U.S. FOOD & DRUG ADMINISTRATION

JUL 23 2018

The Honorable Greg Walden
Chairman
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515

Dear Chairman Walden:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the March 14, 2018, hearing before the Committee on Energy and Commerce, entitled "Reauthorization of Animal Drug User Fees: ADUFA and AGDUFA." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,

John Martin
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for Legislative Affairs

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The committee's questions are restated below in bold, followed by FDA's response.

The Honorable Gus M. Bilirakis

1. **Would you walk us through what actions FDA has taken over the past few years and is currently undertaking with regard to antimicrobial resistance in animals – specifically those for consumption?**

Antimicrobial resistance (AMR) is a serious global public health threat. FDA, in close coordination with other government and public health stakeholders, including the U.S. Department of Agriculture (USDA), has taken a leading role in addressing this critical threat by implementing judicious use policies to promote antimicrobial stewardship and by enhancing surveillance through systems such as the National Antimicrobial Resistance Monitoring System.

Over the past few years, FDA has made a number of important changes with regard to antimicrobial use in animals.

In December 2013, FDA requested through guidance for industry (GFI) #213 that animal drug sponsors of medically-important antimicrobials used in animal feed and water revise the labels of these products to remove indications for growth promotion and to require veterinary oversight for the remaining therapeutic uses. The policy outlined in GFI #213 was fully implemented in January 2017, with all affected animal drug sponsors making the requested changes to their labels. It is important to note that the cooperation of the affected animal drug sponsors was voluntary; however, because they have now revised their labeling consistent with the recommendations in GFI #213, the use of these products in the feed or drinking water of food-producing animals for production (e.g., growth promotion) purposes is now illegal in the U.S. and their use for therapeutic purposes requires authorization from a licensed veterinarian.

To build on the progress made by GFI #213, FDA sought public input on establishing appropriately-targeted durations of therapeutic use of medically-important antimicrobial drugs in food-producing animals. FDA has evaluated the comments received and is in the process of developing a specific strategy for addressing this issue. The strategy developed will need to consider the approved use conditions of these products on a product-by-product basis and any changes to such use conditions will need to be based on sound science and available evidence.

FDA also has issued a final rule revising the annual reporting requirements for drug sponsors of antimicrobials sold or distributed for use in food-producing animals. The additional data FDA will gather as a result of that rulemaking will improve our understanding of how antimicrobials are sold or distributed for use in major food-producing species and help further target efforts to ensure judicious use of medically-important antimicrobials.

FDA is also funding two grants for antimicrobial use data collection. These collection efforts are intended to provide part of the baseline information on antimicrobial use practices in the

four major food-producing animal species (cattle, swine, chickens, turkeys), which is a critical element in measuring the overall impact of FDA's judicious use strategy. We also expect these data collection efforts to provide important information on methodologies to help optimize long-term strategies to collect and report such antimicrobial use data.

Finally, FDA has also been working in close collaboration with the USDA Animal and Plant Health Inspection Service (APHIS) Center for Epidemiology and Animal Health, and has provided input on surveys they have conducted on antimicrobial use in certain animal agriculture settings. We also expect the results of these surveys to provide useful information for assessing antimicrobial use practices in veterinary settings.

2. How do these user fee programs foster innovation in drug development?

ADUFA and AGDUFA are highly successful programs that have accelerated the review of innovative new animal drugs – and more affordable generic alternatives – advancing both animal and human health. The programs have enabled FDA to dramatically reduce the time needed to review pioneer and generic animal products for premarket approval, improve timely communications with sponsors, and achieve other efficiencies in the drug review process, while helping ensure that the drugs are safe and effective.

Innovative new animal products and approaches are being developed that offer the promise of a longer and healthier life for our pets and other animals. In recent years, FDA has approved new oncology treatments for dogs targeting canine-specific tumors and innovative therapies targeting bone changes in horses to treat a common cause of performance-ending lameness. We also approved the first generic version of a vital heartworm treatment that alleviated a shortage of this critically important treatment for dogs. And promising new stem cell therapies offer future veterinary treatments and cures.

FDA employs cutting edge methods of analysis and approaches to arrive at safety and efficacy conclusions including the following:

- Use of pharmacokinetic/pharmacodynamic information
- In vitro testing of product characteristics
- Meta-analysis of broad sources of information such as published literature
- New statistical analyses and presentations of data
- Risk analysis methodologies

The Honorable Frank Pallone, Jr.

Dr. Solomon, it's clear that the user fee programs for animal drugs have been a success, just as the other user fee programs at FDA have been. I'm pleased that FDA, the animal drug industry, and other stakeholders have once again worked together to reach agreement on a path forward.

1. **Since the implementation of the animal drug user fee programs, how has FDA's new animal drug review process improved?**

Before these programs were initiated, FDA's Center for Veterinary Medicine had a large backlog of overdue submissions, and sponsors had to wait, on average, 500 days for pioneer drug review responses and 700 days for generic drug review responses. Because of additional resources provided through the animal drug user fee programs, FDA maintains a stable scientific and technical workforce and provides the animal drug industry with more timely and predictable premarket product review. These programs have been highly successful and have enabled CVM to eliminate the backlog in applications, dramatically reduce the time needed to review animal drug applications and other submissions, improve timely communications with drug sponsors, and achieve other efficiencies in the drug approval process. FDA has met or exceeded virtually all performance goals established under both programs, without sacrificing scientific standards for safety and efficacy.

2. **What has FDA learned since the first authorization of the animal drug user fees and how have the agreements evolved over time to further streamline the review process since the first authorization?**

The five-year reauthorization cycles for ADUFA – and AGDUFA – have supported continuous program innovation, evaluation, and improvement. Through successive reauthorizations, program enhancements have evolved and expanded to include extensive communication and consultation between drug sponsors and FDA throughout drug development.

Under the current ADUFA III agreement, FDA has made multiple enhancements to the chemistry, manufacturing, and controls (CMC) technical section of the new animal drug application (NADA) – one of the most complex components of the new animal drug submission – which have reduced overall review time. The Agency now permits the submission and review of early completed CMC information, permits comparability protocols to be submitted as protocols without substantial data in an investigational new animal drug (INAD) file, and permits certain prior approval manufacturing supplements to be resubmitted as Supplements – Changes Being Effected in 30 Days (CBE-30s).

FDA continues to improve communications, timeliness, and predictability of foreign pre-approval inspections. Sponsors may now voluntarily submit a list of foreign manufacturing facilities they anticipate including in their applications subject to pre-approval inspections for the following fiscal year, permitting better planning and timely execution of FDA good manufacturing practice (GMP) inspections.

Under the current AGDUFA II agreement, FDA added flexibility with a second-cycle shortened review process for key submission types, such as protocols, data submissions, and applications that significantly impact the generic new animal drug approval timeline. Qualifying submissions receive a significantly reduced second-cycle review to shorten approval timelines. FDA also made multiple enhancements to the CMC technical section, similar to the ADUFA changes noted above.

FDA also added a pre-approval foreign inspection goal to improve communications, timeliness, and predictability of these inspections. FDA also developed question-based review (QbR) for bioequivalence submissions, and deployed a QbR for blood-level bioequivalence protocol submissions. Additional templates to further enhance the review of bioequivalence submissions are currently under development.

The ADUFA IV and AGDUFA III agreements build on the achievements of these highly successful programs. They will help ensure FDA has the resources needed to conduct timely reviews and assist drug sponsors in bringing more animal drugs to the market. They also will foster innovation and provide enhanced access to safe and effective animal therapies.

3. Without the animal drug user fee programs, would animal drug development suffer?

The animal drug user fee programs have enabled FDA to dramatically reduce the time needed to review pioneer and generic animal products for premarket approval, improve timely communications with sponsors, and achieve other efficiencies in the drug review process, while helping ensure that the drugs are safe and effective.

In the absence of these programs, FDA would be forced to lay off a significant share of our scientific workforce, delaying the review of new animal drugs, creating uncertainty and frustration for industry, and delaying the availability of new safe and effective treatments. In the AGDUFA program, approximately 60 percent of our staff are funded by user fees. In the ADUFA program, approximately 35 percent of CVM's workforce is funded by user fees. The loss of such a large number of staff would be devastating.

4. In your opinion, what are the most significant new proposals in ADUFA IV and AGDUFA III and how do they further improve the animal drug review process at FDA?

Both agreements build on the success of prior program achievements, propose additions to current performance goals to further enhance review, and include financial recommendations to enhance program stability.

In ADUFA IV, FDA adds an additional four new performance goals to enhance the exchange of scientific information. FDA will reduce timeframes for certain medicated feed applications and environmental impact submissions from 180 days to 60 days. We also establish new goals for timely pre-submission conferences and tissue residue method demonstrations.

The ADUFA IV recommendations also require 100 percent electronic submission starting in FY 2019 to help facilitate efficient review and an FDA commitment to work on implementing the U.S.-European Union Good Manufacturing Practices Inspection Mutual Recognition Agreement for animal drug facilities.

The AGDUFA III negotiated agreement includes a significant, additional financial commitment from the animal generic drug industry that reflects the industry's growth. These resources will help support significantly decreased review times for generic submissions and provide greater review predictability. Like the ADUFA IV recommendation, AGDUFA III also requires 100 percent electronic submission starting next year.

Dr. Solomon as you have previously explained, these animal drug user fee agreements are critical to ensuring animal health and safety and streamlining FDA's animal drug approval process.

These user fee programs help to maintain a stable workforce at the agency to review new animal drug applications, while cutting down on review times and improving FDA's efficiency. In addition, the agreements also help to bring certainty to industry regarding the review and approval of innovative and generic animal drugs, provide necessary treatments for animal healthproviders, and ensure the health and well-being of our animals.

5. **Can you explain why it is so critical that the animal drug user fee and animal generic drug user fee programs are reauthorized before the sunset date?**

6. **What will happen if the animal drug user fee agreements are not reauthorized in a timely manner? Could there be disruptions in the approval process?**

7. **Would delays impact the agency's ability to retain subject matter experts to review new animal drug applications?**

If reauthorization is delayed, we could risk having to lay off many employees. As a longer-term consequence, a delay will make it more difficult for FDA to attract and retain skilled scientists and medical reviewers, and undermine product innovation.

The loss of large numbers of dedicated staff would be devastating. In the AGDUFA program, approximately 60 percent of our staff are funded by user fees. In the ADUFA program, approximately 35 percent of the FTE are funded by user fees. With the loss of FTE, review times would return to the pre-user fee timeframes which exceeded 500 days for pioneer products and 700 days for generic products.

If there's a reasonable expectation that ADUFA and AGDUFA will not be reauthorized by September 30th, FDA would have to notify those employees affected no later than 60 days prior to their expected release date. The Agency, however, would have to perform a substantial analysis prior to sending out the RIF notices to determine what steps would be necessary to adjust drug review and the personnel engaged in those activities.

A topic that often comes up in relation to the reauthorization of animal drug user fees is antimicrobial resistance given that the Center for Veterinary Medicine at FDA is also charged with evaluating antimicrobial animal drugs. Dr. Solomon, as you know, antibiotic

resistance is a grave public health threat as the use of antimicrobials in food-producing animals can result in the emergence of antimicrobial resistance in bacteria that can be transferred to humans and can ultimately reduce the effectiveness of antibiotics in humans.

8. **Can you discuss the steps FDA has taken recently to address the public health concerns related to antimicrobial resistance and help reduce or limit the use of antimicrobials in food-producing animals?**

Antimicrobial resistance (AMR) is a serious global public health threat. FDA, in close coordination with other government and public health stakeholders, including USDA, has taken a leading role in addressing this critical threat by implementing judicious use policies to promote antimicrobial stewardship and by enhancing surveillance through systems such as the National Antimicrobial Resistance Monitoring System.

Over the past few years FDA has made a number of important changes with regard to antimicrobial use in animals.

In December 2013, FDA requested through guidance GFI #213 that animal drug sponsors of medically important antimicrobials used in animal feed and water revise the labels of these products to remove indications for growth promotion and to require veterinary oversight for the remaining therapeutic uses. The policy outlined in GFI #213 was fully implemented in January 2017, with all affected animal drug sponsors making the requested changes to their labels. It is important to note that the cooperation of the affected animal drug sponsors was voluntary; however, because they have now revised their labeling consistent with the recommendations in GFI #213, the use of these products in the feed or drinking water of food-producing animals for production (e.g., growth promotion) purposes is now illegal in the U.S. and their use for therapeutic purposes requires authorization from a licensed veterinarian.

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FDA also has issued a final rule revising the annual reporting requirements for drug sponsors of antimicrobials sold or distributed for use in food-producing animals. The additional data FDA will gather as a result of that rulemaking will improve our understanding of how antimicrobials are sold or distributed for use in major food-producing species and help further target efforts to ensure judicious use of medically-important antimicrobials.

FDA is also funding two grants for antimicrobial use data collection. These collection efforts are intended to provide part of the baseline information on antimicrobial use practices in the four major food-producing animal species (cattle, swine, chickens, turkeys), which is a critical element in measuring the overall impact of FDA's judicious use strategy. We also expect these data collection efforts to provide important information on methodologies to help optimize long-term strategies to collect and report such antimicrobial use data.

Finally, FDA has also been working in close collaboration with the USDA APHIS Center for Epidemiology and Animal Health, and has provided input on surveys they have conducted on antimicrobial use in certain animal agriculture settings. We also expect the results of these surveys to provide useful information for assessing antimicrobial use practices in veterinary settings.

9. How do we balance the need for medically important uses of antimicrobials in food producing animals with efforts to limit or reverse resistance concerns?

FDA believes that the concept of "antimicrobial stewardship" in the animal agriculture setting encompasses a number of important principles, including the following judicious use principles: 1) Antimicrobial drugs should only be used in food-producing animals when necessary to treat, prevent, or control disease, and not for production (e.g., growth promotion) purposes; and 2) when antimicrobial use is necessary, they should be used in an optimal manner under the supervision of a licensed veterinarian.

10. How has access to antimicrobial drug sales and distribution data helped to improve FDA's efforts to address antimicrobial resistance?

FDA believes this information enhances the Agency's understanding of antimicrobials entering the marketplace and supports the assessment of FDA's ongoing efforts to encourage the judicious use of antimicrobials in food-producing animals to help ensure the continued availability of safe and effective antimicrobials for animals and humans.

While sales data provide insight regarding antimicrobial drugs being sold and distributed, FDA believes additional data should be considered when assessing the progress of efforts to foster judicious antimicrobial use, including actual use data, animal demographics and animal health data, and data on resistance. FDA continues to work with Federal, academic, and industry partners to obtain more information about how, when, and why animal producers and veterinarians use medically important antimicrobial drugs.

11. For the first time this past year FDA's summary report on antimicrobials sold or distributed for use in food-producing animals included species-specific estimates. How did FDA determine these estimates and what advantage does inclusion of specific estimates have in data collection efforts?

Since 2008, sponsors of approved or conditionally approved new animal drug applications for a drug containing an antimicrobial active ingredient, must annually report to FDA on the amount of each such ingredient in these drug products sold or distributed for use in food-producing animals. FDA summarizes this information and makes it available to the public in its annual summary reports.

The species-specific estimates were reported for the first time as part of the 2016 annual summary report. FDA established, through notice and comment rulemaking, the additional requirement that drug sponsors submit species-specific estimates as part of their annual report on the quantity of antimicrobials sold or distributed for use in food-producing animals. Drug sponsors are required to provide a species-specific estimate of the percentage of each product that was sold or distributed domestically in the reporting year for use in any of the following animal species categories, but only for such species that appear on the approved label: cattle, swine, chickens, turkeys. The total of the species-specific percentages reported for each product must account for 100 percent of its sales and distribution; therefore, a fifth category of "other species/unknown" must also be reported. Sponsors must submit each year's report to FDA no later than March 31.

Given that many antimicrobial new animal drug products are approved and labeled for use in more than one animal species, the additional species-specific data improves our understanding of how antimicrobials are sold or distributed for use in major food-producing species and will help further target efforts to ensure judicious use of medically important antimicrobials.

Dr. Solomon, the public health crisis resulting from antimicrobial resistance is very concerning and I'm interested in FDA's guidance on judicious use of antimicrobials for food-producing animals and whether FDA's policy has improved veterinary practice in this area.

There is wide agreement that antibiotics should only be used when necessary. As you discussed briefly in your testimony, greater awareness of the harms of antibiotic resistance should result in changes to how antibiotics are utilized in animal agriculture and how FDA is monitoring antimicrobial usage in food-producing animals.

12. Will you further discuss FDA's policy on judicious use of antimicrobials in food producing animals, which aims to maximize therapeutic efficacy while also minimizing the selection of resistant microorganisms?

The goal of FDA's judicious use strategy is focused on mitigating antimicrobial resistance by eliminating the use of medically important antimicrobials in food-producing animals for production (e.g., growth promotion) purposes and limiting therapeutic use to legitimate animal health needs (i.e., disease treatment, control, and prevention) that are under veterinary oversight.

It's essential that we take steps to ensure that all uses of antimicrobials, in both veterinary and human healthcare settings, are judicious and consistent with the principles of antibiotic stewardship. FDA continues to work with Federal, academic, and industry partners to obtain more information about how, when, and why animal producers and veterinarians use medically important antimicrobial drugs. Additional information about how these antimicrobials are being used on the farm will help the agency to assess associations between antibiotic use practices and antimicrobial resistance.

13. Why is it so important to have veterinary oversight or consultation when utilizing medically important antimicrobials in food-producing animals?

Veterinarians play a critical role in diagnosing disease and in the decision-making process related to instituting measures to treat, control, or prevent disease. Veterinary oversight of medically important antimicrobials ensures that prescribing decisions are based on professional judgements about the risk of a specific bacterial disease and whether it would be appropriate in a particular situation to use medically important antimicrobials for prevention purposes. Such factors include whether: (1) there is evidence that the drug will be effective in treating the particular disease; (2) such preventive use is consistent with accepted veterinary practice; (3) the use is intended to address particular bacteria; (4) the use is appropriately targeted to animals at risk of developing a specific disease; and (5) there are no reasonable alternatives for intervention.

14. What is the status of implementation on FDA's judicious use policy and how has implementation progressed since the guidance was first published in 2013?

In January 2017, FDA completed its three-year initiative to eliminate the use of medically important antimicrobial drugs for production purposes (e.g., growth promotion) and require veterinary oversight for the remaining therapeutic uses of these drugs in the feed or drinking water of food producing animals. All affected animal drug sponsors voluntarily worked with FDA to make the requested changes to their product labels. All 292 affected animal drug applications were either aligned with the Agency's recommendations or, in some cases, were voluntarily withdrawn by the drug sponsor. As a result of the changes made by animal drug sponsors to align their products with FDA's recommendations in GFI #213, medically-important antimicrobials can no longer legally be used in the feed or drinking water of food-producing animals for production (e.g., growth promotion) purposes and can only be used for therapeutic purposes in the feed or water of food-producing animals with the oversight of a licensed veterinarian.

FDA finalized updated Veterinary Feed Directive (VFD) regulations in June 2015 to facilitate veterinary oversight of feed-use antibiotics. These regulations went into effect October 1, 2015. The updated VFD regulations provide veterinarians a framework for authorizing the use of medically important antimicrobials in feed.

Based on inspection activities carried out by FDA's Office of Regulatory Affairs (ORA) and state feed regulatory programs, implementation of the VFD Final Rule has generally gone

well. Of the approximately 190 VFD orders inspected during the 2017 VFD Inspection Assignment, nearly 100% have been signed by a veterinarian aware of the state or federal veterinarian-client-patient relationship (VCPR) requirements that apply in the state where they are issuing the VFD order. Based on this observation, we believe affected stakeholders have been learning and adopting the practices necessary for ensuring compliance with the VFD regulation and supporting antimicrobial stewardship.

15. What additional steps do you believe FDA and industry should be taking to further address the harms of antimicrobial resistance? Are there additional tools that FDA needs to better address antimicrobial resistance?

Last January, FDA published its key initiatives for the next five years, which include the following:

- Align antimicrobial drug products with the principles of antimicrobial stewardship in veterinary settings.
- Support efforts to foster stewardship of antimicrobials in veterinary settings.
- Assess the impact of strategies intended to curb the emergence of antimicrobial resistance associated with the use of antimicrobial drugs in veterinary settings.

FDA continues to work with Federal, academic, and industry partners to obtain more information about how, when, and why animal producers and veterinarians use medically important antimicrobial drugs. Should FDA identify further steps that are necessary to address the potential harm of antimicrobial resistance, we will work with our Congressional partners to request additional tools or authorities, as appropriate.