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Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program

Guidance for Industry, Clinical Laboratories, and Food and Drug Administration Staff

Document issued on June 20, 2023.

For questions about this document regarding CDRH-regulated devices, contact the Office of In Vitro Diagnostics at OncologyPilotCDRH@fda.hhs.gov. For questions about this document regarding CDER-regulated oncology drug products, contact Reena Philip (OCE) at 301-796-6179, or by email at Reena.Philip@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)

Preface

Public Comment

This guidance is being issued to announce a voluntary pilot for oncology drug products, which treat serious and life-threatening disease, and certain corresponding in vitro diagnostic tests. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices. Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to https://www.regulations.gov. All comments should be identified with the docket number FDA-2022-D-2275 and complete title of the guidance in the request.

Additional Copies

CDRH

Additional copies are available from the Internet. You may also send an email request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please include the document number 22001 and complete title of the guidance in the request.

CDER

Additional copies are available from the Center for Drug Evaluation and Research (CDER), Office of Communication, 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor, Silver Spring, MD 20993-0002, or by calling 1-855-543-3784 or 301-796-3400, by email, druginfo@fda.hhs.gov or from the Internet at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. INTRODUCTION

FDA is issuing this guidance to announce and describe FDA's voluntary pilot program for certain Center for Drug Evaluation and Research (CDER)-regulated oncology drug products[1] used with certain in vitro diagnostic tests, as described in the scope below.

Given the public health importance of such in vitro diagnostic tests for determining a patient's cancer treatment, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the FD&C Act). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

[1] For the purposes of this guidance, references to *oncology drug products* include both human drug products and biological products regulated by CDER, unless otherwise specified. This pilot is currently only available for oncology drug products within CDER.

the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

An in vitro companion diagnostic test (also known as an in vitro companion diagnostic device and hereafter referred to as an in vitro companion diagnostic) provides information that is essential for the safe and effective use of a corresponding therapeutic product.[2] As described in the FDA guidance titled "In Vitro Companion Diagnostic Devices"[3] in most circumstances, an in vitro companion diagnostic should be granted marketing authorization[4] contemporaneously with the approval of the corresponding therapeutic product for the use indicated in the therapeutic product labeling. As also described in that guidance, FDA may decide to approve a therapeutic product even if, at the time of the therapeutic product's approval, an in vitro companion diagnostic has not yet received marketing authorization, when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an in vitro companion diagnostic with marketing authorization.[5] Consistent with this policy, FDA has approved some oncology drug products that require use of in vitro companion diagnostics without contemporaneous marketing authorization of a corresponding in vitro companion diagnostic. In these cases, tests offered as laboratory developed tests (LDTs)[6] are being used for patient treatment decisions. FDA has generally exercised enforcement discretion for LDTs, meaning that, at this time, FDA generally does not exercise its authority to enforce the regulatory requirements for these devices, although it maintains that authority.

FDA intends to pilot a new approach to provide greater transparency regarding performance characteristics that certain tests for oncology biomarkers should meet. Through this transparency FDA seeks to support better and more consistent performance of certain LDTs used to identify

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[2] For the purposes of this guidance and as used in FDA's *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* (August 2014), references to *therapeutic product* includes therapeutic, preventive, and prophylactic drugs and biological products. This includes oncology drug products. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] See the guidance for industry and Food and Drug Administration Staff *In Vitro Companion Diagnostic Devices* (August 2014), page 8.

[4] For purposes of this guidance, the term "marketing authorization" means FDA's approval of a premarket approval application, granting of a *de novo* request, or clearance of a premarket notification (510(k)).

[5] See the guidance for industry and Food and Drug Administration Staff *In Vitro Companion Diagnostic Devices* (August 2014), page 9.

[6] For the purposes of this guidance, the term laboratory developed test (LDT) means an in vitro diagnostic device that is intended for clinical use and designed, manufactured and used within a single laboratory certified under the Clinical Laboratory Improvement Amendments (CLIA) (42 U.S.C. 263a) that meets the requirements to perform tests of high complexity, as described in 42 CFR 493.17(c)(4) and 493.25, and is a location that has its own CLIA certificate as described in 42 CFR 493.43(a).

patients for treatment with certain oncology drug products, resulting in better drug selection and improved care for patients with cancer.

This pilot does not alter the standards for approval of the oncology drug products or for marketing authorization of the corresponding companion in vitro diagnostics.

III. SCOPE

This guidance document and the pilot program described herein are intended for drug product sponsors with regard to:

(1) CDER-regulated oncology drug products for which FDA determines that

   (a) use of an in vitro diagnostic test is needed to identify the intended patient population,

   (b) no satisfactory alternative treatment exists, and

   (c) the anticipated benefits from the use of the drug product are so pronounced as to outweigh the anticipated risks from approval of the drug product without an FDA-authorized companion diagnostic; and

(2) corresponding clinical trial assay(s)

   (a) that use the same technology as a previously FDA-authorized companion diagnostic for any indication (e.g., next generation sequencing, immunohistochemistry, and fluorescent in situ hybridization)[7]; and

   (b) for which there is a well-validated reference method, well-validated comparator method, and/or well-characterized materials (e.g., appropriate clinical samples, cell lines) that can be used to support test accuracy.

This pilot is intended for the tests described above because FDA believes that, in general, they are the tests for which it is appropriate to extrapolate clinical validity of the test(s) used in a drug trial to other tests of the same type with similar analytical performance.

Many tests used in selection of oncology drugs in clinical practice employ established technologies and have appropriate methods and materials to support leveraging clinical validity established for another test of the same type. Further, there is an urgent public health need to recommend minimum performance characteristics for tests used to identify patients for oncology treatment to address safety risks posed by the use of LDTs that are not properly validated and/or are unable to identify the appropriate population for the corresponding drug products.

[7] https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

IV. PILOT PROGRAM

This pilot is intended to improve oncology patient care by providing transparency regarding minimum performance necessary for in vitro diagnostic tests used with oncology drug products enrolled into the pilot program. Under this pilot, if FDA concludes that the drug product meets the applicable standards for its approval,[8] FDA intends to rely on the same pivotal clinical trial(s) that support approval of the drug product to establish the clinical validity for the clinical trial assays (CTAs) used in those trial(s). Further, FDA intends to recommend minimum analytical performance characteristics for other tests that, when established through properly conducted validation studies, FDA believes would support extrapolation of the clinical validity of the CTA(s) to additional tests of the same type. If FDA approves an oncology drug product enrolled in this pilot program, FDA expects that at the time of drug product approval, it will recommend minimum performance characteristics for in vitro diagnostic tests to be used to identify patients for treatment with that drug product.

The minimum performance characteristics are intended to serve as a benchmark for test developers seeking to design tests that are accurate and reliable for such use. Test developers would be able to leverage the clinical validity of the CTAs established through the drug trial to help streamline validation of additional tests for the same use. Ultimately, this may bring new treatment options to appropriate patients sooner.

Under this pilot program, FDA anticipates that the approved drug labeling will specify that the drug is indicated for patients identified as exhibiting a named biomarker by in vitro diagnostic tests that have FDA's recommended performance characteristics. FDA's Center for Devices and Radiological Health (CDRH) intends to provide on its website the recommended minimum performance characteristics for these tests. FDA also anticipates that both the approved drug labeling and CDRH's website will specify relevant test characteristics for the in vitro diagnostic tests for use with the drug, such as the biomarker detected and test method, including the specimen type(s). The specified test characteristics will be determined based on the characteristics of the CTAs used for enrollment of the pivotal clinical trial(s) which helped to define the indicated biomarker-selected patient population for which that use of the drug is approved, including the validation and performance characteristic information reviewed for those tests. For example, if all CTAs detect [DNA biomarker] in formalin-fixed paraffin-embedded (FFPE) tissue by polymerase chain reaction (PCR), the drug labeling and CDRH website would specify tests for the detection of [DNA biomarker] in FFPE tissue by PCR.

V. PARTICIPATION AND PROCEDURES

A. Participation

Drug product sponsors may be accepted into the pilot program, starting June 20, 2023, based on evaluation of the following factors:

[8] See FD&C Act Section 505 and PHS Act Section 351.

1. CTAs for the enrollment of the pivotal clinical trial(s) are of a test type described in the scope above.

2. The oncology drug sponsor agrees to discuss with FDA analytical validation data and performance characteristics for clinical trial assays prior to enrollment of the pivotal clinical trial(s).

3. Pivotal clinical study protocol(s) use tests that have specified performance characteristics recommended by FDA for acceptance into the pilot.

4. The oncology drug sponsor is able to collect the analytical validation data and performance characteristics as recommended in FDA templates (see section VI) for all CTAs used for the enrollment of the pivotal clinical trial(s).

5. The owner(s) of the data supporting the safety and effectiveness of the oncology drug product and CTAs agree to FDA's use of such data to recommend minimum analytical performance characteristics for tests used to identify patients for treatment with the oncology drug product. Such minimum recommended performance characteristics will be publicly available on FDA's website and could be used by test developers, including in premarket submissions, for tests with the same use.

Pivotal clinical trials can take months to years. To begin the pilot program as soon as possible, FDA may opt not to consider factor (2) for oncology drug products where the pivotal clinical trial(s) started prior to June 20, 2023. Further, FDA recognizes that there may be circumstances in which obtaining the analytical validation data may not be possible. Drug product sponsors that are able to collect and provide validation data and performance characteristics for virtually all CTAs, provide a scientifically and statistically sound justification for any missing validation data, and demonstrate that the missing information does not impact the ability to determine minimum performance characteristics for the tests used to demonstrate that the drug product is safe and effective, might also be accepted into this pilot. If adequate validation data are not available for a sufficient number of CTAs used in the trial, the drug product likely will not be accepted into this pilot.

B. Procedures

In the initial phase of the pilot, FDA will evaluate no more than 9 sponsors for possible acceptance into the pilot. FDA anticipates the initial phase to last up to one year. Evaluation of the pilot program will occur at set timepoints with review of comments submitted to the docket, evaluation of the experience of the pilot participants, and a public meeting within three years.

To be considered for the voluntary pilot program, drug product sponsors should submit correspondence titled "a Statement of Interest in Participation in the Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program" with their Investigational New Drug (IND) applications, New Drug Applications (NDA), or Biologic License Applications (BLA), as

appropriate. Submission of this statement affirms the sponsor's commitment to provide the following information, if subsequently requested by FDA:

1. Status of the enrollment of the pivotal trial(s). For example, complete, initiated but not complete, not initiated. For those that are complete or initiated but not complete, the date the trial(s) start and number of enrolled patients should also be provided.

2. IND, NDA, or BLA number if already submitted to FDA or a timeline for submission of an IND, NDA, or BLA if not already submitted.

3. List of clinical trial assays that were used or are planned for use for enrollment of the pivotal trial(s). The number of subjects enrolled into the trial by each CTA, the total number of subjects enrolled into the trial, and the total number of subjects that were evaluated by each CTA but not enrolled into the trial should also be provided for completed trials.

4. Analytical validation and performance characteristic information recommended in the templates available on FDA's website for each CTA (see section VI).

5. Right of reference from the owner(s) of the data supporting the safety and effectiveness of the oncology drug product and the CTAs, agreeing that (a) FDA may use the provided analytical validation data and performance characteristics to recommend minimum performance characteristics that FDA will make publicly available on CDRH's website, (b) clinical laboratories may use in developing LDTs, and (c) FDA may reference to approve, authorize or clear premarket submissions for in vitro companion diagnostic tests.

Upon receipt of the statement of interest, FDA will follow up with no more than 9 sponsors to request specific information to enable FDA to make a decision concerning acceptance into the pilot, based on evaluation of the factors outlined in section V.A. and provide written feedback that either accepts or rejects the drug product for the pilot program.

For oncology drug products where the pivotal clinical trial(s) have not started as of June 20, 2023, FDA will work with each sponsor to provide feedback in the form of recommended minimum validation and performance characteristics for CTAs to be used to enroll the drug product's pivotal clinical trial(s), prior to the start of the trial. FDA expects that the CTAs to be used for enrollment in the trial will meet or exceed these validation and performance characteristics. In the event that the drug is ultimately approved, FDA will recommend minimum performance characteristics for in vitro diagnostic tests to be used with the approved oncology drug product based upon submission of data and information regarding performance of the CTAs actually used in the clinical trials that supported the drug's approval, as these CTAs may have exceeded the minimum recommendations for performance provided prior to trial enrollment.

For oncology drug products where the pivotal clinical trial(s) were initiated prior to June 20, 2023, FDA will work with drug product sponsors accepted into the pilot program to

review the performance characteristic and validation information for each CTA and, provided the data are sufficient, recommend the minimum performance characteristics within the timeframe for review of the NDA/BLA application.

Based on the experience during the initial phase, FDA intends to update this guidance to include more specific procedures with specific information to provide the Agency and anticipates expanding the pilot to evaluate additional sponsors for acceptance into the pilot.

VI. AVAILABILITY OF TEMPLATES AND PERFORMANCE CHARACTERISTICS

FDA has made available through download from CDRH's website a series of templates that oncology drug product sponsors who have submitted the statement of interest described above may use to facilitate the provision, when requested by FDA, of performance characteristic and validation information for CTAs used in the pivotal clinical trial(s) for the drug product. FDA will also make available on CDRH's website the minimum recommended performance characteristics for in vitro diagnostic tests to be used with each approved drug product under the pilot.