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Daily News

FDA Drug User Fee Talks Nearly Done, Negotiations On Other Fees To Begin

Posted: February 23, 2011

FDA is concluding negotiations with stakeholders on the reauthorization of prescription drug fees, an agency official said, as the agency is preparing to accelerate talks with industry on fees for medical devices, generic medicines and biosimilars, the latter of which is expected to include non-traditional discussions because of the inclusion of competing industry groups, agency officials said at a drug and device policy forum last week. The officials added that the user fees are particularly important during the tough budget climate where the agency's funds could be cut.

Theresa Mullin, director of the Office of Planning and informatics in FDA's drug center, said the agency intends to complete negotiations with industry soon on the reauthorization of the Prescription Drug User Fee Act. Recommendations will then be taken to agency leadership, and next passed along to HHS and the White House's Office of Management and Budget, with Capitol Hill briefings on the recommendations expected to occur in the summer, she said.

Mullin added that once those negotiations are finished, she plans to turn her attention to user fees for biosimilars. She said the agency is examining potential ways to structure the process and expects a traditional approach to user fee negotiations won't work for the fees, as there is not a single industry voice. "It's such a nascent industry," she said at the 2011 Health Leaders Dialogue conference last Thursday. "We're trying to come up with a process that gets to the concerns of all the stakeholders."

Brand-name and innovator drug trade groups have indicated that they intend to participate in FDA's negotiations on a user fee for biosimilars, with the Biotechnology Industry Organization contending that its inclusion would provide a voice to ensure that reviews of innovative therapies are not slowed by assessments of biosimilars ([see FDA Week, Feb. 4](#)).

Nevertheless, it is still very early in the process, Mullin added, and the agency plans to publish a notice in the *Federal Register* describing negotiation procedures in the next few months. FDA intends to gain resources from a biosimilars user fee in the future, but it is not in the agency's fiscal 2012 budget request released this week.

Additionally, Peter Beckerman, a senior policy adviser to the FDA commissioner, said the agency will start to meet with industry at the end of the month to negotiate a new generic drug user fee. FDA indicated that it is anticipating the new user fee in the fiscal 2012 budget request it released earlier this week.

Beckerman noted that FDA is considering a range of proposals to address the fee, but has yet to settle on a particular structure. The agency has received two different types of proposals -- a traditional sponsor and review-based user fee conception, being pushed by the Generic Pharmaceutical Association, and more non-traditional inspection-based proposals, backed by Mylan. "We think there are benefits to each of these approaches that we may want to try to have incorporated into any final program that we settle on," he said at the forum.

Furthermore, FDA Assistant Commissioner for Planning Malcolm Bertoni said the agency just commenced medical device user fee negotiations with industry last month. While progress has been made in recent years on meeting its review goals, he said the agency must improve program outcomes. "We need to seize this opportunity for reauthorization to improve the program," he said.

He noted that while user fees have led to improved performance for 510(k) reviews, it has been more gradual for premarket approval applications. Nevertheless, he said the agency has recently improved performance. "We're not where we want to be, [but] things have been getting a bit better."

However, he added that FDA has observed some "paradoxes" in the performance of the medical device program. He noted that though FDA is meeting its goals for the 510(k) program, the total time to market has expanded because the number of review cycles has increased. Furthermore, the average time of reviews is also increasing, and FDA is "taking a very close look" at the reasons behind those outcomes, he said. "We're trying to look at root causes, and we're trying to figure out why those undesired outcomes are happening," he said at the forum.

He offered a few possible explanations behind the increase in total review times, such as that the program is operating at full capacity, there are gaps in important specialty topics, and there is high staff turnover.

While the agency has regular talks with industry planned over the next few months, it also plans to meet monthly with consumer and patient advocates, he added. The agency hopes to finish device user fee negotiations by this summer.

Furthermore, agency officials said the user fee programs would help the agency maintain its effectiveness, particularly as increased FDA funding could be threatened by cost-cutting GOP efforts. "User fees may be an important hedge to ensure program stability," Bertoni said.

Mullin added that the agency is aware of the detrimental impact of the economic downturn on drug companies, but said user fees are essential to shoring up funding gaps. "We need to ensure this program has a sound basis going forward, so we can continue to be predictable and efficient," she said. "The last thing companies need is for us to become less predicable and introduce even more uncertainty into the process." -- *Sara Ditta* (sditta@iwpress.com)

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The Business of Health Care

FEBRUARY 18, 2011, 6:22 PM

F.D.A. Chief Backs Fees for Generic Drug Reviews

By *DUFF WILSON*

Dr. Margaret Hamburg, commissioner of the Food and Drug Administration, called on Friday for a new process to allow makers of generic drugs to pay user fees to the F.D.A. to speed up approval of the low-cost drugs.

Speaking at the Generic Pharmaceutical Association's annual meeting in Orlando, Dr. Hamburg said the user fees would be "vital" to reduce backlogs in agency safety reviews. In a round-table discussion, many of the industry leaders at the meeting agreed.

The F.D.A. plans to meet with industry representatives later this month to try to agree on a plan to carry out the new fees and an accelerated review process within two years. The change may require legislation.

Major pharmaceutical companies have paid user fees to the F.D.A. since the 1990s to speed up approval of their new patented drugs.

Some critics say the system leaves the government beholden to industry and creates a conflict of interest.

"Without a fair system of user fees, we simply cannot achieve for the public what we otherwise could," Dr. Hamburg said in a keynote address at the event, which had [an audio Webcast](#).

"The user fee model has seen many major successes with other F.D.A. regulated items, including innovator prescription drugs, medical devices, animal drugs, and generic animal drugs, to name a few. This is the only major medical product industry in which F.D.A. provides marketing review that doesn't have a program.

"So I think this is really a critical time, and the user fee program is clearly, clearly important, vital, to the future of the generic drug industry," she said.

Several drug makers agreed, including the heads of Mylan and Watson Pharmaceuticals. They said it took an average of two and a half years to get some generic drugs approved. The process is slowed by manufacturing inspections. The F.D.A. has a backlog of more than 2,000 applications.

Dr. Hamburg said the agency might also create a user fee process for generic biologic drugs.

Greg Howard, a spokesman for the association, said generic drugs accounted for 75.4 percent of all prescriptions in the United States.

[In a recent report](#), the association and IMS Health, an industry consultant, estimated generic drugs had saved the United States health care system \$824 billion over the last decade.

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FDA Week - 02/04/2011

Innovator Trade Groups Seek To Participate In Biosimilars Fees Talks

Posted: February 3, 2011

The brand-name and innovator drug trade groups hope to participate in FDA's negotiations to establish a user fee for the health reform-created biosimilars pathway, with their involvement likely to focus on ensuring that resources are not drained from the review of novel biopharmaceuticals to support approval of the follow-on products, sources said.

Aside from the innovator firms and trade groups, the generic drug industry, as expected, will also play a major role in the development of the biosimilars user fee program. "I expect it's going to be a wide berth," a generic drug lobbyist said. "I know the major generic companies have all put their names in there."

Both the Biotechnology Industry Organization and the Pharmaceutical Research and Manufacturers of America -- the two top brand-name drug industry trade groups -- informed FDA that they plan to participate in biosimilars user fee discussions, according to officials from the associations. During the healthcare reform debate, the brand-name drug industry lobbied for positions that many analysts contend made the new pathway not favorable to biosimilars sponsors, such as the 12-year exclusivity period established under the law (see *FDA Week*, Jan. 28).

As FDA establishes user fees to fund reviews of biosimilar products, the agency asked both industry and interested stakeholders on whether they intend to participate in the negotiations. BIO sent FDA a letter earlier this month expressing interest helping to shape the new user fee program.

"We responded that BIO should be part of that process in order to ensure that such user fees adequately reflect the time and resources that FDA will need to thoroughly review biosimilar applicants, so that resources are not drained away from agency review of innovator products," a BIO official said. "We did not ask to represent biosimilar manufacturers in such discussions."

Similarly, PhRMA informed the agency that it will also participate in biosimilars user fee discussions because some of its members have expressed an interest in the new pathway.

"PhRMA's membership includes research-based biopharmaceutical companies, including some that have indicated publicly that they intend to develop biosimilar medicines," a PhRMA official said. "In response to the FDA's question, PhRMA stated that we would like to be a party in the biosimilar user fee negotiations."

The brand-name drug industry is facing a changing landscape, as many blockbuster drugs are going off patent in the coming years and will be open to generic competition. Similarly, the creation of the biosimilars pathway now enables firms to develop lower cost drugs to be swapped for some of the most expensive biologic therapies that represent billions of dollars in annual revenues.

"[The trade groups] have to participate in that. They have to keep track of this. It's too much money," a drug industry lobbyist said. "They can't just turn around and let FDA create a user fee program and not participate in it."

Both trade groups are active participants in the the reauthorization of the Prescription Drug User Fee Act, which provides agency funding to review innovator product applications. That user fee program, up for reauthorization in 2012, could help inform FDA's development of a biosimilars user fee, including metrics and the proportion of agency appropriations used to supplement money provided by industry.

"I suspect that what they're both trying to do is make sure that ... there's at least programmatic consistency or constituency of thought as FDA is implementing both of these programs," the lobbyist said. "They have to make sure that FDA isn't creating a program that isn't somehow going to divert money or change incentives somehow from the innovator side."

However, members of the groups -- such as PhRMA member Pfizer -- have expressed at least some interest in biosimilars, as this emerging area could be lucrative as less truly innovative and game-changing products come through drug firm's pipelines. Moreover, some traditionally generic companies have growing innovator portfolios, such as generic drug giant Teva Pharmaceuticals, which is seeking membership in BIO, although sources suggest the application will not likely be granted after it is reviewed.

"Depending on how strongly they're pushed by members on the biosimilars side within their organizations will determine the nuance on certain policies," the lobbyist said.

User fee programs are intended to reduce the length of FDA reviews. Assessments of biosimilars applications could range anywhere from a few months to years, especially in the beginning when FDA is only developing the approval pathway. Innovator drugs are supposed to be reviewed within 10 or 6 months, depending on whether the new pharmaceutical is deemed a priority. Reviews of biosimilars could be shorter than that time-frame because the sponsors of those products will have to provide -- at least theoretically -- less data in order to incentivize the development of these products.

"How can you possibly say longer," a drug industry source said. "Otherwise, your review (involves) more data because it's about the data burden and the review burden."

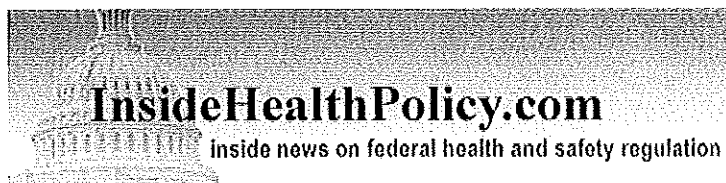
However, the agency has been pressured to ensure that biosimilars are safe, therefore longer reviews would help provide more certainty on the risk-benefit assessment of these drugs.

"It's a new field, so FDA, I would assume, will be encouraged to err on the side of caution," the lobbyist said. "I don't think it's realistic to assume that it will be less, it may be equivalent," the source said, referring to the review timeframes of innovator and biosimilar drugs.

Having longer review times for the biosimilars sponsors might further disincentivize firms from filing these applications because longer review clocks suggests that the agency is requiring more data from sponsors, one of the sources said.

"That's insane. ... How do they conceivably think anybody is going to apply for these things," one of the industry sources said. "If the review clock is longer and the fee is more, they're not going to get any. ... You're sending the message that you're asking for more materials as a biosimilar than an innovator." -- *Ben Moscovitch*

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Inside CMS - 02/17/2011

Generics Press FDA To Tone Down Concerns On Equivalence

Posted: February 16, 2011

Representatives of the generic drug industry recently urged top FDA officials in a closed-door meeting to ease agency criticism of generic products' bioequivalence with reference therapies in order to maintain consumer confidence in these lower-cost pharmaceuticals and the FDA approval process, sources said. FDA is studying bioequivalence of generic drugs, and is assessing whether to change standards for narrow-therapeutic index drugs. The discussions come as increased generic drug use is widely viewed as a cost-saving health reform measure.

Officials from several major drug companies and the Generic Pharmaceutical Association met with FDA Commissioner Margaret Hamburg and other top agency personnel last month, with the industry representatives expressing concern about recent comments from FDA drug center personnel that generic firms should develop more consistent products. At a joint GPhA-FDA conference last year, drug center chief Janet Woodcock drew the ire of the generic drug industry after she urged companies to change their products' coatings, sizes, odors and other factors to more closely resemble the brand-name reference pharmaceuticals (see *FDA Week*, Oct. 22, 2010).

"Woodcock has had a propensity to say some pretty stupid things about the generic industry," an industry official familiar with the meeting said. "She can't continue to have these silly comments that puts us in a bad position and, quite frankly, puts FDA in a bad position. ... Off-the-cuff discussion is hurtful, not only for the industry, but also for the agency."

The generic industry has countered suggestions that their products are not bioequivalent to the brand-name reference drug, even though concerns with some types of pharmaceuticals - such as epilepsy medicines - have been viewed warily by critics. Generic manufacturers contend that FDA's approval of the products suggest that there is no reason to be concerned about the drugs.

"Are they not believing in their reviewers and the job that they're doing?" the industry source said. "They determine it's bioequivalent. That's it. ... There have been no studies that show anything otherwise."

Concurrently with Woodcock's comments last year, though, FDA also sent a letter to a New Jersey state lawmaker contending that there is no reason to consider generic drugs not bioequivalent to the reference product (see *FDA Week*, Nov. 12, 2010).

An FDA official said the agency is continually studying generic drugs' bioequivalence, and will make any regulatory decisions based on the available science.

"FDA continually monitors the scientific literature and performs research of its own, in order to ensure that its standards for establishing bioequivalence are consistent with current scientific knowledge in this field," an FDA official said. "Regulatory policies can have a significant impact on the availability of safe and efficacious drugs. As such, setting and changing FDA's policies must be done with great care. FDA's regulatory policies must be based on conclusions from scientific studies that meet rigorous standards and are statistically valid."

However, the agency is assessing narrow-therapeutic index drugs, which are products whose therapeutic and lethal dosage levels are close. As part of that examination, the agency is reviewing whether to change bioequivalence standards for these products.

"FDA continues to re-examine the standards as they are applied to narrow-therapeutic index drugs; and continues to examine the available bioequivalence data for these drugs," the FDA official said. "As such, it is currently in the process of assessing the need for and the anticipated impacts of changing its bioequivalence standards for narrow therapeutic index drugs."

Regardless of the assessment of narrow-therapeutic index drugs, FDA has not received evidence questioning the equivalence of most generic drugs.

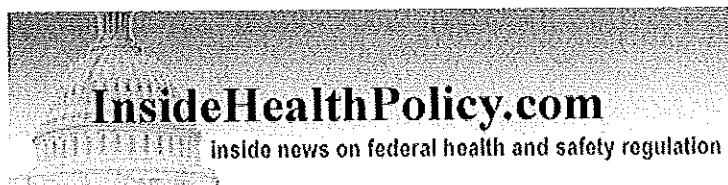
"The vast majority of the thousands of FDA-approved generic drugs have not received complaints or anecdotal reports of safety or efficacy issues," the FDA official said.

Even though the generic drug industry broached several outstanding FDA issues - such as the establishment of generic drug user fees - with Hamburg, the FDA concerns on equivalence and perception still garnered attention from the parties to ensure open dialogue between the agency and product sponsors.

"It was one of those itches you have to scratch," the industry source said. "If we don't have a good dialogue, it's just not helpful." - *Ben Moscovitch*

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Daily News

Obama Seeks Medicare/Medicaid Savings -- Including New Biosimilars Policy, Pay-For-Delay Limits -- To Fund SGR

Posted: February 14, 2011

President Obama's fiscal 2012 budget request proposes a slew of Medicare and Medicaid cuts, anti-fraud legislative initiatives, a controversial change to biosimilars policy and limits on so-called "pay-for-delay" settlements to come up with \$54 billion to pay for a CMS physician reimbursement patch. HHS Secretary Kathleen Sebelius heads to Capitol Hill this week to make the case for that proposal, as House Republicans consider blocking funds for health reform implementation as part of a measure to fund the government through the rest of this year.

The White House budget request, unveiled Monday morning, calls for two sets of adjustments to the sustainable growth rate formula used by Medicare to reimburse physicians — a two-year patch budgeted at \$54 billion, and "relief from 2014 onward" that the administration says would cost \$315 billion.

The proposed offsets include:

- Reducing the Medicaid provider tax threshold (\$18 billion in estimated savings).
- Banning "pay-for-delay" patent settlements between brand-name and generic drug companies (\$8 billion).
- Cutting Medicaid payments for durable medical equipment (\$6.4 billion).
- Recovering improper Medicare Advantage payments (\$6.2 billion).
- Rebased payments to disproportionate share hospitals (starting in 2021) (\$4.2 billion).
- Tracking the highest utilizers of prescription drugs in Medicaid (\$3.4 billion).

Also this week, the House is slated to begin debate on a continuing resolution for the rest of 2011, which also contains steep cuts to a range of programs. Appropriations Committee Chair Hal Rogers (R-KY) said before releasing the latest CR draft that he intended to cut \$100 million across the entire federal government, and Republicans traded quotes in the press about how and whether the CR would or could be used to cut off funds for the implementation of health care reform. The draft he released over the weekend prohibits the use of any funds to enforce the reform law's unpopular "1099" tax reporting requirement, which will likely be repealed before it takes effect and could be enforced. And it would prevent the Executive Office of the President from paying a director of the White House Office of Health Reform "or any substantially similar position." But the future of that office is already in doubt following the ascension of its former director, Nancy-Ann DeParle, to the position of White House deputy chief of staff, and the CR only specifically denies funding for a White House office — not the newly created CMS Center for Consumer Information and Insurance Oversight.

Some Republicans have vowed to introduce a more comprehensive blockage of health reform funds as a floor amendment, though some have also said they've run into roadblocks because cutting off the flow of money to certain programs would require a change to the reform law itself and could not be accomplished through the appropriations process. -- Sam Baker (sbaker@ivpnews.com)

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SPECIAL ARTICLE

SHATTUCK LECTURE

Innovation, Regulation, and the FDA

Margaret A. Hamburg, M.D.

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N Engl J Med 2010;363:2228-32.
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MORE THAN A CENTURY AGO, CONGRESS PASSED THE 1906 PURE FOOD and Drugs Act, which transformed a small scientific bureau in the basement of the Department of Agriculture building into a federal regulatory agency charged with protecting the nation's supply of food and drugs. This regulatory agency would eventually become the Food and Drug Administration (FDA). Since the agency was founded, advances in science and medicine have transformed our understanding and treatment of many diseases. And the FDA has evolved in response to our changing world, taking on new responsibilities and playing a critical role in promoting and protecting the health of the public.

Despite the essential and unique contributions of the FDA, the agency's regulatory role is periodically questioned, including in recent litigation that challenges, on First Amendment grounds, the permissible scope of the FDA's regulatory capacity and its ability to assess and ensure the safety and effectiveness of medications, vaccines, and medical devices. With history and these lawsuits as a backdrop, I offer a perspective on the important role that the FDA has played — and must continue to play — in protecting health and safety and facilitating the interplay among innovation, evidence, and medicine.

A HISTORY OF REGULATION

Although the FDA was not known by its current name until 1930, its modern regulatory functions began with the passage of the 1906 Pure Food and Drugs Act, a law, more than a quarter of a century in the making, that prohibited interstate commerce in adulterated and misbranded food and drugs. Harvey Wiley, the chief chemist of the Bureau of Chemistry in the Department of Agriculture, had been the driving force behind the legislation, and in the early years, he headed enforcement of the law, which provided basic elements of protection that consumers had not previously known.

In 1902, one advertisement for a medical product claimed, “No other preparation has had its therapeutic value more thoroughly defined or better established . . . [as] a remedy in the treatment of coughs, bronchitis . . . asthma, laryngitis, pneumonia, and whooping cough.”¹ This wonder drug was heroin — a drug that made people feel better but had an addictive potential that made its medicinal use dangerous and inappropriate.

At the turn of the 20th century, companies marketed their “patent or proprietary medicines” — some deadly, others comprising just sugar water — with a variety of unproven claims. It took decades for American medicine to emerge from what pharmacologist Louis Goodman called a “therapeutic jungle.” As the years passed, important scientific advances in pharmacology, toxicology, and clinical research were central to this transformation. The FDA embraced these advances — insisted on them, in fact — and helped pull medicine into the modern era. This

effort was propelled by two critical public health events that triggered new regulatory authorities for the FDA.

In 1937, a drug company in Tennessee manufactured Elixir Sulfanilamide, sulfanilamide mixed with diethylene glycol, and although the company tested the product for flavor, appearance, and fragrance, the food and drug laws at the time did not require toxicologic analysis. As a result, more than 107 people died from ingestion of the adulterated elixir,² and Congress passed the Food, Drug, and Cosmetic Act the following year. The law established that drugs that are intended to prevent or treat disease must be proved to be safe for use as labeled and must include safety data from the manufacturer in the application that is submitted to the FDA. This law ended the practice of marketing new proprietary mixtures of a wide range of untested ingredients. For the first time, before pharmaceutical companies could market a drug, they had to show at least that the product was safe.

At first, it was unclear to the pharmaceutical industry, scientists, and the agency what safety really meant. Gradually, the fields of pharmacology and toxicology began to answer these questions. Standardized assessments were developed, and as these advances were incorporated into the FDA's premarket review, they became standard practice across the pharmaceutical industry.

The FDA continued to expand its regulatory scope, thanks in part to the defining case of thalidomide — the medication that was widely marketed in Europe as a sedative and antiemetic agent and was even recommended for use by women in their first trimester of pregnancy. The drug proved to be highly teratogenic. Many babies died, and thousands more were born with severe defects, including phocomelia, a devastating disorder in which the long bones of the limbs fail to develop. But the drug was never approved in the United States. Thanks to the perceptiveness and determination of a single new reviewer at the FDA, Dr. Frances Kelsey, the drug was denied approval because its sponsor failed to show basic aspects of the product's pharmacologic and toxicologic characteristics. She kept thalidomide off the market and protected the American people.³ In a fundamental way, her actions represented the embrace of modern, innovative scientific methods.

Soon thereafter, in 1962, a pivotal regulatory advance occurred in the form of a set of amendments to the Food, Drug, and Cosmetic Act —

amendments that institutionalized some basic patient protections and had major consequences for the FDA and American medicine. Congress now required drug manufacturers to show substantial evidence of effectiveness and stipulated that such evidence must be based on “adequate and well-controlled studies.” This requirement has changed the face of modern therapeutics by dramatically raising the standard of evidence and the likelihood that a marketed drug will really work.

The law emerged from broad concern over the state of the market for pharmaceuticals. At that time, companies were required to show that their products passed basic tests of safety, but there was still wide latitude for marketing a drug for many different uses, and there was no explicit standard for showing that a product did indeed do what it was supposed to do. This meant that unproven drugs at times supplanted those with known effectiveness. For example, potent psychiatric drugs were widely marketed for minor conditions. Mellaril (thioridazine, Novartis), for instance, was promoted to general practitioners for the treatment of patients with insomnia, pregnant women who were anxious about childbirth, patients with “vague digestive disorders,” and “tense, nervous patients seen in everyday practice.”⁴

Many ineffective drugs also had serious adverse effects, subjecting patients to harm without providing any benefit. One such drug was diethylstilbestrol (DES), which was promoted to prevent miscarriage, despite a large, randomized, controlled study in 1953 showing that DES was ineffective for this use.⁵ By the time the devastating, multigenerational reproductive effects of DES^{6,7} became known in the 1960s and 1970s, 5 million to 10 million American women and their children had been needlessly exposed.⁸

Increasingly, clinicians and pharmacology experts started to complain that there was little evidence to support the use of many medications in clinical care, which meant that the passage of the 1962 legislation marked an important change. From then on, before a drug could be marketed, the FDA had to review the manufacturers' claims and the data supporting them and conclude that effectiveness had indeed been shown.

In the case of drugs that were already on the market in 1962 and that had been approved on the basis of the FDA's prior review of their safety, sponsors now had to submit evidence of effectiveness to the agency. The FDA turned to the National Academy of Sciences for help in review-

ing this massive amount of information. The academy found that 70% of the claims it reviewed could not be substantiated. Almost one third of all marketed drugs lacked even a single effective use and were removed from the market entirely.⁹

As the FDA set standards for effectiveness, many companies, for the first time, conducted large, randomized, controlled trials to support their claims of efficacy. Major therapeutic breakthroughs ensued, and because of the evidence now required for FDA review, the best drugs, rather than the most aggressively marketed drugs, could rise to the top. In other words, the increasingly rigorous standards of the FDA created the conditions for innovation and progress in the pharmaceutical market, and together, American medicine and the FDA have accomplished an enormous amount. Now our challenge is to continue to move forward.

LAWSUITS THREATENING THE FDA'S AUTHORITY

Several recent lawsuits have challenged the FDA's authority to review the safety and effectiveness of products before they are marketed. In the first case,¹⁰ which has now been dropped, a drug company contested the FDA's authority to require premarket review of new, "off-label" uses of drugs that have already been approved before companies may promote such uses to physicians and patients — the so-called off-label promotion issue. In the second case, tobacco companies are challenging the FDA's ability to prevent companies from marketing products with claims of reduced risk before the evidence has been reviewed.¹¹

In both suits, the companies argued that premarket review violates their First Amendment right to engage in free speech. According to these arguments, companies have a constitutional right to disseminate health claims about their products without first submitting evidence to the FDA showing the accuracy of those claims. The companies argue further that the FDA may step in to stop such claims only after it can produce sufficient evidence to convince a court that the claims are false or misleading. Developing such evidence would be very expensive and time-consuming, and the evidence of ineffectiveness or harm would emerge only after patients — possibly many patients — had suffered avoidable serious adverse effects. If these types of challenges

are successful in obtaining the broad relief that certain companies appear to seek, they could undermine the premarket review system that has been in place for drugs since 1962 and for devices since 1976. Indeed, they place at risk efforts that are currently under way at the agency to ground FDA practices more solidly in public health practice.¹²

Without question, such legal challenges, if successful, would turn back the proactive role of the FDA in American medicine, threaten current efforts to ground FDA practices in public health science,¹² and jeopardize the safety of patients, as well as the future of innovation and medical progress. Quite simply, they would ignore the lessons of history.

In the scenario sought by the plaintiffs in the first case, companies would need to generate sufficient evidence to support approval of only a single, perhaps relatively trivial, indication and would then be free to promote all other uses without any requirement to justify those uses to the agency. Under the current system, each potential use is subject to the same systematic analysis of risk versus benefit. Without the current system, companies with truly innovative and effective products could have a difficult time penetrating the confusion generated by efficacy claims made by their competitors that were not based on the kind of strict evidence that would meet the agency's current standards.

If the tobacco companies prevail in the second case, premarket approval of health claims will be abolished in its entirety (even for first indications). The pending lawsuit would leave our country vulnerable to a repeat of the "low tar" fiasco, when makers of low-delivery cigarettes urged Americans to switch to these "modified-risk" products instead of quitting, even though there was no scientific evidence that these products provided any health benefits whatsoever.¹³ It was one of the most costly public health charades of the 20th century and one that Congress intended to prevent from happening again when it passed the landmark Family Smoking Prevention and Tobacco Control Act in 2009.

PREMARKET REVIEW VERSUS PEER REVIEW

The FDA plays a critical — and science-based — role in evaluating new therapeutic products in the medical marketplace by helping companies

design trials that answer key questions regarding safety and efficacy and insisting that all available data be provided for review. Some people who are opposed to FDA review have suggested that it should be replaced by peer review and publication in the scientific literature.

Peer review is an essential part of scientific dialogue, and medical journals play a critical role in shaping the field of medical research. However, peer review is not a replacement for a strong FDA. The FDA uses multidisciplinary teams — physicians, pharmacologists, toxicologists, chemists, and statisticians, as well as experts in the conduct of clinical trials and in the fields of clinical medicine and biopharmaceuticals, among other areas — to independently analyze the raw data from the studies. The reviewers assess the data for integrity and often conduct audits of the sponsor or clinical investigator. Peer review, on the other hand, is generally conducted by a more limited set of experts and involves only the article under consideration for publication. According to one survey, peer reviewers generally spend an average of 2 to 3 hours reviewing an article.¹⁴ Even if peer reviewers have access to study protocols, they do not have access to the primary data, and they cannot reanalyze the original data supporting the report. In contrast, FDA reviewers have the protocols and the data at hand and may spend hundreds of hours reviewing a submission.

For many reasons, positive studies are much more likely to be published than are negative studies, although that is changing. In one study, only 43% of the trials for FDA-approved drugs were published, with larger, pivotal trials that show statistically significant results more likely to be published.¹⁵ In another study, all but 1 of the 38 trials of antidepressant agents viewed by the FDA as having positive results were published. In contrast, of the 36 studies viewed by the FDA as having negative or questionable results, 22 were not published and 11 were reported in the literature as if they had positive results.¹⁶ Thus, whereas FDA analyses showed that only 51% of the relevant trials were positive, physicians reading the published literature would have concluded that 94% were positive.

REGULATORY SCIENCE
AND INNOVATION

History has made the dangers of an unregulated marketplace clear. Restricting the FDA's ability

to conduct premarket review would effectively set science and public health back to an earlier, more dangerous time. We must look forward to a new paradigm of scientific efforts to support innovation and medical progress.

Recent scientific advances in fields as diverse as genomics and nanotechnology hold out the promise of major therapeutic breakthroughs. Yet scientific discovery is moving much faster than is the ability to translate those advances into real-world products. We are failing, as a scientific community and as a nation, to adequately deliver the promise of science to diagnose, treat, prevent, or cure disease.

We can bridge this gap, but success will require that we work together on a new set of flexible standards of product review for the 21st century through the emerging field of regulatory science. Regulatory science is the science of the assessment and evaluation of the safety, effectiveness, potency, quality, and performance of a product. We must invest in regulatory science to develop new methods, assays, standards, and models that will help speed the development, review, and approval of medical products that patients need and can rely on.

The knowledge generated from this process would inform a whole body of innovation and could help solve some of the most pressing medical and public health challenges of the 21st century. For example, before patients with Parkinson's disease can benefit from promising stem-cell therapies for restoring brain function, we must develop scientifically valid standards and manufacturing processes to ensure that the therapies are produced reliably and safely. Before we can realize the era of "personalized medicine," we need new science to identify genetic markers and subpopulations for treatment and to guide the evaluation and use of new diagnostic tests. And before we can finally cure drug-resistant tuberculosis with the use of effective combinations of drugs, we need a new pathway to evaluate earlier in the regulatory process drugs that are administered in combination.

These challenges are not the FDA's alone. To truly leverage advances in science and technology, there must be a collaboration of all relevant stakeholders, including government, academia, and industry. The FDA must work with its partners to promote innovation and creativity at various points throughout the development process. For example, instead of simply waiting at the end

of the pipeline to approve or reject a product, the FDA can help make clinical trials more efficient by identifying qualifying biomarkers that accurately predict outcomes and by encouraging investigators to use innovative trial designs that are as effective as standard designs but less burdensome and time-consuming. And instead of accepting that the only way to test for drug safety is to expose cadres of patients to new products, the FDA can help develop innovative assays for safety that can better predict toxic effects in the liver and kidney early on. The FDA can become more transparent, so that knowledge and insights can be shared and the field of drug discovery can move forward more quickly.

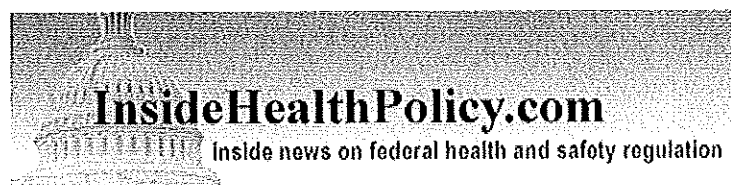
Regulatory science is a field that must be widely embraced as an essential and dynamic component of the broader biomedical research enterprise. As we look to the new and emerging challenges of the 21st century, we require, now more than ever, an invested industry, an engaged academy, a strong FDA, and most of all, the recognition that together we can harness scientific progress for patients and for public health. Together, we can begin the next phase of innovation in science and medicine.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Thursday, February 24, 2011

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Daily News

Collins Counters Criticism That FDA Puts Brakes On NIH Innovation

Posted: February 16, 2011

National Institutes of Health Director Francis Collins rejected congressional criticisms this week that FDA is hampering patients' ability to access innovative therapies developed by federal researchers, with the Obama administration's top biomedical investigator calling on lawmakers to ensure timely access to new medicines by increasing funding for FDA drug investigations and regulatory science initiatives.

"FDA has an incredibly tough job. They are under resourced, and they're constantly buffeted by some who say that they're too slow in making approvals and some who say they're not careful enough in their approvals and they're letting things through that they shouldn't. So I have great sympathy with the FDA," Collins told *FDA Week*. "I don't know that it's fair to look at the difficulties we're having right now to put such a heavy blame load on FDA."

NIH supporter Rep. Brian Bilbray (R-CA) criticized FDA for not approving new drugs fast enough to provide patients with the most innovative therapies, many of which were developed, at least initially, by NIH. Bilbray, whose daughter is battling cancer, said breakthrough treatments are not available to his daughter and the public because FDA has not yet approved the drug, thereby making the pharmaceuticals' distribution illegal. He made the remarks Wednesday (Feb. 16) at a Capitol Hill event hosted by United for Medical Research, an NIH advocacy group.

"As a congressman, I cannot assure her that the best possible treatment will be legal for her to receive under the existing system," Bilbray said. "There is going to be this economic barrier of what treatments can be finished off and made available to the consumer by the private sector, and at the same time which treatments will be held up by government, by the FDA."

However, Collins told *FDA Week* that these criticisms of FDA are not sound, as the agency must balance providing timely access to new medications with ensuring the safety of these products. He said the solution is for lawmakers to support regulatory science efforts pushed by the Obama administration.

Starting in last year's budget request, the White House requested funding for the FDA regulatory science program, which includes boosting the agency's expertise on how to review emerging therapies, such as nanotechnology.

In the fiscal 2011 budget proposal, FDA requested \$25 million for this effort, which was nearly doubled in the fiscal 2012 budget plan released earlier this week. However, some lawmakers have criticized the regulatory science fund, thereby threatening whether FDA can obtain the money necessary to fully actualize the program.

"It would certainly not help" with developing new drugs, Collins said of potential cuts to the regulatory science program. "I think there's a great opportunity to encourage scientists who have potential projects out there that could be used to inform FDA about new approaches to review. ... I would be very disappointed if somehow someone thought that that was a bad investment."

"I think (FDA Commissioner) Peggy Hamburg would agree that there's a great opportunity to build a stronger science base for regulation, and she and I have been working together on a research program to support that," Collins said. "I think there is a way in which some of the more creative ways and approaches to speeding up review of drugs that are safe and effective could be pushed forward and she would like to see that too. ... I think if someone is concerned about the future and about having a regulatory system that's responsive to the new developments in science, you should support the ability to do that better."

Overall NIH funding is even more threatened than FDA's regulatory science program. Even though the Obama administration's fiscal 2012 budget request included an increase of approximately 2 percent to nearly \$32 billion for NIH, House GOP lawmakers proposed a major cut to the research hub. In their fiscal 2011 continuing resolution to fund the government through September, Republicans pushed for an over \$1 billion reduction to the NIH budget.

Collins said that cut would be extremely detrimental to developing new drugs. "It would be devastating to the research efforts that so many investigators are now actively engaged in," Collins told reporters after speaking at the United for Medical Research event.

Supporters of NIH said investments in the agency help fuel the economy and boost development of life-saving and life-changing new products. Collins said the agency has helped reduce heart disease deaths by 63 percent and stroke deaths by 70 percent in the last few decades. He also noted that the average American's investment in NIH, which accounts to \$3.70 per taxpayer, helps reduce overall healthcare spending. For example, a 1 percent reduction in cancer deaths saves \$500 billion, Collins said.

"None of those reductions would have been possible without the bedrock of research conducted by the NIH," Collins said in a speech at the event. "In this current climate where we are all deeply concerned about the cost of anything the federal government is spending money on, we have to think about economics as well."

Collins added that NIH helps boost employment, as the agency's grants support high paying and high skill jobs that "are contributing in a major way to U.S. competitiveness." -- *Ben Moscovitch* (bmoscovitch@iwppnews.com)

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Perspective

Development of Novel Combination Therapies

Janet Woodcock, M.D., Joseph P. Griffin, J.D., and Rachel E. Behrman, M.D., M.P.H.

Innovative drug development requires science and regulation to advance in concert. Nowhere is this need more apparent or urgent than in the development of combination therapies. Advances in geno-

mics and cell biology have increased the opportunity for rational design of targeted drugs to inhibit the function of specific molecules, including those contributing to the proliferation of cancer cells and pathogenic microorganisms. Although targeted therapies may offer enhanced efficacy and improved selectivity (and therefore less toxicity), most often their effects are not durable when they are used alone.

Cellular pathways operate more like webs than superhighways. There are multiple redundancies, or alternate routes, that may be activated in response to the inhibition of a pathway. This redun-

dancy promotes the emergence of resistant cells or organisms under the selective pressure of a targeted agent, resulting in drug resistance and clinical relapse. For this reason, combination therapies are often needed to effectively treat many tumors and infectious diseases.

Yet traditionally, new drug development has been pursued one agent at a time, even for diseases for which combination therapy is necessary, such as mycobacterial diseases and many other chronic infections. For those diseases, many investigational drugs are tested for efficacy in add-on trials in which the new drug

added to a standard regimen is compared with the standard regimen alone.

Successful development of future targeted therapies will require modernizing this paradigm to provide the flexibility needed to rapidly evaluate combination regimens involving new targeted agents in a single development program. Increasingly, tumors will be screened for pertinent pathway dependencies, as is currently done for breast cancer, and patients will be treated with drug combinations on the basis of screening results and experience with patterns of resistance. Similarly, combination antimicrobial therapy will increasingly be targeted, and susceptibility determined, at a molecular level. For example, the antiretroviral drug Selzentry (maraviroc), in combination with other antiretrovirals,

is indicated only to treat strains of human immunodeficiency virus type 1 that rely on the CCR5 protein receptor to infect cells. Development programs evaluating combinations of targeted agents, including investigational agents, are an essential part of this evolving paradigm.

Concern has been expressed that the policies of the Food and Drug Administration (FDA) on the development of combination therapies, which heretofore have focused primarily on fixed-dose combinations (i.e., combined in the same tablet or vial) of already-marketed drugs, are a barrier to the development of novel combination regimens using targeted therapies.¹ FDA regulations for fixed-dose combinations require demonstration of the contribution of each component of the combination to the treatment effect. Often, a large clinical trial, using a multi-group factorial design to demonstrate that the combination is superior to each of the individual components alone, is needed to meet this requirement. For example, a factorial study for a two-drug combination could have four groups so that the combination can be compared with each of the individual components alone, as well as with either the standard of care or placebo.

The FDA recognizes that for diseases in which innovative targeted combination therapies are likely to be used, such studies will often be unethical because of the potential for promoting the development of resistance and rendering a new therapy ineffective. For instance, hepatitis C virus (HCV) can develop resistance to antiviral monotherapy within only days, so a factorial study of sufficient duration (24 to 48 weeks) to demonstrate the

efficacy of the individual new drugs in an anti-HCV combination would not be possible and could not be required.²

To ensure that the regulatory expectations are clear, the FDA has drafted guidance about testing and developing two or more novel agents together in a single development program (termed “co-development” in the guidance).³ The guidance provides general recommendations for all facets of co-development, including preclinical testing for proof of concept and safety, clinical pharmacology studies, phase 1 safety studies, and phase 2 and 3 clinical efficacy studies. It also makes clear that the FDA’s regulations and policies pertaining to the amounts and types of data needed to demonstrate the contribution of each drug to the overall effect provide adequate flexibility to facilitate the development of novel targeted therapies for use in combination regimens in diseases for which a large factorial study (requiring monotherapy treatment groups) would not be possible. And it emphasizes that a range of potential data sources could be used to help establish the contribution of the individual drugs and provides examples of potential alternative study designs, including the use of data from *in vivo* models and pharmacodynamic studies.

Although co-development of innovative drug combinations directed simultaneously at multiple therapeutic targets has the potential to dramatically improve the response to treatment and survival rates among patients with difficult-to-treat diseases, it does introduce additional uncertainty. Because it will usually not be possible to fully characterize the

effects of the individual components of the combination, co-development may yield considerably less information about the safety and effectiveness of the drugs than would be obtained if they were developed individually. For this reason, co-development should be used only for therapies intended to treat serious and life-threatening diseases for which there are no satisfactory alternatives — a situation in which patients and physicians tend to accept heightened uncertainty — and only when there is potential for an important effect on human disease. There should also be a compelling biologic rationale for use of the combination, evidence of substantial *in vivo* or *in vitro* activity, and strong reasons why the components cannot be developed as individual agents.

Because co-development results in greater uncertainty about the performance of the individual agents, it will be important to ensure that the risks, benefits, and appropriate uses of the combination are communicated to prescribers and that those risks are effectively managed. The FDA’s guidance recommends that companies developing novel drugs for use in combination devise pharmacovigilance plans to address these risks, including the potential for the use of the drugs individually or in combination with different therapies. For example, if it is essential that the drugs in the combination be used only together, there should be careful consideration of ways to ensure that the individual agents are not misused.

To date, interest in combination development has focused primarily on cancer and infectious diseases. However, the FDA in-

tends the guidance to serve as a roadmap for co-development in any appropriate therapeutic category.

A clear regulatory path is a prerequisite to successful co-development, but it is not sufficient. Drug developers must embrace a new paradigm that emphasizes sharing of information and collaboration in testing combinations. In some cases, third parties such as academic consortia or other nonprofit cooperative groups may enable such activities. For example, in 2010, the Biomarkers Consortium — a public-private partnership that includes the National Institutes of Health, the FDA, patient groups, and pharmaceutical and biotechnology companies — initiated a groundbreaking trial in breast cancer to predict drug responsiveness based on the presence or absence of genetic and biologic markers, the Investiga-

tion of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis, or I-SPY 2 (ClinicalTrials.gov number, NCT01042379).⁴ The trial is evaluating tumors' response to multiple investigational drugs, albeit not in combination. The Global Alliance for TB Drug Development and similar groups may also be in a position to facilitate these kinds of studies.

The development of effective therapies for serious diseases is a primary FDA objective. The agency recognizes the therapeutic potential of innovative combination therapies and is committed to fostering their development. The FDA also recognizes the uncertainties inherent in combination development programs and is equally committed to effectively managing those risks.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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This article (10.1056/NEJMp1101548) was published on February 16, 2011, at NEJM.org.

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The New York Times

Prescriptions

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FEBRUARY 8, 2011, 3:44 PM

F.D.A. Offers Device Proposals

By [ANDREW POLLACK](#)

The [Food and Drug Administration](#), responding to criticism that it is hindering innovation, proposed a new system on Tuesday that would speed the approvals of pioneering medical devices.

The F.D.A. said it would try to review devices, through a new “Innovation Pathway,” within about five months, roughly half the time it now takes to review the most innovative medical devices.

“We must assure that our oversight doesn’t stifle innovation but rather encourages innovation, while maintaining a commitment to safety and effectiveness upon which Americans rely,” Dr. Jeffrey Shuren, director of the agency’s device division, told reporters Tuesday.

The F.D.A. has been heavily criticized by medical device companies, which say the agency has been overly stringent, inconsistent and too slow in approving medical devices. Companies say this hurts not only them but also patients who then may not have access to the latest technology.

On Monday, [President Obama](#), in a talk with the [United States Chamber of Commerce](#), a powerful business lobbying group, said that improving medical device reviews was one step his administration was taking to reduce unnecessary regulations and rebuild its ties with the business community.

Some consumer advocates and lawmakers, on the other hand, have criticized the F.D.A. for being too lax, approving devices that endangered patients and had to be recalled.

Buffeted from both sides, the F.D.A. is trying to walk a tightrope. Its solution, it says, is to make the regulatory process smoother, quicker and more predictable without lowering the standards for approval.

In January, it announced a series of measures to improve review of somewhat less innovative devices that go through the so-called 510(k) approval process.

The [new measures announced Tuesday for innovative devices](#) are still only proposals, subject to public comment, including at a meeting scheduled for March 15. And Dr. Shuren said that because the F.D.A. has limited resources, it may be able to review only

one or two of the most groundbreaking and important new devices a year through the new program.

The first such device will be a flexible prosthetic arm and hand with supposedly near normal function. The device, being developed by the Defense Department, would be controlled by a user's thoughts through a computer chip implanted on the surface of the brain.

The F.D.A. already has a program for expedited review for the most innovative medical devices. What is new here, Dr. Shuren said, is that the agency will become involved with the device developer earlier in the process.

Such devices would be assigned a "case manager" from the F.D.A. to help the company navigate the regulatory system. Within 120 days of a device's acceptance into the pathway, the F.D.A. and the developer will craft a memorandum laying out the road map for testing the device and for regulatory review.

The F.D.A. also proposed various measures on Tuesday to improve the ability to test medical devices in trials. It also said it would provide better guidance on when data accumulated overseas can be used to help a device win approval in the United States.

The Medical Device Manufacturers Association, a trade group, welcomed the announcement but called for speedier reviews for the vast majority of devices that will not go through the Innovation Pathway.

"It is critical that we continue to work together to ensure that the countless other therapies attempting to navigate the F.D.A. are provided a reasonable, timely and predictable regulatory pathway," it said in a statement.

The New York Times

Prescriptions

The Business of Health Care

FEBRUARY 24, 2011, 4:23 PM

F.D.A. Grants Hearing on Avastin as Treatment for Breast Cancer

By [ANDREW POLLACK](#)

The [Food and Drug Administration](#) has granted a hearing for [Genentech](#) to argue in favor of preserving the approval of its drug [Avastin](#) as a treatment for [breast cancer](#).

The hearing will take place June 28-29, the F.D.A. [said in a letter](#) to Genentech's lawyer and to a lawyer for the F.D.A.

The F.D.A. announced in December that it planned to revoke the approval of Avastin for breast cancer because new studies did not show the drug was helping women live longer or to delay the progression of their cancers very long, while at the same time exposing them to dangerous side effects. The decision has split the breast cancer community.

While Genentech, a subsidiary of Roche, will get its day in court, so to speak, it will not get the jury it wanted. The hearing will be in front of the F.D.A.'s Oncologic Drugs Advisory Committee. That committee voted 12 to 1 last July that the approval of Avastin for breast cancer should be withdrawn.

In its request for the hearing, Genentech argued that the committee did not have enough breast cancer specialists and therefore could not properly evaluate the importance of Avastin for that disease.

But in her letter to the company's lawyer, Dr. Karen Midthun, the F.D.A. officer who will oversee the hearing, said she would not add breast cancer experts to the committee. "We must face the reality," she wrote, "that many experts in this area have already expressed a view on this issue and/or might be considered as having conflicts because of their association with one of the parties to the hearing or competitors to Genentech."

The letter sets out other ground rules. The first day of the hearing will be devoted to presentations by witnesses chosen by Genentech and by the F.D.A.'s drug division, with each side given equal time. On the second day, the advisory committee will make recommendations.

Members of the public can submit written testimony but will not be allowed to speak at the meeting. The ultimate decision will be made by the F.D.A. commissioner, Dr. [Margaret Hamburg](#).

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