July 16, 2019

Dr. Steven Solomon
Director, Center for Veterinary Medicine
U.S. Food and Drug Administration
5630 Fisher Lane, Rm. 1061
Rockville, MD 20852

RE: FDA's RECENTLY ANNOUNCED FUNDING OPPORTUNITY TO HELP DEFINE DURATION OF USE FOR CERTAIN MEDICALLY IMPORTANT ANTIMICROBIAL DRUGS FOR FOOD ANIMALS

Dear Dr. Solomon:

The Pew Charitable Trusts (Pew) and the Infectious Diseases Society of America (IDSA) appreciate the work that the U.S. Food and Drug Administration (FDA) is undertaking to establish appropriate, science-based duration of administration limits for all medically important antibiotics as part of its five-year plan to improve antibiotic use in food animals[1]. We recognize the practical challenges associated with establishing appropriate durations of use for more than 80 animal drugs and encourages the agency to prioritize its efforts based on factors such as each drug's importance to animal health.

Slowing the emergence of resistant bacteria requires appropriate use of antibiotics in all settings, including animal agriculture[2]. However, many medically important antibiotics can still be[3] legally given to animals in ways that do not meet the Food and Drug Administration's definition of judicious use[4]. For example, many antibiotic labels allow[5] for very long or undefined durations of use[6], meaning that they can be given to animals for weeks or months, or even indefinitely. Additionally, some label duration limits are tied to subjective or poorly defined external factors, such as when the animal experiences "times of stress."

FDA has publicly recognized [7]that "long-term or open-ended use of medically important antibiotics is a significant stewardship issue" and that labeling medically important antibiotics "for continuous or undefined durations of use is not consistent with judicious use." Using the

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[1] https://www.pewtrusts.org/en/research-and-analysis/articles/2018/12/11/highlights-of-fdas-5-year-plan-to-improve-antibiotic-use-in-food-animals
[2] https://www.pewtrusts.org/en/research-and-analysis/articles/2017/07/11/link-reaffirmed-between-antibiotic-use-in-animal-agriculture-and-the-public-health-risk
[3] https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2016/10/judicious-animal-antibiotic-use-requires-drug-label-refinements
[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-209-judicious-use-medically-important-antimicrobial-drugs-food-producing-animals
[5] https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2016/10/judicious-animal-antibiotic-use-requires-drug-label-refinements
[6] https://www.pewtrusts.org/en/research-and-analysis/articles/2018/09/13/antibiotic-stewardship-in-animal-agriculture-requires-defined-durations-of-use
[7] https://www.federalregister.gov/documents/2016/11/29/2016-28660/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing

right antibiotic for the optimal amount of time is fundamental to antibiotic stewardship[8]. It protects the health of food animals, slows the emergence of resistance, and maximizes the probability of achieving the desired clinical response. FDA's current[9] animal drug approval process requires the establishment of science-based duration limits, but the agency approved many animal antibiotics long before these requirements were in place.

Adding defined, science-based duration limits will be relatively easy and straightforward for many of the nearly 30 percent[10] of animal antibiotics labels that lack them. For example, where data exist, drug sponsors can use information from comparable antibiotics already approved for identical or similar indications that have well-defined duration limits. Still, the collection of new data will be necessary for some antibiotics. And because generating new data is time- and resource-intensive, FDA must put the highest priority in this process on those drugs most critical to animal and public health.

FDA should develop a robust, transparent, and evidence-based process to decide the animal antibiotics on which to collect new data first, based on the following criteria:

- **Are new data really needed?** Or are other relevant data sources available, such as in the scientific literature or in dossiers of approved drugs, that drug sponsors can use to establish scientifically valid duration limits without having to initiate new research?
- **What other antibiotics with defined durations of use are available to address the same diseases?** Is the product that lacks a defined duration of use the only viable option to address a disease?
- **What antibiotic or non-antibiotic options, such as vaccines or changes in management practices, could help address the disease?** Table 1 summarizes these data.
- **How important are the diseases addressed by the antibiotic?** Does the disease have a high impact on animal health, public health, or the U.S. agricultural economy?

For example, FDA should put the higher priority on collecting data for antibiotics with limited alternatives. Because the agency has approved several antibiotics with comparable human health importance that do have durations of use for treating pneumonia or bacterial enteritis in cattle and swine, collecting new data to establish such limits for other antibiotics to treat these diseases should be a lower priority. In contrast, there are few or no treatment options with duration limits in other diseases important to animal health. Therefore, collecting new data to establish appropriate limits for these drugs should be a higher priority.

In conclusion, having publicly recognized the lack of duration limits as a problem for several years, FDA must now move quickly on implementing duration limits where data exist for comparable products, while establishing a systematic, data-driven process for prioritizing the

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[8] https://www.pewtrusts.org/en/research-and-analysis/articles/2018/12/17/comprehensive-framework-is-established-for-antibiotic-stewardship-in-animal-agriculture
[9] https://www.federalregister.gov/documents/2016/09/14/2016-21972/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing
[10] https://www.pewtrusts.org/en/research-and-analysis/articles/2016/10/04/judicious-animal-antibiotic-use-requires-changes-to-drug-labels

remaining animal antibiotics that need additional data most urgently. This will help ensure the efficiency and effectiveness of FDA actions on these issues and better protect animal and public health. In addition, duration of use label instructions provide veterinarians with information that is needed to make judicious antibiotic prescribing choices and advance antibiotic stewardship in the field of animal production.

Sincerely,

The Pew Charitable Trusts
The Infectious Diseases Society of America (IDSA)

Table 1

Antibiotics to Treat Certain Animal Diseases Lack Defined Durations of Use

FDA should collect data to set limits promptly for drugs most important to animal health and without alternatives

Diseases for which antibiotics without duration limits are approved	Number of approved antibiotics without duration limits[*]	Availability of approved antibiotics with defined durations for use in...[†]		Disease identified by U.S. Department of Agriculture-led expert group as high priority for development of antibiotic alternatives[‡]
		...feed or water	...other administration routes (e.g., injection)	
Cattle				
Anaplasmosis	Few	None	Few	Yes
Bacterial enteritis	Few	Several	Several	-
Liver abscesses	Several	None	None	Yes
Pneumonia	Few	Several	Several	Yes
Swine				
Atrophic rhinitis	Several	Few	None	Yes
Pneumonia	Few	Several	Several	Yes
Inestinal parasites	Few	Non-antibiotic parasiticides available		-
Bacterial enteritis/swine dysentery	Several	Several	Few	Yes
Jowl abscesses (Group E Streptococci)	Few	Yes for other Streptococci/animal species		
Chickens				
Infectious coryza	Few	Several	N/A[§]	-
Chronic respiratory disease	Few	Several	N/A[§]	-
Necrotic enteritis/ colibacillosis	Several	Few	N/A[§]	Yes
Fowl cholera	Few	Several	N/A[§]	-
Intestinal parasites	Few	Non-antibiotic parasiticides available		-
Coccidiosis	Few	Several	N/A[§]	Yes
Turkeys				
Coccidiosis	Few	Several	N/A[§]	Yes
Fowl cholera	Few	Several	N/A[§]	-

Note: The table provides an overview of FDA-identified animal diseases for which antibiotics without duration limits are approved, as well as information regarding the availability of other treatment options for those diseases. "Few" refers to one or two approved antibiotics; "several" indicates three or more. Determining the availability of viable substitutes for an antibiotic without duration limits in a specific situation requires additional data and must occur under the guidance of a veterinarian. Not every existing option may be a feasible substitute. For instance, different strains of bacteria can cause pneumonia and may not all be susceptible to each of the available antibiotics. Additionally, some antibiotics may be approved only for certain production classes or specific animal age groups. In some cases, extra-label uses of approved drugs may be a viable option but may be prohibited in other cases. Similarly, switching from feed or water administration to other routes may logistically be more feasible in some situations.

[*] The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Establishing Appropriate Durations of Therapeutic Administration; Request for Comments, 81 Fed. Reg. 63187 (Sept. 14, 2016), https://www.federalregister.gov/documents/2016/09/14/2016-21972/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing.

[†] U.S. Food and Drug Administration, "Animal Drugs at FDA," accessed March 28, 2019, https://animaldrugsatfda.fda.gov/adafda/views/#/search.

[‡] United States Department of Agriculture, "Alternatives to Antibiotics, Research Gap Analysis Workshop"(Cattle, Poultry, and Swine Working Group Reports, 2nd International Symposium on Alternatives to Antibiotics, Paris, Dec. 12-15, 2016), https://www.ars.usda.gov/alternativestoantibiotics/Symposium2016/ATAWorkshop2016.html.

[§] Other administration routes are not practically feasible.