th Congress, 1st Session.
2. *Food and Drug Modernization Act of 1997, Summary prepared by the Biotechnology Industry Organization*. November 21, 1997. <http://www.bio.org/laws/modernization.dgw>.
3. Prepared statement of Alan Holmer, President of the Pharmaceutical Research and Manufacturers of America (PhRMA), before the House Commerce Committee, October 7, 1998.
4. Loose cannons. *BioCentury*. 1998;6(21):A4-A5.
5. Robinson ML. FDA and industry embark on new collaborative era. *Reg Aff Focus*. 1998;3(1):18-21.
6. Woodcock J. An FDA perspective on the drug development process. *Food & Drug Law J*. 1997;52(2):145-150.
7. Versteegh LR. Science and regulatory rituals associated with the drug development process. *Food & Drug Law J*. 1997;52(2):155-161.
8. Opening Statement of Chairman James M. Jeffords, Hearing on FDA Modernization Act: implementation of the law, Senate Health, Education, Labor & Pensions Committee, October 21, 1999. http://www.senate.gov/~gregg/body_index.htm.
9. Investigational New Drug Applications; clinical holds. *Federal Register*. 1998 Dec. 14;63(239):68676.
10. Prepared statement of Alan Holmer, President of the Pharmaceutical Research and Manufacturers of America, before the Senate Committee on Health, Education, Labor, and Pension, October 21, 1999.
11. USFDA "Converting to regulation by guidance." *Pharma Marketletter*. 1998 Oct. 26;25(42):15.
12. *Guidance for industry: qualifying for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act*. Rockville, MD: Food and Drug Administration; September 1999.
13. *Guidance for industry: qualifying for pediatric exclusivity under section 505A of the Federal Food, Drug, and Cosmetic Act*. Rockville, MD: Food and Drug Administration; June 1998.
14. Industry active role in guidance development urged by Wyeth's Burlington. *Pink Sheet*. 1999 Oct. 4; 61(40):24.
15. Prepared Statement by Jane E. Henney, MD, Commissioner of Food & Drugs, Food and Drug Administration, before the Senate Committee on Health, Education, Labor and Pensions, October 21, 1999. <http://www.senate.gov/~labor/heari...>
16. Food and Drug Administration, Summary of FDA Public Meeting on Section 406(b) of FDA Modernization Act of 1997, September 14, 1998. http://www.fda.gov/oc/fdama/comm/mtg_91498.html.
17. *CBER Stakeholders Meeting, Summary of Proceedings*. Aug. 14, 1998. <http://www.fda.gov/cber/minutes/cber814.htm>
18. Opening Statement of Edward M. Kennedy, Hearing on FDA Modernization Act: Implementation of the Law, October 21, 1999. http://www.senate.gov/~gregg/body_index.htm.
19. Suydam LA, Elder DK. FDAMA update. *Food & Drug Law J*. 1999;54(1):21-33.
20. Federal Administrative Procedure Act, 5 U.S.C. §551 et seq., §sec. 551 (4), 1991.
21. Koch CH. *Administrative Practice and Procedure*. Second Edition. Charlottesville VA; Michie; 1991: 627-628,19.
22. Gellhorn E, Levin RM. *Administrative Law and Process*. 3rd Edition. St. Paul, MN: West; 1991:310.
23. Testimony of Ms. Janice Bourque, Massachusetts Biotechnology Council, Hearing on the Modernization of the Food and Drug Administration, before the Senate Health, Education, Labor and Pensions Committee, October 21, 1999. <http://web.lexis-nexis.com/congcomp/docu>.
24. Merrill RA. Modernizing the FDA: an incremental revolution. *Health Aff*. 1999;18(2):96-111.
25. Fisher LD. One large, well-designed, multicenter study as an alternative to the usual FDA paradigm. *Drug Inf J*. 1999;33(1):265-271.
26. *Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products*. Rockville, MD: Food and Drug Administration; May 1998.
27. Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act of 1997, House Report 105-310, to accompany H.R. 1411, 105th Congress, 1st Session.
28. *Guidance for industry: standards for the prompt review of efficacy supplements, including priority efficacy supplements*. Rockville, MD: Food and Drug Administration; May 1998.
29. *FY 1998 Performance report to Congress for the Prescription Drug User Fee Act of 1992 as amended by the FDA Modernization Act of 1997*. Rockville,

- MD: Food and Drug Administration; January 1999. <http://www.fda.gov/ope/pdufa/report98/default.htm#Outcomes>.
30. *Efficacy supplements approved in CY 99*. Rockville, MD: Food and Drug Administration; Center for Drug Evaluation and Research; 1999. <http://www.fda.gov/cder/rdmt/escy99ap.htm>.
 31. *Efficacy supplements approved in CY 98*. Rockville, MD: Food and Drug Administration; Center for Drug Evaluation and Research; 1998. <http://www.fda.gov/cder/rdmt/eff98.htm>.
 32. Dissemination of information on unapproved/new uses for marketed drugs, biologics, and devices; final rule. *Federal Register*. 1998 Nov. 20;63(224):64555.
 33. Remicade off-label RA campaign cleared with balancing statement. *Pink Sheet*. 1999 Jun. 7;61(23): 3–4.
 34. United States District Court for the District of Columbia, *Washington Legal Foundation v. Jane E. Henney and Donna Shalala*, Order Granting Summary Judgment and Permanent Injunction, Civil Action No.1:94CV01306 (RCL). <http://www.FDCReports.com/RULING.HTM>.
 35. Testimony of Jane Henney, Commissioner, Food and Drug Administration, Hearing on the Modernization of the Food and Drug Administration, before the Senate Health, Education, Labor and Pensions Committee, October 21, 1999.
 36. Wechsler J. Sailing the straits, Henney on FDA, FDAMA & marketing. *Pharma Exec*. Dec. 1998; 18(12):42–48.
 37. Regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. *Federal Register*. 1998 Dec. 2;63(231):66632.
 38. Remarks by Linda Suydam, Senior Associate Commissioner, Food and Drug Administration, presented at Food and Drug Law Institute, Educational Conference, Washington, D.C., December 17, 1999. <http://www.fda.gov/oc/speeches/fdli991s.html>.
 39. Milne C-P. Pediatric research: coming of age in the new millennium. *Am J Therapeutics*. Sep. 1999;6(5): 263–282.
 40. Standard NDA reviews most affected by downturn in first-cycle NDA approvals Lumpkin asserts. *U.S. Reg Reporter*. Oct. 1999;16(4):1–3.
 41. Cocchetto DM, Jones DR. Faster access to drugs for serious or life-threatening illnesses through use of the accelerated approval regulation in the United States. *Drug Inf J*. 1998;32(1):27–35.
 42. DiMasi JA, Manocchia M. Initiatives to speed new drug development and regulatory review: the impact of FDA-sponsor conferences. *Drug Inf J*. 1997; 31(3):771–788.
 43. Fast track drugs may lose designation if criteria are no longer met-FDA. *Pink Sheet*. 1998;60(47):32.
 44. Morrison J. Ombudsman's corner: CDER's pet peeves—part II. *News Along the Pike*. 2000;6(1):3.
 45. An interview with Director of the Division of Cardio-Renal Drug Products Raymond Lipicky, M.D. *U.S. Reg Reporter*. Oct. 1999;16(4):3–7.
 46. Patients or profits? *Economist*. 1998 Mar. 7:15.
 47. Healy EM, Kaitin KI. The European Agency for the Evaluation of Medicinal Products' centralized procedure for product approval: current status. *Drug Inf J*. 1999;33(4):969–978.
 48. Pharma outpaced in global rankings. *Scrip*. 1999; #2454:9.
 49. US retail Rx sales to rise 18%. *Scrip*. 1999;#2470:15.