THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 1700 215.575.9050 Phone
Philadelphia, PA 19103-7077 215.575.4939 Fax

901 E Street NW, 10th Floor 202.552.2000 Phone
Washington, DC 20004 202.552.2299 Fax
www.pewtrusts.org

September 13, 2019

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

RE Docket No. FDA-2019-N-2281: FDA's PUBLIC MEETING ON ALTERNATIVE APPROACHES IN CLINICAL INVESTIGATIONS FOR NEW ANIMAL DRUGS

Dear Dr. Solomon:

The Pew Charitable Trusts (Pew) supports the U.S. Food and Drug Administration's (FDA) efforts to strengthen the stewardship of antibiotics in animal agriculture and to develop industry guidance on the appropriate use of alternative approaches in clinical investigations of antibiotics and other animal drugs, as mandated by the 2018 reauthorization of the Animal Drug User Fee Act.[1] Many animal antibiotics requiring updated product labels have a long history of use and are subject to unique market constraints associated with drugs for food producing animals. Therefore, alternative investigative approaches that balance the need for rigorous safety and efficacy evaluations with the efficiencies afforded by appropriate use of existing data sources hold considerable promise. FDA's recent public meeting on this topic was a valuable first step and Pew appreciates the opportunity to provide additional written comments.

For food animal drugs, alternative clinical investigative approaches, such as the use of real-world evidence (RWE), data from foreign trials, biomarkers, and surrogate trial endpoints, can promote antibiotic stewardship by fostering innovation in the development of antibiotic alternatives and by optimizing the use of medically important antibiotics through the expeditious establishment of evidence-based duration limits for drugs that currently lack them. The labels of many medically important antibiotics still allow for very long or undefined durations of use. [2,3] This makes it legal to give these drugs to animals for extended periods of time that may span many months – a practice not consistent with judicious use.[4,5] As FDA has publicly recognized, these drugs were approved long before the current, stringent animal drug approval process was created and retroactively establishing defined durations of use for them will be central to the agency's stewardship efforts. For many of the drugs, existing data sources may support the establishment of appropriate duration limits, although the collection of some new data may be necessary.[6] Because generating new data is time and resource-intensive, guidance on the appropriate use of existing data, including RWE and foreign trials, in the clinical investigation of new animal drugs is needed. This information will be critical to optimize scarce resources, prioritize new data collection efforts, and enable the expeditious establishment of evidence-based duration limits.

To ensure the guidance will be optimally useful and appropriately supports FDA's stewardship efforts, Pew recommends the following:

1. **FDA should appropriately tailor the guidance to the unique characteristics of animal drugs while seeking alignment with corresponding guidance for human drug development where appropriate**

In many cases, FDA can and should learn from and, where appropriate, utilize resources that have already been developed to address similar issues in human drug development. For instance, last year FDA revised its guidance on the acceptability of foreign clinical studies during human drug development to ensure the quality and integrity of the resulting data and to adequately protect the study subjects.[7] Similarly, the 21st Century Cures Act (Cures Act) has mandated FDA's exploration of the use of RWE in regulatory decision making for human drugs. In response, FDA's Center for Drug Evaluation (CDER) published industry guidance[8] and put forth a framework[9] detailing the appropriate use of RWE. FDA has also published draft guidance on adaptive designs of clinical trials for human drugs[10] and established a biomarker qualification program.[11] To avoid duplication of efforts, minimize the potential for unnecessary discrepancies and confusion, and learn from applicable prior experience, FDA should draw on these and other pertinent existing documents and involve agency staff with relevant experience in the development of the new guidance. Experience from human drug development may, for instance, help define how 'alternative' evidence can be used most effectively given the inherent limitations of data not gathered through traditional clinical trials performed in the US, and inform methodologies for how best to surveil and conduct research with the newly acquired data. Learning from human drug development can be particularly valuable because experience with the use of RWE and other 'alternative' data sources in the veterinary sector has so far remained scarce. For RWE, for instance, veterinary experiences have so far been limited to few currently ongoing projects in companion animals.[12]

However, animal drugs pose several unique challenges that need to be carefully considered during guidance development. For example, animal populations may be more (or less) homogenous in genetics, age, nutrition and disease history than the human population, and subject to more significant influences of external factors such as weather, housing, or other environmental stressors that may affect their health. These factors may also be highly variable across operations, production systems, or geographic regions, and advances in animal husbandry practices or breeding can have significant effects over relatively short periods of time—thus possibly limiting the applicability of even relatively recent data. Electronic health, production and treatment record systems in animal agriculture are highly fragmented, limited in detail and functionality, typically not standardized across industry segments, supply chains, or operations, and differ significantly from human health records. Certain data sources in human medicine—such as billing databases—may not be applicable to (most) parts of the animal sector at all, and some data requirements, such as food safety related data needs, are unique to animal drugs. Finally, because many of the antibiotics that currently lack duration limits have been in use for decades, farmers and veterinarians may be able to access a richer and more diverse body of evidence regarding their optimal use than would be typical for human drug development.

To strike the right balance between drawing upon applicable experiences from human drug development and appropriately accounting for the unique requirements of the animal drug development process, FDA should establish a transparent and robust development plan for the

guidance document that actively engages relevant human and animal drug development experts throughout the process and that provides ample opportunity for public engagement. The public meeting FDA held earlier this year was an important step in that direction, but additional periodic opportunities for public input are needed.

2. FDA should provide specific guidance to drug sponsors on how alternative clinical approaches can be used to support the establishment of duration limits for antibiotics that lack them or approvals for non-antibiotic alternatives that have a long history of use

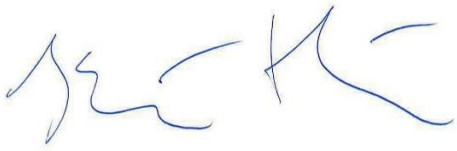
Many animal drugs that currently lack duration limits, as well as certain antibiotic alternatives that are not currently approved as animal drugs for such indications, have a very long history of use in veterinary medicine and ample 'alternative' data available—such as RWE or foreign data. In these cases, the available relevant data may be unusual in type, amount, detail, geographic representation, and time since collection. For instance, FDA has already solicited various kinds of information to support the establishment of evidence-based duration limits for antibiotics that lack them, including current use practices, times animals are at increased risk, veterinary decision-making around the use of the product – including duration of use – and available alternative treatment approaches.[13] Guidance is needed on what types of information may be usable in these specific circumstances, what minimum requirements and data quality standards may apply, and how those data can be used efficiently – for instance to inform trial design, generate research hypotheses, identify or refine trial endpoints or biomarkers, or support data extrapolations (potentially in combination with bridging studies). Such explicit guidance will be important to foster the development of antibiotic alternatives and enable the expeditious establishment of duration limits for drugs that currently lack them.

3. FDA should balance transparency and privacy protection for sensitive and/or proprietary data

Appropriate access to sensitive and/or proprietary data that strikes a balance between transparency and privacy protection is a longstanding, significant concern in the agricultural space. The issue is somewhat distinct from related concerns in human drug development. For instance, many data privacy concerns in the animal space are related to the product end-users, including potential food product liability, reputational risks for the food brand, and adequate protection of competitive advantages related to animal rearing. FDA has a long history of successfully navigating this issue. For instance, since 2009 FDA has been collecting, aggregating, analyzing, and publishing data on the quantities of antibiotics sold for use in food-producing species on an annual basis, and the agency has worked closely with the United States Department of Agriculture (USDA) on the collection of on-farm antibiotic use data.[14,15,16] Such prior experiences, as well as lessons learned during human drug development, will be valuable for FDA in establishing guidance on this issue. The agency will have to work closely with producers, drug sponsors, USDA, other relevant federal and state agencies, and other key stakeholders to find adequate, workable data infrastructure solutions. Pilot projects, in close partnership between public and private entities, would be useful to identify and overcome challenges related to data transparency and privacy. Such pilot projects could also provide the proof-of-concept needed to secure broader stakeholder buy-in on this important topic, and FDA should actively explore opportunities to establish such pilot programs.

In conclusion, Pew commends the agency for developing guidance on the appropriate use of alternative approaches to collect data for the clinical investigation of new animal drugs, recognizing the potential promise - and perils - these approaches hold for improving antibiotic stewardship. Given the urgency of the antibiotic resistance threat, FDA must move quickly to establish science-based duration limits for drugs that currently lack them, and to foster the development of new alternatives. FDA has an opportunity to accelerate this process and sustainably foster innovation in food animal drug development by providing guidance on the appropriate use of existing 'alternative' data sources such as RWE or foreign data that strikes a balance between ensuring rigorous scientific evaluations and promoting efficiency. Pew is looking forward to continuing work with FDA and other key stakeholders on this important issue, as well as antibiotic stewardship more broadly.

Sincerely,



Kathy Talkington, Director
Antibiotic Resistance Project
The Pew Charitable Trusts

Karin Hoelzer, Senior Officer
Antibiotic Resistance Project
The Pew Charitable Trusts

[1] Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (2018), https://www.congress.gov/bill/115th-congress/house-bill/5554/text.

[2] The Pew Charitable Trusts, "Judicious Animal Antibiotic Use Requires Drug Label Refinements" (The Pew Charitable Trusts, 2016), https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2016/10/judicious-animal-antibiotic-use-requires-drug-label-refinements.

[3] K. Hoelzer, "Antibiotic Stewardship in Animal Agriculture Requires Defined Durations of Use," The Pew Charitable Trusts, September 14th, 2018, https://www.pewtrusts.org/en/research-and-analysis/articles/2018/09/13/antibiotic-stewardship-in-animal-agriculture-requires-defined-durations-of-use.

[4] Food and Drug Administration, "FDA Releases Five-Year Plan for Supporting Antimicrobial Stewardship in Veterinary Settings" (2018), https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-five-year-plan-supporting-antimicrobial-stewardship-veterinary-settings.

[5] Food and Drug Administration, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals, Guidance for Industry #209" (2012), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-209-judicious-use-medically-important-antimicrobial-drugs-food-producing-animals.

[6] K. Hoelzer and N. Wong, "FDA Must Ensure That All Animal Anbtibiotics Have Defined Durations of Use," The Pew Charitable Trusts, April 1st, 2019, https://www.pewtrusts.org/en/research-and-analysis/articles/2019/04/01/fda-must-ensure-that-all-animal-antibiotics-have-defined-durations-of-use.

[7] Food and Drug Administration, "FDA Acceptance of Foreign Clinical Studies Not Conducted under an IND: Frequently Asked Questions" (2012), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-acceptance-foreign-clinical-studies-not-conducted-under-ind-frequently-asked-questions.
[8] Food and Drug Administration, "Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics, Draft Guidance" (2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drugs-and-biologics-guidance.
[9] Food and Drug Administration, "Framework for FDA's Real-World Evidence Program" (2018), https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence.
[10] Food and Drug Administration, "Adaptive Designs for Clinical Trials of Drugs and Biologics, Draft Guidance" (2018), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics.
[11] Food and Drug Administration, "Qualifying a Biomarker through the Biomarker Qualification Program," Food and Drug Administration, August 2nd, 2018, https://www.fda.gov/drugs/cder-biomarker-qualification-program/qualifying-biomarker-through-biomarker-qualification-program.
[12] E.M. Lund, "Power of Practice: Using Clinical Data to Advance Veterinary Medicine," *Veterinary Record* 176, no. 2 (2015): 46, http://veterinaryrecord.bmj.com/content/176/2/46.abstract.
[13] Food and Drug Administration, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Establishing Appropriate Durations of Therapeutic Administration; Request for Comments", 81 Fed. Reg. 63187-91 (September 15th, 2016), https://www.federalregister.gov/documents/2016/09/14/2016-21972/the-judicious-use-of-medically-important-antimicrobial-drugs-in-food-producing-animals-establishing.
[14] R.S. Singer and L. Porter, "Estimates of on-Farm Antimicrobial Usage in Broiler Chicken and Turkey Production in the United States, 2013 – 2017" (Mindwalk Consulting Group, 2019).
[15] United States Department of Agriculture, "Antimicrobial Use and Stewardship on U.S. Feedlots, 2017" (2019).
[16] United States Department of Agriculture, "Antimicrobial Use and Stewardship on U.S. Swine Operations, 2017" (2019).