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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2014-N-0731]

Methodological Considerations in Evaluation of Cancer as an Adverse Outcome Associated With Use of Non-Oncological Drugs and Biological Products in the Postapproval Setting; Public Meeting; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of public meeting; request for comments.

The Food and Drug Administration (FDA), in collaboration with the National Cancer Institute (NCI), is announcing a public meeting entitled "Methodological Considerations in Evaluation of Cancer as an Adverse Outcome Associated With Use of Non-Oncological Drugs and Biological Products in the Postapproval Setting." The purpose of the public meeting is to engage in constructive dialogue and information sharing among regulators, researchers, the pharmaceutical industry, public health agencies, health care providers, and the general public concerning challenges in designing and implementing postapproval studies to evaluate the risk of cancer associated with use of non-oncological drugs and biological products. The input from this meeting and public docket will be used to inform the Agency on best study design and methodological options to consider when evaluating cancer risk in the postapproval setting.

Dates and Time: The public meeting will be held on September 10, 2014, from 8 a.m. to 5 p.m., and September 11, 2014, from 8 a.m. to 5 p.m.

Location: The public meeting will be held at The DoubleTree by Hilton Hotel Washington DC--Silver Spring, The Maryland Ballroom, 8727 Colesville Rd., Silver Spring, MD 20910 (Metro: Silver Spring Station on the Red Line).

Contact Person: Paul Tran, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, 301-796-9029, FAX: 301-796-9832, Paul.Tran@fda.hhs.gov.

Registration and Requests for Oral Presentations: Registration is free and available on a first-come, first-served basis. You must register online by August 27, 2014. Seating is limited, so register early. FDA may limit the number of participants from each organization. If time and space permit, onsite registration on the day of the meeting will be available. To register for this meeting, please visit FDA's Drugs News & Events--Meetings, Conferences, & Workshops calendar at http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm and select this meeting from the events list. If you need special accommodations due to a disability, please contact Paul Tran (see Contact Person) by September 3, 2014. Those without Internet access should contact Paul Tran to register.

This meeting includes a public comment session. If you would like to present at the meeting on topics related to challenges in designing and implementing postapproval studies to evaluate the risk of cancer associated with use of non-oncological drugs and biological products, please identify during registration the topic(s) you will address (see section II).

FDA will do its best to accommodate requests to speak. FDA urges individuals and organizations with common interests to coordinate and give a joint, consolidated presentation. Following the close of registration, FDA will allot time for each presentation and notify

presenters by September 3, 2014. Do not present or distribute commercial or promotional material during the meeting. Registered presenters should check in before the meeting.

Comments: FDA is holding this meeting to seek input on the study design and methodological options for conducting postapproval studies to evaluate cancer as an adverse outcome associated with use of non-oncological drugs and biological products. FDA is soliciting from interested persons electronic or written comments on all aspects of the meeting topics through October 9, 2014.

Attendees and non-attendees may 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. Send only one set of comments. When sending comments, please include the docket number from the heading of this notice. In addition, when addressing specific topics (see section II), please identify the topic. Received comments may be viewed 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.

Transcripts: After the meeting, FDA will post a transcript at http://www.regulations.gov. The transcript may be viewed at the Division of Dockets Management (see Comments). A transcript will also be available in either hardcopy or on CD-ROM upon submission of a Freedom of Information request. Send requests to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is holding this meeting to seek input from industry, academia, public health agencies, the clinical community, and other stakeholders regarding the study design and methodological options for conducting studies to evaluate cancer as an adverse outcome associated with use of non-oncological drugs and biological products in the postapproval setting.

Questions about whether a drug causes or influences cancer development and how this cancer risk can be evaluated are frequent concerns posed to FDA. Cancer signals can arise from premarket non-clinical and clinical trial data, and also from spontaneous adverse event reports or other studies conducted following a drug's approval. Unfortunately, further evaluation of these cancer signals is hindered by methodological limitations of tools and data available in the postapproval setting, particularly in light of the often complex exposure patterns and expected long latency of certain cancer outcomes. In the preapproval setting, randomized controlled trials (RCTs) are considered the gold standard in evaluating drug efficacy, and can evaluate frequently occurring and short-latency adverse events. However, due to certain limitations, RCTs are not best suited to identify the occurrence of cancer as an adverse outcome associated with drug treatment, although cancer events observed in trials raise concerns. Preapproval RCTs have important limitations, such as use of restricted populations, limited number of participants, as well as short duration and followup time. Postapproval studies, frequently observational, better reflect real-world-use patterns and capture the clinical experience for a larger number of individuals over time. In theory, these studies are better positioned to evaluate rare and longer-latency drug safety signals, including cancer signals. In practice, however, evaluating drug-related cancer outcomes using observational data is hampered by important methodological limitations, including difficulties in determining the timing of the outcome occurrence

accurately, difficulties in identifying the biologically relevant period of risk, and challenges in handling complex exposure patterns over time, among others.

Given the many methodological challenges in the postmarketing evaluation of adverse cancer outcomes associated with use of non-oncological products and current gaps in knowledge, FDA, in collaboration with NCI, is sponsoring a public meeting to seek input from industry, academia, public health agencies, the clinical community, and other stakeholders.

The meeting will include multiple sessions over 2 days.

II. Scope of the Meeting

The objective of the meeting is to engage researchers, industry, public health agencies, health care providers, and the public through presentations and panel discussions on the following topics:

Topic 1: Determination of exposure and identification of relevant risk window. The ability to accurately capture complex drug-use patterns over a period of time, to determine the most appropriate exposure metric(s), and to identify the most biologically relevant risk periods are essential elements in the appropriate postapproval evaluation of cancer-related outcomes associated with use of non-oncological drugs and biological products. There is currently no consensus on how these elements should be considered in postapproval studies that evaluate cancer outcomes. Discussions will explore methodologies for determining informative exposure metric(s), thresholds, latency period, and length of followup. These discussions will be based on current knowledge of carcinogenesis, potential underlying biological mechanisms, and particular types of cancers (according to site or histology). Given uncertainties around defining some of these metrics, discussions may consider strategies beyond testing of hypotheses, including the

use of exploratory hypotheses and sensitivity analyses, as well as consideration of scenarios under which postapproval studies are unlikely to be informative.

Topic 2: Identification of cancer-related outcome(s). The insidious nature of cancer events makes identification and timing-of-event occurrence challenging. Discussions will focus on relevant methodologies to identify cancer-related outcomes, as well as considerations regarding the challenges involved in identifying the sequence of symptoms that eventually lead to an accurate cancer diagnosis, a sequence that may be initiated before or during drug exposure.

Topic 3: Identification of population/data source. Identifying the relevant characteristics of the data or population source is crucial in conducting and interpreting postapproval evaluations of cancer signals. Discussions will focus on the essential characteristics of population/data source (e.g. administrative databases, registries, clinical encounters, surveys/interviews); the ability to appropriately capture medical history over time; and other information relevant to the evaluation of cancer outcomes, sample size, and participant followup.

Topic 4: Current thinking on cancer biology to inform epidemiology study design. It is noteworthy that recommendations for postapproval study designs to date have been based on the concept that cancer develops over a period of time, long after initiating drug treatment (long latency period). Nonetheless, several cancer-related signals have been observed during preapproval RCTs of non-oncological therapies, trials which typically have short duration of followup. Discussions will focus on the current thinking of potential biological mechanism(s) underlying purported drug-related increase in initiating, promoting, or detecting cancerous tumors, with particular consideration given to scenarios where cancer signals arise at any time following drug exposure. Discussions will also focus on cancer biology (and the different types

of tumors) to inform postapproval evaluation of cancer signals and to better identify the most relevant exposure metric and risk windows.

Information about this meeting, including registration and the agenda, will be posted at http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm as it becomes available.

Dated: June 10, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

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