Welcome To Today's Webinar

Thanks for joining us!
We'll get started in a few minutes

Today's Topic:
Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program

Date
December 12, 2023

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

and

Templates for Collecting and Providing Performance Characteristics and Validation Information for Clinical Trial Assays (CTAs)

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U.S. Food and Drug Administration

Opening Remarks

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

Templates for Collecting and Providing Performance Characteristics and Validation Information for Clinical Trial Assays (CTAs)

Final Guidance

- **Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program**
  - www.fda.gov/regulatory-information/search-fda-guidance-documents/oncology-drug-products-used-certain-in-vitro-diagnostic-tests-pilot-program

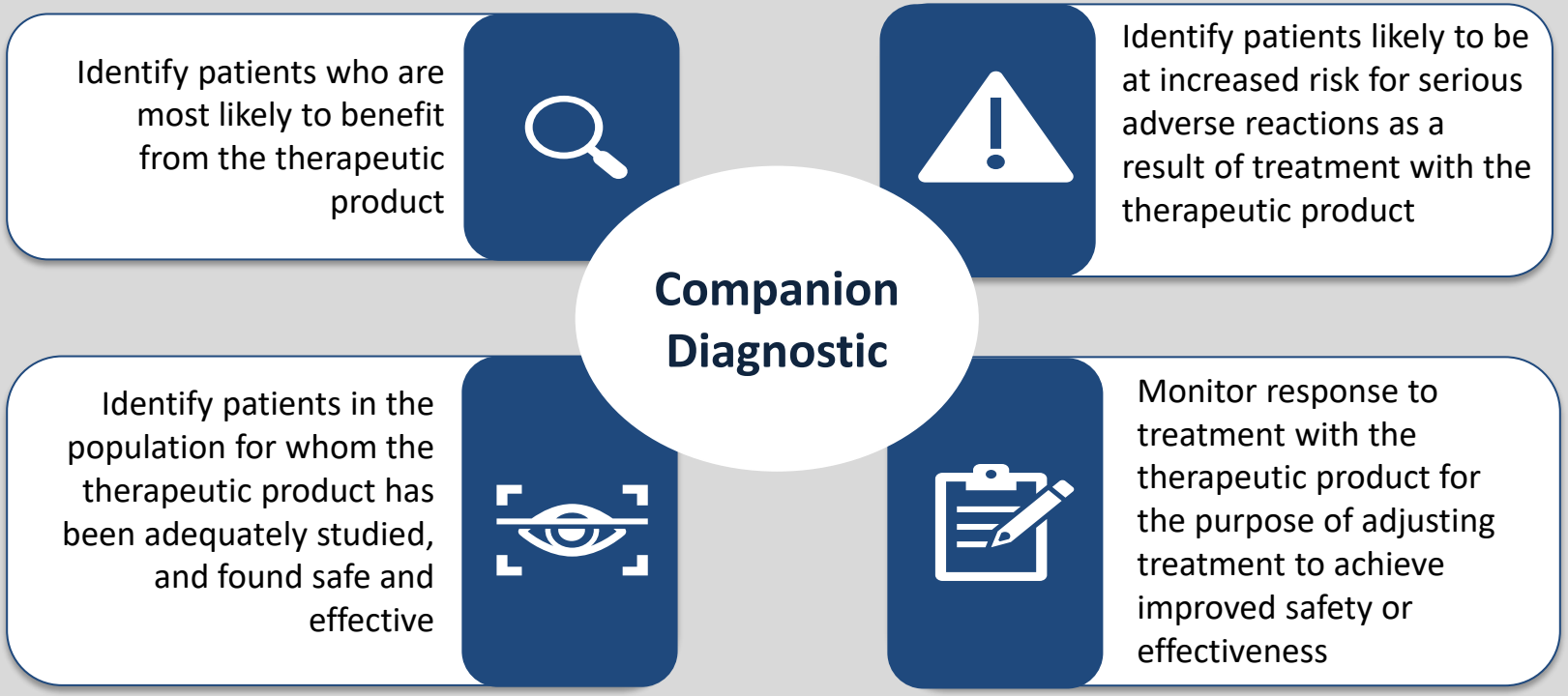
Learning Objectives

- Identify the scope and goals of the new voluntary pilot program for certain oncology drugs used with certain in vitro diagnostic tests
- Describe how to complete FDA templates to provide analytical validation and performance characteristic information for CTAs used in the pivotal trial(s) for drug products under the pilot, when requested by FDA

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

Background: Companion Diagnostics (CDx)

An in vitro diagnostic (IVD) that provides information that is essential for the safe and effective use of a corresponding therapeutic product



Background: CDx (cont.)

The FDA issued final guidance "In Vitro Companion Diagnostic Devices", August 2014
(www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-companion-diagnostic-devices)

Ideally, a therapeutic product and its corresponding CDx should be developed and authorized contemporaneously,

- With the clinical performance and clinical significance of the companion diagnostic established using data from the clinical development program of the corresponding therapeutic product

The use of a CDx with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product

Current Environment

As described in FDA's CDx guidance, there are specific circumstances where FDA may decide to approve a drug without clearing, approving, or authorizing a corresponding CDx at the same time.

1. New Therapeutic Products to Treat Serious or Life-Threatening Conditions

FDA may decide to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared 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 approved or cleared IVD companion diagnostic device. This will be determined by FDA during product review.

www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-companion-diagnostic-devices

Current Environment (cont.)

- In these cases, tests offered as laboratory-developed tests (LDTs) with unknown performance are being used for patient treatment decisions.
    - An 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).
- Historically, FDA generally has exercised enforcement discretion with respect to most LDTs, such that, except in certain circumstances, FDA generally has not enforced applicable requirements with respect to most LDTs.

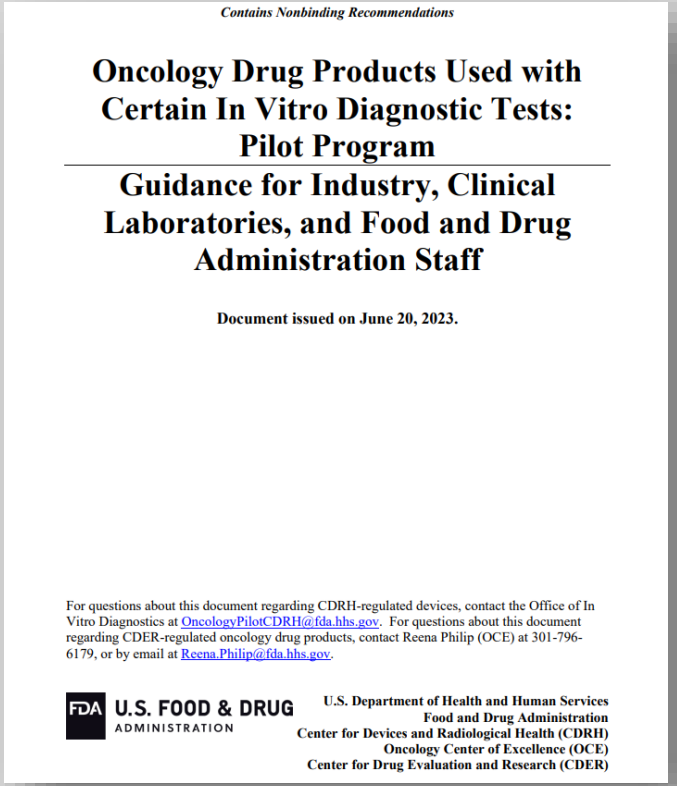
Current Environment (cont.)

- FDA is concerned that LDTs used to identify patient biomarkers may not be accurate or reliable
- FDA is particularly concerned that LDTs used to identify patients for drug treatment when there is not an FDA authorized companion diagnostic may not perform well
- Pilot Program: Recommend minimum performance characteristics for tests used to identify patients for certain oncology drugs to address safety risks posed by LDTs

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

FDA is piloting a new approach to provide greater transparency regarding minimum performance characteristics that certain tests for certain oncology drugs should meet

- One step that may be helpful in reducing the risk of using LDTs for oncology drug treatment decisions.
- 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.



Contains Nonbinding Recommendations

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)

Pilot Program Limitations

The scope of this voluntary pilot program is limited to 9 drug sponsors and:

CDER-regulated oncology drug products for which FDA determines that:

- ☑ use of an in vitro diagnostic test is needed to identify the intended patient population,
- ☑ no satisfactory alternative treatment exists, and
- ☑ 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

CDRH-regulated corresponding clinical trial assay(s):

- ☑ for which there is a well-validated reference method, well-validated comparator method, and/or well-characterized materials that can be used to support test accuracy
- ☑ that use the same technology as a previously FDA-authorized CDx

Pilot Program

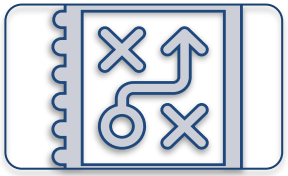
FDA intends to rely on the same pivotal clinical trial(s) that support approval of the drug product to establish the clinical validity for the clinical trial assays (CTAs) used in those trial(s).

Given the type of tests eligible for use in the pilot program, FDA believes that, in general, the clinical validity of these CTAs can be extrapolated to additional tests of the same type with similar analytical performance, when established through properly conducted validation studies.

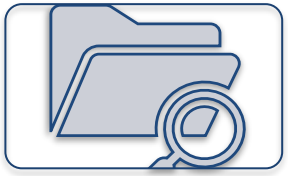
Pilot Program

FDA will request performance information for the tests used to enroll patients into the clinical trials that support drug approval

FDA will post to its website the minimum performance characteristics recommended for similar tests that may be used to select patients for treatment with the approved drug



Laboratories may use this information to guide their development of LDTs to identify specific biomarkers used for selecting cancer treatment



This transparency aims to help facilitate better and more consistent performance of these tests, resulting in better drug selection and improved care for patients with cancer

Pilot Program: Templates

CDRH's website includes a series of templates that oncology drug product sponsors may use to facilitate the provision of performance characteristic and validation information for CTAs used in the drug product pivotal clinical trial(s), **when requested by FDA**

Templates for Collecting and Providing Performance Characteristics and Validation Information for Clinical Trial Assays:

- Next generation sequencing test template
- Polymerase chain reaction test template
- Sanger sequencing test template
- Immunohistochemistry test template
- Fluorescence in situ hybridization test template

www.fda.gov/medical-devices/in-vitro-diagnostics/oncology-drug-products-used-certain-in-vitro-diagnostics-pilot-program

Pilot Program: Procedures

Oncology drug pivotal trial(s) **have not started** as of June 20, 2023

- FDA will provide minimum validation and performance characteristics for CTAs to enroll the drug product's pivotal clinical trial(s), prior to the start of the trial
- FDA expects the CTAs for trial enrollment will meet or exceed these validation and performance characteristics
- If the drug is approved, FDA will recommend minimum performance characteristics for IVDs to be used with that drug based upon performance of the CTAs used in the clinical trials

Pilot Program: Procedures (cont.)

Oncology drug pivotal trial(s) **were initiated prior** to June 20, 2023

FDA will work with drug sponsors accepted into pilot to review the performance characteristic and validation information for each CTA and recommend the minimum performance characteristics within the New Drug Application (NDA)/Biologics License Applications (BLA) application review timeframe

Key Takeaways

FDA believes transparency regarding **minimum recommended performance characteristics** will help facilitate development of better and more consistently performing tests, resulting in better drug selection and improved care for patients with cancer

However, this pilot program **will not** assure that LDTs available to patients are safe and effective

Separately, **FDA issued a notice of proposed rulemaking**, proposing a policy under which FDA intends to phase out its general enforcement discretion approach for LDTs

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

Templates for Collecting and Providing Performance Characteristics and Validation Information for CTAs under the Pilot Program

CTA Templates: Scope and Purpose

The templates on CDRH's website are intended for use by oncology drug product sponsors who have submitted the statement of interest (SOI) for the pilot program

- Oncology drug sponsors interested in participating in the pilot should submit an SOI to their IND, NDA, or BLA

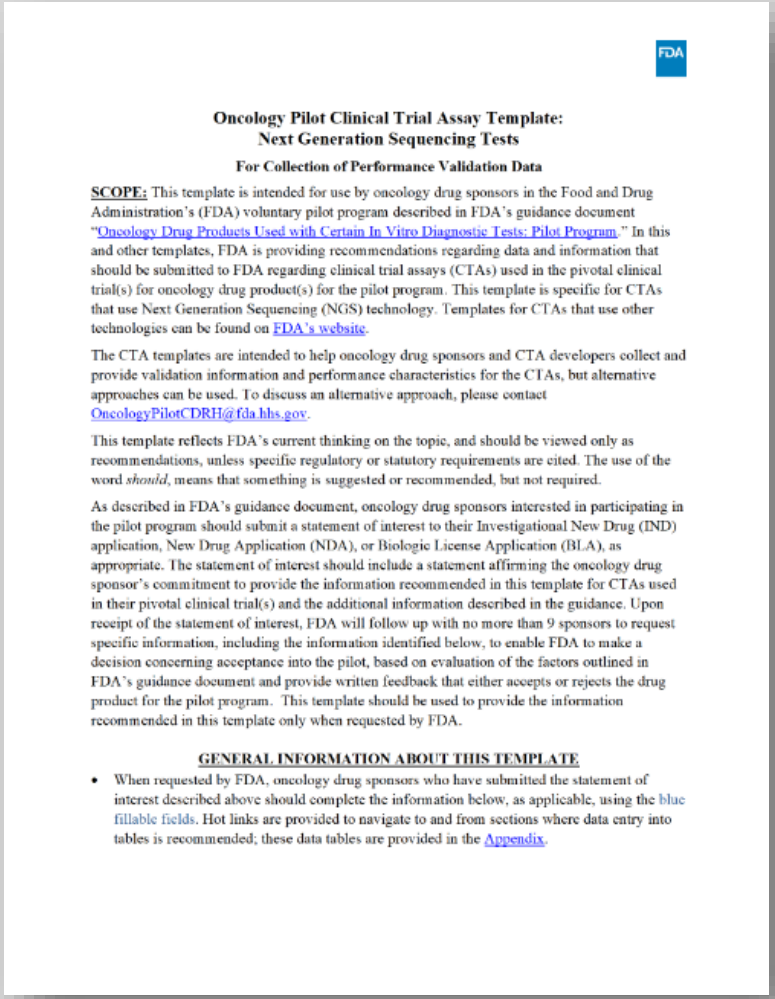
The templates should be used to provide the information recommended in the templates **only when requested by FDA**

The templates are to help oncology drug sponsors collect and provide validation information and performance characteristics for **each CTA** used in the pivotal clinical trial(s) for the drug product

CTA Templates: General Sections

- I. General Laboratory Information
- II. General Test Information
- III. Validation Studies
- IV. Data Tables

Template Demo: Next Generation Sequencing (NGS) Test Template



Oncology Pilot Clinical Trial Assay Template:
Next Generation Sequencing Tests

For Collection of Performance Validation Data

SCOPE: This template is intended for use by oncology drug sponsors in the Food and Drug Administration's (FDA) voluntary pilot program described in FDA's guidance document "Oncology Drug Products Used with Certain In Vitro Diagnostic Tests: Pilot Program." In this and other templates, FDA is providing recommendations regarding data and information that should be submitted to FDA regarding clinical trial assays (CTAs) used in the pivotal clinical trial(s) for oncology drug product(s) for the pilot program. This template is specific for CTAs that use Next Generation Sequencing (NGS) technology. Templates for CTAs that use other technologies can be found on FDA's website.

The CTA templates are intended to help oncology drug sponsors and CTA developers collect and provide validation information and performance characteristics for the CTAs, but alternative approaches can be used. To discuss an alternative approach, please contact OncologyPilotCDRH@fda.hhs.gov.

This template reflects FDA's current thinking on the topic, and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should*, means that something is suggested or recommended, but not required.

As described in FDA's guidance document, oncology drug sponsors interested in participating in the pilot program should submit a statement of interest to their Investigational New Drug (IND) application, New Drug Application (NDA), or Biologic License Application (BLA), as appropriate. The statement of interest should include a statement affirming the oncology drug sponsor's commitment to provide the information recommended in this template for CTAs used in their pivotal clinical trial(s) and the additional information described in the guidance. Upon receipt of the statement of interest, FDA will follow up with no more than 9 sponsors to request specific information, including the information identified below, to enable FDA to make a decision concerning acceptance into the pilot, based on evaluation of the factors outlined in FDA's guidance document and provide written feedback that either accepts or rejects the drug product for the pilot program. This template should be used to provide the information recommended in this template only when requested by FDA.

GENERAL INFORMATION ABOUT THIS TEMPLATE

- When requested by FDA, oncology drug sponsors who have submitted the statement of interest described above should complete the information below, as applicable, using the blue fillable fields. Hot links are provided to navigate to and from sections where data entry into tables is recommended; these data tables are provided in the Appendix.

www.fda.gov/media/169619/download?attachment

General Laboratory and Test Information

I. General Laboratory Information

a. Laboratory name and address: Enter laboratory's name and address
b. Laboratory contact name and email: Enter person's name and email address
c. Test name: Enter test name

II. General Test Information

A. Test information

Please provide a general description of the test including:

a. Is the test/CTA commercially available? ☐ Yes; ☐ No
    i. if yes, provide the following information:
        1. name of the kit and manufacturer: Enter kit name(s) and manufacturer(s) here
        2. if any modifications to the kit were made, describe them: Summarize here
    ii. if not, provide the following information:
        1. analyte(s) (e.g., single nucleotide variants for T790M in the *EGFR* gene in DNA): Enter analyte(s)
        2. test method, including specimen type (e.g., gene panel, PCR-based target amplification, hybrid-based capture from formalin-fixed paraffin-embedded [FFPE] breast tumor tissue): Enter test method including specimen type
b. CTA components (e.g., probes, reaction mixes, enzymes): Enter CTA components
c. Extraction method(s): Enter extraction method(s)
d. Instrument(s)/platform(s) used: Enter instrument(s)/platform(s)
e. Minimum tumor content: Enter amount
f. Minimum nucleic acid amount/range: Enter amount/range
g. Describe the positive control, its use, and what it measures: Positive control
h. Describe the negative control, its use, and what it measures: Negative control
i. Provide a brief summary of the bioinformatic workflow used for the test (e.g., sequence alignment process, germline filter, variant calling): Summarize here

Determination of Calling Rules and Clinical Cut-off

- Prespecified variant classification rule(s) to identify presence or absence of analytes
- Acceptable sequencing quality metrics at the sample, variant, and flow cell level (Table 1)
- Summary of the prespecified clinical cut-off used to enroll subjects

Table 1: Sequencing quality metrics for run acceptability

Sample level	
Coverage uniformity	Enter information or data
Base quality score	Enter information or data
Mapped reads	Enter information or data
Other	Enter information or data
Variant level	
Strand bias	Enter information or data
Variant allele frequency (VAF)	Enter information or data
Minimum # of mutant reads	Enter information or data
Other	Enter information or data
Flow cell level	
% pass quality filter	Enter information or data
% > Q30	Enter information or data
Other	Enter information or data

Validation Studies

- Samples used (Table 2)
- Comparator/orthogonal method(s) (Table 3)
- Analytical accuracy – concordance (Table 4)
- Limit of Detection (LoD) (Table 5)
- Precision (Table 6)
- Interfering substances (Table 7)
- Inclusivity/Cross-reactivity
- Stability
- NGS liquid biopsy (LBx) specific information

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Comparator/Orthogonal Method(s)

Table 3: Comparator/orthogonal method(s)

For sample selection or characterization					
Orthogonal method	Information	Analytical accuracy - concordance	Limit of detection	Precision	Interfering substances
Name	Enter information	☐ Yes; ☐ No	☐ Yes; ☐ No	☐ Yes; ☐ No	☐ Yes; ☐ No
Technology	Enter information				
Performed in-house	☐ Yes; ☐ No				
For test/CTA validation					
Comparator method (If different from the orthogonal method)	Information	Analytical accuracy - concordance			
Name	Enter information	☐ Yes ☐ No			
Technology	Enter information				
Performed in-house	☐ Yes; ☐ No				

Analytical Accuracy - Concordance

Analytical accuracy of the CTA is determined relative to a reference method or validated comparator method (orthogonal method). If a comparator method is used, it should have similar panel content and sensitivity to that expected from the CTA (based on the test method and/or previous analytical testing). Well characterized samples should be tested with both the CTA and comparator method.

Information Requested:

- Summary of study design to determine analytical concordance
- Details on samples tested to demonstrate accuracy
- If the analytes are not individually validated, details on the samples tested to demonstrate panel-wide accuracy for representative panel variants
- Summary of analytical concordance between NGS CTA and comparator for variant(s) and gene(s) evaluated for patient enrollment (Table 4)

Table 4: Summary of analytical concordance between CTA NGS (CTA) and comparator (Comp) for the variant(s) and gene(s) evaluated for patient enrollment

Gene, variant and type	Sample type	CTA (+), Comp (+)	CTA (+), Comp (-)	CTA (-), Comp (+)	CTA (-), Comp (-)	Possible variants (n)	Samples (n)	PPA (% CI*)	NPA (% CI*)
Enter gene (e.g., *EGFR*), variant (e.g., T790M), variant type (e.g., SNV)	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data
Enter gene (e.g., *EGFR*), variant (e.g., exon 19), variant type (e.g., deletion)	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data
Enter gene (e.g., *ALK*), variant (e.g., *NPM1-ALK*), variant type (e.g., fusion)	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data
For panel-wide data									
Panel-wide SNVs	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data
Panel-wide indels	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data

* CI: Confidence Interval

Validation Studies

- Samples used (Table 2)
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Precision

Precision studies are performed to evaluate sources of variation in the test procedure to determine the repeatability and reproducibility of the test.

Information Recommended:

- Brief study design
- Number of runs, days, instruments, reagent lots, operators, replicates tested per sample
- Whether precision evaluated at multiple sites
- If details not provided for each analyte, details on samples tested to demonstrate panel-wide precision
- If study not conducted with end-to-end workflow, information on part of workflow included and rationale
- Summary of statistical/data analysis methods to determine CTA precision
- Summary of PPA and NPA for variant(s) in gene(s) used for patient enrollment and panel-wide precision, if applicable (Table 6)

Table 6: Variant PPA/NPA summary for precision

Sample ID	Alteration (i.e., gene, variant)	Level (e.g., VAF, chimeric reads, tumor content)	Fold LoD (e.g., 1xLoD, 3xLoD)	Number positive / number expected	PPA (% CI)	NPA (% CI)
Enter information	Enter gene1 and variant1 (e.g., *EGFR* T790M)	Enter data	Enter data	Enter data	Enter data	Enter data
Enter information	Enter gene2 and variant2 (e.g., *EGFR* L858R)	Enter data	Enter data	Enter data	Enter data	Enter data
Enter information	Enter gene3 and variant3 (e.g., *EGFR* Exon 19 Del, E746_A750del)	Enter data	Enter data	Enter data	Enter data	Enter data
For panel-wide data						
Panel-wide SNVs	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data
Panel-wide indels	Enter information	Enter data	Enter data	Enter data	Enter data	Enter data

Validation Studies

- Samples used (Table 2)
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Limit of Detection (LoD)

The lowest amount of genomic target that the test can consistently detect with a stated probability.

Table 5: Call/detection/hit rate for LoD

Sample ID	Gene, variant and variant type	Measurand levels (list examples)	Level selected for LoD (Y/N)	Level (e.g., VAF, chimeric reads, CNV, tumor content)	Replicates called (n)/total replicates (n) (%)
Enter information	Enter gene (e.g., *EGFR*) Enter variant (e.g., T790M) Enter variant type (e.g., SNV)	Enter high level	☐ Yes; ☐ No	Enter data	Enter data
		Enter medium level	☐ Yes; ☐ No	Enter data	Enter data
		Enter low level	☐ Yes; ☐ No	Enter data	Enter data

Interfering Substances

Studies that evaluate the effects of potentially interfering endogenous and exogenous substances on test performance.

Table 7: Summary results for interfering substances study

Substances	Substance level tested	LoD levels used for variant allele frequency/chimeric reads/copy number/tumor content, etc.	# Samples	Replicates/ sample	Failure rate*	Detection rate**	Call rate (% CI)
Enter information (e.g., no interferent)	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data
Enter information (e.g., hemoglobin)	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data	Enter data

Inclusivity/Cross-Reactivity

Studies that evaluate the specificity of the primers or probes used to target specific genes and/or genomic regions.

Validation Studies

- Samples used (Table 2)
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NGS LBx-Specific Information

- Quality measures for circulating tumor DNA (ctDNA) samples, such as fragment analysis
- Whether germline and/or clonal hematopoiesis of indeterminate potential (CHIP) variants were excluded
- Limit of Blank (LoB) study description, if performed
- Description of assessment of interferents (such as short draws and unique components derived from the blood collection process can contribute to interference)

Questions and Comments

- Please submit questions regarding the templates and CTA validation to OncologyPilotCDRH@fda.hhs.gov

- Please submit comments on the oncology diagnostics pilot guidance and templates to the docket (www.regulations.gov/docket/FDA-2022-D-2275)

Summary

- Pilot CTA templates are intended to facilitate the provision, when requested by FDA, of analytical validation and performance characteristic information for CTAs used in pivotal trial(s) for drug products under the pilot.
- The pilot program is one step that may be helpful in reducing the risk of using unauthorized LDTs for oncology drug treatment decisions.


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Let's Take Your Questions

- **To Ask a Question:**
  - Raise your hand in Zoom 

  - Moderator will announce your name and invite you to ask your question
  - Unmute yourself when prompted in Zoom to ask your question

- **When Asking a Question:**
  - Ask one question only
  - Keep question short
  - No questions about specific submissions

- **After Question is Answered:**
  - Mute yourself and lower your hand
  - If you have more questions - raise your hand again

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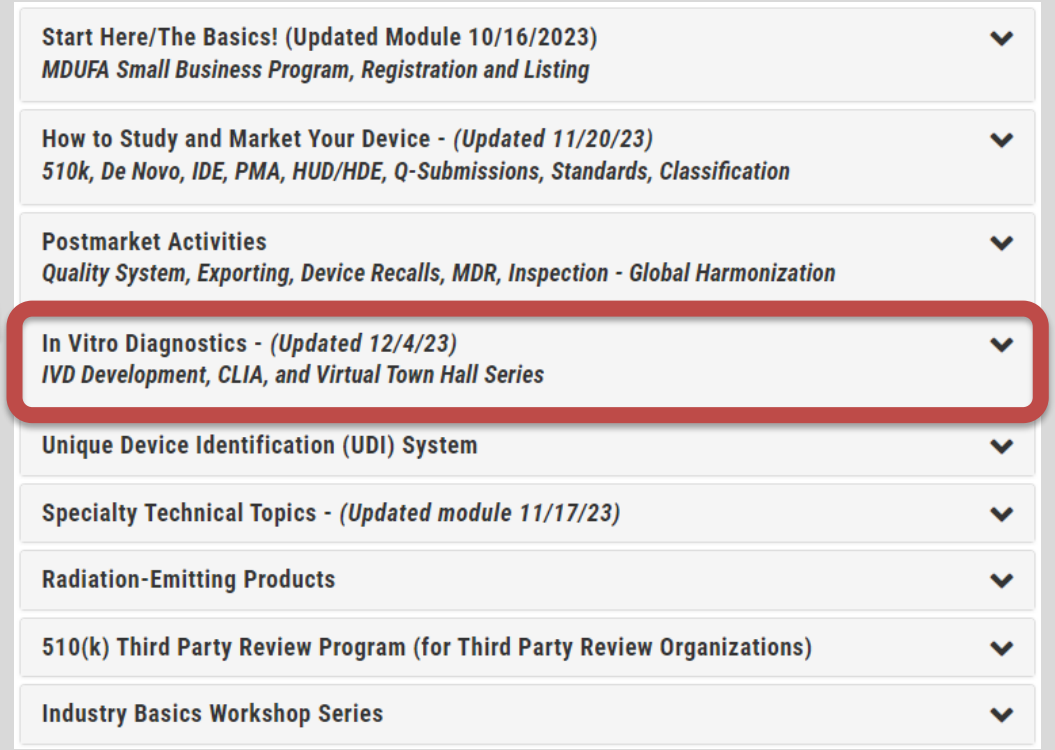


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