



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

MAY 30 2007

The Honorable Edward Kennedy
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate
Washington, D.C. 20510-6300

Dear Mr. Chairman:

Thank you for the opportunity to testify at the March 14, 2007, hearing entitled, "Drug User Fees: Enhancing Patient Access and Drug Safety," before the Senate Committee on Health, Education, Labor, and Pensions. The Food and Drug Administration (FDA or the Agency) is responding to the March 23, 2007, e-mail you sent containing follow-up questions for the record. Below we have reprinted the question in bold followed by our response.

Senator Kennedy:

- 1. The user fee program has allowed for significant resources to improve drug review and approval times at FDA. However, there are concerns that while user fees have strengthened drug reviews, resources for other functions such as drug safety have stagnated or fallen. What more, beyond money in the user fee agreement, does the agency need to ensure that safety can remain a top priority for the agency?**

Ensuring the safety of drugs and other medical products regulated by FDA has always been a key focus of our commitment to protect and promote the public health. In the past few years, FDA has reassessed its drug safety programs because of rapid advances in science and technology that have resulted in increasingly complex medical products. We take very seriously our response to safety-related issues from all sources, including those raised by consumer advocates, health professionals, academic researchers, and Members of Congress. Some examples of what the Agency is doing to ensure the safety of drugs are described below.

Included in the fiscal year (FY) 2008 President's budget is a proposal for a significant additional investment in FDA to modernize the process for ensuring drug safety. With the funds requested, FDA expects to strengthen the science and tools that support the product safety system at all stages of the product life-cycle from pre-market testing and development through post-market surveillance and risk management. Also, FDA expects to improve communication and information flow among all stakeholders engaged in promoting the safe use of medical products. These additional appropriations, combined with PDUFA IV resources, will support FDA's ability to effectively detect, communicate, and act on important safety issues thereby improving patient safety.

On September 22, 2006, the Institute of Medicine (IOM) released its report entitled, *The Future of Drug Safety – Promoting and Protecting the Health of the Public*. The report recognized the progress and reform already initiated by the Agency. The IOM report makes substantive recommendations about additional steps FDA can take to improve our drug safety program. The recommendations are consistent with the Agency's commitment to drug safety, including: (1) strengthening the science that supports our medical product safety system, (2) improving communication and information flow among key stakeholders, and (3) improving operations and management. Our Prescription Drug User Fee Act (PDUFA) proposal would, in part, support some of these initiatives.

We are working diligently on the actions we have committed to in our response to the IOM Report and have already made significant progress on several projects. For example, in March 2007, we issued final guidance that describes FDA's current approach to communicating drug safety information, including emerging safety information, to the public. The guidance affirms the Agency's commitment to communicate important drug safety information in a timely manner, including in some situations when the Agency is still evaluating whether to take any regulatory action. FDA's communication about drug safety information is available through FDA's website.

In addition, we are well on our way to implementing an electronic drug safety tracking system. This system, which replaces multiple office and division specific systems, is already helping the Center for Drug Evaluation and Research (CDER) reviewers and managers to prioritize their work on safety issues. In March 2007, FDA issued guidance designed to make the advisory committee process more rigorous and transparent so that the public has confidence in the integrity of the recommendations made by its advisory committees.

We have implemented an aggressive effort to strengthen our drug safety program, including developing new tools for communicating drug safety information to patients. Through our Critical Path initiative, we are working with our health care partners to improve the tools we use to more effectively evaluate products and processes.

- 2. I think we agree Congress should increase the FDA's appropriation, and that it would be better for the FDA not to have to rely on user fees for its budget. But some have gone a step further, and have called on Congress to discontinue the user fee program. Can you describe for the Committee what effect it would have on FDA and on medical innovation if Congress were to discontinue the user fee program?**

In FY 2008, FDA expects to collect approximately \$438 million in PDUFA fees, after the workload adjustment is made. These fee revenues will provide the funds that will pay for about 60 percent of the staff that FDA will use for drug review in FY 2008.

If PDUFA is not reauthorized, and if the \$438 million anticipated from PDUFA fee revenue is not available in FY 2008 through fees or made up by appropriations, then FDA could no longer employ the 60 percent of review staff paid for through the fees. FDA also would be responsible for severance pay and the payment of unused annual leave. The loss of 60 percent of the drug review staff would have a devastating impact on the drug review process

in the United States. FDA would be unable to meet the 6- and 10-month review timelines that have existed under PDUFA. In the initial few years after such a reduction, the drug review process in America would most likely revert to review times that average three or more years, as was the case prior to the enactment of PDUFA. The U.S. would cease to be the first market of entry for most new pharmaceutical and biotechnology products that enter into world commerce, and "drug lag" would re-emerge—meaning that most new pharmaceutical and therapeutic biotechnology products would again only be available to U.S. citizens long after they were first approved and available in other countries.

- 3. The Institute of Medicine report on drug safety raised concerns over the culture at the FDA. The report described the agency as "an organizational culture in crisis." We asked you about this issue at your confirmation hearing and you promised to address the problem. Please describe in detail what you have done.**

Addressing the organizational culture issue is a top priority for FDA. Significant culture change is an evolving process that has already begun. As noted in FDA's written statement, FDA's Center for Drug Evaluation and Research (CDER or the Center) has initiated a series of changes designed to effect a true culture change that will strengthen the drug safety system. CDER has moved to reinvigorate its senior management team and charged its members with the responsibility to lead the Center in an integrated manner that crosses organizational lines.

CDER has already implemented process improvements recommended by CDER's Office of Surveillance and Epidemiology (OSE) and Office of New Drugs (OND) staff including their recommendations to (1) establish an Associate Director for Safety and a Safety Regulatory Project Manager in each OND review division within CDER and (2) conduct regular safety meetings between OSE and all of the OND review divisions are now being implemented. We are committed to providing the necessary management attention and support to effect sustained culture change in our drug safety program.

Also, as noted in FDA's written statement, we have recently engaged external management consultants to help CDER develop a comprehensive strategy for improving CDER/FDA's organizational culture. In addition to the ongoing FDA activities to improve how our organization supports the individuals who work on safety issues in FDA, we are enlisting the help of external experts in organizational improvement to help us identify additional opportunities for change and assist us with carrying out those needed changes.

- 4. I'm intrigued by the plan to review the available information about a drug, 18 months after approval. But this innovation suggests something very disturbing about the current drug safety system: FDA doesn't currently look proactively at the information about the safety of a drug. Instead, it only does so if something truly striking happens, like several liver failures, or the termination of a clinical trial for safety reasons. In the absence of something such as this, a drug simply isn't looked at now. Is that correct?**

This is not correct. Staff in OSE and OND review post-marketing safety continuously. FDA reviews reports of serious and unexpected adverse experiences that drug companies are

required to submit within 15 days, periodic safety reports that are submitted by drug companies quarterly for the first three years following approval and annually thereafter, and reports of serious problems sent directly by health care professionals and consumers, in addition to information from medical literature, clinical trials, other members of a class of drugs, and other sources.

With the rapidly increasing number of adverse event reports that the Agency receives (under 200,000 in 1996 and over 470,000 in 2006), we are focusing on making our post-marketing drug safety review processes more effective and efficient. We embarked on the New Molecular Entity Pilot Evaluations to examine whether we can more rapidly and predictably detect problems in newly approved drugs. In the pilot program, we are closely examining all available safety data of a few drugs selected for the pilot after they have been on the market for a period of time, such as 18 months or two years. We are examining the analyses needed, the most efficient approaches to communicating and discussing the data, the timeframes in which it can be accomplished, and how this systematic look compares to the review processes already in place. We will also be measuring the resources needed to conduct these scheduled reviews. At least four drugs will be studied initially. Then, FDA will assess the pilot program for possible wider implementation.

- 5. I am concerned about antibiotics used for human treatment and how use of these antibiotics in animals may contribute to the development of drug-resistance in bacteria. I have several questions related to the use of antibiotics in animals. Do you think Congress should give the FDA the authority to collect data on how much of an antibiotic is used for treatment of animals and on which animals it is used in a way that protects legitimate confidential business information? What programs does the FDA's Center for Veterinary Medicine now have in place to collect and compile information on post-approval antibiotic use?**

FDA currently requires that drug sponsors provide information on the distribution of each approved new animal drug product. Title 21, *Code of Federal Regulations* (CFR) 514.80(b)(4)(i). This requirement applies to all approved new animal drugs and does not include any provisions specific to antimicrobial new animal drugs. The required information must include the total number of distributed units of each size, strength, or potency. However, the current requirements are limited to drug distribution (sales) data. Furthermore, depending on whether a given product is approved for multiple animal species or indications, the current requirements do not necessarily provide information for each intended use or type of animal for which the drug is approved.

- 6. FDA Guidance Document # 152 focuses on the impact of animal drugs on food-borne infections in people. The World Health Organization has issued a report examining the impact on all human infections. Do you think the FDA, when considering approval of medically important antibiotics for use in animals, should follow WHO's approach and consider the impact of such use on all human infections?**

FDA recognizes that food-borne human exposure to antimicrobial resistant bacteria is complex and often involves the contributions from other sources of exposure; for example, direct contact between animals and humans and the introduction of resistant bacteria and

resistance determinants into the environment. However, FDA believes that evaluating antimicrobial new animal drug safety relative to the most significant exposure pathway, i.e., food-borne pathway, is the best way to qualitatively assess the risk of antimicrobial drug use in food-producing animals. Nonetheless, as stated in Guidance 152, non-food-borne bacteria may be considered when deemed necessary; for example, uncertainties regarding the contribution of other exposure pathways may be considered during the development of appropriate risk management strategies.

In developing criteria for ranking antimicrobial drugs with regard to their importance in human medicine, FDA considered broad issues associated with the efficacy of drugs in human medicine and factors influencing the development of antimicrobial resistance. Specific factors include the usefulness of the drug in food-borne infections, the types of infections treated, the availability of alternative therapies, the uniqueness of the mechanism of action, and the ease with which resistance develops and is transferred between organisms.

The World Health Organization (WHO) has also developed a system for ranking antimicrobial drugs with regard to their importance to human medicine. However, the WHO approach differs somewhat from the approach adopted by FDA. WHO determines the critical nature of an antimicrobial drug based on its use as the sole therapy or one of few alternatives to treat serious human disease and on its use to treat diseases caused by organisms that may be transmitted via non-human sources or diseases caused by organisms that may acquire resistance genes from non-human sources. WHO is looking broadly at diseases worldwide that may not be present in the U.S.

As mentioned previously, FDA believes that human consumption of animal-derived foods represents the most significant pathway for human exposure to antimicrobial resistant bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals.

- 7. Does the FDA have legal authority to place extra-label use restrictions on an animal drug prior to the drugs' being marketed when either a drug sponsor's own risk assessment or an internal FDA risk assessment finds that a potential drug approval presents a high risk of resistance adversely affecting human health? Does the FDA have the legal authority to act proactively to put in place an extra-label prohibition on an antimicrobial drug in cases where research shows that the drug is likely to select for resistance that would harm human health, but because the drug has not yet been marketed there is no evidence that extra-label use has caused a problem?**

FDA has the legal authority to prohibit the extra-label use of an approved new animal drug or human drug if it has evidence to support the conclusion that the extra-label use in question presents a risk to public health. Such evidence could be based on a risk assessment, published literature, surveillance data, or any other available information. FDA issued an order in May 1997 (62 FR 27944) to prohibit the extra-label use of fluoroquinolone and glycopeptide drugs in food-producing animals. At the time of issuance of that order, fluoroquinolone drugs were approved and marketed for use in certain animal species. Although certain glycopeptide drugs were approved for use in humans at that time, no glycopeptide drugs were approved or marketed for use in animals nor are any drugs in the glycopeptide class approved for use in animals today. To date, FDA has not issued an order

to prohibit the extra-label use of a drug concurrently with the approval of that drug in animals. However, FDA believes it has the authority to do so if evidence supports a finding that extra-label use of the drug presents a risk to public health.

FDA's extra-label use regulation defines *presents a risk to public health* to mean FDA has evidence that demonstrates that the use of the drug has caused or likely will cause an adverse event. (21 CFR 530.3(e)). The most recent example of FDA exercising its authority to prohibit extra-label use was the order issued on March 22, 2006, to prohibit the extra-label use by veterinarians of anti-influenza adamantane and neuraminidase inhibitor drugs in chickens, turkeys, and ducks. Although these anti-influenza drugs are approved for use in humans, these drugs are not approved or marketed for use in animals. Nevertheless, FDA compiled sufficient evidence to meet the statutory standard that such extra-label use presents a risk to public health.

- 8. Section 17 of the Best Pharmaceuticals for Children Act required the Food and Drug Administration to issue within a year a final rule to require that FDA-approved drugs be dispensed with the toll-free MedWatch number, so patients can report adverse events. FDA issued a proposed rule on April 22, 2004, more than 2 years after the date of enactment of the BPCA. FDA has yet to issue the final rule, more than 5 years after enactment. When will FDA issue the final rule required by BPCA?**

The proposed rule on Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products published on April 22, 2004, with the comment period ending July 21, 2004. In the proposed rule FDA solicited comments on the wording of the proposed labeling statements. We received a number of comments suggesting changes to the specific wording of the proposed statements. We have been conducting studies designed to resolve issues raised by the comments and to optimize consumer understanding of the labeling statements. We plan to finalize the rule upon completion of these studies.

Senator Enzi:

- 1. Some PDUFA IV resources are focused on giving FDA more ability to use some of the large patient databases to conduct drug safety studies. How many new information sources would the PDUFA IV funds allow access to? How many studies the user fees might these increased fees support?**

PDUFA IV proposes to increase funding directed to purchasing access to databases for post-marketing research to about five times the current funding level (from about \$1,000,000 to \$5,000,000). The funding will support formal epidemiologic drug safety studies and active surveillance. We cannot determine how many databases or studies we will be able to support with these funds because the cost depends on a number of factors such as size of the database, type of study, i.e., epidemiological or active surveillance research, and other study design elements. One study alone could cost as much as \$500,000 to \$1,000,000, or even more.

- 2. Right now, if a safety issue arises after a drug is marketed, can the agency require a study or clinical trial to follow up on the issue? My understanding is that you can request it, but not require it. Is that correct?**

Yes, that is correct, but post-marketing studies may occur in the following circumstances:

- A post-marketing study might be conducted because an applicant and FDA agree, in writing, that one or more such study should be conducted. These agreements can be made at the time of approval or after FDA grants marketing approval.
 - In addition, an applicant may be required to conduct a post-marketing study under certain circumstances. FDA can require an applicant to conduct studies to verify and describe clinical benefit for a drug or biological product approved in accordance with the accelerated approval provisions at 21 U.S.C. 356(b)(2)(A); 21 CFR 314.510 and 601.41.
 - For a drug or biological product approved on the basis of animal efficacy data because human efficacy studies are not ethical or feasible, an applicant must conduct studies when ethical and feasible to verify and describe clinical benefit and to assess the product's safety.
 - The Pediatric Research Equity Act of 2003 authorized FDA to require pediatric studies of marketed drugs that are not adequately labeled for children.
3. **I think there's a lot to like in the PDUFA IV proposal for drug safety. However, I believe FDA needs new authorities to really do its job. Do you agree? If not, why not?**

We believe it is important that FDA have appropriate resources and the capacity to develop better scientific tools and approaches to drug review and safety. We have provided technical assistance on drug safety bills and FDA and the Administration are currently evaluating whether new authorities are necessary or appropriate. FDA will use our current authority to the best of our ability.

Senator Hatch:

1. **On January 11, 2007, FDA announced that "serious questions remain about the validity of bioequivalence data" of 140 marketed generic drugs. As FDA has previously said, "bioequivalence is critical for drawing the conclusion that both the original and generic drugs will produce similar therapeutic results." If FDA has "serious questions" about whether 140 generic drugs actually work like the brand drugs for which they are substituted, how can FDA allow those questionable drugs to stay on the market?**

FDA had serious questions about the conduct of bioequivalence studies done by MDS Pharma Services (MDS Pharma) that were submitted to the Agency in support of various abbreviated new drug applications (ANDAs). MDS Pharma is a contract company that performs bioequivalence studies for a number of pharmaceutical companies.

FDA conducted a series of lengthy inspections of MDS Pharma bioequivalence studies covering laboratory analyses and analytical results, and found significant deficiencies with several studies that were conducted by MDS Pharma from 2001 to 2005. As a result of these

deficiencies, FDA was unable to verify the results reported from these studies. The bioequivalence studies for these particular products in question were either re-analyzed or repeated by the ANDA sponsors, and this additional work by the sponsors confirmed the accuracy of the bioequivalence findings from the initial studies. It is important to note that FDA inspected many other MDS Pharma bioequivalence studies conducted during the 2001 to 2005 time period and found those studies acceptable.

The Agency then focused on those remaining bioequivalence studies conducted by MDS Pharma during the 2001 to 2005 time period that had not been inspected by FDA and that were submitted in support of 140 approved ANDAs. Although the Agency had serious concerns about the conduct of some of the bioequivalence studies by MDS Pharma based on its previous inspection findings, the Agency did not have any adverse inspection findings for these specific studies that would undermine the Agency's bioequivalence conclusions regarding these products. In addition, these products had satisfied the Agency's rigorous chemistry and manufacturing standards for approved drugs.

Nevertheless, FDA took additional steps to assure that the bioequivalence data for these 140 products were reliable. To obtain these necessary assurances, on January 11, 2007, FDA sent written requests asking that the ANDA sponsors do one of the following, in order of FDA preference, within 6 months:

- a. Repeat the bioequivalence studies;
- b. Re-assay the samples at a different bioanalytical facility. For this option, the integrity of the original samples must be demonstrated for the frozen storage period; and
- c. Commission a scientific audit by a qualified independent expert, who is knowledgeable in the area of bioequivalence studies and bioanalytical data, selected by the manufacturer rather than by MDS, to verify the results obtained by MDS.

Confirmatory data received from sponsors thus far have supported the bioequivalence determinations that were made. At the end of the six month period, FDA will reassess whether any additional steps will need to be taken.

2. Why did FDA announce it had "serious questions" about these 140 marketed drugs, but not disclose their identities to the American public, so they could decide for themselves whether they wanted to take these questionable products?

FDA took these actions described in response to Question 1 as a precautionary measure to ensure that data submitted to the Agency and used to support approval decisions were accurate. FDA's routine adverse event surveillance monitoring program has not detected any signals or evidence that any of the drugs involved pose a safety risk or that there has been any impact on efficacy. FDA does not have any evidence that there are problems with the quality, purity, or potency of the affected drug products. Moreover, the studies at issue were conducted by MDS Pharma, a contract research organization with which the ANDA holders had a contractual arrangement, and the information was considered to be confidential commercial information and not releasable to the public.

- 3. Absence of evidence is not evidence of absence. FDA says it has no evidence that the 140 drugs pose a safety risk or have impaired efficacy. I question how you can be sure. You stated, "FDA's routine adverse event surveillance monitoring program" has not detected any problems. This is the same monitoring that the recent IOM Report found inadequate for new drug adverse event reporting, and which current drug safety legislative proposals seek to improve. If FDA's current monitoring system is inadequate, how can you be sure none of the 140 drugs have problems?**

Approval of a generic product depends on meeting standards for purity and potency of the drug substance as well as bioequivalence. These products have all met the usual chemistry and manufacturing standards for approved drugs. As noted in the answer to Question 1, FDA has asked all sponsors of the 140 relevant products to follow one of the three options within 6 months to confirm that bioequivalence standards have been met.

While FDA generally relies on AERS and MedWatch and post-marketing safety reporting as the sources for surveillance monitoring, the Office of Generic Drugs (OGD) also receives reports of potential bioequivalence problems from many other sources, and follows up on these reports from sources including individual patients, and problems reported in the literature.

- 4. Please explain how FDA's adverse event monitoring system tracks generic drugs. Do you track adverse events by manufacturer?**

The Adverse Event Reporting System (AERS) is a computerized information database designed to support FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products (including both brand and generic products). The goal of this system is to improve the public health by providing the best available tools for storing and analyzing safety reports.

FDA receives adverse drug reaction reports from manufacturers as required by regulation. Health care professionals and consumers send reports voluntarily through the MedWatch program. These reports become part of a database. The structure of this database is in compliance with the international safety reporting guidance (ICH E2B) issued by the International Conference on Harmonization.

The reports in AERS are evaluated by clinical reviewers in the Office of Surveillance and Epidemiology in CDER to detect safety signals and to monitor drug safety. Reports about generic drugs are tracked in the same manner as reports about new drug products. The analyses of reports are usually done to assess the potential adverse effects of the molecule, and not the drug product of an individual manufacturer.

- 5. Does FDA have any monitoring system capable of detecting bioequivalence problems? If so, what data are incorporated into the monitoring program that would provide a signal of a bioequivalence problem? If not, on what scientific basis can FDA confer a judgment that the absence of evidence of safety and efficacy problems is a**

sufficient validation that ANDA sponsors have submitted information showing bioequivalence?

Although bioequivalence problems are difficult to detect because of the large amount of variability between individuals, and from time to time within the same individual, regarding the therapeutic response to a drug, the AERS database and MedWatch post-marketing safety reporting are capable of detecting bioequivalence problems. It is acknowledged that the voluntary reporting on which the systems are based is a limiting factor. However, OGD also receives reports of potential bioequivalence problems from many other sources, and follows up on these reports from other sources including individual patients, and problems reported in the literature. See the response to Question 1 for a description of the steps FDA has taken with respect to the 140 products at issue in the MDS Pharma case.

6. Please provide the Committee with a list of the 140 generic drugs subject to the January 11th announcement.

We are unable to provide the list of products because information about companies that have contractual arrangements with MDS Pharma is confidential commercial information.

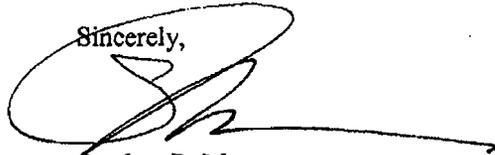
Senator Burr:

1. I know that this is off subject, but last week we held a hearing on follow-on biologics, I like to call them biosimilars. Do you think that the Clinton-Schumer bill sets up a good pathway for the FDA to approve biosimilars?

Given the complex scientific and legal considerations addressed in this legislation, we are still looking at this and other bills in relation to our developing thoughts on this issue. We would be happy to speak with you or appropriate staff about this legislation.

Please let us know if you have further questions.

Sincerely,



Stephen R. Mason
Acting Assistant Commissioner
for Legislation