4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0872]

Draft Guidance for Industry on Use of Histology in Biomarker Qualification Studies; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Use of Histology in Biomarker Qualification Studies." This guidance is intended to assist sponsors that conduct biomarker qualification studies for which histology is a reference standard. This guidance discusses the processes that should be considered to ensure the quality and integrity of histology data in biomarker studies, and outlines the scientific standards for histology used in biomarker characterization and qualification. The recommendations in this guidance are intended for studies in biomarker qualification designated to justify the proposed context of use, where scientifically rigorous evaluation of biomarker performance in relation to histologic changes is essential. The principles outlined in this guidance are also applicable to exploratory biomarker studies.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

Submit either electronic or written comments concerning the proposed collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to http://www.regulations.gov.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.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Use of Histology in Biomarker Qualification Studies." The discovery, characterization, qualification, and implementation of biomarkers have been identified by the FDA Critical Path Initiative as an important means for improving the efficiency and success rate of medical product development. Biomarkers have been broadly applied to describe the following:

- Structural features from the molecular to the anatomic level (e.g., genetic composition, receptor expression patterns, radiographic appearances);
- Biochemical measurements (e.g., serum levels of electrolytes, enzyme activity levels, prostate-specific antigen);
- Physiologic organ system function (e.g., creatinine clearance, pulmonary function tests, cardiac ejection fraction, electrocardiography).

The studies to be submitted in support of a biomarker qualification will depend upon the proposed context of use and the ultimate goal of the submission. If a biomarker becomes qualified, analytically valid measurements of it can be relied upon to have a specific and interpretable meaning (e.g., physiologic, toxicologic, pharmacologic, or clinical) in drug development and regulatory decisionmaking. Industry can then employ the biomarker for the qualified context of use during premarketing drug development, and FDA reviewers can be confident about the qualified context of use without the need to reconfirm its applicability or utility. Accordingly, biomarker qualification studies are held to the same Good Laboratory Practice standards as are other premarketing studies.

Traditionally, histology has been used to identify morphologic changes in the context of nonclinical safety assessment, clinical diagnosis, and evaluation of response to therapy. There is a strong correlation between specific histology findings, clinical outcomes, and some clinical

chemistry parameters. Because of this history, histology is currently used in biomarker qualification as a reference standard to evaluate the sensitivity and specificity of potential biomarkers and their ability to indicate temporal correlation with the evolution and reversibility of morphologic changes. Because of the many variations in the practice of histology, this guidance is offered to facilitate quality, consistency, and scientific rigor in biomarker qualification studies where histology is used as a reference standard.

Although great benefit may accrue from use of a qualified biomarker, a poorly characterized biomarker can do considerable harm. A poorly characterized biomarker may lead to inappropriate removal of a drug from development, encourage development of a drug that is unlikely to be approved, or lead to an erroneous perception of safety. Thus, for biomarkers to achieve the desired goal, the science that identifies, characterizes, and informs the biomarker use should be unbiased and of the highest quality.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on the use of histology in biomarker qualification studies. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed 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.

III. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information that they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)), requires Federal Agencies to provide a 60-day notice in the Federal Register for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing this notice of the proposed collection of information set forth in this document.

With respect to the collection of information associated with this draft guidance, FDA invites comments on the following topics: (1) Whether the proposed information collected is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimated burden of the proposed information collected, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of information collected on the respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

This draft guidance refers to previously approved collections of information found in FDA regulations. Sections II, IV, V, and VI of the guidance request that certain information be submitted to FDA and certain records be maintained by the sponsor. We may request this

information under 21 CFR 58.81, 58.120, 58.185, 312.23, and 312.53. The collections of information for 21 CFR parts 58 and 312 have been approved under OMB control numbers 0910-0119 and 0910-0014, respectively.

The draft guidance discusses certain information that should be described in the standard operating procedures (SOPs) and recommends that sponsors document and maintain records of the SOPs. In addition to the SOPs already covered by previously approved collections of information, the draft guidance recommends that two new procedures be included in the SOPs. The new procedures that require OMB approval for the collection of information are as follows: (1) Procedures for describing and documenting the type and extent of background lesions and (2) a detailed description of the pathology peer review process, including how disagreements among reviewers will be adjudicated. Based on FDA's data on the number of sponsors that would be covered by the draft guidance, we estimate that approximately 180 SOPs related to histologic evaluation will include the new procedures, and that sponsors will need approximately 30 minutes to document, maintain, and update their SOPs with the new procedures.

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Recordkeeping Burden[1]

	Number of Recordkeepers	Number of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping (in Hours)	Total Hours
SOP New Procedures	30	6	180	0.5	90
Total					90

[1] There are no capital costs or operating and maintenance costs associated with this information collection.

IV. Electronic Access

Persons with access to the Internet may obtain the document at either http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or http://www.regulations.gov.

Dated: December 22, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

[FR Doc. 2011-33553 Filed 12/29/2011 at 8:45 am; Publication Date: 12/30/2011]