4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-2281]

Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs; Public Meeting; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comment.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing a public meeting entitled "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs." This public meeting and request for comments is intended to support FDA guidance development as required by the Animal Drug and Animal Generic Drug User Fee Amendments of 2018. The topics to be discussed will inform the development of guidance to assist sponsors in incorporating complex adaptive and other novel investigation designs, data from foreign countries, real world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs under the Federal Food, Drug, and Cosmetic Act (FD&C Act). FDA is seeking comments from stakeholders, including representatives of regulated industry, consumer groups, academia, veterinarians, and food producers.

DATES: The public meeting will be held on July 16, 2019, from 8:30 a.m. to 5 p.m. Submit either electronic or written comments on this public meeting by August 17, 2019.

ADDRESSES: The public meeting will be held at Johns Hopkins University – Montgomery County, Gilchrist Hall, 9601 Medical Center Dr., Rockville, MD 20850. Free parking is available on site.

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before August 17, 2019. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of August 17, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2019-N-2281 for "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its

consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Susan Storey, Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Pl. HFV-131, Rockville, MD, 20855, 240-402-0578, susan.storey@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing a public meeting entitled "Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs." This public meeting and request for comment is

intended to support FDA guidance development as required under section 305 of the Animal Drug and Animal Generic Drug User Fee Amendments of 2018 (Pub. L. 115-234). Section 305 directs FDA to develop guidance to address several alternative approaches in clinical investigations for new animal drugs, including incorporating complex adaptive and other novel investigation designs, data from foreign countries, real world evidence (including ongoing surveillance activities, observational studies, and registry data), biomarkers, and surrogate endpoints into proposed clinical investigation protocols and applications for new animal drugs under sections 512 and 571 of the FD&C Act (21 U.S.C. 360b, 360ccc). Section 305 also directs FDA to conduct a public meeting to allow the Agency to gather input from stakeholders, including representatives of regulated industry, consumer groups, academia, veterinarians, and food producers before developing the guidance.

II. Topics for Discussion at the Public Meeting

The purpose of this public meeting is to facilitate discussion and obtain input from stakeholders about the use of complex adaptive and other novel investigation designs, data from foreign countries, real world evidence, and biomarkers and surrogate endpoints in drug development and regulatory decision making.

The meeting is expected to include four sessions that focus on the following topics: (1) Complex adaptive and other novel investigation designs; (2) data from foreign countries; (3) real world evidence; and, (4) biomarkers and surrogate endpoints. Within each session and following all sessions there will be an opportunity for public comment. To facilitate the development of guidance on these topics, please consider the following questions. When responding please identify the topic and question in your response.

Topic 1: Complex adaptive and other novel investigation designs

1. In September 2018, FDA published draft Guidance for Industry: Adaptive Designs for Clinical Trials of Drugs and Biologics, which applies to human drugs and biologics (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics). How should these apply to study designs for animal drugs? What are the potential study adaptation features that could be applied to animal drug investigations? What are the challenges and possible solutions to apply these adaptations to studies for animal drugs? To what type of studies for animal drugs would these study designs be most applicable?
2. How does complex adaptive design differ from adaptive design? What constitutes other novel investigation designs? What examples are directly applicable to animal drug development?
3. Are there partnerships that can be formed between FDA and the regulated industry, academia, or other groups to facilitate the development or use of these novel investigational designs for animal drug development? What strategic work is needed to enable the regulated industry to make full use of these novel investigational designs for animal drug development? What methods are needed, such as the use of simulations or modeling, to facilitate the use of these novel investigational designs for animal drug development?

Topic 2: Data from foreign countries

For the purposes of this meeting, FDA considers data from foreign countries to be data from investigations or studies conducted outside the United States (U.S.). FDA can accept data from studies conducted outside the United States to support a new animal drug application, provided the applicant demonstrates that the data are adequate under applicable standards to support approval (section 569B of the FD&C Act; 21 U.S.C. 360bbb-8b). FDA also accepts data

from studies conducted outside the United States to support a food additive petition for a food additive intended for use in animal food, when provided by the petitioner (section 409(k)(1) of the FD&C Act; 21 U.S.C. 348(k)(1)). While the regulatory standards for approval differ between animal drugs and animal food additives, data from foreign countries can be used to support either approval if the data meet the appropriate regulatory standards.

1. What challenges and potential solutions do you have in meeting the requirements of substantial evidence of effectiveness, as defined in 21 CFR 514.4, when using data from foreign countries for an animal drug?
2. Typically in the United States, when we wish to show a test drug is no worse than an active control, that active control is an approved animal drug in the United States. A non-inferiority analysis is used to statistically demonstrate this relationship. In studies conducted outside the United States, an active control may be used that is not approved for that use in the United States. In the absence of a U.S. approval for the active control, FDA cannot interpret non-inferiority to the unapproved active control. What challenges exist in utilizing these studies? What criteria should FDA use to accept a study where the active control is not approved in the United States? What are potential options or solutions to enable FDA to use these studies?
3. What challenges exist in demonstrating that data from foreign countries were generated under conditions representative of typical conditions in the United States for an animal drug or food additive? What are potential solutions to these challenges?
4. What challenges exist in designing studies for an animal drug or food additive to meet the approval requirements of different jurisdictions? What are possible solutions to these challenges?

5. What challenges exist in study conduct and the collection and interpretability of data from foreign countries (both manual and electronic) that may influence study quality and data integrity to support the approval of an animal drug or food additive? What are possible solutions to these challenges?
6. What other challenges have you encountered and what potential solutions would you propose with regard to providing data from foreign countries to FDA?

Topic 3: Real world evidence

There is significant activity within FDA aimed at clarifying how to determine if real-world data (RWD) are sufficient to generate real-world evidence (RWE) that could be used for regulatory decision making by the Agency. In August 2017, FDA published a guidance document entitled, "Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices" (available at https://www.fda.gov/media/99447/download) and, in accordance with the 21st Century Cures Act (Pub. L. 114-255), released a draft framework entitled "Framework for FDA's Real-World Evidence Program" (available at https://www.fda.gov/media/120060/download) in December 2018 for human drug and biological products.

1. How should FDA define RWE for making regulatory decisions for animal drugs? What sources of RWD should FDA consider to generate RWE for animal drugs?
2. What challenges exist for the use of RWE for animal drug approvals? What are possible solutions to these challenges?
3. In what contexts might RWD/RWE be used to generate clinical evidence for regulatory decision making for animal drugs?
4. What factors should FDA consider when evaluating RWE for animal drugs?

Topic 4: Biomarkers and surrogate endpoints

Biomarkers have long been a part of veterinary medicine. Examples include routine tests such as body temperature, heart rate, complete blood cell count and clinical chemistry, radiographs, and intraocular pressure. Numerous technological advancements have greatly increased the number of available biomarkers while reducing their cost. Unfortunately, many potential biomarkers are not validated for their use and interpretation in clinical investigations. FDA's Center for Drug Evaluation and Research (CDER) has a formal Biomarker Qualification Program, related guidance, and affiliated consortia to support the development and use of biomarkers in regulatory decision making for human drugs (https://www.fda.gov/drugs/drug-development-tool-qualification-programs/cder-biomarker-qualification-program). FDA is seeking stakeholder feedback on how to best support the identification and development of new biomarkers for new animal drug applications and on ways to better incorporate biomarkers and surrogate endpoints into animal drug development.

1. What are the expectations of sponsors, researchers, veterinarians, and producers for the use of biomarkers in the context of animal drug regulation and how might biomarkers be used in addition to surrogate endpoints in the design and conduct of clinical studies?
2. Biomarkers are commonly used for diagnosing disease to enroll patients, sample size estimations, and pilot/proof-of-concept studies. What information should be provided to FDA to support their use in these contexts (e.g., analytical validation, clinical validation, establishing clinical utility, companion diagnostics etc.)?
3. What are the major challenges in translating potential biomarkers and/or surrogate endpoints into practical tools in clinical trials? What are possible solutions to these challenges?
4. How do we determine the evidentiary criteria for evaluating biomarker use?

5. Should FDA's Center for Veterinary Medicine develop a biomarker qualification program like CDER's? Would such a program be beneficial, and is it something that stakeholders (e.g., drug sponsors) would use? Are there other approaches to the development and acceptance of biomarkers for animal drugs?

III. Information about the Public Meeting

Additional information about the public meeting is available on our website at https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs. If time and space permit, onsite registration on the day of the public meeting will be provided beginning at 8 a.m. We will post a notice on the above website no later than July 12 as to whether onsite registration is available.

Streaming Webcast of the Public Meeting: This public meeting will also be webcast. Registration for the webcast is required. Information to register for the webcast is available at https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs. You can register for the webcast up until the time of the meeting.

If you have never attended a Connect Pro event before, test your connection at https://collaboration.fda.gov/common/help/en/support/meeting_test.htm. For a quick overview of the Connect Pro program, visit https://www.adobe.com/go/connectpro_overview. FDA has verified the website addresses in this document, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

Transcripts: Please be advised that as soon as a transcript of the public meeting is available, it will be accessible at https://www.regulations.gov. It may be viewed at the Dockets

Management Staff (see ADDRESSES). A link to the transcript will also be available at https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/public-meeting-incorporating-alternative-approaches-clinical-investigations-new-animal-drugs.

Dated: July 2, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2019-14528 Filed: 7/8/2019 8:45 am; Publication Date: 7/9/2019]