THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

March 13, 2017

Cindy Burnsteel
Director-Division of Therapeutic Drugs for Food Animals
Center for Veterinary Medicine (HFV-130)
Food and Drug Administration
7500 Standish Pl.
Rockville, MD 20855

ATTN: Comment Docket No. FDA-2016-D-2635; The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals; Establishing Appropriate Durations of Therapeutic Administration

Dear Dr. Burnsteel:

The Pew Charitable Trusts (Pew) strongly supports the U.S. Food and Drug Administration (FDA)'s efforts to establish appropriately targeted durations of use for all antimicrobial drugs of importance to human medicine (i.e., medically important antimicrobial drugs). However, Pew urges the agency to go further and announce a concrete plan and timeline for making all necessary label revisions and to not restrict actions solely to durations of use. FDA needs to ensure that the labels of medically important antibiotics are consistent with all aspects of judicious use, which also includes specifying clear dosages and revising questionable indications. To signal a clear path forward for all stakeholders and to minimize administrative efforts, all necessary label revisions should take place at the same time and as soon as possible.

Pew is an independent non-partisan research organization which applies a rigorous, analytical approach to improve public policy, inform the public, and stimulate civic life. In our work on antibiotic resistance, we seek to reduce the inappropriate use of antibiotics in human healthcare and animal agriculture and to foster innovation in drug development.

To evaluate which revisions are still needed after full implementation of GFI #213 to bring the labels of medically important antibiotics into full compliance with judicious use principles , Pew recently conducted an analysis of all 389 labels for medically important antibiotics approved for food producing species (submitted as Appendix 1). This analysis provides the basis for our public comments.

1. **Labels with undefined durations of use are an important issue FDA needs to address, but injudicious indications and inappropriate dosage ranges are also important ways in which the labels of many medically important antibiotics fall short of judicious use and these shortcomings need to be addressed.**

Our analysis found that, after full implementation of GFI #213, more than 1 in 3 labels still will not fully meet judicious use standards, sometimes in more than one respect. Over 100 labels lack adequate restrictions on the duration of use, and nearly 80 labels raise concerns about whether the specified indication (e.g., maintenance of weight gain during times of stress) is judicious.[i] In addition, not all drug labels provide veterinarians with a clearly defined dosage. For example, as many as 30 drug labels specify an excessively wide dosage range, defined as a range that equals or exceeds 100 percent (e.g., 100-200 milligrams per kilogram). *The appended issue brief provides additional details on these important shortcomings.*

THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

2. In many cases, the necessary scientific information to establish evidence-based duration limits already exist and FDA needs to take action now to appropriately restrict duration of use in these cases.

Our analysis of labels without duration limits demonstrates that for many of the problematic antibiotic labels with no defined duration, other labels exist for the same or similar indications in the same animal species that do specify a duration of use. Therefore, scientifically based duration limits are in many cases available, although product-specific differences have to be considered, for example in administration routes (i.e., via feed, water, or other routes such as injection) or product formulation. In fact, for the most common antibiotics lacking a specified duration (i.e., sulfonamides, chlortetracycline, oxytetracycline, tylosin, lincomycin, virginiamycin, and penicillin), the majority of available labels clearly define durations. *The appended issue brief provides additional details on the labels with and without clearly defined durations.*

3. FDA should issue a new guidance setting forth deadlines by which companies would submit plans and timelines for evaluating all problematic labels

Publicly announcing next steps now has several advantages. With notice, drug companies that sponsor labels without appropriate duration limits as well as labels that are not judicious in other respects can incorporate all necessary changes into that process, avoiding multiple label revisions. Additionally, an announcement of FDA's plans on this issue will give stakeholders notice of impending changes, and provide an opportunity to collect data and conduct research as needed to support label changes.

4. FDA should specify the administrative process through which such label changes should be made, including specific guidelines for sponsors to make scientifically-based changes to problematic labels

To ensure revisions of problematic labels are based on strong scientific evidence, FDA could issue guidance outlining the administrative process for making the required label changes. Specifically,

a. **With regard to duration limits:** the guidance could clarify the extent and conditions under which drug sponsors can rely on already-existing information when establishing evidence-based duration limits on their labels. In other circumstances, such as 505(b) (2) applications, FDA recognizes that drug sponsors may reference existing data to support their applications, even if for some of the data the drug sponsor has not obtained the right of reference (e.g., because the drug sponsor was not involved in the study), and even if the drug sponsor may not have access to all of the raw data. FDA should clarify whether and how animal drug sponsors may rely on existing information, including information in the approval packages for other products, to support evidence-based duration limits. FDA could specify in guidance how drug sponsors are expected to demonstrate the applicability of existing duration data to their specific products (e.g., what bridging studies may be required), and what safety and efficacy studies the agency would require to approve such label changes. Similarly, FDA could clarify under which conditions evidence

THE PEW CHARITABLE TRUSTS

2005 Market Street, Suite 2800 215.575.9050 Phone
Philadelphia, PA 19103-7077

901 E Street NW 202.552.2000 Phone
Washington, DC 20004
www.pewtrusts.org

submitted in other jurisdictions may be applicable to the establishment of scientifically-based duration limits.

b. With regard to the withdrawal of certain problematic indications: FDA could specify that drug sponsors choosing to withdraw problematic indications that are not deemed to be judicious will have the option of utilizing the same regulatory approach as outlined in Guidance 213 for the voluntary withdrawal of growth-promotion indications from the labels of existing animal drugs. If drug sponsors instead choose to amend indications to comply with judicious use guidelines, the guidance could indicate that the process outlined above for relying on existing data to support scientifically based, medically appropriate duration limits would also be available to support scientifically-based indications.

c. With regard to dosage: FDA could specify the approach by which drug sponsors can modify dosage ranges. For instance, the agency could indicate that drug sponsors can voluntarily restrict dosage ranges within the limits of the already-approved dosage range for their product without the need for additional safety or efficacy studies because of a presumption of safety and efficacy across the entire dosage range.

In conclusion, Pew's analysis shows that the problem of injudicious labels, while not only restricted to labels without duration of use, is manageable. The analysis identifies the biggest issue areas, which can help FDA decide how to prioritize resources for the review and revision of antibiotic labels. Moreover, the analysis also demonstrates that in many cases the necessary scientific evidence may already exist to establish evidence-based restrictions that bring the labels into compliance with judicious use. Pew appreciates the opportunity to comment on this important topic and would value the opportunity for further dialogue.

Sincerely,

Kathy Talkington, Director
Antibiotic Resistance Project
The Pew Charitable Trusts

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

[i] See Appendix A- Table 1.