COMMITTEE PRINTS ON ADMINISTRATION LEGISLATIVE PROPOSALS ON THE ANIMAL DRUG USER FEE ACT AMENDMENTS OF 2008 AND THE ANIMAL GENERIC DRUG USER FEE ACT OF 2008

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

ONE HUNDRED TENTH CONGRESS

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CONTENTS

COMMITTEE PRINTS ON ADMINISTRATION LEGISLATIVE PROPOSALS ON THE ANIMAL DRUG USER FEE ACT AMENDMENTS OF 2008 AND THE ANIMAL GENERIC DRUG USER FEE ACT OF 2008

THURSDAY, JUNE 5, 2008

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 10:13 a.m., in room 2123 of the Rayburn House Office Building, Hon. Frank Pallone, Jr. (chairman) presiding.

Members present: Representatives Pallone, Waxman, Towns, Green, Schakowsky, Matheson, Deal, Buyer, and Murphy.

Staff present: William Garner, Jessica McNiece, Melissa Sidman, Ryan Long, Lance Kotschner, Chad Grant, Jodi Seth, Lauren Bloomberg, and Bobby Clark.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. The meeting of the subcommittee is called to order.

Today we are going to have a hearing on two committee prints of the Administration's legislative proposals on first, the Animal Drug User Fee Act amendments of 2008, and second, the Animal Generic User Fee Act of 2008, and I am going to recognize myself initially for an opening statement.

Prior to 2003, the FDA's review of animal drug submissions was taking over a year and a half to be completed. This obviously led to serious concerns that new and innovative pharmaceutical products were not making their way into the marketplace in order to treat our Nation's pets as well as food animals that help sustain the Nation's food supply. Accordingly, in 2003, Congress enacted the Animal Drug User Fee Act, ADUFA, which was modeled after the successful user fee programs for the review of human drug and medical device submissions. Like the user fee programs that preceded it, ADUFA authorized the FDA to collect fees to help ensure that the agency had the resources it needed to provide a timely review of animal drug applications. ADUFA also set new performance goals for FDA to review and act upon submissions within a stated timeframe. By the fifth year of the authorization period,

FDA was supposed to review 90 percent of submissions within the statutorily required time frame of 180 days. According to the required annual performance reports for the most recent fiscal years, FDA says that the agency has been meeting or exceeding the timeliness goals established under the program, and I am looking forward to hearing more from FDA about how this program has been working over the past 5 years and how it can be improved upon.

Now, under the Administration's legislative proposal to reauthorize ADUFA, the review times would remain the same as the existing performance goals for fiscal year 2008. The proposal would increase the amount of fees collected from $15 million to $24 million over 5 years for a total of $98 million. Revenues would be derived from a mix of application product, establishment, and sponsor fees. Other important provisions of the Administration's proposal include a new end-review amendment process and improved communications between FDA and the regulated industries. Absent from the Administration's proposal, however, is any provision relating to the issue of antimicrobial resistance. I recognize that there is a growing concern among stakeholders and members of this subcommittee about the use of antibiotics in food animals for prophylactic and/or growth purposes. As these practices become more commonplace, bacteria that are resistant to antibiotics begin to proliferate and this poses a significant threat to humans who may come into contact with antibiotic-resistant bacteria through eating contaminated or undercooked meat, by caring for livestock, or through polluted waterways.

So clearly we face significant challenges when it comes to maintaining the effective use of antibiotics with fewer and fewer innovative antibiotic products coming down from the pharmaceutical pipeline. It is even more important that we keep the antibiotics that are currently on the market working, and I am anxious to hear testimony both from the FDA and the witnesses on our second panel about the problem of antibiotic resistance and what, if any, consideration should be made regarding this issue as we move forward with reauthorizing ADUFA.

In addition to the reauthorization of ADUFA, the Administration has offered a proposal to establish a new animal generic drug user fee. According to FDA, the average review time of an animal generic drug submission was 570 days in fiscal year 2007 in spite of a 180-day statutory requirement. At the end of last year, there was a recorded backlog of 446 submissions waiting for review and agency action. As more and more brand pharmaceuticals come off patent over the next 5 years, we need to make sure that FDA has the resources it needs to effectively review generic animal drug submissions in a timely manner. Accordingly, the agreement between the FDA and the industry would provide for the collection of user fees increasing annually from $4.8 million to $6 million over 5 years for a total of $27 million, including the yearly cost of inflation. These additional revenues are designed to help speed up the review process, and by year 5 of the authorization period, most reviews of generic animal drug submissions would occur in 270 days or less, a substantial improvement over the time it now takes FDA to conduct such reviews. I am pleased that the industry and the FDA have been able to work out this agreement. I am looking forward

to hearing more about it today. If implemented, AGDUFA, we are calling it, will speed lower cost animal drugs to the marketplace and bring significant savings to ranchers, farmers, and pet owners. While this is an important and noteworthy goal, I also think it is equally, if not more important, to ensure the timely review of generic human drug applications.

Over the past few years, I have tried to work to improve the speed in which the agency works to review generic applications for human drugs. We have lobbied appropriators for additional monies for the Office of Generic Drugs. Additionally, last year we included a provision in the FDA Amendments Act of 2007 to reform the citizen petition process, which has been abused in an effort to delay agency approval of generic applications. While steps have been taken to improve the efficiency in which the agency is reviewing generic human drug applications, more can and should be done to help ensure patients have access to cheaper and safer medications, and I see that Mr. Waxman is here and I know that he has always been a champion of trying to improve generics, get them on the market and try to bring costs down. I just mention the human because I do think we have to keep that in mind even as we are talking about the animal drugs today.

Mr. PALLONE. Mr. Waxman is recognized for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you very much, Mr. Chairman. I appreciate your holding this hearing.

As we consider FDA's animal user fee program, we have to recognize it has been successful in speeding new medicines for animals to the market and that is important and that is why we have this user fee program for animals and that is why, quite frankly, we have the user fee program for FDA to approve human drugs as well. This reauthorization of the Animal Drug User Fee Act, or ADUFA, also gives us an opportunity to look at providing FDA with new tools to address what has become a glaring public health crisis. We now have an overwhelming body of evidence showing that the overuse of antibiotics in industrial farm production is threatening to destroy the effectiveness of many of our most important antibiotics for human use. Most recently, the Pew Commission on Industrial Farm Animal Production issued a report concluding that our current system of producing food animals and its reliance on the indiscriminate use of antibiotics poses an unacceptable level of risk to public health. I am glad that the executive director, Robert Martin, will be here today to walk us through some of the Commission's findings.

We also have reports from the Institute of Medicine, GAO, and the World Health Organization, all of which describe the very serious and growing threat to global public health generated by antibiotic resistance. Americans have experienced firsthand the importance of ensuring that we preserve our arsenal to fight the new and emerging superbugs like MRSA. We know that the overuse of antibiotics hampers our ability to do that. So we clearly need to look

at ways to reduce the overuse in animals of these antibiotics that are so vitally important for preventing and curing diseases in humans.

This legislation deals with one critical issue related to animal drugs but clearly there are others. It is our responsibility as a subcommittee concerned with the health of the American public to examine those issues, and I hope in the course of this hearing we might consider evaluating the possibility of adding additional legislation to the reauthorization bill to deal with animal drug antibiotic use that is leading to human resistance to the antibiotics itself.

I yield back the balance of my time, Mr. Chairman. Thank you.

Mr. PALLONE. Thank you, Mr. Waxman, and I would ask unanimous consent to include in the record the statement of Chairman Dingell. Without objection, so ordered.

[The prepared statement of Mr. Dingell follows:]

STATEMENT OF HON. JOHN D. DINGELL

Mr. Chairman, thank you for beginning the consideration of two legislative proposals recently sent up by the Administration, and for your leadership on these important public health matters. Today's hearing is the first step in crafting legislation that will provide the necessary resources for the Food and Drug Administration (FDA) to safely and efficiently review animal drug applications.

The Animal Drug User Fee Act (ADUFA) expires on October 1, 2008, less than 4 months from now. It is the responsibility of this Committee and the Congress to ensure that this program is reauthorized in a timely manner to avoid any personnel disruptions at the FDA. Hardworking, skilled employees at FDA are depending on us to do our job, so they can continue to do their job.

An important component of the Administration's proposals focuses on the need for greater resources at FDA. We have heard from a wide range of stakeholders on this point and I agree. This legislation must provide FDA with the necessary user fee structure to provide resources for the timely and thorough review of new animal drug applications. Equally important, we must ensure that Congress appropriates the requisite funds that have been authorized for FDA.

As we begin this process of reauthorizing ADUFA and considering the proposed legislation to establish an animal generic drug user fee, we must diligently work towards strengthening the safety and effectiveness of the Nation's supply of animal drugs. I thank the Chairman for holding this hearing on the proposals before us today and I look forward to the testimony of the witnesses.

Mr. PALLONE. Next is our vice chair, Mr. Green of Texas.

OPENING STATEMENT OF HON. GENE GREEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

Mr. GREEN. Mr. Chairman, thank you for holding the hearing on today's Animal Drug User Fee Act and the Animal Generic Drug User Fee Act. The Animal Drug User Fee Act was first signed into law in 2003 and allowed the FDA to collect user fees from brand-name drug companies to reduce the backlog of the FDA's review system for brand-name drugs. The Animal Drug User Fee Act and the Animal Generic Drug User Fee Act will provide the FDA with additional funds to supplement their appropriations funding from Congress and for expediting animal drug applications from Congress. These additional resources support FDA's responsibility under the Food, Drug, and Cosmetic Act to ensure that new animal drug products are safe and effective for animals as well as for the public with respect to animals intended for food consumption. The

legislation allows the FDA to expedite and improve its review of the application for new drugs so that safe and effective new drugs will be available more quickly.

The current ADUFA law will expire October 1 and generic drug companies would like a swift review process as well, which is why we are having the hearing today on these bills. I support both the bills and I thank the committee for having the hearing and look forward to the testimony of our witnesses, and I yield back my time.

Mr. PALLONE. Thank you, Mr. Green.

Mr. Towns.

Mr. TOWNS. Thank you very much, Mr. Chairman, for holding this hearing.

The reauthorization of the ADUFA is essential in providing safety measures directed towards animal health and disease prevention. Requiring animal health companies to provide additional funding to the FDA's Center for Veterinary Medicine will enable the Center to meet its performance goals and expectations.

The proposed AGDUFA bill is also a step toward meeting future standards of growth and performance. The AGDUFA bill has potential to provide essential resources to reduce the amount of time to review generic animal drug applications, which is very, very important. This initiative also helps support important health priorities. It supports a priority to transform health through an improved process that makes new drugs available in less time.

In general, it has been proven that companies that research and develop animal drugs have been successful at reducing the review backlog while also increasing the FDA's accountability of the standards it utilizes for its applicants. The reauthorization will also support FDA staff and reviews in place to continue uninterrupted.

Again, let me thank you, Chairman Pallone, of course for having this hearing and I look forward to working with the committee to move these two ideas forward.

On that note, I yield back.

Mr. PALLONE. Thank you, Mr. Towns.

I recognize the gentleman from Indiana, Mr. Buyer, for an opening.

OPENING STATEMENT OF HON. STEVE BUYER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF INDIANA

Mr. BUYER. Thank you, Mr. Chairman.

I am glad we are holding the hearing today and I am hopeful that the process of reauthorizing the Animal Drug User Fee Act will be quick and smooth. It is vital to the business and agriculture in my home State of Indiana that this program is reauthorized quickly. This program is critical to providing for innovative medications for companion and food animals. I strongly support the proposal before us today and commend the animal drug community for the work they did to develop it. I urge the subcommittee to preserve this well-vetted proposal and to restrain from attaching measures that compromise a quick passage.

The Animal Drug User Fee Act has been very successful in speeding the process of getting innovative drugs to our Nation's market. Since its initial authorization in 2003, FDA's review proc-

ess for new animal drugs has decreased significantly from an average of 295 days to 180 days. I look forward to authorizing a process to speed the development of generic animal drugs as well. Currently, FDA's review process for generic animal drugs lasts on average 4 to 5 years. This year we have a new proposal for a generic drug user fee program which will decrease this review time to an average of 270 days.

Again, I strongly support the two proposals before us today. They have been well vetted by the business and regulatory communities and it is critical to our companion and food animal communities that these measures move forward quickly without delay, and I thank the chairman for his good work along with the ranking member.

Mr. PALLONE. Thank you.

The gentleman from Pennsylvania, Mr. Murphy, is recognized for an opening.

Mr. MURPHY. I waive opening, Mr. Chairman.

Mr. PALLONE. The gentleman waives. OK. So I think we are done with the opening statements. We have two panels today. Welcome. The first panel consists of Dr. Bernadette Dunham, who is director of the Center for Veterinary Medicine at the FDA. She is the speaker, and she is accompanied by Dr. Steven Vaughn, who is director of the Office of New Animal Drug Evaluation, and David Wardrop, Jr., who is director of the Office of Management, but I understand you are going to speak and they are going to accompany you for questions. You know the drill, 5-minute opening. We may subsequently send you some written questions at the discretion of the committee.

I now recognize Dr. Dunham. Thank you for being here.

STATEMENT OF BERNADETTE DUNHAM, PH.D., D.V.M., DIRECTOR, CENTER FOR VETERINARY MEDICINE, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY STEVEN VAUGHN, D.V.M., DIRECTOR, OFFICE OF NEW ANIMAL DRUG EVALUATION, CVM, FDA

Dr. DUNHAM. Thank you very much. Good morning, Chairman Pallone and members of the subcommittee. I am Dr. Bernadette Dunham, director of the Center for Veterinary Medicine, referred to as CVM, at the U.S. Food and Drug Administration, which is part of the Department of Health and Human Services. I am accompanied today by Dr. Steven Vaughn, to my right, director of the Center for Veterinary Medicine's Office of New Animal Drug Evaluation, and to my left, Mr. David Wardrop, Jr., executive officer and director of CVM's Office of Management.

FDA appreciates the opportunity to testify on the reauthorization of the Animal Drug User Fee Act and the proposed Animal Generic Drug User Fee Act. This morning I will be presenting an abbreviated oral testimony, if acceptable to the Committee. FDA has submitted a detailed written statement for the record. Thank you.

FDA is the federal agency that regulates almost everything we eat except for meat, poultry and processed egg products, which are regulated by our partners at USDA. FDA's responsibility extends to live food animals and animal feed. The Animal Drug User Fee Act, referred to as ADUFA, enacted in 2003, authorizes FDA to col-

lect user fees from the animal drug industry to enhance the process for the review of animal drug applications. Fees collected under ADUFA are in addition to the base appropriations and they enable FDA to pursue a comprehensive set of review performance goals and commitments designed to improve the timeliness and predictability of the review of new animal drug applications, supplemental NADAs and investigational new animal drug submissions

I am here today to share some very good news with you. Since ADUFA's enactment, FDA has exceeded all the program's review performance goals. Review times for original NADAs have decreased from 295 days to 180 days. Resources provided by ADUFA have allowed CVM's scientists to keep pace with the rapid advances in science and medicine that drive the quality of healthcare and as a part of their work in review the animal drug applications. User fee funding has enabled the agency to hire and retain highly qualified scientific staff to address critical public health issues such as antimicrobial resistance that play a role in the review of new animal drug applications. This legislation has been extremely valuable to FDA to help us fulfill our commitment to promote and protect public and animal health.

The user fee provisions of ADUFA will sunset on October 1, 2008, if not reauthorized. Recognizing that timely reauthorization is needed to ensure there is no disruption to the program, FDA held public meetings, negotiated with the Animal Health Institute, which represents the majority of animal drug industry for pioneer drugs, published negotiated recommendations in the Federal Register, and accepted comments on those recommendations. FDA's proposal to Congress includes input from stakeholders. Our goals for the legislative proposal to reauthorize ADUFA are to sustain and enhance the core program's operation and performance while providing predictable review times and resources sufficient to keep pace with actual costs. Performance improvement enhancements are aimed at reducing costs for some submissions, providing for improved handling of inspections, improving communication between sponsors and the agency, and increasing the flexibility of the application process. FDA's proposal also includes technical changes to increase the administrative efficiency of the user fee program.

Because user fees have not kept up with the increasing costs of the program, FDA is proposing to change the financial provision of ADUFA to place the program on sound financial ground. At the proposed funding level of $98 million over 5 years, FDA has confidence that it will have a stable review workforce over the 5 years covered by ADUFA II. This will enable FDA to commit to a continuation of the fiscal year 2008 performance goals throughout the period covered by ADUFA II as well as to additional performance enhancements.

Now I would like to address the Animal Generic Drug User Fee Act, AGDUFA. Currently, FDA's review of generic animal drugs is funded entirely through appropriations. Under FDA's generic animal drug user fee proposal, the generic animal drug industry would pay user fees that would be available to FDA in addition to the appropriated funds to spend on the process for the review of generic animal drug submissions. The proposed legislation will generate an estimated $27 million in user fees over 5 years. Fees dedicated to

the review process of applications will provide essential resources to improve generic animal drug review times. Review times for generic animal drug submissions have increased significantly in recent years, and at the end of fiscal year 2007, there was a backlog of 446 submissions for generic animal drugs, an increase of 93 percent over fiscal year 2000. The statutory review time is 180 days, but in fiscal year 2007, the actual review time was 570 days. With 49 pioneer animal drugs to come off of patent between 2009 and 2011, review times will increase unless improvements are made. This legislation is critical to FDA to improve its approval process for generic animal drugs. By passing AGDUFA, Congress will provide significant savings to ranchers, farmers, rural communities, and pet owners who struggle to pay the high price of pioneer drugs for their animals. In preparing its AGDUFA proposal for Congress, FDA negotiated with the Generic Animal Drug Alliance, which represents the majority of the animal generic drug industry. FDA'S AGDUFA recommendations ensure that generic animal drug user fee program will have a sound financial footing and strong performance goals. Resources generated through user fees will be sufficient to cover the actual cost of meeting specified performance goals.

AGDUFA's performance goals mirror those of ADUFA. The first goal is to reduce specific review times for sentinel submissions. It is estimated the review of an original generic animal drug application takes approximately 700 days in fiscal year 2009. It will take 270 days by 2013. For generic investigational new animal drug protocols, the 400 days needed to review in 2009 will be reduced to 100 days by 2013. These significant process improvements will help bolster a struggling generic animal drug industry. The AGDUFA proposal includes an amendment process to reduce the time and review cycles associated with similar submissions from a single sponsor and it incorporates several changes aimed at improved communication between sponsors and the agency. Resources generated by AGDUFA will be used to increase review staff, refine FDA's business process for review of generic animal drug submissions, provide training and development for program staff and develop policies targeted at more efficient review. This proposal benefits from FDA's ADUFA experience and will allow FDA to continue to maintain the high standards of safety and effectiveness for animals.

In conclusion, FDA's ADUFA and AGDUFA legislative proposals represent considerable input from and agreement of stakeholders and the agency. FDA urges passage of these proposals and we will work with Congress in any way we can to assist with that effort.

Thank you for the opportunity to present testimony before the subcommittee, and we welcome any questions.

[The prepared statement of Dr. Dunham follows:]

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

STATEMENT OF

BERNADETTE M. DUNHAM, D.V.M., PH.D.

DIRECTOR

CENTER FOR VETERINARY MEDICINE

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

JUNE 5, 2008

For Release Only Upon Delivery

INTRODUCTION

Good morning, Chairman Pallone and Members of the Subcommittee. I am Dr. Bernadette Dunham, Director of the Center for Veterinary Medicine (CVM) at the U.S. Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). I am accompanied today by Dr. Steven Vaughn, Director of CVM's Office of New Animal Drug Evaluation, and Mr. David Wardrop, Jr., Executive Officer and Director of CVM's Office of Management. FDA appreciates the opportunity to testify on the reauthorization of the Animal Drug User Fee Act (AGDUFA) and the proposed Animal Generic Drug User Fee Act (AGDUFA).

I'd like to begin my testimony today by speaking about the reauthorization of ADUFA, including a description of ADUFA's performance to date and a description of how FDA's recommended improvements for ADUFA II fulfill the goals set by the House Committee on Energy and Commerce, the Senate Health, Education, Labor and Pensions Committee, FDA and others. I will then briefly describe the proposed AGDUFA.

ADUFA

BACKGROUND

As authorized by Congress and signed into law in 2003, ADUFA amended the Federal Food, Drug, and Cosmetic Act to authorize FDA to collect user fees from the animal drug industry to enhance the process for the review of animal drug applications. The goal of ADUFA is to better serve public and animal health by providing additional funds to

augment FDA resources dedicated to the application review process. Shorter, more predictable review times are achieved by increasing the review staff at CVM and building better management systems. Fees collected under ADUFA are in addition to base appropriations and enable FDA to pursue a comprehensive set of review performance goals and commitments designed to improve the timeliness and predictability of the review of new animal drug applications (NADAs), supplemental NADAs, and investigational new animal drug (INAD) submissions.

Under ADUFA, FDA committed to meeting the performance goals specified in letters from the Secretary of Health and Human Services to the Chairmen of the House Committee on Energy and Commerce and the Senate Committee on Health, Education, Labor, and Pensions.

ADUFA ACHIEVEMENTS

I'm here today to report to Members of the Subcommittee some very good news. Since the enactment of ADUFA, FDA has exceeded all of the review performance goals established under ADUFA. The performance goals under ADUFA were intended to achieve progressive, yearly improvements in the process for review of NADA's. FDA agreed to review and act on submissions within shorter periods of time each successive year. For example, review times for original NADA's have decreased from 295 days to 180 days. This has been accomplished by hiring additional FDA staff; providing training and educational opportunities for FDA animal drug review staff; developing and disseminating guidance, policy, and procedural documents; and implementing business

process improvements. These actions are an integral part of FDA's commitment to improving the efficiency, quality, and predictability of the new animal drug review process. The best news is that resources provided by ADUFA have allowed CVM scientists to keep pace with the rapid advances in science and medicine that drive the quality of health care as part of their work in reviewing animal drug applications. User fee funding also enables us to hire and retain highly qualified scientific staff to address critical public health issues, such as antimicrobial resistance, that play a role in the review of NADAs.

As the Prescription Drug User Fee Act (PDUFA) enhanced the review of human drugs, so has ADUFA benefited the review of animal drugs. This legislation has been extremely valuable in helping FDA fulfill our commitment to promote and protect public and animal health.

REAUTHORIZATION

The user fee provisions of ADUFA will sunset on October 1, 2008, if not reauthorized. Timely reauthorization is needed to ensure there is no disruption to this program. In preparing our proposed recommendations for ADUFA reauthorization, we held a public meeting on April 24, 2007. We then negotiated, from May through August 2007, with the Animal Health Institute, which represents the majority of the animal drug industry for pioneer drugs. FDA then published the negotiated recommendations in the *Federal Register* on February 21, 2008, held a public meeting for comments on those recommendations on March 11, 2008, and provided a 30-day comment period on the

same (that comment period closed April 14, 2008). The proposal FDA presented to Congress on April 24, 2008, included input from our stakeholders.

PROPOSAL FOR ADUFA II

Our goals for the legislative proposal to reauthorize ADUFA are to sustain and enhance the core program's operation and performance while providing predictable review times and resources sufficient to keep pace with actual costs.

Recommendations presented in the proposal to accomplish these goals fall into two categories:

A. Enhancements to performance provisions; and
B. Enhancements to program funding.

I'd like to describe those recommendations in a bit more detail.

A. Enhancements to performance provisions

FDA's proposal includes several performance-improving enhancements aimed at reducing costs for some submissions, providing for improved handling of inspections, improving communication between sponsors and the Agency, and increasing the flexibility of the application process.

First, a new End-Review Amendment process has been developed in an attempt to reduce review cycles. Under ADUFA I, in cases of an incomplete application, FDA must issue an "incomplete" letter for the application. The sponsor must then correct and resubmit the application, at which time a new review cycle starts. This adds considerable time and expense to those application reviews. Under ADUFA II, for applications that are nearly

satisfactory but need non-substantial changes, a new "End-Review Amendment" process will allow sponsors to provide an amendment within a specified timeframe, allowing the Agency to immediately review the amendment and approve the application, if appropriate, without starting a new review cycle. This change will significantly reduce costs and expenses associated with second reviews.

Another enhancement to the process for reviewing animal drug applications is the creation of a process allowing for the voluntary submission by sponsors of a list of foreign manufacturing facilities that may be subject to a premarket approval inspection during the fiscal year. In addition, a sponsor may notify FDA 30 days prior to submitting an animal drug application, supplemental animal drug application, or investigational animal drug submission that it includes a foreign facility. This change will allow FDA to better predict and organize pre-approval inspections.

In addition, FDA is recommending a number of changes to improve communication between the Agency and sponsors to increase the efficiency of the application submission process. FDA and regulated industry have agreed to participate in ten public workshops by the end of Fiscal Year (FY) 2013 on mutually agreed upon topics. FDA will explore and discuss the applicable use of pharmacokinetic/pharmacodynamic data and will explore opportunities for exchange of information regarding the characteristics of new animal drugs. FDA will use both formal meetings and informal communication with stakeholders to ensure complete submissions.

Finally, FDA will develop an electronic submission tool for industry submissions, thereby allowing online review capability of applications by FDA.

Beyond the stated goals, FDA's proposal includes technical changes to increase the administrative efficiency of the user fee program. These changes are designed to clarify several ADUFA definitions and to remove potential ambiguity. FDA's analysis of the impact of these changes indicates that they would be revenue-neutral and would have a minimal impact on industry.

FDA believes this agreement will continue the sustained performance improvements established by ADUFA, enhance communications between FDA and regulated industry, enable FDA to maintain high standards of safety and effectiveness of animal drugs, and provide revenue for sustained performance while maintaining our critical public health mission.

B. Enhancements to program funding provisions

Although user fees have provided important resources to FDA since the beginning of the program, user fees have not kept up with the increasing costs of the program associated with inflation in pay and benefit costs to the Agency and rent and rent-related costs. FDA is proposing changes to the financial provisions of ADUFA to address these shortcomings and place the program on sound financial footing so FDA can continue with the program and enhance it. The proposed funding level is $98 million over five years.

Based on an analysis of FDA's recent costs history and anticipated costs over the next five years, FDA expects the trend of increasing costs to continue. FDA's proposed recommendation to Congress, after consultation with regulated industry, is that the total fee revenue estimate for each of the five fiscal years of ADUFA II be the amounts set out in the table below:

Fiscal Year	2009	2010	2011	2012	2013	Total
Total Revenue Target	$15,260,000	17,280,000	$19,448.000	$21,768,000	$24,244,000	98,000,000

With the level of funding proposed, FDA has confidence that it will have a stable review workforce over the five years to be covered by ADUFA II. That assurance of a stable animal drug review workforce enables FDA to commit to a continuation of the FY 2008 performance goals throughout the period covered by ADUFA II as well as to additional performance enhancements.

AGDUFA

Currently, FDA's review of generic animal drugs is funded entirely through appropriations. Under FDA's generic animal drug user fee proposal, the generic animal drug industry would pay user fees that would be available to FDA, in addition to appropriated funds, to spend on the process for the review of generic animal drug submissions. The proposed legislation will generate an estimated $27 million in user fees over five years. Fees dedicated to the review process of such applications will

provide essential resources to improve generic animal drug review times. Despite several management initiatives already implemented to make this review process more efficient, there has been a significant increase in review times for generic animal drug submissions. At the end of FY 2007, there was a backlog of 446 submissions for generic animal drugs. That's an increase of 93 percent over the FY 2000 number. The statutory review time frame for ANADAs is 180 days. In FY 2007, the actual review time averaged 570 days. With 49 pioneer animal drugs due to come off patent between 2009 and 2011, review times are certain to increase unless improvements are made. This legislation is critical to FDA improving its approval process for generic animal drugs.

By passing AGDUFA, Congress will provide significant savings to ranchers, farmers, rural communities, and pet owners who struggle to pay the high price of pioneer drugs for their animals. This legislation will provide a 75 percent cost savings to the end user for a food-producing animal drug and a 30 percent cost savings to pet owners for companion animal drugs.

FDA recognizes the great need for improved response times for generic animal drug applications. From September through November 2007, in response to that need, the Agency held negotiations with the Generic Animal Drug Alliance, which represents the majority of the animal generic drug industry. From input gained through those negotiations, FDA formulated recommendations for a generic animal drug user fee program and presented those recommendations to Congress on April 24, 2008.

Similar to the Agency's ADUFA proposal, FDA's AGDUFA recommendations ensure

that the generic animal drug user fee program will have a sound financial footing and strong performance goals. Resources generated through user fees will be sufficient to cover the actual costs of meeting specified performance goals. Revenues generated by the AGDUFA proposal increase annually from $4.8 million to $6 million over five years for a total of $27 million. As with ADUFA, revenue amounts from fees account for yearly cost of inflation, so no further inflation adjustment is necessary.

The AGDUFA fee structure uses three streams to generate revenue – application fees, sponsor fees, and product fees. Sponsor fees are graduated based on the number of approved applications a sponsor holds. In addition, there is a waiver for Minor Use and Minor Species applications/submissions as there is in ADUFA.

FDA's AGDUFA proposal includes an adjustment mechanism for potential sustained increases in workload. The program delays offset collections to the final year and utilizes the same triggers as ADUFA (i.e., Agency level appropriation combined with review process level appropriation).

AGDUFA's performance goals also mirror those of ADUFA. The first of those goals is the reduction of specific review times for sentinel submissions over five years. As an example, it is estimated that the review of an original ANADA that will take approximately 700 days in FY 2009 will take 270 days in FY 2013. For generic investigational new animal drugs (JINAD) protocols, the 400 days needed to review in 2009 will be reduced to 100 days by 2013. These are considerable improvements in the

approval process, and they will go a long way in bolstering a struggling generic animal drug industry.

The AGDUFA proposal also includes an amendment process to reduce the time and review cycles associated with multiple submissions from a sponsor that are similar to one another. This provision is to be implemented no later than FY 2012. Under this provision, in most cases, if FDA requests an amendment to an animal drug application/submission, or if the Agency issues an incomplete letter for such an application/submission, a sponsor may request to amend other, similar applications or submissions. This will reduce the time and review cycles associated with any related submissions from a sponsor.

Again, like ADUFA, AGDUFA includes various changes aimed at improving communication between sponsors and the Agency.

Resources generated by AGDUFA will be used to increase review staff, refine FDA's business process for review of generic animal drug submissions, provide training and development for program staff and develop policies targeted at more efficient review. This proposal benefits from lessons learned through ADUFA and, with it, FDA will continue to maintain high standards of safety and effectiveness for animal drugs and provide sustained revenue for improved FDA review performance.

CONCLUSION

FDA's ADUFA and AGDUFA legislative proposals represent considerable input from and agreement of stakeholders, the public, and the Agency. They represent methods by which FDA will improve its pioneer animal drug user fee program and institute the first generic animal drug user fee program. FDA urges passage of these proposals, and we will work with Congress in any way we can to assist with that effort.

Thank you for the opportunity to present testimony before the Subcommittee. I would be happy to answer any questions.

Mr. PALLONE. Thank you, Doctor. We are going to have some questions now from members of the subcommittee.

You know there is great concern about antimicrobial resistance. While the overuse of antibiotics is certainly a factor, many researchers believe that the use of antibiotics in food animals also poses a great risk. In 2004, the GAO issued a report assessing Federal agencies' efforts to address the risk to humans from the use of antibiotics in animals and the GAO found that while FDA had begun conducting risk assessments, most of these assessments were for drugs other than those that were critically important for human health. Can you tell how much progress the FDA has made in conducting risk assessments on existing approvals that are critically important to human health versus risk assessments at the time of initial review? I am making that distinction between existing approvals and risk assessments at the time of initial review for the drug.

Dr. DUNHAM. The concerns for antimicrobial resistance have been and continue to be a top priority for the agency. Concerns arising from antimicrobials in animal feed was identified more than 30 years ago, and in regard to those responses, FDA has taken into account antimicrobial resistance as part of the animal drug review process, and we do look at all the data on the potential resistance to be selected to the animal and also to be transferred to bacteria that could contaminate food products.

Mr. PALLONE. But do you have any—can you make a distinction in terms of your progress on the existing approvals, you know, the currently approved drugs as opposed to those assessments that are done when you are initially reviewing the drug that haven't been approved yet?

Dr. DUNHAM. Assessment on drugs that have not been approved?

Mr. PALLONE. I think we are trying to make a distinction between those drugs that have been on the market and have been approved for some time as opposed to those that are going through the process now.

Dr. DUNHAM. I understand. We have a review process that is going right now to take a look at some classes of antimicrobials that have been approved for a very long time. Those are classes, not individual drugs, and we are going through and pulling and looking at each one of those. So there is a tremendous amount of work that is being done right now to take a look at those as well as the literature review available for all of those classes of antimicrobials that very, very early on were approved compared to—

Mr. PALLONE. Do you have—and you don't have to give it to me today, you can get back to me but—

Dr. DUNHAM. Oh, I would be happy to get back to you.

Mr. PALLONE. But is there a schedule for conducting these risk assessments for those drugs that have been approved for some time that you can get back to us, you know, more information about how you are going about that and how long it is going to take? I will say a schedule.

Dr. DUNHAM. All right. We would be happy to get that information.

Mr. PALLONE. OK. And my impression is, the FDA has not been able to conduct a lot of risk assessments on those currently approved drugs. I mean, would you want to comment on that? I mean, do you think there is enough? Do you think there should be more?

Dr. DUNHAM. At the moment we are currently going back, as you mentioned, and reviewing that, and we will be glad to give you a further update on that information.

Mr. PALLONE. In getting back to me, if you could indicate the average length of time to conduct a risk assessment on those products that are currently approved and whether you think that length of time is acceptable. I guess that is all I wanted. Just get back to us on that.

Let me get to a second set of questions here. Again, it goes back to antibiotics. We have heard from various stakeholders about FDA's authority to act when they think that the use of an antibiotic in a food-producing animal is harmful to human health. Take, for example, the case of Baytril, manufactured by Bayer. It is my understanding that FDA found that the use of the product in poultry posed a threat to human health and sought to withdraw its approval. After 5 years of appeals and administrative proceedings, the approval was finally withdrawn. So the question is, does the FDA have any concerns about the process which you have to undergo to withdraw a product's approval if you think it poses a threat? Do you think that 5 years that I mentioned in the case of Baytril is an excessive amount before the approval can be withdrawn? Do you think this process deters the agency from conducting risk assessments on products with existing approvals? So essentially this would be the opportunity to change that process and to change the law if you thought that we should, so I just wanted you to comment on it.

Dr. DUNHAM. Thank you very much. As you know right now, our authority does allow us to go through that review process to determine if there is a serious health threat and, if so, we would be addressing that, and as you mentioned with the Baytril procedure, we have to make sure there is reasonable certainty of no harm, and if so, we do investigate and an opportunity to have a notice of hearing at which time we take a look at the information that is there and the safety of that drug, and during that procedure, if we have decided that, then the sponsor has the burden to come back and show us information. In the case of Baytril, as you pointed out, this was withdrawn.

Mr. PALLONE. But it took 5 years. So my question is, do you think that we should do—well, first, do you think that is excessive? And obviously if you think it is a problem, what would you want us to do in reauthorizing the law to correct it?

Dr. DUNHAM. Well, at the moment, that authorization has been working but we would be very happy to work with you if you have anything alternative that we would like to consider. At the moment we follow that procedure and, as you well know, the product would remain on the market during the time that we go—

Mr. PALLONE. So you do feel it is too long and that we should try to address it? I am not trying to catch you in being evil or anything. I am just trying to find honestly if you think that that is

something we should try to correct because you think it is too long a process.

Dr. DUNHAM. Well, as I said, at the moment right now, with our process and what we have a chance to do and how we do it, it has been working and that is the caveat that we undergo the approval process and then the withdrawal process.

Mr. PALLONE. So you are open to a change. OK.

Mr. Deal.

Mr. DEAL. Thank you, Mr. Chairman.

I suppose we ought to ask, in light of the reauthorization issue before us, what would happen if Congress fails to enact the ADUFA reauthorization by September 30, and would there be layoff notices sent to employees, and how many employees would be affected and when would these notices have to go out?

Dr. DUNHAM. Yes, sir. This would be critical if we do not get this reauthorization to the program and all that we have accomplished. We do have to apply notice 60 days in advance of the reenactment time to our employees and we would possibly be impacting 58 employees that we currently have under the ADUFA procedure. So we would lose the talent that we have right now and the impact would really step us back with the whole program that has been incredibly well performing. It has been a successful program and we really would be hurt if we couldn't get this reinstituted.

Mr. DEAL. So time is of the essence, in other words?

Dr. DUNHAM. Yes, sir, it is. Thank you.

Mr. DEAL. Let me ask this question. Does the CVM believe it has enough authority to protect the effectiveness of antibiotics used to treat human illness, especially those that are considered by FDA as critically important to human health, and if not, then what further authorities would you feel like you need from Congress?

Dr. DUNHAM. As you know, we do have the authorities to go through and review, because that is our goal, to approve safe and effective products, and we do look at public health, and if there were indications that any drug on the market was impacting human health, then we can conduct a thorough review and take action, as we mentioned a minute ago, on that.

Mr. DEAL. So you feel like you do have adequate authority in that regard?

Dr. DUNHAM. Yes, sir.

Mr. DEAL. This agreement calls for an end-review amendment of deficiencies in a sponsor's application, and also the creation of electronic submission too. How do you anticipate that these will affect approval times?

Dr. DUNHAM. Oh, it is going to be well welcomed. If we can move into the electronic age, for example, the ease with which the sponsors can provide us that and the ease with which our reviewers can access and modify as well as storage of all the data that comes from the electronic submission will be a great improvement as we move forward in the 21st century. So that would be great. Thank you.

Mr. DEAL. I think that answers my questions. Thank you very much.

I yield back, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Deal.

The gentlewoman from Illinois, Ms. Schakowsky.

Ms. SCHAKOWSKY. Thank you, Mr. Chairman. I wanted to get back to that issue that you had raised, Mr. Chairman, about the potential overuse of antibiotics and the effect that it can have on humans, and maybe you answered this question but I am wondering if you could explain the 2003 FDA guidance for industry that laid out the agency's requirements for evaluating antimicrobial drugs that may pose a risk to public health. Is that what you were referring to in the answer to the chairman's question?

Dr. DUNHAM. Yes, it was part of our procedure. Whenever we do a review, if there was a concern to public health of a specific product, then we can take a very detailed approach and look through that, take a look at the science, and if there is indication of harm, then we will follow through and take that information, review it, and if we have determined that is the case, as was the example with Baytril, then we can put out a notice of opportunity for hearing at which time then the sponsor would have an opportunity to push back and give us information to say whether or not that project is safe or not. The review goes through and a decision would be made at the end of that notice of opportunity for hearing.

Ms. SCHAKOWSKY. And what was the conclusion of that investigation?

Dr. DUNHAM. In the case of Baytril, it was removed and we no longer use that for treatment in poultry.

Ms. SCHAKOWSKY. Is it a matter of a particular drug or is a matter of the quantity of antibiotic present in the animal products that we eat?

Dr. DUNHAM. In the case of the drug, you are looking at the drug itself, and when you take a look at, for example, a residue, as we would follow through in an animal of that drug product, there are limits that we establish courtesy of the review process. In the case of the drug, if, as you mentioned a minute ago, there was an impact to public health, then we take a look at that drug and its impact specifically and how it is being used.

Ms. SCHAKOWSKY. And do we have good scientific data on just what the impact is, the cumulative effect of eating animal products that are treated with antibiotics? Is this an area where we are still doing research and studying this?

Dr. DUNHAM. This area is in fact very complicated. It is not black and white. There are so many venues that impact this and we, yes, are along with many other scientists heavily involved with current studies and review to assess all of this and understand this very complicated procedure.

Ms. SCHAKOWSKY. Because it is very threatening, the fact that we have all these drug-resistant incidents where this could be a major threat to public health over time, and we want to be sure that the FDA is looking ahead.

Dr. DUNHAM. Yes we are, and I think again, with the talent that we have, cutting-edge science to know what is happening, the traceability, surveillance programs, information internationally as well as domestically comes into play. Environmental issues, medicine in general, everything is very much in tune to understand all of this, and I think it is a very exciting area that we have for our scientists to be involved.

Ms. SCHAKOWSKY. And does the FDA have all the authority it needs to enforce its guidance and perhaps enforce new standards that could be set up?

Dr. DUNHAM. Yes, we do.

Ms. SCHAKOWSKY. Do you think there is enough evidence at this point to at least consider phasing out the use of antimicrobials for non-therapeutic use in food animals?

Dr. DUNHAM. That is another area that we are looking at the information right now. It is under review.

Ms. SCHAKOWSKY. And what is the timeline for that?

Dr. DUNHAM. I am going to respond back to Mr. Pallone and you with the information that we will return to you in written documentation.

Ms. SCHAKOWSKY. Yes, but you do have a protocol and a timeline and all that for completing this review or this study?

Dr. DUNHAM. We have information that I will be able to provide to you that will give you an outline of everything we have, yes.

Ms. SCHAKOWSKY. The Union of Concerned Scientists estimates that 70 percent of all antibiotics in the United States are used in healthy pigs, poultry, beef, and cattle. Is that the case?

Dr. DUNHAM. I would have to get back to you to confirm any documentation of that number.

Ms. SCHAKOWSKY. The doubling of the user fee that is being proposed, and so this will mainly be used to shorten the review period? I know you went over it in your testimony, but if you could just summarize, though, how that money would be used?

Dr. DUNHAM. Right now for ADUFA, we will continue with our review times that we have now reached at the end of ADUFA I.

Ms. SCHAKOWSKY. Which is how many days?

Dr. DUNHAM. One-hundred and eighty days without statutory time, which now under ADUFA II will allow us to further enhance working through communication with our sponsors. We will have 10 public workshops over the 5-year period. We will be able to work with our sponsors now to have an understanding of any of the preapproval potentially foreign facility inspections, to work with them in advance to again keep the times down and to complete that information that is collected. We hope very much to move forward into the 21st century with electronic submissions and reviews which will help not only storage but access and free moving of the information that we receive for our reviewers, and we will have an opportunity to further enhance overall communication with sponsors. For example, sometimes they come in at the very, very end and there may be non-substantial information but something that needs to still be reviewed, and we can add that on with very little additional time instead of going back, as we used to under ADUFA I, and have to do another notice of a letter to come back and go through another review cycle. Keeping it down to one review cycle time is very, very critical. This will help get that product that is going through approval on the market without having further delay.

Mr. PALLONE. The gentlewoman is a minute over.

Ms. SCHAKOWSKY. Oh, I am sorry. If I could just ask one more thing about the pet food that we get? Can we be sure that it is safe now?

Dr. DUNHAM. We have our food protection plan and I think we have come a long way since the melamine incident, which has really been fantastic to open up the awareness to people not only for pet food but human food and feed in general. So yes, we have come a long way.

Ms. SCHAKOWSKY. Thank you.

Mr. PALLONE. The gentleman from Indiana, Mr. Buyer.

Mr. BUYER. Thank you, Mr. Chairman.

The FDA had given previous testimony and the Commissioner has also supported for us to give authority to the FDA to destroy counterfeit, adulterated, or misbranded drugs that may be found in any of our ports of entry, and that is with regard to human consumption. Do you not believe that it would make sense that we also extend that authority, that if you find a misbranded, adulterated or counterfeit drug that would be used for animals that you also be given the authority to destroy?

Dr. DUNHAM. I don't believe I have had an opportunity to really address this within our group for CVM. I know it is happening on the human side. We haven't seen as much counterfeit opportunities for animal drugs the way I know you do see it on the human side, but we definitely would appreciate any opportunity to keep only our approved products on the market and be able to intervene whenever we do see adulterated products coming across.

Mr. BUYER. So therefore, following the syllogism of logic, would it not make sense that FDA be given the authority to destroy if in fact you found a misbranded, adulterated, or counterfeit animal drug? If you want to do it for humans, you would think you would want to do it for an animal drug too, would you not?

Dr. DUNHAM. And I would just need to confirm that we have gone through with our counsel on that to let you know that we have had a green light to look at animal drugs as well.

Mr. BUYER. Let me ask about your personal opinion. Do you not in your personal opinion think that it is common sense, if we are going to protect humans, we ought to protect animals equally?

Dr. DUNHAM. We do with our drugs to make sure they are safe and effective and approved. I do agree, yes.

Mr. BUYER. All right. I don't want to do the dance with you, OK? It is easy for me to pick up the phone and ask the Commissioner because the Commissioner is going to say absolutely.

Dr. DUNHAM. Yes, we do. I do.

Mr. BUYER. All right. Now let me ask you in your professional opinion, since we also know, now, would FDA support—if we were to put in language giving you the authority to destroy a counterfeit, adulterated, or misbranded drug, would you not welcome that authority?

Dr. DUNHAM. Yes, I would.

Mr. BUYER. All right. Thank you.

Mr. Chairman, here is my question to you. I think we have an opportunity here. As Mr. Matheson and I are working with you and Chairman Dingell on the food and drug safety side of the bill, not only creating electronic pedigree, but one of the provisions for which you have also agreed is about giving the authority to FDA to destroy these misbranded, adulterated, or counterfeit drugs. It is easier for us to put that provision in this bill with regard to ani-

mals rather than in the other drug and safety bill expanding that and say well, we want to include animals. See what I am saying? We have two different provisions, one dealing with human consumption on food and human use on drugs. Let us leave those provisions to apply to humans. This is our opportunity to take that provision and leave it in the animal bill.

Mr. PALLONE. I think I followed you, and I think we will look into it. I don't want to prejudge it in any way but we will certainly look into it.

Mr. BUYER. I just think we have an opportunity. We have got something that is moving. Earlier when I had proposed this when we were doing the reauthorization of PDUFA, Chairman Dingell said whoa, Steve, hold off, we are going to do a food and drug safety bill, and that is when Mr. Matheson and I began to work together on building an electronic pedigree bill that incorporates what the Commissioner was asking for, and so as we are working cooperatively on that side of the bill to deal with human consumption and medications, I just once again think it makes a lot of sense that we work with you and I will work with Mr. Matheson, that this could be included perhaps in your own manager's amendment that we take care of this issue.

Now, as the lady from the FDA just testified, well, we are not seeing that as much, my sensing would be that if people are beginning to drive toward generics because of costs, it is only a matter of time before the criminal syndicates then move into this economic space because it is highly lucrative, and that is where they are moving. So let us give them the tools to be able to combat this before the syndicates can move into the space would be my argument, and I would like to work with the ranking member and the chairman to do just that. And Mr. Matheson, you and I have not had an opportunity to discuss this. This just came up, but I think this is one that only makes sense. Building a consensus on how to dance. I yield back.

Mr. PALLONE. Let me just explain to you. I think you all understand what we have before us are two drafts based on what the Administration and the industry agreed to. Obviously the purpose of the hearing today is to entertain any other ideas either for or against that, so this is certainly something that we will look into without prejudging whether we would definitely do it. But the whole idea of today's hearing is to get these kinds of ideas. So thank you.

The gentleman from Utah.

Mr. MATHESON. Thank you, Mr. Chairman, and thank you, Mr. Buyer, for raising that issue, by the way.

Dr. Dunham, I wanted to ask you a couple of questions about antibiotics, if I could. The World Health Organization has established a measurement for antibiotic usage data collection called Defined Daily Doses, and Europe has mandatory reporting of the consumption data collection using this measure and it is my understanding that it has enabled comparisons that we are unable to perform right now in the United States. Does the FDA require manufacturers to submit data in this format or some other comparable format using a uniform measurement?

Dr. DUNHAM. At the moment, we do receive the quantity that they produce on anniversary of the approval. We receive that information from them.

Mr. MATHESON. Does the information you receive help you in terms of having a way to better understand patient safety, in this case, animal safety? I mean, is the data you are getting comparable to what the Europeans ask for as mandatory reporting data? I didn't think it was. That is why I am asking.

Dr. DUNHAM. Well, we have adverse drug reporting that we will look at on any individual drug that has been approved. We have that system that is all part of our Federal Food, Drug, and Cosmetic Act.

Mr. MATHESON. Can you tell me the percentage of antibiotic drugs sales that are for humans versus animals?

Dr. DUNHAM. I cannot but I could certainly look into that and get you some information, sir.

Mr. MATHESON. Do you know whether the antibiotics that are used to treat sick animals or animals exposed to disease or—let me rephrase this. Are antibiotics used to treat sick animals or animals exposed to disease or for other purposes such as growth promotion and/or disease prevention?

Dr. DUNHAM. There are products on the market that are approved for growth promotion and feed efficiency and then they are also there to treat disease.

Mr. MATHESON. Does FDA maintain a database of animal antibiotic use data?

Dr. DUNHAM. We again would receive the information as far as quantities and any adverse reaction to those drugs.

Mr. MATHESON. OK. Mr. Chairman, that is all I have to ask. I will yield back.

Mr. PALLONE. The gentleman from Pennsylvania, Mr. Murphy.

Mr. MURPHY. Thank you, Mr. Chairman.

Just a couple quick questions on some issues. I am concerned about the timing of this bill. Before, you were asked about some impacts it would have in terms of layoff notices, you commented on that. I am concerned about the clinical impact of any delays here. Does current status of this or in any additions that would be coming up in this changed legislation impact you? So for example, would the delays hold up any ability to handle any improvements or modernizations in what you do now?

Dr. DUNHAM. Yes, it would, because of the advances we have been looking for, and a specific example would be if we wanted to move forward with the electronic era, it would be impacted by this as well. But more importantly, the biggest impact by far is going to be the lack of the scientific technical expertise and talent that we need to continue to do the reviews and that is going to stall and we are going to have a delay again on having the review to enable safe products to be approved and be used to help both protect companion animals and food animals.

Mr. MURPHY. Would it then negatively impact on your ability to enforce new regulations or, more specifically and more concerning, to respond to any emergencies?

Dr. DUNHAM. Overall, whenever we do receive anything like an emergency reaction, we would have the staff to respond to that.

The biggest impact is going to be again the review of any new products coming through that we would like very much to have come through for approval and be on the market. That would be delayed.

Mr. MURPHY. I see. And just another question I thought of while Mr. Buyer was raising his questions too. With regard to drugs that are used both for animals and for humans, so similar ones or identical ones, and what Mr. Buyer was raising about counterfeit or other drugs coming over on black markets, and it is an issue we have discussed a number of times in this committee, is there jurisdiction now if it is the same drug for both animals and human use that if it came through labeled as an animal drug but was identical to human, would you have the power at this point to take action that he is referring to?

Dr. DUNHAM. If we haven't gone through the approval process of that drug and it is coming from outside the United States, then it is not approved. It has to come through our review process. So many times you will have a drug approved in another country but you wouldn't be able to import it and use it if it hasn't gone through our review process.

Mr. MURPHY. What action would you take if you found it at a port?

Dr. DUNHAM. Then you would be able to prevent entry coming into the port.

Mr. MURPHY. If that drug was approved for human use but not animal drug, I mean, does it go—

Dr. DUNHAM. Well, once again, if it is not approved, the only way that you would be able to possibly have a veterinarian use that is if it is an approved drug through FDA. So a human approved drug through the FDA procedure, not outside of the United States, and only then would a veterinarian be able to use that. So even if it is approved in another country, a human drug, still coming over here it hasn't gone through our review process even on the human side.

Mr. MURPHY. I raise the issue because we hear some people trying to use animal drugs because they are less expensive than human drugs, but that is a discussion for another hearing another day. Thank you very much.

Thank you, Mr. Chairman.

Mr. PALLONE. Thank you, Mr. Murphy.

I am going to have a second round because I for one have some questions I wanted to ask Dr. Dunham, and this is an area that, as I said, we basically took the Administration's proposal so we do have some questions.

Another issue that has been brought to my attention regarding antimicrobial resistance is the lack of data that exists on how antibiotics are sold and used by ranchers, meat producers, farmers, et cetera. As I understand it, currently there are no data sources that FDA can draw upon that show the total quantity of antibiotics used in animals, the species they are used in, the purpose of the use, therapeutic versus prophylactic or growth promotion purposes, or the method used to deliver the antibiotic. Is that correct, in your opinion?

Dr. DUNHAM. We do not have the individual use. We have the drug and what it is approved for and only information on quantity

marketed at the end of the anniversary do we have information coming back unless there were some adverse events, and then we would have data from that.

Mr. PALLONE. OK. Do you think that it is important for FDA in its mission to have access to that additional data, and how would that data enable FDA to better track antimicrobial resistance or determine any threats to the public health?

Dr. DUNHAM. As I said, for that opportunity at the moment, what we have, it comes in strictly as quantity marketed, and we have been complying with that and using that information but we don't have access to anything further.

Mr. PALLONE. Well, do you think it would be burdensome to collect this additional data from manufacturers and those delivering the antibiotics, what I am suggesting?

Dr. DUNHAM. I probably would have to make some inquiries and get back to you.

Mr. PALLONE. You can get back to us. Sure. Get back to me in writing. I would be very happy with that.

Dr. DUNHAM. Thank you.

Mr. PALLONE. I understand that at some point, if Congress does not act to reauthorize ADUFA, you would have to issue the RIF notices. We dealt with this possibility before, when we were dealing with PDUFA and MDUFA. Can you tell me how many employees at FDA might be subject to those RIFs, and what is the agency's deadline for issuing those notices and whether you have any flexibility in determining when the notices will be sent out? Because when the agency was able to hold off sending out RIF notices when we dealt with PDUFA and MDUFA last year, I think what they did is, because they knew the Congress was moving to reauthorize in a timely fashion, they had the flexibility not to send out the notices. Is that true?

Dr. DUNHAM. I would need myself to personally confirm that. Otherwise I do know we are required 60 days before that date to let the employees know they could undergo a RIF, and that is why is so critical that we move this piece of legislation forward.

Mr. PALLONE. Do you know how many employees would be subject to those notices?

Dr. DUNHAM. Approximately 58.

Mr. PALLONE. Fifty-eight. All right. Well, again, get back to us on that issue of flexibility, because I know that there was some flexibility used with regard to PDUFA and MDUFA because they knew that we were moving, and I commit to you that obviously the reason we are having this hearing today is because we do want to move forward with passing a bill and getting it signed into law in a timely fashion.

And then lastly, in your testimony you note that FDA worked and negotiated with industry, both the Animal Health Institute and the Generic Animal Drug Alliance, in putting forward the ADUFA II and the AGDUFA proposals. Did you also meet with consumer groups and incorporate concerns raised by those groups? And if so, what changes did you make to incorporate consumer concerns?

Dr. DUNHAM. With the submitted comments to our documents, the majority of the views were supported of the ADUFA and

AGDUFA proposal, and there were a few that would like us to do a little more, like you mentioned, which is to look at aspects of do we do enough on antimicrobial resistance, and as we have explained to you today, our procedures of the review do incorporate looking at issues of antimicrobial resistance during the review process. So if anything, it would be a chance of where do we do more, and I think we have the capability of doing that and incorporating that into our review right now.

Mr. PALLONE. OK. Thank you.

Any other member want to ask additional questions? Mr. Deal.

Mr. DEAL. Thank you. Can you tell us what is the FDA approval process if we compare the approval process of antibiotics for animals versus the approval process of antibiotics for humans? Is it more or less stringent in the animal environment?

Dr. DUNHAM. If I may, I am going to have Dr. Vaughn go through that review process difference between human and animal.

Mr. DEAL. My understanding is that there may be a benefit analysis in one area versus benefit analysis in the other, but I will let you answer.

Dr. VAUGHN. Thank you, Mr. Deal. On the animal drug side, our evaluations are for primarily human food safety for the products that are derived from those animals and the potential transference of any adverse effects either through chemical residues or antimicrobial resistance or impact of the drugs on human gastrointestinal flora. And so to that end, we are looking strictly from a safety standpoint and it is not offset by the potential benefit that may be derived from that drug in animals.

Mr. DEAL. OK. A related question deals with the definition I guess of a term that we often hear used and that is the term 'therapeutic use' of a drug. Some of these areas I am going to list maybe seem simplistic to ask you the question, but do you feel that it is appropriate to use antibiotics in animals for the following purposes, first of all, disease treatment?

Dr. VAUGHN. For disease treatment, yes, sir.

Mr. DEAL. All right. What about for disease prevention?

Dr. VAUGHN. Disease prevention, if I can explain a little bit, the way we go about establishing indications on our labels for those products that do get approved, we do look at them as therapeutic and non-therapeutic, and for the non-therapeutic, we would include things for growth promotion, average daily gain, feed efficiency, those types of claims, and in those cases, for antimicrobials, we have not approved a single product for quite a few years. Those applications just are not coming to us. And on the therapeutic side, we consider claims such as prevention, control, and treatment, and as a veterinarian, I can tell you that it is important, depending on the disease process, to intervene at the appropriate time to have the best effect for that drug, and in some cases, if we wait until we actually have clinical signs of disease, that we will not be able to get the clinical effect that we need to be able to get from these therapeutic products.

Mr. DEAL. So treatment, prevention, and control would all be considered appropriate therapeutic usage for antibiotics in animals?

Dr. VAUGHN. Yes, sir.

Mr. DEAL. OK. I think that is all. Thank you very much.

Mr. PALLONE. Does any other—yes, Ms. Schakowsky.

Ms. SCHAKOWSKY. I just want to clarify something. You said that the FDA, that you have adequate authority to take action if you conclude there is a problem with antibiotic resistance, but yet in response to the chairman's questions about Baytril, you said that it took 5 years to remove that drug and that is just one drug. So to me, that doesn't seem—either it doesn't seem like adequate authority or that the process is awfully slow. So if the FDA knows that a drug is generating antibiotic resistance, don't you think 5 years is too long to deal with that and that the American people could be at risk for too long?

Dr. DUNHAM. As I mentioned, the procedure that we use in having to go through in this case the review and the court hearing, took that long, and we would be happy to work with you if you have any additional suggestions or ideas you would like to modify to that procedure that currently our jurisdiction allows us to go that way. We had that review, and you are right, it took 5 years before completion. During that entire time, the product would stay on the market. That is currently the system that we operate under. So we would be happy to work with you.

Ms. SCHAKOWSKY. Well, I would appreciate that because in your mind, isn't 5 years an awfully long time if this is something that should be off the market?

Dr. DUNHAM. And it takes a scientific review and the back-and-forth before a decision was made.

Ms. SCHAKOWSKY. But don't you think that is an awfully long time to—obviously the conclusion was that there is some kind of risk. Isn't 5 years too long? Don't we need to work on that, in your view, to figure out how to shorten the process?

Dr. DUNHAM. We would be very happy to work with you on anything that you have that you are willing to provide.

Ms. SCHAKOWSKY. Thank you.

Mr. PALLONE. Mr. Matheson, did you want to ask additional questions? OK.

Thank you, Dr. Dunham and the two that accompany you. I think this was very helpful. And as I said, we basically put these proposals together based on the Administration's agreement and we are just going to follow up after the hearing and try to see if we have any additions or suggestions to change it, but we do intend to move this in a timely fashion, I want to assure you.

Dr. DUNHAM. I appreciate that very much. Thank you for the opportunity.

Mr. PALLONE. And I will ask the second panel to come forward now. Welcome. Let me introduce our second panel. To my left is Dr. Richard Carnevale—I don't know if I am pronouncing that correctly—who is Vice President of Regulatory, Scientific, and International affairs for the Animal Health Institute, and next is Ms. Stephanie Batliner, who is Chairperson of the Generic Animal Drug Alliance and also Director of Pre-market Regulatory Affairs for IVX Animal Health Inc. from St. Joseph, Missouri, and then is Robert Martin, who is Executive Director of the Pew Commission on Industrial Farm Animal Production. We have 5-minute opening statements become part of the record, and the Committee may sub-

mit additional questions in writing for you to answer very quickly after the hearing. And so we will start with Dr. Carnevale.

STATEMENT OF RICHARD CARNEVALE, V.M.D., VICE PRESIDENT OF REGULATORY, SCIENTIFIC AND INTERNATIONAL AFFAIRS, ANIMAL HEALTH INSTITUTE

Dr. CARNEVALE. Good morning, Mr. Chairman and members of the subcommittee. Thank you very much for holding this hearing on this important piece of legislation and for the opportunity to speak to you today about the benefits to human and animal health from FDA-approved animal medicines.

I am Dr. Richard Carnevale. I am a veterinarian and a vice president with the Animal Health Institute, a trade association in Washington that represents companies that make medicines for animals. Our companies share a common mission: we contribute to public health by protecting animal health. As companion animals have become a more important part of our everyday lives, they have moved from the backyard into our living rooms and bedrooms, increasing their importance to humans and requiring attention to their health needs. As medical breakthroughs from human medicine are adapted to animal medicine, our pets are living longer and healthier lives.

Animal health products also give veterinarians and livestock and poultry producers the necessary tools to protect the health and well-being of food-producing animals. A vital first step in producing safe meat, milk, and eggs is keeping animals healthy. Veterinarians work hard to prevent disease in animals. However, it is important for them to have medicines available when they are needed to treat a disease they cannot prevent.

The statutory standard for FDA approval of animal drugs under the Federal Food, Drug, and Cosmetic Act is the same as that for human drugs: they must be proven safe and effective. As a result, the animal drug review process looks much like the human drug review process. Animal drug companies submit data from scientific studies to demonstrate safety, efficacy, and the ability to meet the same stringent manufacturing standards. It is a costly process, requiring as much as $100 million and 7 to 10 years to bring an animal drug to market. In the case of food animals, the standard to ensure that meat, milk, and eggs are safe for human consumption adds an additional set of requirements that increases the costs and time to market.

Animal health companies rely on a rigorous, efficient, predictable, and science-based review process at the Food and Drug Administration's Center for Veterinary Medicine to provide these products to society. That is why our companies supported the first authorization of the Animal Drug User Fee Act more than 5 years ago. ADUFA I made it possible for our companies to bolster funding at CVM so that they could meet performance standards to improve the efficiency and predictability of the animal drug review process.

We believe ADUFA I has been successful. The backlog of overdue pioneer animal drug submissions that existed at the beginning of the program is gone. FDA CVM has successfully met the performance timelines established by the legislation. As a testament to this

progress, 2007 was a banner year for approval of new and innovative products with CVM approving nine new chemical entities, giving veterinarians new medicines to fight diseases and other conditions in animals.

The legislation before you to reauthorize this successful program builds upon this record of achievement. Whereas the total cost of ADUFA I came to around $43 million over 5 years, sponsors will contribute $98 million to this process over the life of the next legislation.

Many will benefit should Congress approve this bill. FDA CVM of course benefits by having additional resources to meet its mission of protecting public health. Animal health company sponsors benefit from a stable and predictable review process, allowing them to make informed decisions about the investment risks of research and development dollars. Veterinarians and animal owners benefit from having new and innovative medical advances to treat, control, and prevent diseases in their patients. And finally, consumers benefit from a safer food supply as a result of the availability of additional tools to keep food animals healthy because healthy animals means healthful and safe food. These widespread benefits are why a broad coalition of companion animal interests and animal agriculture interests support this legislation. Attached to my testimony, Mr. Chairman, is a copy of the coalition letter sent to you earlier this year from a broad mix of groups asking for congressional action on this bill.

The regulatory process this bill will support is one of the most protective of human health in the world. The bill does not in any way alter or change the rigorous pre- and post-approval animal safety and food safety standards. FDA CVM has a rigorous and robust process that takes into account animal and human safety throughout the life cycle of the product. We strongly believe this bill intensifies CVM's public health focus by increasing the resources used to meet that mission. The timely availability of animal medicines approved by FDA protects public health. A process that is cumbersome and inefficient delays those products that are safe and effective and encourages the use of untested and illegally compounded products in an attempt to address unmet animal health needs. The rigorous review process and monitoring systems in place are at the heart of a broad system of protections that ensure that all medicines including antibiotics are safe for animals and humans.

Mr. Chairman, I have attached more information in my written statement on the review process related to antimicrobials.

In summary, Mr. Chairman, CVM has a rigorous science-based review process that provides to society the products necessary to protect public health by protecting animal health. The reauthorization of ADUFA will continue to provide the Agency the resources necessary to maintain and improve this process, provide new and innovative products to allow our pets to live longer and healthier lives, and contribute to food safety and food security by keeping food animals healthy. I urge you to move a clean ADUFA II bill in a timely manner so this program can continue without interruption. Thank you.

[The prepared statement of Dr. Carnevale follows:]

STATEMENT OF RICHARD CARNEVALE

Mr. Chairman and members of the Subcommittee:

Thank you for holding this hearing on this important piece of legislation, and for the opportunity to speak to you today about the important human and animal health benefits that result from using medicines to keep animals healthy.

I am Dr. Richard Carnevale. I am a veterinarian by training with a degree from the University of Pennsylvania and I am here today on behalf of the Animal Health Institute, a trade association that represents companies that make medicines for animals. Our companies share a common mission: we contribute to public health by protecting animal health. With food animals in more demand from our growing global population, the importance of the nexus between animal health and human health has never been greater, and is one of the driving forces behind the Center for Disease Control's "One Health" initiative. Recent highly-publicized threats like avian influenza highlight this nexus. As companion animals have become a more important part of our everyday lives they have moved from the backyard into our living rooms and bedrooms, increasing their importance to humans and requiring greater attention to their health needs. As medical breakthroughs from human medicine are adapted to animal medicine, our pets are living longer and healthier lives.

Animal health products also give veterinarians, and livestock and poultry producers, the necessary tools to protect the health and well-being of food producing animals. More and more evidence demonstrates that a vital first step in producing safe meat, milk, and eggs is keeping animals healthy. Veterinarians work hard to prevent disease in animals, but it is important for them to have medicines available when needed to treat a disease.

The statutory standard for FDA approval of animal drugs under the Federal Food, Drug, and Cosmetic Act is the same as that for human drugs: they must be proven to be safe and effective. As a result, the animal drug approval process looks much like the human drug approval process: animal drug companies submit data packages to demonstrate safety, efficacy, and the ability to meet the same stringent FDA manufacturing standards. It is a costly process, requiring as much as $100 million and 7–10 years to bring an animal drug to market. In the case of food animals, the standard to ensure that meat, milk, and eggs are safe for human consumption adds an additional set of requirements that increases the cost and time to market.

The market for animal drugs, however, is nothing like the market for human drugs. Our products are used to treat seven different major species of animals and many more minor species. A blockbuster animal drug will have sales of $100 million, and the vast majority of animal health products have a market size of around $1 million. There is no Medicare or Medicaid and, except in rare cases, no employer supported health insurance—the cost of animal drugs is borne in full by the animal owner.

Animal health companies rely on a rigorous, efficient, predictable, and science-based review process at the Food and Drug Administration's Center for Veterinary Medicine (CVM) to provide these products. That's why our companies supported the first authorization of the Animal Drug User Fee Act more than 5 years ago. The Animal Drug User Fee Act of 2003 (ADUFA I) made it possible for our companies to bolster funding at CVM so that they could meet performance standards to improve the efficiency and predictability of the animal drug approval process.

As a result of an efficient and predictable regulatory process, animal health companies can be more confident investing research dollars in the United States. According to data AHI collects, in 2006 pioneer animal health companies invested $663 million in research and development of new and innovative products, a seven percent (7%) increase over the preceding year.

We believe ADUFA I has been successful. The backlog of overdue pioneer animal drug submissions that existed at the beginning of the program is gone. FDA/CVM has successfully met the performance goals established by the legislation. Timeframes have been uniformly met, restoring predictability to the review process. As a testament to this progress, 2007 was a banner year for approval of new and innovative products with CVM approving nine new chemical entities, giving veterinarians new medicines to fight diseases and other conditions in animals. Examples include medicine to treat heart failure in dogs, control pain and inflammation from osteoarthritis, and to treat and prevent motion sickness.

The legislation before you to reauthorize this successful program builds upon this record of achievement. Animal health companies approached ADUFA II with the goal of reducing overall review times. CVM came to the table with a need for additional resources to compensate for the gap between the increased employee cost and Congressional appropriations. The end-review amendment process established in this agreement will help reduce the overall review time by reducing the number of

submission cycles. The ten agreed upon workshops will help CVM and sponsors deal with the complex scientific questions that often surround the review of these products.

Whereas the total cost of ADUFA I came to around $43 million over 5 years, sponsors will contribute $98 million to this process over the life of this legislation. The only change in the financial structure is the inflation factor calculated annually during the life of ADUFA I has been agreed to and built into the annual costs of ADUFA II, giving both sponsors and CVM more predictability regarding the program's revenue. Many will benefit should Congress approve this legislation:

1. FDA/CVM benefits by having additional resources to meet its mission of protecting public health.
2. Animal health sponsors benefit from a stable and predictable review process, allowing them to make informed decisions about the investment risks of research and development dollars.
3. Veterinarians benefit from having new and innovative medical advances available to treat, control, and prevent diseases in their patients.
4. Livestock and poultry producers, and the veterinarians on whose advice they rely, also have the tools needed to keep food animals healthy.
5. Pet owners benefit by having their animals live longer and healthier lives, increasing their enjoyment of these companions.
6. Consumers reap the food safety benefits that come as a result of the availability of additional tools to keep food animals healthy.These widespread benefits are why a broad coalition of companion animal interests and animal agriculture interests support this legislation. Attached to my testimony is a copy of a coalition letter sent to you earlier this year from this broad mix of groups asking for congressional action on this bill.

PROTECTIONS IN PLACE TO PROTECT PUBLIC HEALTH

We would like to emphasize that the regulatory process this bill will support is one of the most protective of human health in the world. This bill does not in any way alter or change the rigorous pre- and post-approval animal safety and food safety standards. FDA/CVM's has a rigorous and robust approval process that takes into account safety throughout the lifecycle of the product, including safety to the animal, safety to humans, a thorough process for measuring the potential transfer of antimicrobial resistant bacteria between animals and humans, environmental safety, animal handler safety and drug experience reporting and adverse reaction evaluation to assess post-market safety.

We strongly believe this bill intensifies CVM's public health focus by increasing the resources used to meet that mission. The timely availability of animal medicines approved by FDA protects public health. A process that is cumbersome and inefficient delays those products that are safe and effective and encourages the use of untested and illegally compounded products in an attempt to address unmet animal health needs. These types of treatments can create a health hazard for the animals and jeopardize food safety. Increasing agency resources and setting achievable timeframes will only help improve the agency's ability to meet its high safety standards.

The rigorous review process and monitoring systems in place are at the heart of a broad system of protections that ensure that all medicines, including antibiotics, are safe for animals and humans. Antibiotics for use in animals must meet all the same requirements as antibiotics used in humans, with two additional requirements: first, sponsors must show the meat from animals in which the product is used is safe for human consumption. Second, beginning in 2003, CVM instituted Guidance for Industry (GFI) # 152, which outlines a qualitative risk assessment process that is applied to all antibiotics approved for use in animals. This guidance process is designed to measure the risk of antibiotic resistant bacteria being transferred from animals to humans if the product is approved. Based on this risk, FDA makes decisions to either deny or approve the produce with certain restrictions to significantly reduce risk. Restrictions can include requiring a veterinary prescription, prohibiting extra-label use and prohibiting use in certain species. The methodology is very conservative—meaning it is very difficult to get an antibiotic approved. Further, the guidance is sufficiently broad so that if new, previously unidentified or undescribed, resistant organisms or genes were to become of concern, the Agency can act swiftly to take this information into account. The existing guidance allows the Agency sufficient flexibility to allocate resources appropriately to changing issues of safety related to resistance emergence.

The GFI # 152 process applies not only to new submissions, but to all existing products as well. FDA has established a priority list for the re-evaluation of all antibiotics currently approved and marketed. Most of the drugs on the list are anti-

biotics administered in animal feed for the prevention and control of animal diseases or to increased the weight gains and improve feed efficiency. The re-review under Guidance 152 was stimulated by new funding that FDA received and continues to receive via annual appropriated money specifically earmarked for these reviews. Bear in mind, though, the evaluation of these products did not begin with Guidance 152. In response to concerns raised some 30 years ago, the Bureau of Veterinary Medicine in FDA, in the 1970s, required sponsors of these products to conduct tests to determine the potential for resistance to be selected in the animals and to be transferred to bacteria that could cause human disease. While the standards and science may have changed over the years, the safety of these products has been an ongoing exercise at FDA. Moreover, published quantitative risk assessments performed by both the agency and individual product sponsors have generally affirmed that the risks to human health from these antibiotics in animal feed under approved conditions of use are quite low.

We fully support efforts by the agency to continue to evaluate the safety of these products using all available scientific data under a sound risk assessment approach in order the determine the true risk to public health and guide appropriate risk management interventions to protect public health.

In addition to the rigorous review process and the additional public and private risk assessments that have been conducted, there are other post-approval layers of protection to ensure the safe use of antibiotics.

MONITORING PROGRAMS

USDA's Food Safety and Inspection Service monitor meat samples for the presence of antibiotic residues as a check on the observance of the withdrawal times set by FDA. It is very uncommon for FSIS to find a violative residue, an indication that products are being used according to label directions.

The National Antimicrobial Resistance Monitoring System (NARMS) is a multi-agency program coordinated by FDA to monitor the possible emergence of antibiotic resistant bacteria and allow for implementation of management and control measures if needed. The three agencies involved are:

- The USDA Agricultural Research Service (ARS), which collects samples from slaughter and processing facilities to monitor for antibiotic resistance trends in farm animals;
- The FDA, which monitors for resistant bacteria in retail meats;
- The Centers for Disease Control and Prevention (CDC), which collects isolates, or samples, from public health laboratories to monitor for the emergence of antibiotic resistant food-borne pathogens in humans.

To date, the program has produced 7 years of data representing over 50,000 animals and 11,000 human Salmonella isolates. Most bacterial species isolated from humans and tested for resistance against drug classes potentially related to animal usage have shown stable or declining resistance patterns. Most of the multiple-drug resistance types, such as Salmonella typhimurium DT104 show stable or declining prevalence in both food animals and humans since 1996, according to an expert report issued in 2006 by the Institute of Food Technologists entitled "Antimicrobial Resistance: Implications for the Food System."

JUDICIOUS USE PRINCIPLES

Responsible, or judicious, use programs that are specific to different livestock species give veterinarians and producers specific guidelines to help them safely and properly use of antibiotics in their health management systems. Generally, these guidelines have been prepared collaboratively by FDA, CDC, and veterinary groups.

There remains a great deal of confusion about how antibiotics are used in animal agriculture. CVM approves these products for four specific purposes:

1. Disease treatment
2. Disease prevention
3. Disease control
4. Growth promotion, as measured by the amount of feed needed to produce a pound of animal weight or increased rate of weight gain.

Many assume in-feed uses equate to growth promotion, but this confuses the use with the route of administration. In fact, any of the four uses can be administered via feed, as that is the only practical way to administer medication to large flocks or herds. In most cases, a veterinarian is involved in this process, recommending feed that is specifically formulated for the health management system used for the flock or herd.

Perhaps the most discussed, and most misunderstood use, is the growth promotion use. The Animal Health Institute collects annual data from its members on

the amount of antibiotics sold for use in animals. As part of that survey, we ask members to estimate the amount sold that is used for growth promotion. In 2006, that amount was 4.6 percent of the total. Each year we publically release the results of this survey, and a copy of the 2006 results is attached to my testimony.

There is one other note about growth promotion: when the European Union phased out the use of antibiotics for growth promotion, according to data from the Danish government, animal death and disease rose, requiring a greater amount of antibiotics to be used to treat disease. Clearly, as has been discussed in many peer-reviewed articles, this use also had the effect of suppressing disease that did not necessarily produce symptoms.

Mr. Chairman, CVM has a rigorous, science-based approval process that provides to the American public the products necessary to protect public health by protecting animal health. Every year scientists uncover new diseases in animals, some of which potentially pose a threat to human health. As more animals are raised to feed the planet and as animals are reared closer to people, we will continue to need new medicines to protect animal and human health.

The reauthorization of ADUFA will continue to provide the agency the resources necessary to maintain and improve this approval process, provide new and innovative products to allow our pets to live longer and healthier lives and contribute to food safety by keeping food animals healthy. I urge you to move a clean ADUFA bill in a timely manner so this program can continue without interruption.

Mr. PALLONE. Thank you, Doctor.

Ms. Batliner.

STATEMENT OF STEPHANIE BATLINER, CHAIRPERSON, GENERIC ANIMAL DRUG ALLIANCE; DIRECTOR, PRE-MARKET REGULATORY AFFAIRS, IVX ANIMAL HEALTH, INC.

Ms. BATLINER. Good morning. I appreciate the opportunity to be here this morning. My name is Stephanie Batliner and I am here in my capacity as the chairperson of the Generic Animal Alliance. The Generic Animal Drug Alliance is an independent professional trade organization that represents the interests of sponsors, manufacturers and distributors of generic animal drugs before regulatory agencies and Congress.

FDA approved and regulated generic animal drugs are essential to both pet owners and food producers to reduce costs and increase accessibility to important pharmaceuticals. Through access to and affordability of therapeutic pharmaceuticals, the generic animal health industry aids in the protection of our Nation's food supply and the safety of our Nation's pet owners. It is critical to the success of the animal health generic drug industry to have a predictable and efficient CVM review process for the approval of abbreviated new animal drug applications, or ANADAs. The current review cycle time frames, as we have discussed earlier this morning, are an untenable situation both for industry and for CVM. The statutory review time frame for an ANADA is 180 days. Currently, review times for ANADAs are over 600 days and climbing, and this is far beyond anything that is reasonable and practical. It is important to point out that often an animal drug application will go through multiple cycles of review so right now it is pretty well accepted that it will take 4 or 5 years from first submission to time of approval for a generic animal drug.

Our support for a user fee program stems from our experience in witnessing the successes accomplished under ADUFA. The performance goals were consistently met by the Center for Veterinary Medicine resulting in shortened regulatory review cycle time frames. During our discussions with CVM on how to approach the

problem of generic review times, we were able to define boundaries necessitated by the economics of the generic animal drug industry and still arrive at an outcome that ensures a stable, reliable revenue source to support the review process at CVM in a manner not currently met by appropriated funds.

The legislative language and associated performance goals contained within the proposal for AGDUFA are very similar to that enacted with ADUFA 2003. There are, however, several important differences between the two programs. In AGDUFA, participants will not pay an establishment fee. The sponsor fee prescribed within AGDUFA is tiered to provide relief to sponsors who hold fewer ANADA approvals and the performance goals for AGDUFA do not return generic application review times to statutory requirements. Rather, 270 days is the highest level of performance that the generic animal drug industry could afford. While we are pleased with the overall content of the legislative proposal, additional funding requirements for CVM became apparent during our negotiations. The purpose of AGDUFA is to supplement the resources used specifically for review of applications and administration of the regulatory process, not to alter the existing stringent requirements for approval of a generic animal drug.

Generic Animal Drug Alliance believes that it is important also to express our support for the reauthorization of ADUFA. Many of our member companies do participate in user fee activities on the pioneer side and as such have been contributing user fees over this past 5 years of the first round of ADUFA.

In summary, GADA supports the legislation to authorize the Animal Generic Drug User Fee Act. The current review process is untenable for sponsors of legal, safe and effective products and is favorable to entities who would promote untested and illegally compounded products to fulfill unmet animal health needs. Access to generic animal drugs that have been approved and are regulated by CVM increases the public health through improved quality of life for companion animals and increased safety of the food supply. Thank you.

[The prepared statement of Ms. Batliner follows:]

GADA

GENERIC ANIMAL DRUG ALLIANCE

June 4, 2008

U.S. House of Representatives
Committee on Energy and Commerce
Subcommittee on Health

Dear Honorable Members:

The Generic Animal Drug Alliance (GADA) is providing testimony to the Subcommittee on Health of the Committee on Energy and Commerce in support of the Animal Generic Drug User Fee Act of 2008 (AGDUFA) and the Animal Drug User Fee Act Amendments of 2008 (ADUFA). The GADA is an independent professional trade organization that represents the interests of generic animal health companies before Federal regulatory agencies and Congress. We are the only trade organization that represents the interests of sponsors, manufacturers and distributors of generic drugs in the animal health industry. Our products and processes are regulated by the Food and Drug Administration, Center for Veterinary Medicine (FDA/CVM). We have been assured by FDA/CVM that our organization represents a solid majority of firms so engaged in generic animal drugs.

It is critical to the success of the animal health generic drug industry to have a predictable and efficient FDA/CVM review process for approval of abbreviated new animal drugs (ANADAs). As in the human generic market, generic animal drugs account for a high volume of units sold at dramatically lower prices than pioneer products. Generic animal drugs are essential to both pet owners and food producers to reduce costs and increase accessibility of therapeutic pharmaceuticals. Through access to and affordability of therapeutic pharmaceuticals, the generic animal health industry aids in the protection of our nation's food supply and the safety of pet owners. The current review process is an untenable situation both for the generic drug industry and FDA/CVM. The statutory timeframe for review of an ANADA is 180 days. The initial review cycles for ANADAs today are approaching 600 days – far beyond reasonable and practical review times, and more than one review cycle is now routinely required before an ANADA is approved. Therefore, from filing an ANADA to ultimate approval is now in the range of 4 to 5 years. For this reason, GADA believes the generic review process is at a critical juncture. Despite efforts on behalf of industry and FDA/CVM to resolve this issue without the implementation of a user fee act, the appropriations shortfall for dedicated generic application resources is currently insurmountable without funding from an additional source.

Our support for AGDUFA arises from our collective experience that ADUFA 2003 performance goals were consistently met by FDA/CVM, resulting in shortened regulatory review cycle timeframes. The FDA/CVM is the regulatory agency that oversees the pioneer and generic animal drug approval process. As should be expected by U.S. citizens, the approval of all animal drugs requires a thorough and rigorous, science-based process. A sponsor must demonstrate that their drug is safe and effective for the animal, the environment and for humans consuming the

food from treated animals and meets quality manufacturing standards and practices. Therefore, building from the success of ADUFA 2003, GADA and FDA/CVM entered into negotiations to establish a similar user fee program (AGDUFA) for ANADAs. The member companies of GADA worked with FDA/CVM to establish appropriate parameters for a user fee program that allows a more predictable and efficient review process. We were able to define the boundaries necessitated by the economics of the generic animal drug industry and still arrive at an outcome that ensures a stable, reliable revenue source to support the review process at FDA/CVM in a manner not currently met by appropriated funds. The shortened review cycles that will result from the agreed upon performance goals will provide predictability and practicality and encourage further investment in research and development for generic animal drugs.

The legislative language and associated performance goals contained within the proposal for AGDUFA are very similar to that enacted in ADUFA 2003. We were able to utilize the framework already in place within FDA/CVM for the administration of the user fee program and learn from previous experiences. There are, however, several important differences between AGDUFA and ADUFA 2003: 1) AGDUFA participants will not pay an establishment fee, 2) the sponsor fee prescribed within AGDUFA is tiered to provide relief to sponsors who hold fewer ANADA approvals, 3) the performance goals for AGDUFA do not return generic application review times to statutory requirements, (180 days), rather 270 days is the highest level of performance that the generic animal drug industry can afford. While we are pleased with the overall content of the legislative proposal, additional funding requirements for FDA/CVM became apparent during our negotiations.

The success of AGDUFA will help maintain a competitive and thriving generic animal drug industry. Ultimately, this will provide alternatives for the end-user that will help contain cost while maintaining safety of the U.S. food supply and pet owners. We would emphasize that AGDUFA does not reduce the robust requirements in place for approval of a generic animal drug. The purpose of AGDUFA is to supplement resources used specifically for review of applications and administration of the regulatory process - not to alter the existing stringent requirements for approval of a generic animal drug. All pre-approval animal safety, efficacy and human food safety requirements remain the same. In fact, we could argue that AGDUFA will allow for more comprehensive reviews of generic animal drug applications by providing the resources necessary for FDA/CVM to adequately staff the review teams and remain current on advances in science and technology. In addition, all post-approval requirements to account for safety throughout the lifecycle of the product remain the same. These post-approval requirements include drug experience reporting and adverse reaction evaluation.

In addition to AGDUFA, GADA supports the reauthorization of ADUFA. Many of the GADA member companies currently participate in the ADUFA 2003 user fee activities. It is estimated that our member companies paid approximately 10% of the total fees collected by FDA/CVM from ADUFA. Furthermore, GADA representatives attended the two ADUFA Public Meetings held in Rockville, MD on April 24, 2007 and March 11, 2008. GADA presented comments either at the public meeting or to the meeting docket in support of ADUFA.

We are aware that some controversy exists over the reauthorization of ADUFA, and possibly the enactment of AGDUFA. At both the 2007 and 2008 public meetings on ADUFA, a

representative of the Union of Concerned Scientists on behalf of the Keep Antibiotics Working Coalition (KAW) stated that they could not support the reauthorization of ADUFA because they believe the funding provided alters the priorities of the agency from public health to efficient approvals. Instead, KAW proposed that FDA/CVM direct resources to areas relative to antimicrobial resistance. On this issue, GADA supports the comments made to the March 11, 2008 public meeting docket by the Animal Health Institute (AHI), including their position and statements regarding antimicrobial resistance. In addition, we support the robust, science-based approval process implemented by FDA/CVM. We believe that the AGDUFA and ADUFA legislative proposals are unrelated to the issue of antimicrobial resistance. The proposed User Fees will supplement review resources – not alter the requirements necessary for approval of an animal drug or alter the post-approval surveillance requirements. Furthermore, the issue of antimicrobial resistance is outside the scope of the generic industry. The approval of a generic drug does not introduce a new drug entity to the animal population, nor does it result in increased utilization of an animal drug.

In conclusion, GADA supports the proposed legislation to authorize the Animal Generic Drug User Fee Act. We believe it is critical for the continued viability of the animal generic drug industry that the FDA/CVM review process becomes more efficient and predictable while continuing to meet the rigorous standards for drug approval. The current review process is untenable for sponsors of legal, safe and effective products and is favorable to the entities who would promote untested and illegally compounded products to fulfill unmet animal health needs.

Access to generic animal drugs that have been approved and are regulated by FDA/CVM improves the public health through improved quality of life for companion animals and increased safety of the food supply.

Sincerely,

The Generic Animal Drug Alliance

Generic Animal Drug Alliance Member Companies

AgriLabs, Ltd.
AmPharmCo., American Animal Health
Bimeda Animal Health, Inc.
First Priority, Inc.
Gaddy & Associates
IVX Animal Health, Inc.
Ivy Animal Health, Inc.
Lloyd, Inc.
Med-Pharmex, Inc.
Norbrook, Inc.
PRN Pharmacal/Trophy Animal Health
Putney, Inc.
Top Choice LLC

Mr. PALLONE. Thank you.
Mr. Martin.

STATEMENT OF ROBERT MARTIN, EXECUTIVE DIRECTOR, PEW COMMISSION ON INDUSTRIAL FARM ANIMAL PRODUCTION

Mr. MARTIN. Good morning, Mr. Chairman and members of the Healthcare Subcommittee. My name is Robert Martin and I am the executive director of the Pew Commission on Industrial Farm Animal Production and I very much appreciate the opportunity to appear here today at this important hearing.

The Pew Commission on Industrial Farm Animal Production is an independent commission funded by a grant from the Pew Charitable Trust to Johns Hopkins Bloomberg School of Public Health to investigate the problems associated with industrial farm animal production operations and to make consensus recommendations to solve them. Fifteen commissioners with diverse backgrounds began meeting in early 2006 to start their evidence-based review of the problems caused by industrial farm animal production.

Over the last 2 years the Commission conducted 11 meetings and received thousands of pages of material submitted by a wide range of stakeholders and interested parties. Two public hearings were held to hear concerns from the generic public with IFAP issues. Eight technical reports were commissioned from leading academics to provide information on the Commission's areas of interest, and the commissioners themselves brought expertise in animal agriculture, public health, animal health, medicine, ethics and rural sociology to our discussion. In addition, the Commission visited several IFAP production facilities. We visited broiler production, swine production, dairy production, egg production as well as a large cattle feedlot.

The Commission's findings make clear that the present system of producing food animals in the United States is not sustainable and presents an unacceptable level of risk to public health, damage to the environment as well as unnecessary harm to the animals we raise for food. In addition, the current system of industrial food animal production is detrimental to rural communities.

The Commission released its full report on April 29, 2008, that included 24 primary recommendations. The Commission was so concerned about the indiscriminate use of antibiotics in food animal production and the potential threat that causes to public health that five of those main recommendations deal with antibiotic use, and those five general recommendations are, number one, restrict the use of antimicrobials in food animal production to reduce the risk of antimicrobial resistance to medically important antibiotics; number two, clarify antimicrobial definitions to provide clear estimates of use and facilitate clear policies on antimicrobial use, improve monitoring and reporting of antimicrobial use in food animal production in order to accurately assess the quantity and methods of antimicrobial use in animal agriculture, improve monitoring and surveillance of antimicrobial resistance in the food supply, the environment, animal health and the human population in order to refine our knowledge of antimicrobial resistance and its impact on human health, and five, to increase veterinary oversight of all antimicrobial use in food animal production to prevent this overuse.

One of the things that I think shocked the Commission more than anything was when we started looking at these issues and in particular antimicrobial use that we couldn't get a definitive amount that is used in food animal production. The range is 30 percent on the low side to 70 percent on the high side but they were quite concerned that no entity is compiling the amount used and how it is used and the types used, and even at the low end, 30 percent, that is a significant amount of antibiotics being fed to animals indiscriminately and on the high end, it would be quite alarming. I think that they were also very concerned about the lack of post-market activities in food animal use and hence the development of several of our recommendations on monitoring and assessing the impact.

With that, again, thank you for the opportunity to appear and I will be happy to answer any questions.

[The prepared statement of Mr. Martin follows:]

PEW COMMISSION ON
INDUSTRIAL FARM
ANIMAL PRODUCTION

Statement by Robert P. Martin, Executive Director
Pew Commission on Industrial Farm Animal Production
June 5, 2008
Health Subcommittee of the House Energy and Commerce Committee

Good morning Mr. Chairman and members of the Health Subcommittee. My name is Robert P. Martin and I am the executive director of the Pew Commission on Industrial Farm Animal Production. I appreciate the opportunity to appear today.

The Pew Commission on Industrial Farm Animal Production (PCIFAP) is an independent commission funded by a grant from The Pew Charitable Trusts to the Johns Hopkins Bloomberg School of Public Health to investigate the problems associated with industrial farm animal production (IFAP) operations and to make recommendations to solve them. Fifteen Commissioners with diverse backgrounds began meeting in early 2006 to start their evidence-based review of the problems caused by IFAP.

Over the last two years, the Commission conducted 11 meetings and received thousands of pages of material submitted by a wide range of stakeholders and interested parties. Two public hearings were held to hear from the general public with an interest in IFAP issues. Eight technical reports were commissioned from leading academics to provide information in the Commission's areas of interest. The Commissioners themselves brought expertise in animal agriculture, public health, animal health, medicine, ethics, and rural sociology to the discussion.

In addition, the Commission visited broiler, hog, dairy, egg, and swine IFAP operations, as well as a large cattle feedlot.

The Commission's findings make clear that the present system of producing food animals in the United States is not sustainable and presents an unacceptable level of risk to public health, damage to the environment, as well as unnecessary harm to the animals we raise for food. In addition, the current system of industrial food animal production is detrimental to rural communities.

The Commission released its full report on April 29, 2008, that included 24 primary recommendations. The Commission was so concerned about the indiscriminate use of antibiotics in food animal production, and the potential threat to public health, that five of those recommendations deal with antibiotic use. Those recommendations follow.

Recommendation #1: **Restrict the use of antimicrobials in food animal production to reduce the risk of antimicrobial resistance to medically important antibiotics.**

a. Phase out and ban use of antimicrobials for non-therapeutic (i.e. growth promoting) use in food animals[1] (see PPCIFAP definition of "non-therapeutic").

b. Immediately ban any new approvals of antimicrobials for non-therapeutic uses in food animals[2] and retroactively investigate antimicrobials previously approved.

[1] The PCIFAP defines nontherapeutic as any use of antimicrobials in food animals in the absence of clinical disease or known (documented) disease exposure; i.e. any use of the drug as a food or water additive for **growth promotion**, feed efficiency, weight gain, disease prevention in the absence of documented exposure or any other "routine" use as non-therapeutic.

[2] The PCIFAP defines nontherapeutic as any use of antimicrobials in food animals in the absence of clinical disease or known (documented) disease exposure; i.e. any use of the drug as a food or water additive for **growth promotion**, feed efficiency, weight gain, disease prevention in the absence of documented exposure or any other "routine" use as non-therapeutic.

c. Strengthen recommendations in FDA Guidance #152 which requires the FDA determine that the drug is safe and effective for its intended use in the animal prior to approving an antimicrobial for a new animal drug application.

d. To facilitate reduction in IFAP use of antibiotics and educate producers on how to raise food animals without using nontherapeutic antibiotics, the USDA's extension service should be tasked to create and expand programs that teach producers the husbandry methods and best practices necessary to maintain the high level of efficiency and productivity they enjoy today.

Background

In 1986 Sweden banned the use of antibiotics in food animal production except for therapeutic purposes and Denmark followed suit in 1998. A WHO (2002) report on the ban in Denmark found that "the termination of antimicrobial growth promoters in Denmark has dramatically reduced the food animal reservoir of enterococci resistant to these growth promoters, and therefore reduced a reservoir of genetic determinants (resistance genes) that encode antimicrobial resistance to several clinically important antimicrobial agents in humans." The report also determined that the overall health of the animals (mainly swine) was not affected and the cost to producers was not significant. Effective January 1, 2006, the European Union also banned the use of growth-promoting antibiotics (Meatnews.com, 2005).

In 1998, the National Academy of Sciences (NAS) Institute of Medicine (IOM) noted that antibiotic-resistant bacteria increase U.S. health care costs by a minimum of $4 billion to $5 billion annually (IOM, 1998). A year later, the NAS estimated that eliminating the use of antimicrobials as feed additives would cost each American consumer less than $5 to $10 per year, significantly less than the additional health care costs attributable to antimicrobial resistance (NAS, 1999). In a 2007 analysis of the literature, another study found that a hospital

stay was $6,000 to $10,000 more expensive for a person infected with a resistant bacterium as opposed to an antibiotic-susceptible infection (Cosgrove *et al*, 2005). The American Medical Association, American Public Health Association, National Association of County and City Health Officials, and National Campaign for Sustainable Agriculture are among the more than 300 organizations representing health, consumer, agricultural, environmental, humane, and other interests supporting enactment of legislation to phase out nontherapeutic use in farm animals of medically important antibiotics and calling for an immediate ban on antibiotics vital to human health.

The Preservation of Antibiotics for Medical Treatment Act of 2007 (PAMTA) amends the Federal Food, Drug, and Cosmetic Act to withdraw approvals for feed-additive use of seven specific classes of antibiotics[3]—penicillins, tetracyclines, macrolides, lincosamides, streptogramins, aminoglycosides, and sulfonamides—each of which contains antibiotics also used in human medicine (2007a). The PAMTA provides for the automatic and immediate restriction of any other antibiotic used only in animals if the drug becomes important in human medicine, unless FDA determines that such use will not contribute to the development of resistance in microbes that have the potential to affect humans. FDA Guidance #152 defines an antibiotic as potentially important in human medicine if FDA issues an Investigational New Drug determination or receives a New Drug Application for the compound (2007a).

Most antibiotics currently used in animal production systems for nontherapeutic purposes were approved before the Food and Drug Administration (FDA) began giving in-depth consideration

[3] Fluoroquinolones are approved in animals only for therapeutic use (not for nontherapeutic use), and thus are not covered under PAMTA.

to resistance during the drug approval process. The FDA has not established a schedule for reviewing existing approvals, although Guidance #152 notes the importance of doing so. Specifically, Guidance #152 sets forth the responsibility of the FDA Center for Veterinary Medicine (CVM), which is charged with regulating antimicrobials approved for use in animals: "prior to approving an antimicrobial new animal drug application, FDA must determine that the drug is safe and effective for its intended use in the animal. The Agency must also determine that the antimicrobial new animal drug intended for use in food-producing animals is safe with regard to human health (FDA-CVM, 2003)." The Guidance also says that "the FDA believes that human exposure through the ingestion of antimicrobial-resistant bacteria from animal-derived foods represents the most significant pathway for human exposure to bacteria that have emerged or been selected as a consequence of antimicrobial drug use in animals." However, it goes on to warn that the "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, the guidance describes the Agency's current thinking on the topic and should be viewed only as guidance, unless specific regulatory or statutory requirements are cited. The use of the word 'should' in Agency guidance means that something is suggested or recommended, but not required" (FDA-CVM, 2003).

The Commission believes that the "recommendations" in Guidance #152 should be made legally enforceable and applied retroactively to previously approved antimicrobials. Additional funding for FDA is required to achieve this recommendation.

Recommendation #2. **Clarify antimicrobial definitions to provide clear estimates of use and facilitate clear policies on antimicrobial use.**

a. The Commission defines as *non-therapeutic*[4] any use of antimicrobials in food animals in the absence of microbial disease or known (documented) microbial disease exposure; thus, any use of the drug as an additive for growth promotion, feed efficiency, weight gain, routine disease prevention in the absence of documented exposure, or other routine purpose is considered non-therapeutic.[5]
b. The Commission defines as *therapeutic* the use of antimicrobials in food animals with diagnosed microbial disease.
c. The Commission defines as *prophylactic* the use of antimicrobials in healthy animals in advance of an expected exposure to an infectious agent or after such an exposure but before onset of laboratory-confirmed clinical disease as determined by a licensed professional.

Background

In 2000 the WHO, United National Food and Agriculture Organization (FAO), and World Organization for Animal Health (OIE, *Fr.* Office International des Épizooties) agreed on definitions of antimicrobial use in animal agriculture based on a consensus (WHO 2000). Government agencies in the United States, including the USDA and FDA, govern aspects of antimicrobial use in food animals but have varying definitions of such use. Consistent definitions should be adopted for the use of all U.S. oversight groups that estimate types of antimicrobial use and for the development of law and policy. Congress recently revived a bill to address the antimicrobial resistance problem: the Preservation of Antibiotics for Medical Treatment Act of 2007 (PAMTA) defines non-therapeutic use as "any use of the drug as a feed or water additive for an animal in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose (2007a)." If the

[4] For the Commission's recommendations, the members considered many definitions; a complete list of sources is in Appendix 1.

[5] This definition is adapted from PAMTA.

bill becomes law, this will be the legal definition of non-therapeutic use for all executive agencies and therefore legally enforceable.

Recommendation #3. **Improve monitoring and reporting of antimicrobial use in food animal production in order to accurately assess the quantity and methods of antimicrobial use in animal agriculture.**

a. Require pharmaceutical companies that sell antimicrobials for use in food animals to provide a calendar-year annual report of the quantity sold. Companies currently report antibiotic sales data on an annual basis from the date of the drug's approval, which makes data integration difficult. The FDA is responsible for oversight of the use of antimicrobials in food animals and needs consistent data on which to report use.
b. Require reporting of antimicrobial use in food animal production, including antimicrobials added to food and water, and incorporate the reported data in the USDA's National Animal Identification System (NAIS).[6] The FDA CVM regulates feed additives but does not have the budget or personnel to oversee their disposition after purchase. In addition, CVM and USDA are responsible for monitoring the use of prescribed antimicrobials in livestock production, but rely on producers and veterinarians to keep records of the antibiotics used and for what purpose.
c. Institute better integration, monitoring, and oversight by government agencies by developing a comprehensive plan to monitor antimicrobial use in food animals, as called for in a 1999 National Research Council (NRC) report (NAS, 1999). An integrated national database of antimicrobial resistance data and research would greatly improve the organization, amount, and types of data collected and would facilitate necessary policy changes by increasing data cohesion and accuracy. Further, priority should be given to linking data on both antimicrobial

[6] The USDA APHIS has begun implementing an animal tracking system, the National Animal Identification System (NAIS; http://animalid.aphis.usda.gov/nais/index.shtml). Announced in May 2005, the NAIS tracks both premises and 27 species of food animals (including cattle, goats, sheep, swine, poultry, deer, and elk). The data are linked to several databases run by private technology companies, while the USDA shops for a technology company with data warehousing expertise to run the full national database. The United Kingdom uses a similar database system for its Cattle Tracing System (CTS; http://www.bcms.gov.uk/), which facilitates tracking and is accessible online to users and administrators. See PCIFAP Recommendation #6 in this section for more information.

use and resistance in the National Antimicrobial Resistance Monitoring System (NARMS). This could be accomplished by full implementation of Priority Action 5 of *A Public Health Action Plan to Combat Antimicrobial Resistance,* which calls for the establishment of a monitoring system and the assessment of ways to collect and protect the confidentiality of usage data ((CDC/FDA/NIH, 1999). Since the USDA already provides antimicrobial use data in fruit and vegetable production it seems logical that usage information can be obtained from either agriculture producers and/or the pharmaceutical industry without undue burden.

Background

There are no reliable data on antimicrobial use in U.S. food animal production. Rather, various groups have reported estimates of use based on inconsistent standards. For example, in 2001 the Union of Concerned Scientists (UCS) estimated that 24.6 million pounds of antimicrobials were used per year for non-therapeutic purposes (Mellon *et al*, 2001) in animal agriculture (only cattle, swine, and poultry), whereas the Animal Health Institute (AHI) figure for the same year was only 21.8 million pounds for *all* animals and uses (therapeutic and non-therapeutic) (AHI, 2002). These disparities make it difficult to get a true picture of the state and extent of antimicrobial use and its relationship to antimicrobial resistance in industrial farm animal production.

Recommendation #4. **Improve monitoring and surveillance of antimicrobial resistance in the food supply, the environment, and animal and human populations in order to refine knowledge of antimicrobial resistance and its impacts on human health.**

a. Integrate, expand, and increase the funding for current monitoring programs.
b. Establish a permanent interdisciplinary oversight group with protection from political pressure, as recommended in the 1999 NRC report *The Use of Drugs in Food Animals: Risks and Benefits*. The group members should represent agencies involved in food animal drug regulation (e.g., the FDA, CDC, USDA), similar to the Interagency Task Force (CDC/FDA/NIH, 1999). In order to gather useful national data on antimicrobial resistance in the United States, the group should review progress on data collection and reporting, and

should coordinate both the organisms tested and the regions where testing is concentrated, in order to better integrate the data. Agency members should coordinate with each other and with the NAIS to produce an annual report that includes integrated data on human and animal antimicrobial use and resistance by region. Finally, the group should receive appropriate funding from Congress to ensure transparency in funding as well as scientific independence.

c. Revise existing programs and develop a comprehensive plan to incorporate monitoring of the farm environment (soils and plants) and nearby water supplies with the monitoring of organisms in farm animals.
d. Improve testing and tracking of antimicrobial-resistant infections in health care settings. Better tracking of AMR infections will give health professionals and policymakers a clearer picture of the role of antimicrobial-resistant organisms in animal and human health and will support more effective decisions about the use of antimicrobials.

Background

Monitoring and surveillance of antimicrobial resistance in the United States are covered by the National Antimicrobial Resistance Monitoring System (NARMS), a program run by FDA in collaboration with CDC and USDA. CDC is responsible for monitoring resistance in humans, but other federal agencies also conduct antimicrobial resistance research activities. For instance, the USDA National Animal Health Monitoring System (NAHMS) compiles food animal population statistics, animal health indicators, and antimicrobial resistance data. The USDA Collaboration in Animal Health and Food Safety Epidemiology (CAHFSE) is a joint effort of the department's Animal and Plant Health Inspection Service (APHIS), Agricultural Research Service (ARS), and Food Safety and Inspection Service (FSIS) to monitor bacteria that pose a food safety risk, including AMR bacteria. The USGS studies the spread of antimicrobial-resistant organisms in the environment. To achieve a comprehensive plan for monitoring and responding to antimicrobial resistance in the food supply, the environment, and animal and human populations, these agencies should work together to create an integrated plan with independent

oversight, and should upgrade from a passive form of monitoring to an active, comprehensive, uniform, mandatory approach.

The U.S. and state geological surveys (Krapac, 2004; USGS, 2006) as well as several independent groups (Batt, Snow et al. 2006; Centner 2006; Peak, Knapp et al. 2007) have looked closely at the spread of antimicrobial-resistant organisms in the environment, specifically in waterways, presumably from runoff or flooding. A recent study by the University of Georgia suggested that even chickens raised without exposure to antibiotics were populated with resistant bacteria. The authors suggested that an incomplete cleaning of the farm environment could have allowed resistant bacteria to persist and re-infect naïve hosts (Idris, Lu et al. 2006; Smith, Drum et al. 2007). In Denmark, it took several years after the withdrawal of antimicrobials for antimicrobial resistance to diminish in farm animal populations. These experiences emphasize the importance of monitoring the environment for antimicrobial contamination and responding with careful and comprehensive planning.

Recommendation #5. **Increase veterinary oversight of all antimicrobial use in food animal production, to prevent overuse and misuse of antimicrobials.**

a. Restrict public access to agricultural sources of antimicrobials.
b. Enforce restricted access to prescription drugs. By law, only a veterinarian may order the extra-label use of a prescribed drug in animals, but in fact prescription drugs are widely available for purchase online, directly from the distributors or pharmaceutical companies, or in feed supply stores without a prescription. Without stricter requirements on the purchase of antimicrobials, extra-label (i.e., non-therapeutic) use of these drugs is possible and even probable. For that reason, *no* antibiotics should be available for over-the-counter purchase.
c. Enforce veterinary oversight and authorization of all decisions to use antimicrobials in food animal production. The extra-label drug use (ELDU) rule under the Animal Medicinal Drug

Use Clarification Act (AMDUCA) permits veterinarians to go beyond label directions in using animal drugs and to use legally obtained human drugs in animals. However, the rule does not permit ELDU in animal feed or to enhance production. ELDU is limited to cases in which the health of the animal is threatened or in which suffering or death may result from lack of treatment. Veterinarians should consider ELDU in food-producing animals only when no approved drug is available that has the same active ingredient in the required dosage form and concentration or that is clinically effective for the intended use (1994). North Carolina State University, the University of California-Davis, and the University of Florida run the Food Animal Residue Avoidance Databank (FARAD) (http://www.farad.org/), which includes useful information for food animal veterinarians, including vetGRAM, which lists label information for all food animal drugs. To be effective, AMDUCA and ELDU must be enforced. In addition, the FDA CVM should compel veterinarians to submit prescription and treatment information on farm animals to a national database to allow better tracking of antibiotic use as well as better oversight by veterinarians, as technology allows. Veterinary education for food animal production should teach prescription laws and reporting requirements.

d. Encourage veterinary consultation in these decisions.
e. AMDUCA requires the veterinarian to properly label drugs used in a manner inconsistent with the labeling (i.e., extra-label) and to give the livestock owner complete instructions about proper use of the drug. Further, ELDU must take place in the context of a valid, current veterinarian-client-patient relationship—the veterinarian must have sufficient knowledge of the animal to make a preliminary diagnosis that will determine the intended use of the drugs. The producer should be encouraged to work with the veterinarian both to ensure the health of the animal(s) and to conform to antibiotic requirements. For example, the National Pork Board Pork Quality Assurance program encourages consultation with veterinarians to maintain a comprehensive herd health program (NPB, 2005).

Background

Presenters at a 2003 NRC workshop concluded that unlike human use of antibiotics, non-therapeutic uses in animals typically do not require a prescription (certain antimicrobials are sold over the counter and widely used for purposes or administered in ways not described on the label) (Anderson *et al*, 2003). After the passage of AMDUCA, veterinarians gained the right to

prescribe/dispense drugs for "extra-label" use but the FDA limits such use to protect public health (1994), (before AMDUCA, veterinarians were not legally permitted to use an animal drug in any way except as indicated on the label). ELDU occurs when the drug's actual or intended use is not in accordance with the approved labeling. For instance, ELDU refers to administration of a drug for a species not listed on the label; for an indication, disease, or other condition not on the label; at a dosage level or frequency not on the label; or by a route of administration not on the label. Over-the-counter sale of antimicrobials opens the door to the non-therapeutic, unregulated use of antibiotics in farm animals.

The issues being considered today by this Subcommittee are of great concern to the members of the Pew Commission, the medical community, and the veterinary community. The members of the Pew Commission look forward to working with you as you continue consideration of this very important issue. Mr. Chairman and members of the Subcommittee, thank you again for allowing me to testify.

Mr. PALLONE. Thank you, Mr. Martin. Thank all of you. We will take some questions now and I will start with myself.

I did want to start with Mr. Martin. In your testimony, you discussed the need to pass legislation such as the Preservation of Antibiotics for Medical Treatment Act of 2007 as introduced by Representative Slaughter. My understanding of this bill is that it shifts the burden of proving that the use of an antibiotic drug in food animals is no longer safe for human health from the FDA to the manufacturer of that product. Is that correct?

Mr. MARTIN. Yes.

Mr. PALLONE. Can you tell us why you think it is important for the manufacturer to bear that burden as opposed to the FDA?

Mr. MARTIN. Well, I think the manufacturer bears some responsibility in the sales of the product and I think we looked at frankly a lack of resources at the FDA.

Mr. PALLONE. Now, can you talk about the differences between the provisions in that bill, PAMTA, I guess it is, and the Guidance for Industry Number 152 that was issued by the FDA?

Mr. MARTIN. I am not an expert on PAMTA or Guidance 152.

Mr. PALLONE. So you don't want to comment. All right. Do you want to get back to us?

Mr. MARTIN. I will.

Mr. PALLONE. All right. Get back to us in writing. That would be fine. Now, another question. One thing that the ADUFA and AGDUFA proposals have been criticized for is their lack of any post-market safety provisions. Specifically, there is no authorization for the use of ADUFA funds for post-market safety activities. We spent a lot of time talking about antimicrobial resistance today and I think that fits in this category of post-market safety as well as pre-market safety but I am wondering if there are any other types of post-market activity that you think the committee should consider authorizing for use of ADUFA funds. I will give you an example. Under PADUFA from last year, we allowed monies to go for collecting, developing, and reviewing safety information on the drugs including adverse event reporting, and we expanded the list of authorities that FDA could use PADUFA feeds for and expanded the amount of user fees collected to fund those authorities. What is your opinion?

Mr. MARTIN. I think that would be appropriate. The Pew Commission did not actually review that specifically but given our position, I think that would be appropriate. I think that a portion of the fees could go to activities like reviewing animal antibiotics already on the market under FDA's new standards for pre-market approval and collecting data on how it is used in animals and expanding the national antimicrobial resistance surveillance system.

Mr. PALLONE. OK. Do you want get back to us with a list of authorities you think that the FDA should have to improve post-market safety?

Mr. MARTIN. Sure.

Mr. PALLONE. And I guess also how much funding you think we would need to expand those authorities. I will ask you another question, Mr. Martin, and then I will move to Ms. Batliner. One complaint I have heard about ADUFA is that there been a shift in resources away from other missions so that CVM could meet the

requirements of ADUFA. Are you aware of that criticism and could you comment on what functions might not be adequately funded at FDA due to ADUFA funding?

Mr. MARTIN. We didn't really get into that in any detail, and our recommendations and positions are consensus, so I really can't stray too far from what has been presented.

Mr. PALLONE. All right. Ms. Batliner, do you care to comment on that? Do you think that ADUFA funding has had any impact on shifting resources away from the review of generic animal drug submissions to meet timeliness goals of ADUFA?

Ms. BATLINER. Well, certainly the generic application review times have grown during the time that ADUFA was in effect. My understanding from discussions with the Center for Veterinary Medicine is that in 2003, the appropriated monies devoted to generic application review were locked in place, so to speak. Since we as an industry were not supplying user fees, we continued to receive the amount of appropriated funds for generic review that we had received in 2003. In that time, the workload has increased dramatically, so I do not believe that they have shifted resources but rather limited the resources that were engaged in generic application review.

Mr. PALLONE. Now, is that the only thing that has led to the increase in the review times or are there other things you want to mention?

Ms. BATLINER. I really believe that is a resource issue at CVM and the number of reviewers that they are allocating for generic application review.

Mr. PALLONE. OK. Now, I understand that the Administration's proposal would bring enough fees to improve the review time for the generic animal submissions but as you mentioned, FDA still would not be able to complete reviews by the statutory deadline, 180 days. Do you want to give us a sense of how much more money it would have taken in terms of collecting additional fees to reach that goal?

Ms. BATLINER. I believe $47 million was the figure that we were provided when we began discussions with CVM about returning to statutory review times.

Mr. PALLONE. Forty-seven million dollars?

Ms. BATLINER. I believe so.

Mr. PALLONE. All right. Thank you very much.

Mr. Deal.

Mr. DEAL. Thank you. Mr. Martin, you heard my questioning of the prior panel about this question of what is an appropriate use of antibiotics, antimicrobials with regard to therapeutic versus non-therapeutic usage, and I think the first panel agreed that appropriate therapeutic usage of these drugs would be for disease prevention, disease control and disease treatment. Do you agree with that?

Mr. MARTIN. Well, the Commission defines therapeutic use as appropriate in food animals with diagnosed microbial disease. So ours is narrower than—

Mr. DEAL. So you would be only at the point that they have been diagnosed with something, not for prevention of something?

Mr. MARTIN. Right.

Mr. DEAL. Why would you think that it would be humane or even in the public health if an animal is going to be subject to a disease to use an antibiotic to prevent that from occurring?

Mr. MARTIN. Well, we do have a definition of prophylactic use that states that they can be used in healthy animals in advance of an expected exposure to an infectious agent or after such exposure but before a laboratory confirmed clinical disease is determined by a licensed professional. So we do have a provision for prophylactic.

Mr. DEAL. It is still a little bit narrower than the general prevention, right?

Mr. MARTIN. Right.

Mr. DEAL. Let me ask you this. As we know, we think we are the food basket of the world but we still import a lot of food products into this country. Did your commission undertake to determine what foreign counties that are importing food into this country, meat products in particular, for example, how their use of antibiotics compared or contrasted with the usage here in the United States?

Mr. MARTIN. No, we did not. I mean, we looked at some developments in Europe for the impact on the pool of resistant bacteria but we did not have the time to do an in-depth analysis.

Mr. DEAL. Probably at some point that is something somebody needs to take a look at, wouldn't you think?

Mr. MARTIN. Yes.

Mr. DEAL. Because we are in a competitive world market and what other countries do, especially if they import in our country, we need to be at least on hopefully a proverbial level playing field in a competitive environment. Now, back to the definition of therapeutic versus non-therapeutic. The non-therapeutic usage would be what?

Mr. MARTIN. We define that as use for additive or for growth promotion, feed efficiency, weight gain, routine disease prevention in the absence of documented exposure or other routine purposes in animal production. So I think our linchpin is documented exposure.

Mr. DEAL. So where does the Pew Commission come down with regard to use of antimicrobials for those purposes, the non-therapeutic purposes?

Mr. MARTIN. Well, we would like to phase out and ban the use of antimicrobials for non-therapeutic uses.

Mr. DEAL. OK. Just in general knowledge without having done an in-depth survey, I think you know that the usage for those non-therapeutic usages is pretty universal around the world, that they are being used for those non-therapeutic purposes, are you not?

Mr. MARTIN. Well, I think there have been some restrictions recently in Europe since 1996—well, I think 1989 in Sweden, 1986 in Denmark and now I think the E.U. is moving—

Mr. DEAL. That is the growth hormones, et cetera?

Mr. MARTIN. Yes. Well, and non-therapeutic use of antimicrobials.

Mr. DEAL. All right. Thank you all.

Mr. PALLONE. The gentlewoman from Illinois, Ms. Schakowsky.

Ms. SCHAKOWSKY. To follow up on that, I was looking at the other countries that have banned. It was Sweden in 1986, Denmark it says in 1998, and the European Union in 2006, but I was

interested to see that the report also determined that the overall health of the animals, mainly swine, was not affected and the cost to producers was not significant, and I imagine that one of the arguments that would be used in favor of continuing the use as we do for these antibiotics would be the cost. So your report found otherwise. Can you expand on that at all?

Mr. MARTIN. Yes. We looked at, I think, the data in Denmark and it showed that therapeutic use went up for a short time but once the instituted better animal husbandry practices, spreading the animals out and cleaning their stalls more frequently, that the therapeutic use went down. We have done an economic analysis, one of our technical reports, that compares that industrial farm model that is common today with gestation crates and liquid waste management systems compared to a, it is another intensive-type operation called a hoop barn for swine, that requires a little more interaction by the managers. They have to be a little more involved with the animals instead of them being housed in rows in gestation crates, and we have actually found that the cost when you account for the environmental and health impacts of the current system, internalize those costs instead of externalizing that and compare them to the hoop barn system, that the hoop barn systems are actually cheaper.

Ms. SCHAKOWSKY. I wonder if—pronounce your name again for me, Doctor.

Dr. CARNEVALE. Carnevale.

Ms. SCHAKOWSKY. I wonder if you wanted to comment on that. It seems as if, if in fact the animals are as healthy and the costs may even be somewhat less and therefore the impact on public health would be improved, that this is kind of a no-brainer. Why wouldn't we ban the use for, we are saying for non-therapeutic use? Why wouldn't we?

Dr. CARNEVALE. Well, let me comment on that. First of all, the AVMA, American Veterinary Medical Association, defines therapeutic use as prevention, treatment, and control, and in fact, so do other international organizations like Codex and the World Health Organization. They also define those uses as therapeutic, to get back to Mr. Deal's question. With regard to the information we have from Europe, there was a study in Denmark by the World Health Organization called the Fullam Report and in fact it is not true that there was no impact to animal health. There was. There was a tremendous loss of baby pigs when they withdrew those antimicrobials.

Ms. SCHAKOWSKY. Well, Mr. Martin acknowledged that at first there was some effect but that with a change in various procedures, that that is no longer true.

Dr. CARNEVALE. Well, what happened is, they had to increase their use of therapeutic antibiotics, and in fact, that use continues to go up. Now, the overall use of antimicrobials is down but the other important thing in that report that I want to emphasize is the experts in that report concluded that any human health impact before or after the ban was negligible. So in fact, there is not really good enough that the ban in Denmark or the European Union has had any impact on human health at all.

Ms. SCHAKOWSKY. Well, do you think the use of antibiotics in general does have an effect? I mean, what is your conclusion on human health?

Dr. CARNEVALE. Yes, certainly the use of antimicrobials in humans and animals can lead to resistance, absolutely. There is no question about that. That is why we need to use them prudently and that is why the AVMA has adopted a set of prudent use guidelines—

Ms. SCHAKOWSKY. But why would you conclude that if the decrease in use has had a negligible effect?

Dr. CARNEVALE. Why I would conclude that?

Ms. SCHAKOWSKY. Why would you conclude that it actually does have an impact, significant impact on human health if the reduction in its use doesn't—you are arguing two things, that the reduction didn't really matter but that in fact reducing the use does matter.

Dr. CARNEVALE. Well, I am saying that uncontrolled use could have adverse consequences. We do not have uncontrolled use in the United States.

Ms. SCHAKOWSKY. Do we have a good percentage of how many of our food animals are treated with antibiotics?

Dr. CARNEVALE. I do not know the percentage. I do know—

Ms. SCHAKOWSKY. Does anybody? No, I don't mean just on this panel. Is it known? Is it documented? Do we know that? Because didn't you say, Mr. Martin, that it was hard to figure out if it was 30 percent or 70 percent?

Mr. MARTIN. Yes, we couldn't find anybody that was documenting it.

Dr. CARNEVALE. There are data, I recall, from USDA called the National Animal Health Monitoring System, and they have recorded periodically in doing studies on various classes of livestock and poultry, they have concluded how much use. I don't have those numbers available to me but I think they are in those reports.

Ms. SCHAKOWSKY. I see I have gone over time. Thank you, Mr. Chairman.

Mr. PALLONE. I don't have any additional questions so if any member wants to continue. Go ahead, Mr. Matheson.

Mr. MATHESON. Thank you. It sort of plays again on what my colleague was just asking, and on the first panel I was asking about use data and the fact we don't have enough use data, so I think you are on the right track.

Mr. Martin, I wanted to just ask you a couple of quick questions. By way of introduction, I and a number of my colleagues on this committee have introduced the Strategies to Address the Antimicrobial Resistance Act. We call it the STAAR Act. It is a bill that provides a multi-pronged approach to address the threat of antibiotic resistance including enhanced research, surveillance, and data collection, and specifically, my bill requires animal and human antibiotic drug manufacturers to provide the FDA with human and animal antibiotic use data. In the case of animals, the information would be submitted on a calendar-year basis by volume separately for use by species. In summaries the data would be publicly available but the bill would protect confidential business information. A few years ago, the Government Accountability Office looked at the

possible impact on humans of animal antibiotic use. Specifically the GAO stated that Federal agencies do not collect the critical data on antibiotic use in animals that they need to support research on the human health risk. So that kind of led into my question, which is, do you believe we need this type of data to better determine any relationship between use in animals and antibiotic resistance in humans?

Mr. MARTIN. Yes, and the Commission was aware of your legislation and the companion bill in the Senate by I believe Senators Brown and Hatch.

Mr. MATHESON. Yes.

Mr. MARTIN. There is a similar bill there.

Mr. MATHESON. It seems to me it is another piece of the puzzle to help determine whatever public policy strategies we need to address antibiotic resistance.

Mr. MARTIN. Yes.

Mr. MATHESON. It is my understanding that European countries have purchased data from IMS Health Global Services to support their epidemiological research. Are you familiar with this data?

Mr. MARTIN. No, I am not.

Mr. MATHESON. I am glad you mentioned there is a companion bill in the Senate as well, and I think it helps address some of the issues we raised today.

Mr. Chairman, that concludes my line of questioning. I will yield back.

Mr. PALLONE. I am going to go around again if anybody has additional questions. I don't, but Mr. Deal and then Ms. Schakowsky if you do.

Mr. DEAL. I just have a couple of quick ones, and Dr. Carnevale, I would address them to you. What safeguards does the Animal Health Institute have in place to prevent antibiotic resistance? Do you have any safeguards that your organization has put in place?

Dr. CARNEVALE. Well, the Animal Health Institute is a trade association. We don't have any specific safeguards. Our companies certainly do. They have good stewardship programs on their individual products. They have field personnel out there to make sure that producers and veterinarians know how these drugs should be used, know how they should be used according to label and to reduce the presence of antibiotic resistance. I also mentioned before that the American Veterinary Medical Association has gotten together their specialty groups that deal with each class of animals, whether it be poultry, livestock and even companion animals, as a matter of fact, and they put together guidelines for veterinarians to follow on how to appropriately use antibiotics to reduce the chance of resistance development.

Mr. DEAL. And within the agriculture community itself, are you aware of policies that they put in place to try to reduce the use of these antibiotics and especially as they relate to antibiotic resistance in humans?

Dr. CARNEVALE. Yes. As a matter of fact, I can cite one, and that is the Pork Quality Assurance Program, which in fact they have worked very hard, the Pork Board has worked very hard to get their producers to know how to use antibiotics appropriately, know how to control diseases, and that is an integrated program that

they have in operation which at the heart of it involves the use of antimicrobials in an appropriate fashion. So I think that is a model program.

Mr. DEAL. Thank you. That is all.

Mr. PALLONE. Anyone else? Ms. Schakowsky?

Ms. SCHAKOWSKY. Let me just ask Mr. Martin, if you could just elaborate a little bit exactly how antibiotic resistance is generated as a result of using antibiotics in animals because some have argued that we actually can't know whether antibiotic resistance is a result of the use of antibiotics in animals as opposed to humans, and I wondered if you could respond to that, and Ms. Batliner, if you wanted to say something, go ahead.

Mr. MARTIN. Dr. Carnevale even said that all antibiotic use leads to resistance, some resistance, and I think it gets a little bit back to the data collection issue. If 30 percent of the antibiotics used in the country are fed to animals for growth promotion and non-therapeutic ways, that by logic has to add to the antimicrobial resistance pool in the environment. If it is 70 percent, it is quite a problem. We had two physicians on the Commission and one veterinarian, and their beliefs are that once it is in the environment, that—and it is not their beliefs, their training and learning. You know, once it is excreted out of the animal and goes, in the case of a swine facility, flushed into an open cesspool where it is collected for a few weeks and then sprayed on the ground without treatment, that is the method of disposal of swine waste, that gets into the groundwater. Johns Hopkins is doing a study now, the School of Public Health is doing a study now. They are looking into antibiotic-resistant bacteria that were found in dolphins off Woods Hole in Massachusetts that has been linked back to effluents in North Carolina, coastal effluents in North Carolina. So the transmission—I mean, bacteria are like any living thing. When they are put under stress, they adapt and change to survive, and bacteria uniquely can transfer their resistance and antimicrobial-resistant bacteria can transfer that resistance to a bacteria that has never been exposed.

Ms. SCHAKOWSKY. Is it not a matter of eating the treated meat?

Mr. MARTIN. No, that is not the real exposure risk.

Ms. SCHAKOWSKY. That is not the exposure risk. OK.

Mr. MARTIN. That is the Commission's viewpoint. It is in the environment, and workers that are in industrial farm animal production facilities for prolonged periods can carry that resistant bacteria out into the community. In traditional farming systems, the farmer may be interacting with the animals for several short periods of time over a day. In an industrial production facility, the workers are in the barns with the animals for extended periods of time being exposed. So it is more that kind of transmission out into the community—

Ms. SCHAKOWSKY. What about milk from cows that are treated?

Mr. MARTIN. The FDA has very strict rules about anything showing up in milk. I mean, they are very strict about hormones and antibiotics. We found it is more of an environmental concern and particularly with swine production, getting into groundwater, whether some of the lagoons will overflow into rivers in a flood or a heavy rain. The University of Iowa has done studies about higher rates of asthma and exposure to pathogens up to 5 miles in a

downwind plume from hog CAFOs, and the EPA now is undergoing a fairly intensive monitoring program to see exactly what is in the air coming out of industrial operations. But it is really not, from the Commission's viewpoint, it is not—you don't ingest it in the meat because it is being fed to the animal. It is more in the environmental impact.

Ms. SCHAKOWSKY. Thank you. Go ahead.

Dr. CARNEVALE. Can I comment on that? Yes, certainly you can find resistance. A lot of the resistance that might be in the environment frankly could be due to human use as well as animal use. You can find resistance. The issue is not finding resistance. The issue is, what is the risk of the presence of that resistance to human health, and that is why it is important that we stress risk assessment. That is why the FDA and international organizations have taken on the task of trying to determine what the risk of this potential resistance that might occur is to human health. In many cases, when they look at the data, they look at the farm-to-table continuum, if you will. They find that for many of these antibiotics, there is a very low risk of this resistance leading to a human health concern. That doesn't mean we don't use the antibiotics properly to try to make sure that we don't create—we create as little resistance as we can. Resistance also is not permanent. In many cases you can use a drug, you can get resistance to it. As soon as you remove the drug, the resistance goes away. So it is not an all-or-none situation. It is a very complex area, and this is why we think risk assessment is the way to get at the concerns. We fully support the FDA conducting risk assessments on a pre- and post-approval basis. In fact, Mr. Chairman, I would note that the House Agriculture Appropriations Committee in fact gave FDA about $1 million 5 years ago and it appears in their budget every year to conduct post-approval reviews of these antibiotics, so that process is going on with funding from Congress. Thank you.

Mr. PALLONE. Thank you. You know, it was kind of interesting because I listened to all the comments about the dangers from diseases that can be borne by animals yet you also read these articles or statements about how—I remember reading something the other day about how it is good for kids to have pets because if they don't have pets, they don't go out on the street and get exposed to diseases and things and they don't develop resistance to it. So who knows. I guess it is very complicated.

I think we are done. Thank you. This was very helpful. And as I mentioned, we do intend to move this bill in a timely fashion because we know the deadline is looming for the authorization. I guess it expires at the end of the fiscal year, so we are well aware of that and we appreciate your comments today. And I will say again that if members want to submit written questions, they will be submitted to the clerk within the next 10 days and then you will be notified soon after that.

So thank you again, and without objection, this meeting of the subcommittee is adjourned.

[Whereupon, at 11:56 a.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

[COMMITTEE PRINT]

110TH CONGRESS
2D SESSION

H. R. _____

To amend the Federal Food, Drug, and Cosmetic Act to amend and reauthorize the animal drug user fee program, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

M__. _____ introduced the following bill; which was referred to the Committee on _____

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to amend and reauthorize the animal drug user fee program, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE; REFERENCES IN ACT.

(a) SHORT TITLE.—This Act may be cited as the "Animal Drug User Fee Amendments of 2008".

(b) REFERENCES IN ACT.—Except as otherwise specified, amendments made by this Act to a section or other provision of law are amendments to such section or other

provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.).

SEC. 2. DEFINITIONS.

Section 739 (21 U.S.C. 379j-11) is amended—

(1) in paragraph (6), by striking ", except for an approved application for which all subject products have been removed from listing under section 510," and inserting "that has not been withdrawn";

(2) in paragraph (10), by striking "year being 2003" and inserting "month being October 2002";

(3) by redesignating paragraph (11) as paragraph (12); and

(4) by inserting immediately after paragraph (10) the following:

"(11) The term 'person' includes an affiliate thereof.".

SEC. 3. AUTHORITY TO ASSESS AND USE ANIMAL DRUG FEES.

(a) TYPES OF FEES.—Section 740(a)(1)(A) (21 U.S.C. 379j-12(a)(1)(A)) is amended—

(1) in clause (i), by inserting ", except an animal drug application subject to the criteria set forth in section 512(d)(4)" after "for an animal drug application"; and

(2) by amending clause (ii) to read as follows:

"(ii) A fee established in subsection (b), in an amount that is equal to 50 percent of the amount of the fee under clause (i), for—

"(I) a supplemental animal drug application for which safety or effectiveness data are required; and

"(II) an animal drug application subject to the criteria set forth in section 512(d)(4).".

(b) FEE AMOUNTS.—

(1) TOTAL FEE REVENUES FOR APPLICATION AND SUPPLEMENT FEES.—Section 740(b)(1) (21 U.S.C. 379j-12(b)(1)) is amended—

(A) by striking "and supplemental animal drug application fees" and inserting "and supplemental and other animal drug application fees"; and

(B) by striking "$1,250,000" and all that follows through the period and inserting "$3,815,000 in fiscal year 2009, $4,320,000 in fiscal year 2010, $4,862,000 in fiscal year 2011, $5,442,000 in fiscal year 2012, and $6,061,000 in fiscal year 2013.".

(2) TOTAL FEE REVENUES FOR PRODUCT FEES.—Section 740(b)(2) (21 U.S.C. 379j-12(b)(2)) is amended by striking "$1,250,000" and all that follows through the period and inserting "$3,815,000 in fiscal year 2009, $4,320,000 in fiscal year 2010, $4,862,000 in fiscal year 2011, $5,442,000 in fiscal year 2012, and $6,061,000 in fiscal year 2013.".

(3) TOTAL FEE REVENUES FOR ESTABLISHMENT FEES.—Section 740(b)(3) (21 U.S.C. 379j-12(b)(3)) is amended by striking "$1,250,000" and all that follows through the period and inserting " $3,815,000 in fiscal year 2009, $4,320,000 in fiscal year 2010, $4,862,000 in fiscal year 2011, $5,442,000 in fiscal year 2012, and $6,061,000 in fiscal year 2013.".

(4) TOTAL FEE REVENUES FOR SPONSOR FEES.—Section 740(b)(4) (21 U.S.C. 379j-12(b)(4)) is amended by striking "$1,250,000" and all that follows through the period and inserting "$3,815,000 in fiscal year 2009, $4,320,000 in fiscal year 2010, $4,862,000 in fiscal year 2011, $5,442,000 in fiscal year 2012, and $6,061,000 in fiscal year 2013.".

(c) ADJUSTMENTS TO FEES.—Section 740(c) (21 U.S.C. 379j-12(c)) is amended—

(1) by striking paragraph (1);

(2) by redesignating paragraphs (2) through (5) as paragraphs (1) through (4), respectively;

(3) in paragraph (1), as so redesignated—

(A) in the matter preceding subparagraph (A), by striking "After the fee revenues are adjusted for inflation in accordance with paragraph (1), the fee revenues shall be further adjusted each fiscal year after fiscal year 2004" and inserting "The fee revenues established in subsection (b) shall be adjusted each fiscal year after fiscal year 2009"; and

(B) in subparagraph (B), by striking ", as adjusted for inflation under paragraph (1)"; and

(4) in paragraph (2), as so redesignated—

(A) by striking "2008" each place it occurs and inserting "2013"; and

(B) by striking "2009" and inserting "2014".

(d) AUTHORIZATION OF APPROPRIATIONS.—Section 740(g)(3) (21 U.S.C. 379j-12(g)(3)) is amended by

amending subparagraphs (A) through (E) to read as follows:

"(A) $15,260,000 for fiscal year 2009;

"(B) $17,280,000 for fiscal year 2010;

"(C) $19,448,000 for fiscal year 2011;

"(D) $21,768,000 for fiscal year 2012; and

"(E) $24,244,000 for fiscal year 2013;".

(e) OFFSET.—Section 740(g)(4) (21 U.S.C. 379j-12(g)(4)) is amended to read as follows:

"(4) OFFSET.—If the cumulative amount of fees collected under this section during fiscal years 2009, 2010, and 2011, plus the annual amount of such fees estimated to be collected for fiscal year 2012, exceeds the amount of fees specified in aggregate in appropriation Acts for such fiscal years, the aggregate amount in excess shall be credited to the appropriation account of the Food and Drug Administration as provided in paragraph (1), and shall be subtracted from the amount of fees that would otherwise be authorized to be collected under this section pursuant to appropriation Acts for fiscal year 2013.".

SEC. 4. SAVINGS CLAUSE.

Notwithstanding section 5 of the Animal Drug User Fee Act of 2003 (Public Law 108–130), and notwithstanding the amendments made by this Act, part 4 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379j-11 et seq.), as in effect on the day before the date of the enactment of this Act, shall continue to be in effect with respect to animal drug applications and supplemental animal drug applications (as defined in such part as of such day) that on or after September 1, 2003, but before October 1, 2008, were accepted by the Food and Drug Administration for filing with respect to assessing and collecting any fee required by such part for a fiscal year prior to fiscal year 2009.

SEC. 5. EFFECTIVE DATE.

The amendments made by this Act shall take effect on October 1, 2008, or the date of the enactment of this Act, whichever is later, except that, notwithstanding section 5 of the Animal Drug User Fee Act of 2003 (Public Law 108–130), fees under part 4 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act, as amended by this Act, shall be assessed for all animal drug applications and supplemental animal drug applications received on or after October 1, 2008, regardless of the date of the enactment of this Act.

SEC. 6. SUNSET CLAUSE.

Section 5 of the Animal Drug User Fee Act of 2003 (Public Law 108–130) is amended by striking "October 1, 2008" and inserting "October 1, 2013".

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[COMMITTEE PRINT]

110TH CONGRESS
2D SESSION

H. R. _____

To amend the Federal Food, Drug, and Cosmetic Act to establish a program of fees relating to animal generic drugs.

IN THE HOUSE OF REPRESENTATIVES

M__. _____ introduced the following bill; which was referred to the Committee on _____

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to establish a program of fees relating to animal generic drugs.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "Animal Generic Drug User Fee Act of 2008".

SEC. 2. FINDINGS.

Congress finds as follows:

(1) Prompt approval of safe and effective abbreviated new animal drugs is a vital part of reduc-

ing animal health care costs and promoting the well-being of animal health and the public health.

(2) Animal health and the public health will be served by making additional funds available for the purpose of augmenting the resources of the Food and Drug Administration that are devoted to the process for review of abbreviated new animal drug applications.

(3) The fees authorized by this Act will be dedicated toward expediting the abbreviated new animal drug development process and the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions as set forth in the goals identified in the letters of [insert date on letters] from the Secretary of Health and Human Services to the Chairman of the Committee on Energy and Commerce of the House of Representatives and the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate as set forth in the Congressional Record [insert citation of the page].

SEC. 3. FEES RELATING TO ABBREVIATED NEW ANIMAL DRUGS.

Subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 379f et seq.) is amended by adding at the end the following part:

"PART 5—FEES RELATING TO ABBREVIATED NEW ANIMAL DRUG SUBMISSIONS

"SEC. ___. DEFINITIONS.

"For purposes of this part:

"(1) The term 'abbreviated new animal drug application' means an application for approval of any abbreviated new animal drug submitted under section 512(b)(2). Such term does not include a supplemental abbreviated new animal drug application.

"(2) The term 'supplemental abbreviated new animal drug application' means a request to the Secretary to approve a change in an approved abbreviated new animal drug application.

"(3) The term 'abbreviated new animal drug product' means each specific strength or potency of a particular active ingredient or ingredients in final dosage form marketed by a particular manufacturer or distributor, which is uniquely identified by the labeler code and product code portions of the national drug code, and for which an abbreviated new animal

drug application or a supplemental abbreviated new animal drug application has been approved.

"(4) The term 'generic investigational new animal drug submission' means—

"(A) the filing of a claim for an investigational exemption under section 512(j) for an abbreviated new animal drug intended to be the subject of an abbreviated new animal drug application or a supplemental abbreviated new animal drug application; or

"(B) the submission of information for the purpose of enabling the Secretary to evaluate the safety or effectiveness of an abbreviated new animal drug application or supplemental abbreviated new animal drug application in the event of their filing.

"(5) The term 'abbreviated new animal drug sponsor' means either an applicant named in an abbreviated new animal drug application that has not been withdrawn, or a person who has submitted a generic investigational new animal drug submission that has not been terminated or otherwise rendered inactive by the Secretary.

"(6) The term 'final dosage form' means, with respect to an abbreviated new animal drug product,

a finished dosage form which is approved for administration to an animal without substantial further manufacturing. Such term includes abbreviated new animal drug products intended for mixing in animal feeds.

"(7) The term 'process for the review of abbreviated new animal drug applications' means the following activities of the Secretary with respect to the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions:

"(A) The activities necessary for the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions.

"(B) The issuance of action letters which approve abbreviated new animal drug applications or supplemental abbreviated new animal drug applications or which set forth in detail the specific deficiencies in abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, or generic investigational new animal drug submissions and,

where appropriate, the actions necessary to place such applications or submissions in condition for approval.

"(C) The inspection of abbreviated new animal drug establishments and other facilities undertaken as part of the Secretary's review of pending abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions.

"(D) Monitoring of research conducted in connection with the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions.

"(E) The development of regulations and policy related to the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions.

"(F) Development of standards for products subject to review.

"(G) Meetings between the agency and the abbreviated new animal drug sponsor.

"(H) Review of advertising and labeling prior to approval of an abbreviated new animal drug application or supplemental abbreviated new animal drug application, but not such activities after an abbreviated new animal drug has been approved.

"(8) The term 'costs of resources allocated for the process for the review of abbreviated new animal drug applications' means the expenses incurred in connection with the process for the review of abbreviated new animal drug applications for—

"(A) officers and employees of the Food and Drug Administration, contractors of the Food and Drug Administration, advisory committees consulted with respect to the review of specific abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, or generic investigational new animal drug submissions, and costs related to such officers, employees, committees, and contractors, including costs for travel, education, and recruitment and other personnel activities;

"(B) management of information, and the acquisition, maintenance, and repair of computer resources;

"(C) leasing, maintenance, renovation, and repair of facilities and acquisition, maintenance, and repair of fixtures, furniture, scientific equipment, and other necessary materials and supplies; and

"(D) collecting fees under section 740B and accounting for resources allocated for the review of abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions.

"(9) The term 'adjustment factor' applicable to a fiscal year refers to the formula set forth in section 735(8).

"(10) The term 'person' includes an affiliate thereof.

"(11) The term 'affiliate' refers to the definition set forth in section 735(11).

"SEC. 740B. AUTHORITY TO ASSESS AND USE ABBREVIATED NEW ANIMAL DRUG FEES.

"(a) TYPES OF FEES.—Beginning in fiscal year 2009, the Secretary shall assess and collect fees in accordance with this section as follows:

"(1) ABBREVIATED NEW ANIMAL DRUG APPLICATION FEE.—

"(A) IN GENERAL.—Each person that submits, on or after July 1, 2008, an abbreviated new animal drug application shall be subject to a fee as established in subsection (b).

"(B) PAYMENT.—The fee required by subparagraph (A) shall be due upon submission of the abbreviated new animal drug application.

"(C) EXCEPTION FOR PREVIOUSLY FILED APPLICATION.—If an abbreviated new animal drug application was submitted by a person that paid the fee for such application, was accepted for filing, and was not approved or was withdrawn (without a waiver or refund), the submission of an abbreviated new animal drug application for the same product by the same person (or the person's licensee, assignee, or successor) shall not be subject to a fee under subparagraph (A).

"(D) REFUND OF FEE IF APPLICATION REFUSED FOR FILING.—The Secretary shall refund 75 percent of the fee paid under subparagraph (B) for any abbreviated new animal drug application which is refused for filing.

"(E) REFUND OF FEE IF APPLICATION WITHDRAWN.—If an abbreviated new animal drug application is withdrawn after the application was filed, the Secretary may refund the fee or portion of the fee paid under subparagraph (B) if no substantial work was performed on the application after the application was filed. The Secretary shall have the sole discretion to refund the fee under this paragraph subparagraph. A determination by the Secretary concerning a refund under this paragraph subparagraph shall not be reviewable.

"(2) ABBREVIATED NEW ANIMAL DRUG PRODUCT FEE.—Each person—

"(A) who is named as the applicant in an abbreviated new animal drug application or supplemental abbreviated new animal drug application for an abbreviated new animal drug product which has been submitted for listing under section 510; and

"(B) who, after September 1, 2008, had pending before the Secretary an abbreviated new animal drug application or supplemental abbreviated new animal drug application;

shall pay for each such abbreviated new animal drug product the annual fee established in subsection (b). Such fee shall be payable for the fiscal year in which the abbreviated new animal drug product is first submitted for listing under section 510, or is submitted for relisting under section 510 if the abbreviated new animal drug product has been withdrawn from listing and relisted. After such fee is paid for that fiscal year, such fee shall be payable on or before January 31 of each year. Such fee shall be paid only once for each abbreviated new animal drug product for a fiscal year in which the fee is payable.

"(3) ABBREVIATED NEW ANIMAL DRUG SPONSOR FEE.—Each person—

"(A) who meets the definition of an abbreviated new animal drug sponsor within a fiscal year; and

"(B) who, after September 1, 2008, had pending before the Secretary an abbreviated new animal drug application, a supplemental abbreviated new animal drug application, or a

generic investigational new animal drug submission, shall be assessed an annual fee established under subsection (b). The fee shall be paid on or before January 31 of each year.

"(4) Each abbreviated new animal drug sponsor shall pay only one such fee each fiscal year, as follows:

"(A) 100 percent of the amount of the annual sponsor fee published for that fiscal year under subsection (c)(3) for an applicant with more than 6 approved abbreviated new animal drug applications.

"(B) 75 percent of the amount of the annual sponsor fee published for that fiscal year under subsection (c)(3) for an applicant with 2 to 6 approved abbreviated new animal drug applications.

"(C) 50 percent of the amount of the annual sponsor fee published for that fiscal year under subsection (c)(3) for an applicant with no or 1 approved abbreviated new animal drug applications.

"(b) FEE AMOUNTS.—Except as provided in subsection (a)(1) and subsections (c), (d), (f), and (g), the

fees required under subsection (a) shall be established to generate fee revenue amounts as follows:

"(1) TOTAL FEE REVENUES FOR APPLICATION FEES.—The total fee revenues to be collected in abbreviated new animal drug application fees under subsection (a)(1) shall be $1,449,000 in fiscal year 2009, $1,532,000 in fiscal year 2010, $1,619,000 in fiscal year 2011, $1,712,000 in fiscal year 2012, and $1,809,000 in fiscal year 2013.

"(2) TOTAL FEE REVENUES FOR PRODUCT FEES.—The total fee revenues to be collected in product fees under subsection (a)(2) shall be $1,691,000 in fiscal year 2009, $1,787,000 in fiscal year 2010, $1,889,000 in fiscal year 2011, $1,997,000 in fiscal year 2012, and $2,111,000 in fiscal year 2013.

"(3) TOTAL FEE REVENUES FOR SPONSOR FEES.—The total fee revenues to be collected in sponsor fees under subsection (a)(3) shall be $1,691,000 in fiscal year 2009, $1,787,000 in fiscal year 2010, $1,889,000 in fiscal year 2011, $1,997,000 in fiscal year 2012, and $2,111,000 in fiscal year 2013.

"(c) ADJUSTMENTS.—

"(1) WORKLOAD ADJUSTMENT.—The fee revenues established in subsection (b) shall be adjusted each fiscal year after fiscal year 2009 to reflect changes in review workload. With respect to such adjustment:

"(A) This adjustment shall be determined by the Secretary based on a weighted average of the change in the total number of abbreviated new animal drug applications, manufacturing supplemental abbreviated new animal drug applications, generic investigational new animal drug study submissions, and generic investigational new animal drug protocol submissions submitted to the Secretary. The Secretary shall publish in the Federal Register the fees resulting from this adjustment and the supporting methodologies.

"(B) Under no circumstances shall this workload adjustment result in fee revenues for a fiscal year that are less than the fee revenues for that fiscal year established in subsection (b).

"(2) FINAL YEAR ADJUSTMENT.—For fiscal year 2013, the Secretary may further increase the fees to provide for up to 3 months of operating re-

serves of carryover user fees for the process for the review of abbreviated new animal drug applications for the first 3 months of fiscal year 2014. If the Food and Drug Administration has carryover balances for the process for the review of abbreviated new animal drug applications in excess of 3 months of such operating reserves, then this adjustment will not be made. If this adjustment is necessary, then the rationale for the amount of the increase shall be contained in the annual notice setting fees for fiscal year 2013.

"(3) ANNUAL FEE SETTING.—The Secretary shall establish, 60 days before the start of each fiscal year beginning after September 30, 2008, for that fiscal year, abbreviated new animal drug application fees, abbreviated new animal drug product fees, and abbreviated new animal drug sponsor fees based on the revenue amounts established under subsection (b) and the adjustments provided under this subsection.

"(4) LIMIT.—The total amount of fees charged, as adjusted under this subsection, for a fiscal year may not exceed the total costs for such fiscal year for the resources allocated for the process for the review of abbreviated new animal drug applications.

"(d) FEE WAIVER OR REDUCTION.—The Secretary shall grant a waiver from or a reduction of one or more fees assessed under subsection (a) where the Secretary finds that the abbreviated new animal drug is intended solely to provide for a minor use or minor species indication.

"(e) EFFECT OF FAILURE TO PAY FEES.—An abbreviated new animal drug application submitted by a person subject to fees under subsection (a) shall be considered incomplete and shall not be accepted for filing by the Secretary until all fees owed by such person have been paid. A generic investigational new animal drug submission under section 740A(4)(B) that is submitted by a person subject to fees under subsection (a) shall be considered incomplete and shall not be accepted for review by the Secretary until all fees owed by such person have been paid. The Secretary may discontinue review of any abbreviated new animal drug application, supplemental abbreviated new animal drug application, or generic investigational new animal drug submission from a person if such person has not submitted for payment all fees owed under this section by 30 days after the date upon which they are due.

"(f) ASSESSMENT OF FEES.—

"(1) LIMITATION.—Fees may not be assessed under subsection (a) for a fiscal year beginning after

fiscal year 2008 unless appropriations for salaries and expenses of the Food and Drug Administration for such fiscal year (excluding the amount of fees appropriated for such fiscal year) are equal to or greater than the amount of appropriations for the salaries and expenses of the Food and Drug Administration for fiscal year 2003 (excluding the amount of fees appropriated for such fiscal year) multiplied by the adjustment factor, with the base or comparator being October 2002, applicable to the fiscal year involved.

"(2) AUTHORITY.—If the Secretary does not assess fees under subsection (a) during any portion of a fiscal year because of paragraph (1) and if at a later date in such fiscal year the Secretary may assess such fees, the Secretary may assess and collect such fees, without any modification in the rate, for abbreviated new animal drug applications, abbreviated new animal drug sponsors, and abbreviated new animal drug products at any time in such fiscal year notwithstanding the provisions of subsection (a) relating to the date fees are to be paid.

"(g) CREDITING AND AVAILABILITY OF FEES.—

"(1) IN GENERAL.—Fees authorized under subsection (a) shall be collected and available for obliga-

tion only to the extent and in the amount provided in advance in appropriations Acts. Such fees are authorized to be appropriated to remain available until expended. Such sums as may be necessary may be transferred from the Food and Drug Administration salaries and expenses appropriation account without fiscal year limitation to such appropriation account for salary and expenses with such fiscal year limitation. The sums transferred shall be available solely for the process for the review of abbreviated new animal drug applications.

"(2) COLLECTIONS AND APPROPRIATION ACTS.—

"(A) IN GENERAL.—The fees authorized by this section—

"(i) shall be retained in each fiscal year in an amount not to exceed the amount specified in appropriation Acts, or otherwise made available for obligation for such fiscal year; and

"(ii) shall only be collected and available to defray increases in the costs of the resources allocated for the process for the review of abbreviated new animal drug applications (including increases in such

costs for an additional number of full-time equivalent positions in the Department of Health and Human Services to be engaged in such process) over such costs, excluding costs paid from fees collected under this section, for fiscal year 2008 multiplied by the adjustment factor, with the base or comparator being October 2007.

"(B) COMPLIANCE.—The Secretary shall be considered to have met the requirements of subparagraph (A)(ii) in any fiscal year if the costs funded by appropriations and allocated for the process for the review of abbreviated new animal drug applications—

"(i) are not more than 3 percent below the level specified in subparagraph (A)(ii); or

"(ii)(I) are more than 3 percent below the level specified in subparagraph (A)(ii), and fees assessed for the fiscal year following the subsequent fiscal year are decreased by the amount in excess of 3 percent by which such costs fell below the level specified in subparagraph (A)(ii); and

"(II) such costs are not more than 5 percent below the level specified in subparagraph (A)(ii).

"(3) AUTHORIZATION OF APPROPRIATIONS.—There are authorized to be appropriated for fees under this section—

"(A) $4,831,000 for fiscal year 2009;

"(B) $5,106,000 for fiscal year 2010;

"(C) $5,397,000 for fiscal year 2011;

"(D) $5,706,000 for fiscal year 2012; and

"(E) $6,031,000 for fiscal year 2013;

as adjusted to reflect adjustments in the total fee revenues made under this section and changes in the total amounts collected by abbreviated new animal drug application fees, abbreviated new animal drug product fees, and abbreviated new animal drug sponsor fees.

"(4) OFFSET.—If the cumulative amount of fees collected during fiscal years 2009, 2010, and 2011, plus the annual amount estimated to be collected for fiscal year 2012, exceeds the amount of fees specified in aggregate in appropriation Acts for such fiscal years, the aggregate amount in excess shall be credited to the appropriation account of the Food and Drug Administration as provided in para-

graph (1), and shall be subtracted from the amount of fees that would otherwise be authorized to be collected under this section pursuant to appropriation Acts for fiscal year 2013.

"(h) COLLECTION OF UNPAID FEES.—In any case where the Secretary does not receive payment of a fee assessed under subsection (a) within 30 days after it is due, such fee shall be treated as a claim of the United States Government subject to subchapter II of chapter 37 of title 31, United States Code.

"(i) WRITTEN REQUESTS FOR WAIVERS, REDUCTIONS, AND REFUNDS.—To qualify for consideration for a waiver or reduction under subsection (d), or for a refund of any fee collected in accordance with subsection (a), a person shall submit to the Secretary a written request for such waiver, reduction, or refund not later than 180 days after such fee is due.

"(j) CONSTRUCTION.—This section may not be construed to require that the number of full-time equivalent positions in the Department of Health and Human Services, for officers, employees, and advisory committees not engaged in the process of the review of abbreviated new animal drug applications, be reduced to offset the number of officers, employees, and advisory committees so engaged.".

SEC. 4. ACCOUNTABILITY AND REPORTS.

(a) PUBLIC ACCOUNTABILITY.—

(1) CONSULTATION.—In developing recommendations to Congress for the goals and plans for meeting the goals for the process for the review of abbreviated new animal drug applications for the fiscal years after fiscal year 2013, and for the reauthorization of sections 740A and 740B of the Federal Food, Drug, and Cosmetic Act (as added by section 3), the Secretary of Health and Human Services (referred to in this section as the "Secretary") should consult with the Committee on Energy and Commerce of the House of Representatives, the Committee on Health, Education, Labor, and Pensions of the Senate, appropriate scientific and academic experts, veterinary professionals, representatives of consumer advocacy groups, and the regulated industry.

(2) RECOMMENDATIONS.—The Secretary shall—

(A) publish in the Federal Register recommendations under paragraph (1), after negotiations with the regulated industry;

(B) present the recommendations to the Committees referred to in that paragraph;

(C) hold a meeting at which the public may comment on the recommendations; and

(D) provide for a period of 30 days for the public to provide written comments on the recommendations.

(b) PERFORMANCE REPORTS.—Beginning with fiscal year 2009, not later than 60 days after the end of each fiscal year during which fees are collected under part 5 of subchapter C of chapter VII of the Federal Food, Drug, and Cosmetic Act, the Secretary should prepare and submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report concerning the progress of the Food and Drug Administration in achieving the goals identified in the letters described in section 2(3) of this Act toward expediting the abbreviated new animal drug development process and the review of the abbreviated new animal drug applications, supplemental abbreviated new animal drug applications, and generic investigational new animal drug submissions during such fiscal year.

(c) FISCAL REPORT.—Beginning with fiscal year 2009, not later than 120 days after the end of each fiscal year during which fees are collected under the part described in subsection (b), the Secretary should prepare

and submit to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate a report on the implementation of the authority for such fees during such fiscal year and the use, by the Food and Drug Administration, of the fees collected during such fiscal year for which the report is made.

SEC. 5. SUNSET.

The amendment made by section 3 shall not be in effect after October 1, 2013, and section 4 shall not be in effect after 120 days after such date.

STATEMENT OF HON. JIM MATHESON

Thank you for holding this hearing today, Mr. Chairman and Ranking Member Deal.

I understand that we are here today to consider a timely reauthorization of the Animal Drug User Fee Act as well as the creation of a new program, the Animal Generic Drug User Fee Act. While I look forward to working with my colleagues on the committee on both of these proposals, I would like to use my time today highlighting the issue of antibiotic resistance.

I, along with several of my colleagues on this committee, introduced legislation H.R. 3697, Strategies to Address Antimicrobial Resistance Act. Senators Brown/Hatch/Durbin have introduced the Senate companion bill. The STAAR Act provides a comprehensive approach to the antimicrobial resistance crisis. It provides strategies and authorizes critically needed funding to strengthen federal antimicrobial resistance surveillance, prevention and control, and research efforts. This legislation has the support of several infectious disease leaders including: The Infectious Disease Society, The Pediatric Infectious Disease Society, The American Medical Association, The American Public Health Association, and Premier Hospitals, an alliance of 1700 nonprofit hospitals across America.

Antibiotic use presents unique challenges to drug safety. They are researched and developed to respond to infectious organisms that continue to mutate and build resistance to the product even after approval. Even if we all demonstrate good judgment and use antibiotics wisely, eventually, the bad bugs become resistant.

In 2004, the GAO issued a report entitled: "Antibiotic Resistance Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals". In this report, the GAO states: "Although they have made some progress in monitoring antibiotic resistance, federal agencies do not collect the critical data on antibiotic use in animals that they need to support research on the human health risk. The data that could help this research include the types and quantities of antibiotics sold for use in animals, the purpose of their use (such as disease treatment or growth promotion), the species in which they are used, and the method used to administer them. These types of data are needed to study the linkages between antibiotic use in animals and the human risk from antibiotic resistance and to develop and evaluate strategies for mitigating resistance." While I do not oppose antibiotic use in sick animals—I want to be sure we have the best information to determine the full extent, if any, that antibiotic use in animals contributes to antibiotic resistance in humans.

It will take a coordinated effort and a partnership between manufacturers, federal agencies, providers, and patients to truly make a difference in slowing the trend of antimicrobial resistance. It is my hope that Congress and this committee will address provisions to protect antibiotic safety and effectiveness, as well as improve access to new antibiotics.

I look forward to hearing from our witnesses and will yield back the balance of my time.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

The Honorable Frank Pallone
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

Dear Mr. Chairman:

Thank you for providing an opportunity for the Food and Drug Administration (FDA or the Agency) to testify at the June 5, 2008, hearing before the House Energy and Commerce Committee's Subcommittee on Health. The hearing addressed legislative proposals reauthorizing the Animal Drug User Fee Act (ADUFA) and creating the Animal Generic Drug User Fee Act (AGDUFA).

This letter provides responses for the record to questions asked during the hearing. We have reprinted the questions in bold below, followed by the Agency's response.

The Honorable Frank Pallone

1. **What is FDA's schedule for conducting and completing risk assessments for drugs approved long ago?**

   FDA's ongoing review of previously approved antimicrobial drugs is a labor-intensive process that involves complex scientific and legal issues. Due to the complexity of the issues that arise in the course of conducting these reviews, it is difficult to predict timelines for completion. Therefore, we have not established a schedule for conducting these assessments.

2. **What is the average length of time to conduct risk assessments on drugs currently approved and is it acceptable?**

   Risk assessments are complicated and time-consuming processes. The length of time required to conduct risk assessments varies greatly depending on the questions each risk assessment is intended to address, the drug or class of drugs under consideration, the data available to FDA, and other factors.

The risk assessment process typically includes soliciting and analyzing public comments, developing the risk assessment model, collecting data, conducting research, and formulating the draft assessment. FDA then requests and analyzes comments on the draft assessment, revises the draft, if necessary, and, if all criteria are met, publishes the final risk assessment. If research studies are underway at the time the risk assessment process is undertaken, the risk assessment may be delayed pending completion of those studies.

Given the complexity of the risk assessment process, assessments may take many years to complete. Notwithstanding the considerable time it takes to complete the many steps that are part of the risk assessment process, FDA considers the process a scientifically sound and valuable tool for evaluating such complex issues.

3. **Is it important for FDA in its mission to have access to additional data on the total quantity of antibiotics used in animals, the species they are used in, the purpose of the use (therapeutic, prophylactic, growth promotion), and the method to deliver the antibiotic? How would that data enable FDA to better track antimicrobial resistance or determine threats to the public health?**

Existing FDA regulations require drug sponsors to submit data for the total quantity of drugs marketed, not the total quantity of drugs used. Data for antimicrobial drug usage in animals has been difficult to collect because many drugs are approved and labeled for use in multiple species for a variety of purposes. Though difficult to collect, antimicrobial drug usage data is an important component of FDA's investigations into potential causes of emerging trends in antimicrobial resistance associated with the use of drugs in animals. Such data enable our epidemiologists to make associations between use patterns and emerging trends.

Congress recently enacted additional data reporting requirements. As you know, section 105 of the recently reauthorized ADUFA requires the collection and reporting of certain drug usage data. Beginning in 2009, sponsors of any drug that contains an antimicrobial active ingredient will be required to submit an annual report of each antimicrobial active ingredient in the drug that is sold or distributed for use in food-producing animals. The report must include the quantity of product marketed, both domestically and exported on a monthly basis, each calendar year. It must also include information on the target animals, indications, and production classes that are specified on the approved label of the product. The Secretary of Health and Human Services is required to make summaries of the collected information publicly available.

FDA is currently exploring how best to use the information that will be collected under the new ADUFA reporting requirements.

4. **Does FDA have any flexibility in issuing the RIF notices that would be necessary if ADUFA isn't authorized in a timely fashion?**

Fortunately, because Congress passed ADUFA reauthorization legislation in a timely manner, FDA did not have to pursue the issuance of RIF notices.

The Honorable Janice Schakowsky

5. **Does FDA believe there is sufficient evidence now to phase out the non-therapeutic use of antibiotics? What is the timeline for that activity?**

   FDA has concerns about the nontherapeutic use in animals of antimicrobial drugs of human importance. However, it remains unclear at this time if sufficient evidence is available to initiate regulatory action on any particular animal drug or class of drugs. Due to the complexity of the scientific and legal issues involved, we cannot predict a timeline for making a determination on the sufficiency of the evidence. If a determination is made that a sufficient basis exists for initiating some type of regulatory action, FDA will take the appropriate steps at that time.

6. **The Union of Concerned Scientists estimates that 70% of all antibiotics in the United States are used in beef and pigs. Is that the case?**

   FDA does not have any way of quantifying by percentage the amount of antibiotics used on a per species basis.

The Honorable Steve Buyer

7. **Regarding the Commissioner's request to Congress asking for FDA authority to destroy misbranded, adulterated and counterfeit human drugs, does FDA want the same authority for animal drugs?**

   Yes. In the Administration's Action Plan for Import Safety, the President requests authority for FDA to destroy medical products refused admission into the United States. This would include animal drugs.

The Honorable Jim Matheson

8. **Can you tell me the percent of antibiotic drug sales that are for humans versus animals?**

   FDA does not track sales data for either human or animal drugs.

Thank you again for the opportunity to appear before the Subcommittee. Please let us know if you have any further questions or concerns.

Sincerely,

Stephen R. Mason
Acting Assistant Commissioner
for Legislation

cc: The Honorable John D. Dingell
Chairman, Committee on Energy and Commerce
House of Representatives

The Honorable Joe Barton
Ranking Member, Committee on Energy and Commerce
House of Representatives

The Honorable Nathan Deal
Ranking Member, Subcommittee on Health
Committee on Energy and Commerce
House of Representatives

The Honorable Janice D. Schakowsky
House of Representatives

The Honorable Steve Buyer
House of Representatives

The Honorable Jim Matheson
House of Representatives