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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2012-D-0432]

Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled "Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval." This guidance is intended to assist applicants in designing trials to support marketing approval of drugs to treat breast cancer in the neoadjuvant (preoperative) setting using pathological complete response (pCR) as a surrogate endpoint that could support approval under the accelerated approval regulations. Despite advances in systemic therapy of early-stage breast cancer over the past few decades, there remains a significant unmet medical need for certain high-risk or poor prognosis populations of early-stage breast cancer patients. This guidance is intended to encourage industry innovation and expedite the development of breakthrough therapies to treat high-risk early-stage breast cancer. This guidance finalizes the draft guidance issued May 30, 2012.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, 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 guidance document.

Submit electronic comments on the 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: Tatiana Prowell, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 2112, Silver Spring, MD 20993-0002, 301-796-2330.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval." Under the accelerated approval regulations (21 CFR part 314, subpart H, and 21 CFR part 601, subpart E), FDA may grant marketing approval for a new drug on the basis of adequate and well-controlled trials establishing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (e.g., in early-stage breast cancer, an improvement in disease-free or overall survival), provided that the applicant conducts additional trials or collects additional data after approval to verify and describe the predicted clinical benefit. This guidance is intended to assist applicants in designing trials to support marketing approval of drugs to treat breast cancer in the neoadjuvant

(preoperative) setting using pCR as a surrogate endpoint that could support approval under the accelerated approval regulations. The guidance provides acceptable definitions of pCR for regulatory purposes. The guidance also describes appropriate patient populations for inclusion in neoadjuvant trials conducted with regulatory intent. Finally, the guidance outlines critical design features of trials for both accelerated approval and confirmation of clinical benefit to support regular approval.

FDA recognizes that despite advances in adjuvant systemic therapy of breast cancer over the past few decades, there remains a significant unmet medical need for certain high-risk or poor prognosis populations of early-stage breast cancer patients. Developing highly effective new drugs for these populations is an FDA priority. In providing guidance on the use of pCR as a surrogate endpoint that could support accelerated approval in the neoadjuvant setting, FDA hopes to encourage industry innovation and expedite the development and widespread availability of highly effective novel therapies to treat high-risk early-stage breast cancer.

This guidance finalizes the draft guidance issued May 30, 2012 (77 FR 31858). The current version clarifies appropriate trial designs and development strategies to support accelerated approval in the neoadjuvant setting, defines acceptable endpoints for accelerated approval and confirmation of clinical benefit, standardizes the approach to postoperative systemic therapy, includes guidelines for evaluation of the axillary lymph nodes, and provides detailed recommendations for pathology standard operating procedures.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on use of pCR as an endpoint to support accelerated approval of drug and biological products to treat high-risk early-stage breast cancer patient populations. 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. The Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR parts 312 and 314 have been approved under OMB control numbers 0910-0014 and 0910-0001, respectively. The collections of information for special protocol assessments have been approved under OMB control number 0910-0470.

III. Comments

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.

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: October 1, 2014.

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Leslie Kux,

Assistant Commissioner for Policy.

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