4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-N-0684]

Identification of Alternative In Vitro Bioequivalence Pathways Which Can Reliably Ensure In Vivo Bioequivalence of Product Performance and Quality of Non-Systemically Absorbed Drug Products for Animals; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public meeting; request for comments.

The Food and Drug Administration (FDA) is announcing a public meeting entitled "Identification of Alternative In Vitro Bioequivalence Pathways Which Can Reliably Ensure In Vivo Bioequivalence of Product Performance and Quality of Non-Systemically Absorbed Drug Products for Animals". The purpose of the public meeting is to discuss the use of in vitro methods as a mechanism for assessing the in vivo product bioequivalence (BE) of non-systemically absorbed drug products intended for use in veterinary species. FDA is seeking additional public comment to the docket, and is requesting that any written comments be submitted by [**INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER**].

Date and Time: The public meeting will be held on April 16, 2015, from 9 a.m. to 4 p.m.

Location: The public meeting will be held at the Center for Veterinary Medicine (CVM), Food and Drug Administration, 7519 Standish Pl., 3rd Floor, Conference Room A, Rockville, MD 20855. Parking is free.

Contact Person: Aleta Sindelar, CVM, Food and Drug Administration, 7519 Standish Pl., rm. 144, Rockville, MD 20855, 240-276-9230, FAX: 240-276-9241, email: BioequivalencePublicMeetingRegistration@fda.hhs.gov.

Registration: Registration is free and available on a first-come, first-served basis. Persons interested in requesting an opportunity to speak during the open public comment period must register by April 8, 2015, and must include a brief summary of comments with their registration. Those individuals will be contacted prior to the meeting regarding their participation. Persons interested in attending this meeting who are not requesting an opportunity to speak at the meeting must register by April 14, 2015. For general questions about the meeting, for assistance registering for the meeting, to request an opportunity to make an oral presentation, or to request special accommodations due to a disability, contact Aleta Sindelar (see Contact Person). Please include your name, organization, and contact information. Early registration for the meeting is encouraged due to limited time and space.

SUPPLEMENTARY INFORMATION:

I. Background

Given the imprecision and logistic challenges associated with clinical endpoint BE studies, FDA is exploring alternative pathways that can be applied to help ensure the equivalence of product performance and quality for those products that are non-systemically absorbed (locally acting).

The assessment of in vivo BE of non-systemically absorbed drug products has been a longstanding challenge facing drug manufacturers and regulators of human and animal health products. Although blood level BE trials remain the standard for comparing drug products that are systemically absorbed and that act at a target site reached via the blood (systemic circulation), such studies cannot confirm product in vivo BE when a drug is either not systemically absorbed or when it is associated with therapeutic effects occurring proximal to the site of absorption. To date, unless the active pharmaceutical ingredient met the criteria for highly soluble, as defined in CVM Guidance #171 entitled "Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles," clinical endpoint BE trials have provided the only option for generating inter-product comparisons. FDA is exploring whether an alternative in vitro BE approach may be considered when blood level BE studies are either not feasible or not appropriate, and when products do not meet the criteria for applying a Guidance #171-based biowaiver.

The assumption underlying the application of the in vitro BE approach is that equivalence in product physicochemical attributes and in vitro product performance translates to equivalence in product in vivo behavior. For sponsors with a right of reference to underlying safety and effectiveness data, the criteria for similarity of physicochemical attributes would be defined on the basis of the underlying dataset to confirm the comparability of the original formulation and pre- and post-approval changes in formulation or method of product manufacture. In the case of generic products, a more rigid approach to sameness would be used in terms of product composition and physicochemical characteristics. In both situations, physicochemical comparisons would be based upon a battery of in vitro test procedures, including a comparison of in vitro dissolution behavior under a range of physiologically-relevant conditions.

Examples of the kinds of products where in vitro bioequivalence concepts can potentially be applied include some orally administered products (e.g., Type A medicated articles), solutions, emulsions, ointments, creams, suspensions, transdermal products, and intra-mammary formulations. Due to unique issues raised by products employing modified release technologies, only immediate release formulations would be candidates for the in vitro BE assessment. For orally administered products, in vitro BE would be limited to disintegrated dosage forms. In cases when the administered drug acts both locally and systemically, blood level data may be used to confirm drug product BE of the systemic effects (and to confirm comparability of in vivo product disintegration in cases where multiple drugs are combined in a single solid oral dosage forms), while the additional in vitro dissolution data could be used to support the comparability of the local actions.

The in vitro BE approach should not be construed as a biowaiver, but rather as an alternative set of tests that would be handled in a manner consistent with that of an in vivo BE study. Specifically, (1) because an in vitro BE approach is not a biowaiver, sponsors would still need to meet the same environmental safety and human food safety requirements associated with products undergoing in vivo BE studies; (2) one in vitro study may not suffice when there are multiple product strengths (e.g., varying concentrations of an intra-mammary infusion); and (3) the in vitro method could be applied both to fully soluble and poorly soluble compounds. In vitro BE determinations would be based upon a battery of in vitro dissolution studies and physicochemical tests. Links to additional background material are provided on the Agency's Web site at: http://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm435459.htm.

To assist FDA in developing guidance for demonstrating in vitro BE, with this notice the Agency is convening an open forum, providing a summary of what the Agency envisions as considerations pivotal to the BE assessment and inviting public comment on the various components of an in vitro BE determination.

II. Participation in a Public Meeting

While oral presentations from specific individuals and organizations may be limited due to time constraints during the public meeting, stakeholders may submit electronic or written comments discussing any issues of concern to the administrative record (the docket) for the rulemaking. All relevant data and documentation should be submitted with the comments. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at http://www.regulations.gov.

III. Comments, Transcripts, and Recorded Video

Information and data submitted voluntarily to FDA during the public meeting will become part of the administrative record for the rulemaking and will be accessible to the public at http://www.regulations.gov. The transcript of the proceedings from the public meeting will become part of the administrative record for the rulemaking. Please be advised that as soon as a transcript is available, it will be accessible at http://www.regulations.gov under the docket number found in brackets in the heading of this document, and at FDA's Web site at http://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm43545

9.htm. It may also be viewed at the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. A transcript will also be available in either hardcopy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

Additionally, the public can access the meeting remotely by using the following Adobe Connect link: https://collaboration.fda.gov/cvm_bioequivalence_meeting/. The link will become active shortly before the meeting begins at 9 a.m. on April 16, 2015. Anyone interested in viewing the meeting remotely using this link will need to register as a guest using the registration information in this document. The Agency will be recording the meeting for subsequent viewing by the public. Once the recording has been made 508 compliant, it will be accessible at FDA's CVM Web site at http://www.fda.gov/AnimalVeterinary/NewsEvents/WorkshopsConferencesMeetings/ucm435459.htm.

Dated: March 12, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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