

Fight Antibiotic Resistance: Support a Meaningful Reauthorization of the Animal Drug User Fee Act

Congress will soon be working on reauthorization of the [Animal Drug User Fee Act](#) (ADUFA), which expires on September 30, 2018. ADUFA amends the Federal Food, Drug, and Cosmetic Act (FFDCA), the law that assigns responsibility to FDA for ensuring that animal drug products (including antibiotics) are safe and effective for animals and the public. One of the major safety issues that FDA must address is the spread of antibiotic resistant bacteria that result from the inappropriate use of antibiotics. This urgent public health threat can be addressed in part by stemming the overuse and misuse of antibiotics in food-producing animals. In order to fulfill its mandate to ensure the safety of animal drugs, FDA must collect information to evaluate the extent of antibiotic use and its contribution to resistant pathogens, and it must set limits on the use of animal antibiotic drugs to prevent overuse. To date, the FDA has made only partial progress on each of these critical tasks.

ADUFA reauthorization represents an important opportunity to protect public health, and to enlist the support of animal drug manufacturers in mitigating the threat of antibiotic resistant bacteria. In particular, ADUFA reauthorization should:

- 1) Direct the FDA to set duration limits on the use of medically important antibiotics, consistent with the agency's [Guidance for Industry #152](#) and;
- 2) Allocate a portion of the funds collected under ADUFA to support collection of species- and indication-specific on-farm antibiotic use data.

Background

ADUFA became law in 2003, and Congress has reauthorized it twice, in 2008 and 2013. The Act authorizes FDA to collect fees from animal drug manufacturers to support the review of new animal drugs. It also sets performance goals for FDA drug evaluators, giving drug manufacturers the assurance that new animal drug applications will not languish. Prior to reauthorization every five years, FDA must negotiate a new fee schedule with the regulated industry, represented by the Animal Health Institute. FDA must also consult with other stakeholders, including patient and consumer advocacy groups, although those groups' advice has tended to fall on deaf ears. That is why in 2008, Congress inserted provisions favored by public health advocates in the reauthorization to require FDA to collect data from drug manufacturers on the sales of antibiotics for use in food animals, and to report it publicly.

Almost ten years later, these sales data have proven essential to understanding the extent to which the food animal industry continues to rely upon, and even expand, its use of antibiotics. However, the current data give only an overview and leave many areas uncertain. For example, the FDA currently relies on estimates from drug manufacturers to determine which animal species account for the most use, and does not include information on why antibiotics are used. Without this information, it is impossible to pinpoint the policies that will bring the biggest reductions in inappropriate antibiotics use or to measure the impact of actions to address resistance.

At the same time, over the past ten years FDA has developed guidance for industry to promote better stewardship of antibiotics, and affirmed the need for appropriate duration limits as part of that stewardship¹. However, to date, it has not taken final action to put those duration limits in place.

¹ CVM Update. *FDA Seeks Public Input on Next Steps to Help Ensure Judicious Use of Antimicrobials in Animal Agriculture*. September 12, 2016, <https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm520110.htm>

ADUFA provides an opportunity to address both inadequacies. As described below, both proposals are consistent with long-established FDA policy and commensurate with the policy objectives of the FFDCFA.

1) Require FDA to limit duration of antibiotic use consistent with its guidance.

FDA has long acknowledged that using medically important antimicrobials in food animals for long or unlimited durations increases the risk of antibiotic resistance. As far back as the 1970s, FDA required specific safety studies on antibiotic resistance to support applications for antibiotics administered in feeds for any use over 14 days.² In 2003, FDA issued [Guidance for Industry #152](#) (GFI#152), which establishes a risk management approach to resistance for all antibiotic drugs used in food animals. The Guidance recommends, for example, that antibiotics found to have high or medium risk of an adverse human health effect related to resistance not be administered to a group of animals for more than 21 days (see Tables 7 and 8)³. In 2013, FDA issued [Guidance for Industry #213](#), which calls for “explicitly defined duration of dosing” on new drug label indications because “giving antimicrobial drugs to food-producing animals at low levels for long periods of time and in large numbers of animals may contribute to antibiotic resistance.”

Yet as FDA noted in a September 2016 [announcement of a request for comment](#), some 32% of the products containing medically important drugs for use in in feed or water have label indications without duration limits. FDA’s 2016 [request for comment](#) fostered hope that the agency would take action to “establish appropriately targeted durations of use” for these drugs. However, its formal request for comments includes examples of “acceptable” duration limits that are troubling. By indicating that durations of 112 days in chickens and up to 15 weeks in pigs may suffice—FDA’s request casts doubt on whether the agency intends to undertake meaningful change. Both examples are much longer than the 14 and 21 days in existing regulation and guidance, which were set to protect human health.

To address the inconsistency in FDA policy on duration limits, the ADUFA reauthorization should require FDA to set duration limits for drug labels consistent with GFI#152, by a certain date. In particular, Congress should require FDA to set duration limits for all medically important antimicrobials. For any veterinary drug that the agency has found to have a high or medium risk to human health, based on an FDA assessment under GFI #152 or one submitted to FDA by a drug sponsor, the maximum duration limit should be no more than 21 days.

² See 21 CFR 558.15; https://www.fda.gov/ohrms/dockets/ac/02/slides/3816s2_01_Gilbert.ppt).

³ Guidance for Industry #152 Table 7 ranks extent of use as high, medium, or low. In Table 7, any flock- or herd-wise use is considered high extent of use independent of time and any use in a select group of animals for more than 21 days is ranked as high extent of use. GFI #152 Table 8 describes potential risk management steps based on risk, with more restrictive steps recommended for drugs found to have a higher risk. Table 8 lists low extent of use for high-risk drugs and low or medium extent of use for medium-risk drugs. In either case, according to Table 7 any use over 21 days is considered high or medium, so if the tables are applied as written then a duration of over 21 days would not be considered appropriate for drugs that are found to have high or medium risk.

2) Designate 5% of the ADUFA fees to collect data on how antibiotics are used through sampling of records of medicated feeds delivered to livestock farms.

Better information on antibiotic use on farm is needed to support the drug approval process. Yet none of the ADUFA user fees supports this critical function. Recent changes in federal regulations require feed manufacturers to keep and make available to the FDA records of any feed containing medically important antibiotics delivered to farms⁴. These records, feed distribution records and associated veterinary feed directives, include the indication and type of animal receiving the feed along with other relevant information.

According to FDA, “improved data” would yield “improved information for science-based decision making in the approval and monitoring of safe and effective antimicrobial drugs.”⁵ The FDA Science Board has twice identified the need for these data⁶, the GAO has done so three times⁷, and the [2015 National Action Plan to Combat Antibiotic Resistant Bacteria](#) includes a similar recommendation.

Despite this consensus, FDA has no sustainable system in place to collect data on amounts of antibiotics used on farm, a deficiency that the agency has repeatedly blamed—most recently at a meeting of the Presidential Advisory Council on Combatting Antibiotic Resistant Bacteria in September 2017—on resource constraints. Since 2016, FDA has required⁸ drug makers to estimate sales by species but these estimates are based on national sales, not actual data from the farm, and they provide no information on indication or production class. FDA has also made [several short-term grants](#) to researchers affiliated with universities to collect on farm use data, but the agency has not indicated any intent to build on these grants to create an ongoing sustainable data collection system. Congressional action is sorely needed.

Congress should direct FDA to use ADUFA funds to collect and report data on amounts of antibiotics delivered to farms as medicated feed. Congress should direct FDA to sample feed distribution reports maintained under 21 CFR 558.6 (c) (3) to identify amounts of antibiotics used, the purposes for the use, and the species and production classes receiving the feed. This would require FDA to sample both feed distribution records and associated veterinary feed directives (VFDs) not just VFDs alone, since VFDs may not necessarily be filled.

Reauthorization should allocate at least 5% of fee revenue to surveillance of medicated feeds delivered to farms and require FDA to make the results of that surveillance public.

⁴ 21 CFR 558.6 Veterinary Feed Directives

⁵ Federal Register 77(145):44178 July 27, 2012

⁶ FDA Science Advisory Board. 2007. National Antimicrobial Resistance Monitoring System (NARMS) Program Review. Page 4. Available from: https://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_06_NARMS%20Review%20Update.pdf; FDA Science Advisory Board. 2017. Science Board Review of the National Antimicrobial Resistance Monitoring System. Page 7. Available from: <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM564273.pdf>

⁷ GAO. 2017. Antibiotic Resistance: More Information Needed to Oversee Use of Medically Important Drugs in Food Animals, GAO-17-192. Available from: <http://www.gao.gov/assets/690/683130.pdf>; GAO. 2011. Antibiotic Resistance: Agencies Have Made Limited Progress Addressing Antibiotic Use in Animals, GAO-11-801. Available from: <https://www.gao.gov/products/GAO-11-801>; GAO. 2004. Antibiotic Resistance: Federal Agencies Need to Better Focus Efforts to Address Risk to Humans from Antibiotic Use in Animals, GAO-04-490. Available from: <https://www.gao.gov/products/GAO-04-490>

⁸ Federal Register 81(91):29129 May 10, 2016.