STATEMENT

OF

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FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"REAUTHORIZATION OF THE ANIMAL DRUG USER FEE PROGRAMS"

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Introduction

Good morning, Chairman Guthrie, Ranking Member Eshoo, and Members of the Subcommittee. I am Tracey Forfa, Director of the Center for Veterinary Medicine (CVM) at the Food and Drug Administration (FDA or the Agency), under the Department of Health and Human Services (HHS). I have also had the honor of serving as the Deputy Director of CVM for the last 15 years. I am grateful for this opportunity to discuss FDA's proposals for reauthorization of the Animal Drug User Fee Act and the Animal Generic Drug User Fee Act for an additional five years (ADUFA V and AGDUFA IV).

With the enactment of ADUFA in 2003 and AGDUFA in 2008, Congress brought CVM the needed infusion of funds to resolve a long-standing backlog of animal drug applications and created efficiencies and predictability in the review process. Congress also created an opportunity – at five-year intervals – for CVM and industry to assess these user fee programs with the intention of advancing the animal drug review process to accommodate new developments and address new challenges. These are highly successful programs that facilitate the availability of approved products for food-producing and other animals, and foster a reliable review framework to accommodate drug development. Both programs help FDA maintain a stable scientific and technical workforce, improve timely communications with drug sponsors, and achieve other efficiencies such as reduced review times in the drug application review process while maintaining science-based regulatory standards for animal drug safety and efficacy.

Since Congressional passage of ADUFA, FDA has approved over 360 new animal drugs (both original approvals and major enhancements to these approvals, such as approval for new

indications or new species). Over the 14-year period since AGDUFA was passed, FDA has approved 227 generic new animal drugs. The availability of such drugs makes a difference in the lives of companion animals and pet owners. FDA recently approved three drugs that significantly changed the treatment options for diabetes and pain control in cats. Diabetes in cats is commonly treated with injectable insulin. FDA's recent approval of the first oral treatment for cats with diabetes expands those treatment options. Similarly, FDA's approval of two novel products to control pain in cats with osteoarthritis and following surgery greatly expands pain relief options for these animals.

FDA's recent approval of two generic versions of a commonly used pain medication for horses and dogs gives veterinarians and pet owners even more options to ensure our companion animals can lead pain-free lives. In another significant step to support animal health, FDA approved three drugs and conditionally approved another for canine-specific tumors. Drugs that are made available specifically for our pets reflect the strength of the human-animal companion bond in our society. Also, FDA supported producers of food-producing animals by approving several new generic versions of drugs ranging from parasite control in cattle to control of bacterial disease in honeybees.

During the current ADUFA and AGDUFA reauthorization, Congress has another opportunity to advance CVM's highly successful animal health programs. To that end, we have included several proposals for your consideration for ADUFA V and AGDUFA IV.

FDA is building onto the ADUFA IV performance goals. FDA and industry have agreed to report certain programmatic metrics, as well as engage an independent third-party to assess first

cycle reviews and other review processes, as part of the program's objective of expediting the animal drug development process.

And in addition to resuming some in-person meetings with regulated industry, we have agreed to enhance our pre-submission process by incorporating a new virtual meeting option which allows industry to receive feedback from CVM on their development plans faster, removing the time it takes to coordinate logistics required to have all parties convene face-to-face.

Further, we have agreed to host education conferences once a year that will be open to the public. FDA and industry will work together to choose topics for these conferences, and presentations will be posted publicly to FDA's "for industry" website.

FDA and industry also agreed to form workgroups to explore several potential program enhancements, including tools to enhance the efficiency of the review process, the drug residue analytical method trial process, the current policies and procedures on Animal Drug Availability Act (ADAA) drug combinations, and other areas where CVM could more efficiently provide feedback to sponsors on their drug development plan.

Additionally, for ADUFA V, we offer financial recommendations including implementing an Operating Reserve Adjustment, modifying the Workload Adjuster, and publishing an annual five-year financial plan.

AGDUFA IV proposals include agreements on four program enhancements: formalizing the Bioequivalence meeting process, creating a dosage-form-specific template letter, exploring and implementing a US-European Union (EU) Mutual Recognition Agreement (MRA) and US-

United Kingdom (UK) MRA and future MRAs with additional countries, and adding the request to open a generic investigational new animal drug (JINAD) file as a sentinel submission.

Additionally, for AGDUFA IV, we offer financial recommendations including modifying the Workload Adjuster, updating the fee structure, and adding a shortfall provision.

To further support the Center's ability to best serve the American public going forward, I believe it is also critical for you to understand CVM's role in the context of One Health and the larger U.S. public health system.

The international public health community increasingly recognizes the value of One Health, a collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment. CVM has provided leadership within FDA and HHS to both recognize and expand the use of One Health principles to address emerging threats including climate change and zoonotic diseases.

As the COVID-19 and mpox outbreaks have shown, understanding the pathology and potential interventions for animal infectious diseases can accelerate research into responses to related human diseases. One of the earliest Emergency Use Authorizations by FDA for a COVID-19 treatment was for a compound related to one designed to treat a different chronic coronavirus in cats. Similarly, understanding animal disease can help predict the emergence of novel human diseases; by studying influenza in pig populations, scientists can predict changes to the annual flu virus that circulates in humans and develop vaccines accordingly, all ahead of each flu season.

CVM's mission of "Protecting Human and Animal Health" is human health-led because of the numerous ways that our work intersects with key components of the human health ecosystem. While zoonotic diseases are sometimes the most readily available example of a One Health application, much of CVM's other work is also One Health driven, seated at the intersection of disciplines.

The health and wellbeing of our companion animals, who live in the homes and hearts of an estimated 68 percent of American households,[1] is an important contributor to the mental health of humans. Interacting with animals can directly impact people's physical health as well, by decreasing cortisol and lowering blood pressure. CVM's work to bring safe, effective products to market for these animals is indispensable to the pet-owning population.

In addition to animal safety and effectiveness, new animal drug and abbreviated new animal drug applications also include an assessment of their impact on the environment. And when new drugs are intended to be used in a food animal, part of CVM's evaluation is to ensure that the meat, milk, or eggs from these animals are safe for people to eat. The last decade has brought unprecedented advancement in technologies like gene editing and cell and tissue-based therapies. CVM utilizes our deep expertise in animal physiology and product safety and extensive experience in the review and post-approval monitoring of animal products to ensure the safety and functionality of innovative products. To bolster CVM authorities, we are looking to be able to require animal drug sponsors to make post-approval safety related labeling changes based on new safety information that becomes available after approval.

[1] https://newsinhealth.nih.gov/2018/02/power-pets

CVM is also involved in solution-based discussions of cattle emissions of greenhouse gasses as a focal point for action on climate change, including the potential for these gasses to be reduced by adding specific substances to cattle food. These technological advances continue to create bridges between human and animal health, and CVM's multi-disciplinary expertise is an essential part of bringing products like these from concept to market in a safe, transparent, and reliable way. These products also highlight the need to build more statutory flexibilities into CVM's authorities to better enable it to facilitate innovation in such critical areas.

The explosion of products that cut across the traditional boundaries between human, animal, and environmental health has challenged CVM to assess the paradigms that govern our approval processes. Our current authorities include two product approval pathways: animal drugs and animal food additives. Both pathways require specific information to demonstrate safety and have limited post-market reporting requirements for manufacturers. For some new kinds of products coming to market, applying the specified statutory requirements is not scientifically necessary or appropriate to protect public health, and CVM looks forward to working with Congress to update our authorities over such products. In the interim, CVM is working to be as flexible as possible to facilitate safe and effective novel products coming to market without undue burden on the product sponsors.

Two of these flexibilities were included in the ADUFA IV authorization package. We have fulfilled our promise to fully implement those flexibilities by publishing final guidances on expanded conditional approval and on using alternative data sources and study designs in drug development. These alternatives can potentially reduce time spent on data collection and the need for animal testing.

CVM has taken actions to create flexibility in the product review processes. One achievement is our Veterinary Innovation Program. We started this program in 2019 to facilitate advancements in innovative animal product development by providing greater certainty in the regulatory process, encouraging development and research, and supporting an efficient and predictable pathway to approval for certain cellular products and intentional genomic alterations (IGAs) in animals. To date, there are 49 product developers enrolled in the program. The program produced its first approval in December 2020; this was for an IGA in the GalSafe pig, which was approved for both human food use and potential human therapeutic use. This approval allows for a genetic modification in pigs that eliminates a type of sugar, Alpha-gal sugar, found in red meats (including pork) that has the potential to cause severe allergic reactions in people. The field continues to expand into new territory – while not yet ready for widespread adoption, the first xenotransplantation of kidneys from a genetically modified pig into a human recipient was successfully completed in early 2022.

In 2022, CVM announced the first low-risk determination and intent not to enforce premarket approval for an IGA in an animal for human food use. This action allowed PRLR-SLICK cattle, which are altered to have a "slick" coat or short hair trait that has been reported to help cattle better withstand hot weather, and therefore temperature related stress, to enter the market without FDA approval on the basis of FDA's evaluation of data submitted by the sponsor and determination that the IGA product is low-risk and does not raise any safety concerns. This decision demonstrates CVM's commitment to a flexible, science- and risk-based process that allows innovative animal biotechnology products to efficiently reach the market. Since the SLICK decision, we have heard from developers that they are excited about the prospect of bringing other lower-risk animal biotechnology products forward and we are looking forward to

working on these products that can benefit people and animals, and that can improve the food supply.

I look forward to working with Congress to advance FDA's legislative proposals including strengthening post-market animal drug safety oversight and enhancing the availability of generic animal drugs. Today we are focused on FDA's reauthorization activities, and so I have provided a written summary of information about each program, our achievements to date, and our proposed enhancements and financial recommendations. I appreciate your consideration of these changes. I urge you to also consider the public's need for a stronger animal health system beyond the scope of drug product approvals, but also on post-market drug safety, and to work with us to enact solutions that will protect human and animal health this year and for generations to come.

Status of FDA's Reauthorization Activities

The ADUFA IV and AGDUFA III provisions of the Federal Food, Drug, and Cosmetic (FD&C) Act will sunset on October 1, 2023. Timely reauthorization is needed to ensure FDA's ability to deliver continued high levels of performance and help ensure there are no disruptions to these important programs. The final recommendations were transmitted to Congress in early January, and include, for each program, the goals letter outlining performance metrics, proposed legislative language, and a summary of public comments. Below is a high-level summary of the timeline for both the ADUFA and AGDUFA reauthorizations. All meeting minutes, transcripts, and *Federal Register* notices are available on FDA's website at https://www.fda.gov/industry/animal-drug-user-fee-act-adufa/adufa-meetings for ADUFA and https://www.fda.gov/industry/animal-generic-drug-user-fee-act-agdufa/agdufa-meetings for AGDUFA.

ADUFA	AGDUFA
• Public Meeting: May 2021 • Negotiations with industry: October 2021 through August 2022 • Stakeholder meetings: once every four months during negotiations • Final public meeting: December 2022 • Recommendations Transmitted to Congress: January 2023	• Public Meeting: May 2021 • Negotiations with industry: July 2021 through October 2021 • Stakeholder meetings: once every four months during negotiations • Final public meeting: October 2022 • Recommendations Transmitted to Congress: January 2023

ADUFA Background

The ADUFA Program began in fiscal year (FY) 2004, and the first three authorizations covering FYs 2004 through 2018 have supported enhancements including program innovation, evaluation, reduced timeframes, and predictability to the review process. Through successive reauthorizations, program enhancements have evolved and expanded to include reduced review timeframes, improvements in the review process, and extensive communication and consultation between drug sponsors and FDA throughout animal drug development. Review times prior to ADUFA exceeded 600 days on average, and are now 180 days or fewer, depending on the submission type; FDA has met or exceeded nearly all performance goals in previous and current ADUFA authorizations.

ADUFA IV, our current authorization covering FY 2019 through 2023, included a number of enhancements to the program. FDA moved to require 100 percent electronic submissions, which allows for a more efficient review process. During the current authorization FDA also worked on implementing the US-EU MRA of current good manufacturing practices to allow drug inspectors to rely upon information from drug manufacturing surveillance inspections conducted within each other's borders. The EU and FDA are engaged in ongoing discussions relating to the MRA. Thus far, we have completed the assessments of 16 member states. In September 2021, FDA and

the UK's Veterinary Medicines Directorate (VMD) announced their decision to expand the US-UK mutual recognition agreement to include inspections for animal drugs following the UK's exit from the EU. The pandemic highlighted the value of access to this information during a period when FDA had to postpone non-mission critical inspections to protect our investigators.

ADUFA IV also requires labeling revisions of some animal drugs, specifically, adding the Minor Species Index File number on indexed drugs for minor use and minor species, and adding the statement "Approved by FDA" and the new animal drug application number on all marketed new animal drugs. Additionally, new performance goals for pre-submission conferences and tissue residue method trial demonstrations were included in the authorization.

ADUFA Performance

FDA continues to deliver predictably high levels of performance against ADUFA goal commitments for timely review, as shown in Table 1. Final FY 2021 performance data show FDA exceeded the 90 percent on-time performance level for all nine submission types. Based on a preliminary analysis of FY 2022 performance, FDA currently has the potential to meet or exceed the review-time goal for all nine submission types.

Table 1: FDA Review Performance – ADUFA FY 2021: Final Data
90 Percent of Submissions Acted on by Goal Date

Application/ Submission Type	Filed	On Time	Overdue	Percent on Time
Original NADAs and Reactivations	4	4	0	100%
Administrative NADAs	7	7	0	100%
Non-Manufacturing Supplemental NADAs and Reactivations	7	7	0	100%
Manufacturing Supplemental NADAs and Reactivations	389	374	15	96%
Labeling Supplements	19	19	0	100%
INAD Studies	170	166	4	98%
INAD Study Protocols	158	157	1	99%
Presubmission Conferences	73	69	4	95%
Tissue Residue Method Demonstration	2	2	0	100%

NADA = New Animal Drug Application; INAD = Investigational New Animal Drug

Proposal for ADUFA V

ADUFA V builds on the success of prior ADUFA achievements and offers the following program enhancement recommendations. FDA agrees to maintain all the ADUFA IV performance goals.

FDA and industry have agreed to report certain programmatic metrics. These metrics will provide additional transparency to stakeholders on the success of the program. Some will be reported quarterly on the FDA-TRACK website and others will be reported annually in the ADUFA V performance reports to Congress. FDA will engage an independent third party to conduct an assessment of first cycle reviews as they pertain to the ADUFA program's objective of "expediting the animal drug development process and the review of new and supplemental animal drug applications and investigational animal drug submissions."

While CVM continues to offer in-person consultations, we have agreed to enhance our pre-submission conference process by incorporating a new virtual meeting option that will allow industry to receive feedback from CVM on their development plan faster. To provide helpful

information to external stakeholders on the animal drug approval process, FDA has agreed to conduct an industry education conference once a year that will be open to the public. FDA and industry will work together to choose topics for these conferences, and presentations will be posted publicly to FDA's "for industry" website.

To increase transparency and regulatory predictability for drug sponsors, FDA has agreed to publish a series of documents on topics important to the animal drug industry, including draft guidances and policies and procedures documents on topics such as raw data and chemistry, manufacturing, and controls (CMC) processes.

FDA and industry also agreed to form workgroups to explore:

- additional tools to enhance the efficiency of the review process, such as implementing a Clock Stop feature during review of sentinel submissions, which would allow sponsors to not lose review time while they are responding to amendment questions;
- the drug residue analytical method trial process for drugs intended for food-producing animals;
- the current policies and procedures on ADAA drug combinations to learn why the process is not used frequently and to understand how we might increase utilization to reduce the review time for these products; and
- how CVM could more efficiently provide feedback to sponsors on their drug development plan in a way that works best for both industry and CVM.

Additionally, we offer the following financial recommendations for ADUFA V:

- Implementing an Operating Reserve Adjustment, which creates a target for the range of available carryover funds each year of ADUFA V. The maximum cap on the reserve will be a gradual draw-down from 22 weeks in FY 2025 to 16 weeks in FY 2028. The minimum floor will be 12 weeks for the duration of the authorization. The calculations will not include unappropriated funds, and as part of this provision, FDA will eliminate the collection shortfall provision, the final year adjustment provision, and the provision to offset workload or shortfall by excess collections.
- Modifying the Workload Adjuster to update the base years to a rolling five-year average and a new provision that FDA will not add workload adjuster funds to the target revenue until the workload adjuster is invoked at greater than three percent for a second year and any year thereafter within the authorization.
- Publishing a five-year financial plan with annual updates by the end of the second quarter of each fiscal year.
- Making a technical fix for expanded conditional approval applications that are leveraging data from fully approved applications to be eligible for a 50 percent application fee rate.

The ADUFA V recommendations submitted to Congress include total fee revenue for FY 2024 of $33,500,000; in FY 2025 through FY 2028 this amount is subject to possible adjustments, including for inflation, workload, and the operating reserve adjustment.

AGDUFA Background

The AGDUFA program began in FY 2009 and has also supported enhancements including innovation, reduced timeframes, and predictability to the review process. This provides end users, including producers and pet owners, greater access to safe, effective, and more affordable

generic animal drugs. AGDUFA established a comprehensive set of performance goals to show significant improvement in the timeliness and predictability of the generic new animal drug review process. Review times prior to AGDUFA exceeded 700 days on average, and with the agreements for the current AGDUFA III authorization, are now between 60 and 240 days depending on the submission type; FDA has met or exceeded nearly all performance goals in previous and current AGDUFA authorizations. Since 2009, FDA has eliminated the review backlog, added flexibility through a shortened second-cycle review processes, and developed tools for industry to support submissions including question-based review as a framework for certain submissions.

AGDUFA Performance

FDA continues to review sponsor submissions and deliver predictably high levels of performance against AGDUFA goal commitments for timely review, as shown in Table 2. Final FY 2021 performance data show FDA exceeded the 90 percent on-time goal for all five submission types. Based on a preliminary analysis of FY 2022 performance, FDA currently has the potential to meet or exceed the review-time goals for all five submission types.

Table 2: FDA Review Performance – FY 2021: Final Data
90 Percent of Submissions Acted on by Goal Date

Application/Submission Type	Filed	On Time	Overdue	Percent on Time
Original ANADAs and Reactivations	10	10	0	100%
Administrative ANADAs	19	19	0	100%
Manufacturing Supplemental ANADAs and Reactivations	204	196	8	96%
JINAD Studies	216	205	11	95%
JINAD Protocols	52	50	2	96%

ANADA = Abbreviated New Animal Drug Application; JINAD = Generic Investigational New Animal Drug

Proposal for AGDUFA IV

The AGDUFA IV negotiated recommendations build on the success of the first three authorizations of the generic animal drug review program. They include agreements on four program enhancements:

- Formalizing the Bioequivalence meeting process, which has been tested with industry for over a year. FDA proactively schedules these meetings as soon as a data set is received, so the meeting is on the calendar for after the review is completed (180 days later). If a sponsor has any questions about the outcome of the review, they can use the meeting for a discussion. If there are no questions, the meeting is cancelled.
- Creating a dosage-form-specific template letter to use when a JINAD file is opened by a sponsor. This provides industry with FDA's expectations regarding the publicly available CMC or manufacturing specific information related to their dosage form and is included in our response to their request to open a JINAD file.
- Exploring and implementing a US-EU MRA and US-UK MRA and future MRAs with additional countries to reduce costly and redundant pre-approval inspections.

- Adding the request to open a JINAD file as a sentinel submission with a performance goal that will be reported annually in the performance report to Congress.

Additionally, we offer the following financial recommendations for AGDUFA IV:

- Modifying the Workload Adjuster to update the base years to a rolling five-year average, adding two new submission types that are good indicators of future workload into the calculation, and adding a maximum cap of 25 percent for any workload adjuster annually.
- Updating the fee structure, including the percent of revenue derived from each of the three fee types, and adding a one-time flat-rate JINAD file fee.
- Adding a shortfall provision to allow FDA to add any under-collections to the target revenue during the fee-setting process.

The AGDUFA IV recommendations submitted to Congress include total fee revenue for FY 2024 of $25,000,000; in FY 2025 through FY 2028 this amount is subject to possible adjustments, including for inflation, workload, and collections shortfall.

Additional Statutory Enhancements

In the Animal Drug and Animal Generic Drug User Fee Reauthorization Amendments of 2018, Congress included some additional program enhancements. The first program enhancement was expansion to our conditional approval authority. Conditional approval is a special approval pathway under which a sponsor can make an animal drug available after proving that the drug is safe and showing a reasonable expectation of effectiveness, but before collecting all the effectiveness data needed for full approval. Before this program enhancement, conditional approval was only available for uses in minor species or for minor uses in major species. Now

the expanded conditional approval incentives apply to development of new animal drugs for all species when the drug is intended for serious or life-threatening conditions or unmet animal or human health needs that require particularly difficult studies to demonstrate effectiveness. Antimicrobial drugs, however, are not allowed to use the expanded conditional approval pathway. To stand up the expanded conditional approval program, we published a draft guidance for industry in September 2019 and a final guidance in July 2021 clarifying the criteria for determining a drug's eligibility for the expanded conditional approval pathway. Since the start of ADUFA IV, 20 drugs have been found eligible and FDA has conditionally approved three products for marketing using the expanded authority. The conditional approval of these three drugs using the expanded conditional approval pathway allowed medications that control seizures, delay the onset of congestive heart failure, and manage clinical signs of acute pancreatitis to reach the marketplace more quickly, and are giving dogs suffering from these conditions earlier access to drugs to manage these serious diseases.

As part of ADUFA IV, Congress asked us to assist sponsors in incorporating complex adaptive and other novel investigative designs, data from foreign countries, real-world evidence, biomarkers, and surrogate endpoints in the proposed clinical investigation protocols and applications for new animal drugs. We had a public meeting to begin this work in July of 2019 and then wrote four draft guidances for industry. These draft guidances were published in July 2020; we collected public comments on them and published final guidances in October 2021. We have participated in in-depth conversations with industry stakeholders on how to apply the principles in these guidances over the last several months and will continue to do so.

Congress also asked FDA to address some areas of our animal food ingredient pre-market review program, which included publishing a Guidance for Industry to address pre-submission

considerations for Food Additive Petitions. We finalized this guidance in December 2020. It describes the type of information stakeholders might consider, including recommendations for investigational food additive files, use of foreign data, circumstances when we recommend submitting study protocols, an explanation of our review process, and best practices for communicating with us along the way. Additionally, FDA publishes information on FDA-TRACK for Food Additive Petitions and Generally Recognized as Safe (GRAS) notices including reviews completed on time, number of submissions received, and number of files withdrawn.

The ADUFA IV reauthorization also included provisions related to Antimicrobial Resistance and Veterinary Oversight. In June 2021, FDA issued final Guidance for Industry (GFI) #263 to explain our recommended process for sponsors to voluntarily bring any remaining approved animal drugs containing antimicrobials of human medical importance under the oversight of licensed veterinarians. The process for doing this involves changing the approved marketing status from over-the-counter (OTC) to prescription. GFI #263 has a two-year voluntary implementation period. By June 11, 2023, FDA anticipates that all new covered products entering distribution channels will be labeled as prescription products. FDA intends to allow existing inventory of OTC-labeled products that may already be in distribution channels to deplete.