



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 15

[Docket No. FDA-2014-N-0824]

Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials; Public Hearing;
Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public hearing that will provide a forum to discuss confidentiality of interim results for certain cardiovascular outcomes trials (CVOTs) submitted to the Agency while the trials are still ongoing. The purpose of the public hearing is to initiate constructive discussion among regulators, researchers, health care providers, representatives from the pharmaceutical industry and health care organizations, and the general public, about appropriate handling of interim analysis results of these ongoing CVOTs. FDA is also opening a public docket to receive comments on this topic.

DATES: The public hearing will be held on August 11, 2014, from 8 a.m. to 5 p.m. Individuals who wish to present at the public hearing must register by July 28, 2014. Section IV provides attendance and registration information. To ensure consideration, submit comments by July 28, 2014. Electronic or written comments will be accepted after the public hearing until October 10, 2014.

ADDRESSES: The public hearing will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (rm. 1503), Silver Spring, MD

20993-0002. Entrance for the public hearing participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed. For parking and security information, please refer to

<http://www.fda.gov/AboutFDA/WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm>.

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. Identify comments with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Indira Hills, Food and Drug Administration, Center for Drug Evaluation and Research, 10903 New Hampshire Ave., Bldg. 21, rm. 4508, Silver Spring, MD 20993, 301-796-9686, FAX: 301-796-9907, email: indira.hills@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Requirement for Postmarketing Studies to Assess the Risk of a New Drug

In some cases, studies submitted to FDA as part of a new drug application or biologics license application will demonstrate that a drug is safe and effective for its intended use (i.e., that its benefits outweigh its identified risks), but the Agency will nevertheless require a sponsor to conduct additional postmarketing studies or trials under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(o)(3)) for the following reasons: To assess a known serious risk related to use of the drug, to assess signals of a serious risk related to use of the drug, or to identify an unexpected risk when available data indicate the potential for a serious risk.

B. FDA's Approach to the Approval of Drugs to Treat Type II Diabetes

For most drugs, clinical trials of reasonable size can establish a favorable relationship of benefit to relatively common risks, but they are not large enough to assess the risk of rare serious events such as heart attacks, strokes, or death. Where there is concern about these risks (e.g., concern about drugs to treat Type II diabetes mellitus (T2DM) or to promote weight loss), development programs include CVOTs to help assess the risk to meet the requirements for drug approval. In some cases, applicants have conducted a metaanalysis of cardiovascular (CV) risk from Phase 2/3 trials to help establish the safety of a drug and a separate larger CVOT as a postmarketing requirement under section 505(o)(3) of the FD&C Act. In other cases, analyses of interim data from a single CVOT will demonstrate that a drug is safe with regard to CV risk for its intended use, and, if the overall risk-benefit analysis supports approval, the applicant will further assess the CV risks by continuing the trial as a postmarketing requirement.

The Agency has described its expectations for CV outcome data for drugs to treat T2DM in the guidance for industry “Diabetes Mellitus Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2” (available at Diabetes”(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071627.pdf>), which was issued based on the discussion at an advisory committee meeting,¹ as well as in other available data and information. The guidance makes recommendations about how to demonstrate that a new therapy to treat T2DM is not associated with an unacceptable increase in CV risk.

The guidance states that before submission of a new drug application (NDA) or biologics license application, the premarketing CV outcome data should show that the incidence of

¹ On July 1 and 2, 2008, the Endocrinologic and Metabolic Drug Advisory Committee met to discuss the role of CV assessment in the premarketing and postmarketing settings (<http://www.fda.gov/ohrms/dockets/ac/cder08.html#endocrinologicmetabolic>).

important CV events occurring with the investigational agent is not more than 80 percent increase compared to the control group (i.e., that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio for CV events is less than 1.8). The guidance also states that if the risk ratio is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval, a postmarketing trial will generally be necessary to show that the upper bound of the 2-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This showing can be achieved by conducting an adequately powered new postmarketing trial, by combining results of separate premarketing and postmarketing trials, or by continuing a large CVOT in which a planned interim analysis is the basis for concluding that the risk ratio is less than 1.8. If the risk ratio of 1.3 is ruled out based on premarket data, then a postmarketing requirement may not be necessary.

C. Interim Analyses, the Importance of Their Confidentiality, and the Role of the Data Monitoring Committee

Interim analyses are analyses of study data conducted partway through an ongoing clinical trial. They can play an integral role in clinical trials by allowing for the safety of enrolled patients to be monitored at various intervals in the study and also by allowing for the possibility of stopping the trial early for safety concerns, for futility, or for early evidence of efficacy that would make it unethical for the trial to proceed. Confidentiality of interim data is a paramount concern: The 1998 International Conference on Harmonization (ICH) guidance for industry “E9 Statistical Principles for Clinical Trials” (ICH E9 guidance) (available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf>) reflects a collective view across regulatory agencies in the European Union, Japan, and the United States when it states that “All staff involved in the conduct of the trial

should remain blind to the results of such analyses, because of the possibility that their attitudes to the trial will be modified and cause changes in the characteristics of patients to be recruited or biases in treatment comparisons.”

An independent Data Monitoring Committee (DMC) is usually established to review the interim analysis results and make recommendations to the sponsor about any action needed based on those results, allowing the sponsor and other personnel associated with the trial to remain masked to interim results. In 2006, FDA issued the guidance for clinical trial sponsors “Establishment and Operation of Clinical Trial Data Monitoring Committees” (DMC guidance) (available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf>) that reiterated many of the best practices for interim analyses and DMCs outlined in the ICH E9 guidance. Specifically, the guidance states that “[p]rocedures should be established to safeguard confidential interim data from the project team, investigators, sponsor representatives, or anyone else outside the DMC and the statistician(s) performing the interim analyses (see 21 CFR 314.126(b)(5) (drugs) and 21 CFR 860.7(f)(1) (devices)).” An exception is made in considering the need to disseminate safety data to allow for appropriate monitoring of patients’ safety.

D. Potential Adverse Consequences of Disclosure of Interim Results

The concern with widespread disclosure of interim results in an ongoing trial, as described in the DMC guidance, stems from the potential of the disclosure to negatively affect the conduct of the remaining portion of the trial. The impact could include unanticipated changes in recruitment, treatment administration, or other aspects of trial conduct, as well as loss of objectivity in safety event reporting. Sponsors and other interested parties with access to interim data may have difficulty managing the remainder of the trial in an objective manner, particularly if changes to the trial protocol are needed for other reasons. Knowledge of interim

data may influence decisions about the trial going forward, and it is nearly impossible to assess the impact of that influence on the trial's final results. To ensure the integrity of the trial and the validity of its findings, the DMC guidance strongly recommends maintaining the confidentiality of interim data until the trial completion.

E. Partial Disclosure of Interim Trial Results by FDA and the Purpose of This Hearing

Once FDA sends an approval letter for a new drug, the FD&C Act and FDA regulations require that a summary or summaries of the safety and effectiveness data and information submitted with or incorporated by reference in the application be made available immediately for public disclosure, with certain limited redactions. FDA's analyses of the safety and effectiveness data and information from clinical studies that support the approval of a new drug are typically disclosed with little or no redaction. However, data relied on to make approval decisions are ordinarily derived from fully completed clinical trials. In the case of T2DM therapies where a single, large CVOT to rule out CV risk was designed to meet both the requirement for approval and the postmarketing requirements, approval would indicate that the study had indeed ruled out the risk ratio of 1.8, so this aspect of the interim results would be known. But that fact would not reveal the detailed result, e.g., a finding that CV events were actually reduced by the drug in the interim analysis. Disclosure of detailed and more extensive information or analyses from an ongoing trial, that is, the results of an interim analysis, could undermine the integrity of the trial and jeopardize its continuation, which could delay or even prevent obtaining the safety data about serious risks that were required to be assessed at the time of approval.

For example, in connection with a recent approval decision of a drug to treat T2DM (see MEMORANDA: Disclosure of Interim Cardiovascular Risk Study Data, NDA 22271, Nesina (alogliptin) tablets, and Its Fixed-Dose Combination Product NDAs 22426 and 203414, dated

March 12, 2013, and Disclosure of Interim Cardiovascular Risk Study Data and Information Relied on to Approve, NDA 22271, Nesina (alogliptin) tablets, and Its Fixed-Dose Combination Product NDAs 22426 and 203414, dated March 12, 2013, available at <http://www.fda.gov/Drugs/NewsEvents/ucm398454.htm>), FDA released information at the time of approval that was considered not likely to undermine the integrity of the ongoing trial, including (1) general background and study information; (2) high-level summary conclusions that the trial ruled out the prespecified risk margin recommended by FDA guidance; and (3) other data and information from the trial unrelated to CV risk. FDA decided, however, to delay disclosure of other information that it determined could jeopardize successful completion of the trial, specifically point estimates of hazard ratios and associated confidence intervals for CV risk and detailed data on CV events and rates. Based on the circumstances of this case, FDA determined that delaying disclosure of these data was appropriate for a limited time. This information would become available when FDA completed its review of the final CV risk study report and had taken any related regulatory action based on the final results.

The Agency is holding this hearing to solicit input from stakeholders on the effects of disclosing information or analyses, at various levels of detail, from an ongoing trial, and whether general information about the trial can be disclosed without significant risk to the integrity of the trial or its completion. Making a determination about the effect of disclosure on a particular trial requires consideration of the details of that trial and relevant context.

II. Scope of Public Input Requested

FDA is seeking input from the various stakeholders on the following issues:

- When a trial to evaluate CV safety of a new treatment is ongoing at the time a drug is approved, do stakeholders agree that disclosure of detailed analyses (such as point

estimates of hazard ratios and the associated confidence intervals) could undermine the integrity of an ongoing trial and jeopardize its continuation, potentially eliminating or substantially delaying the Agency's ability to obtain needed long-term safety information?

- What interim findings, if disclosed, would represent the greatest risk to trial integrity or jeopardize trial continuation?
- Can partial disclosure of interim findings at the time of approval, essentially disclosing only that the standard for approval has been met, offer protection of trial integrity and also provide health care practitioners with the essential scientific information needed to inform their use of the drug?
- If the detailed interim results were disclosed at the time of approval, and the ongoing study was discontinued at that time, would it be feasible to conduct a new large trial as a postmarketing requirement that would fulfill the original study objective?
- Are there other, alternative trial designs that would allow for disclosure of interim results on safety risks at the time of product approval while also allowing for further information to be obtained postmarket?

III. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner and the Center for Drug Evaluation and Research.

Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation.

Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10, subpart C (21 CFR part 10, subpart C)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b) (see section VI for more details). To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

IV. Attendance and Registration

The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Individuals who wish to attend the public hearing must register on or before July 28, 2014, by visiting <https://www.surveymonkey.com/s/7L8Z66Q> and contacting Indira Hills (see FOR FURTHER INFORMATION CONTACT). Early registration is recommended. Registration is free and will be on a first-come, first-served basis. However, FDA may limit the number of participants from each organization based on space limitations. Onsite registration on the day of the hearing will be based on space availability.

FDA will provide additional background information at the time the Federal Register notice is published and an agenda approximately 2 weeks before the hearing at FDA Meeting Information page, which is available online at <http://www.fda.gov/Drugs/NewsEvents/ucm398454.htm>.

Time will be reserved during the hearing for planned presentations from the audience. If you would like to present at the hearing, please indicate this in your hearing registration. Time for audience presentations is limited and will be assigned on a first-come, first-served basis.

Note also that time will be designated throughout the day for general comments and questions from the audience following the panel discussions.

In this Federal Register notice, FDA has included specific issues that will be addressed by the panel. If you wish to address one or more of these issues in your presentation, please indicate this at the time you register so that FDA can consider that in organizing the presentations. FDA will do its best to accommodate requests to speak, and will determine the amount of time allotted to each presenter and the approximate time that each oral presentation is scheduled to begin.

If you need special accommodations because of disability, please contact Indira Hills (see FOR FURTHER INFORMATION CONTACT) at least 7 days before the hearing.

A live webcast of this hearing will be viewable at <https://collaboration.fda.gov/dmcidcvtpart15/> on the day of the hearing. A video record of the hearing will be available at the same Web address for 1 year.

V. Comments

Regardless of attendance at the public hearing, interested persons may submit either electronic comments regarding this document to <http://www.regulations.gov> or written comments to the Division of Dockets Management (see ADDRESSES). 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>.

VI. Transcripts

As soon as a transcript is available, it will be accessible at <http://www.regulations.gov>. It may be viewed at the Division of Dockets Management (see ADDRESSES). A transcript will also be available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. Written requests are to be sent to Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857.

Dated: July 8, 2014.

Leslie Kux,

Assistant Commissioner for Policy.

[FR Doc. 2014-16374 Filed 07/14/2014 at 8:45 am; Publication Date: 07/15/2014]