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ADMINISTRATION

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Oncology Center of Excellence

# **Biomarker Based Cancer Drug Development and Authorization in US**

CDDF Multi-Stakeholder Workshop

The critical role of Biomarkers in delivering drug development-related precision oncology  
13 -14 November 2023, HYBRID WORKSHOP – Amsterdam (NL)

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# Outline

- Biomarkers in Oncology Drug Development
  - Biomarkers vs IVDs
  - Companion Dx
  - Tissue Agnostic Drug Development
  - Group labeling
  - Rare Molecular Subsets
- Biomarker INDs
- Oncology Diagnostics Pilot

# Key Points

- Precision Oncology is critical to many drug development programs
- Rapidly evolving Biomarker landscape for drug development
- Collaboration with OCE/CDER/CBER/CDRH

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## Biomarkers in Drug Development

- Dramatic increase in biomarker-targeted drug development programs.
  - In the early 1990s, 5% of new drug approvals were for targeted therapies.
  - Personalized medicine account for more than a third of new drug approvals for four of the last five years  
(Source: Personalized Medicine Coalition report 2021)
- NCI has a List of Targeted Therapy Drugs Approved for Specific Types of Cancer

# Accelerated Approvals in Precision Oncology\*



- 42 accelerated approvals for solid tumor indications in precision oncology
- *The identification of several targetable mutations in NSCLC has led to the development and accelerated approvals of therapies that target EGFR, ALK, MET, RET and KRAS. Overall, these approvals have corresponded to a sharp decline in population-level mortality from NSCLC in the USA from 2013 to 2016. This has contrasted with relatively stable population-level mortality from small cell lung cancer, in which no actionable targets have been identified.*

\*As of 9/30/22

Vivek Subbiah, Lori J. Wirth, Razelle Kurzrock, Richard Pazdur, Julia A. Beaver, Harpreet Singh and Gautam U. Mehta. [Nat Med Oct 2022](https://www.nature.com/articles/s41591-022-01984-z)  
<https://www.nature.com/articles/s41591-022-01984-z>

# Biomarkers vs *In Vitro* Diagnostics (IVDs)

## Biomarker (BEST Definition)

- Defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.

## *In Vitro* Diagnostic (IVD)

- those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. 21 CFR § 809.3



# Biomarkers vs *In Vitro* Diagnostics (IVDs)

## Biomarkers

- Types of biomarkers: Molecular, histologic, radiographic, or physiologic **characteristics**
- Analyte(s): Tissue morphology, blood analytes, protein, DNA, RNA
- A biological measure associated with disease state

## *In Vitro* Diagnostic Test

- Well-defined **system** with a defined performance that is used to measure a biomarker status in the patient population
- **system** includes the specimen, the analyte, the instruments, the protocol and type of test (i.e. quantitative or qualitative), and the clinical decision point, (i.e. clinical cut off) for the test system

# FDA Approved/Cleared IVD Tests

## Analytical/Clinical Validation Summary

- Decision summaries of 510(k)s

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>

- SSED of PMAs

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>

## 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
- (<https://www.fda.gov/media/81309/download>)
- FDA applies a risk-based approach to determine the regulatory pathway for CDxs, as it does with all medical devices
- 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



# Example drug label and CDx labeling

## Companion Dx Labeling:

The thescreen PIK3CA RGQ PCR Kit is a real-time qualitative PCR test for the detection of 11 mutations in.....

The **test is intended to aid clinicians in identifying** breast cancer patients who may be eligible for treatment with PIQRAY® (alpelisib) based on a PIK3CA Mutation Detected result.....

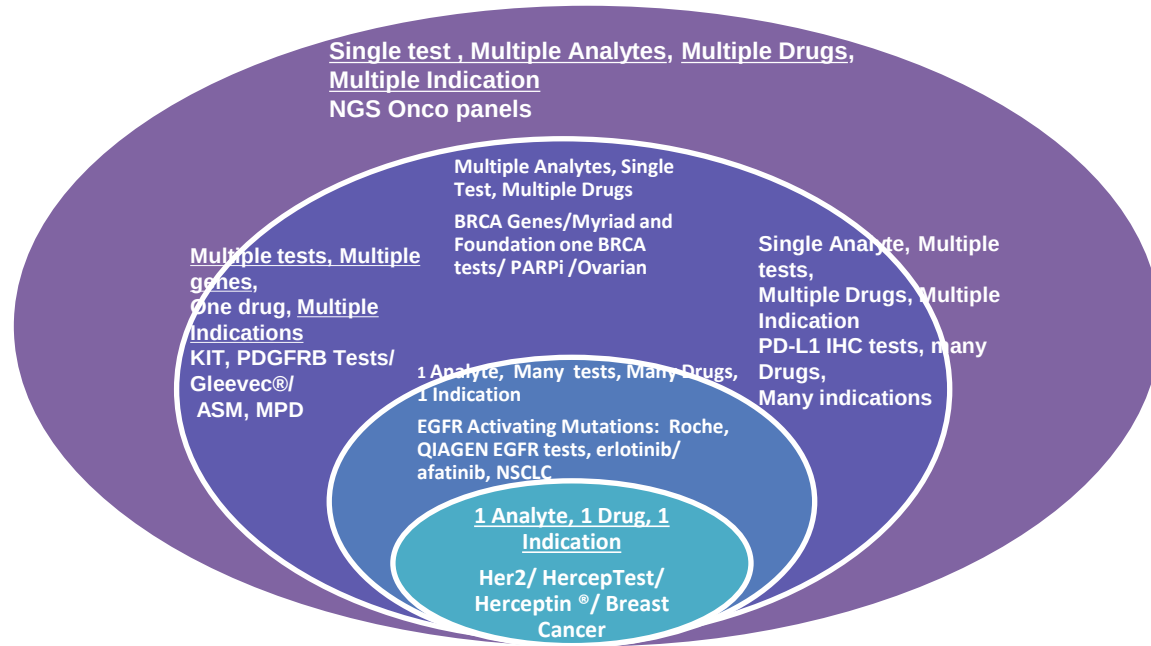
## Alpelisib drug labeling:

PIQRAY is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer **as detected by an FDA-approved test** following progression on or after an endocrine-based regimen

# Outline

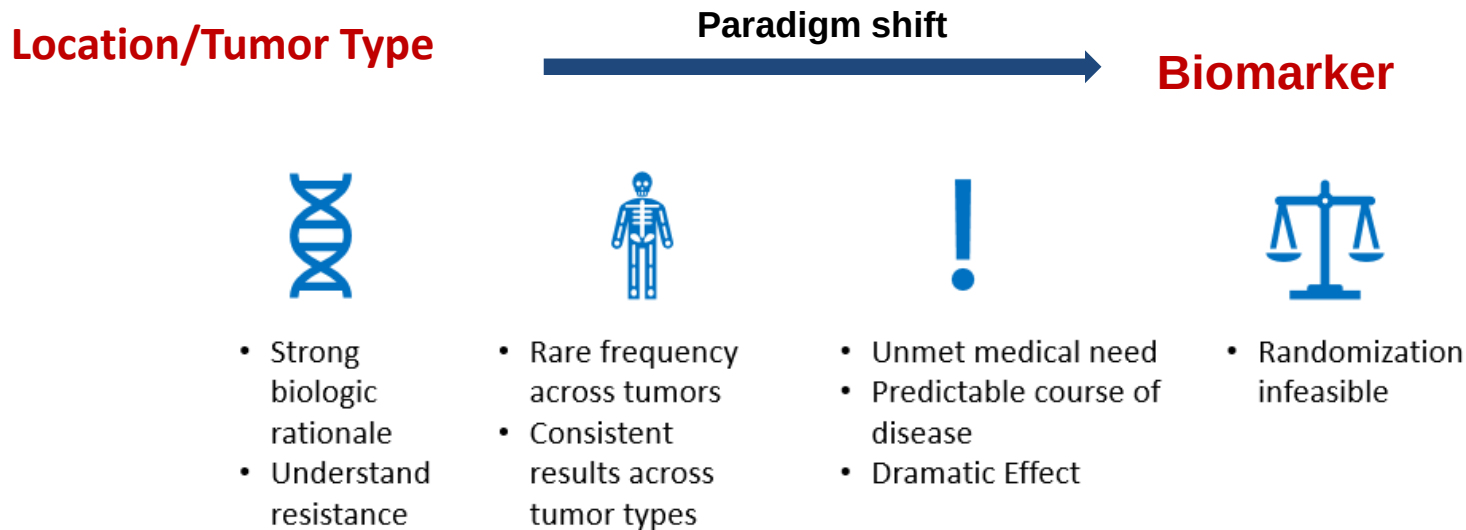
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# Shifting Regulatory Paradigm for CDx



NEW Paradigm: Disease was defined based on a biomarker and not the cancer type

# Tissue Agnostic Drug Development



**Pre-requisite:** detailed biologic understanding + clinical data showing large magnitude and consistency of effect

# Tissue Agnostic Approvals



| Drug                                                  | Indication              | Efficacy<br>ORR (9% CI) | Post<br>Approval<br>Studies | Device<br>with<br>Approval |
|-------------------------------------------------------|-------------------------|-------------------------|-----------------------------|----------------------------|
| 2017: <b>Pembrolizumab</b><br>N=149                   | MSI-H; dMMR             | 40% (32, 48)            | Yes                         | No                         |
| 2018: <b>Larotrectinib</b><br>N=55                    | NTRK-fusions            | 75% (61, 85)            | Yes                         | No                         |
| 2019: <b>Entrectinib</b><br>N=54                      | NTRK-fusions            | 57.4% (43, 77)          | Yes                         | No                         |
| 2020: <b>Pembrolizumab</b><br>N=102                   | TMB-H                   | 29% (21, 39)            | Yes                         | Yes                        |
| 2021: <b>Jemperli</b><br>N = 209                      | dMMR                    | 41.6% (34.9,<br>48.6)   | Yes                         | Yes                        |
| 2022: <b>dabrafenib plus<br/>trametinib</b><br>N= 131 | BRAF V600E<br>mutations | 41% (33, 50)            | Yes                         | No                         |
| 2022: <b>selpercatinib</b><br>N=41                    | RET fusions             | 44% (28, 60)            | Yes                         | No                         |

## Tissue Agnostic: Challenges include

- Companion diagnostics
- Incidence of biomarker across tumor types
- Logistical challenges

Tissue Agnostic Drug Development in Oncology: Draft  
Guidance

<https://www.fda.gov/media/162346/download>

Published: Oct 2022

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# CDx Challenges

## Background for Group labeling guidance

- Trials designed to support approval of a specific therapeutic product and a specific companion diagnostic (CDx) have led to companion diagnostic labels that reference only a specific therapeutic product(s).
- Several drugs with identical indications (including the same mutation/s) with different CDxs

# CDx Challenge



FDA approved CDx labeled for identifying NSCLC patients whose tumors have EGFR exon 19 deletions or exon 21 substitution mutations

| FDA<br>Approved<br>CDx             | Therapeutic Products included on CDx Label |           |           |             |             |
|------------------------------------|--------------------------------------------|-----------|-----------|-------------|-------------|
|                                    | Afatinib                                   | Gefitinib | Erlotinib | Osimertinib | Dacomitinib |
| Therascreen<br>EGFR RGQ<br>PCR Kit | X                                          | X         | -         | -           | X           |
| Cobas EGFR<br>Mutation Test<br>V2  | -                                          | -         | X         | X           | -           |
| Oncomine Dx<br>Target Test         | -                                          | X         | -         | -           | -           |
| Foundationone<br>CDx               | X                                          | X         | X         | -           | -           |

## Group labeling guidance - Background

- Specificity in labeling can limit a potentially broader use of a companion diagnostic that may be scientifically appropriate.
- Practicing oncologist **is only likely to order one test** to determine mutation status of a patient
- Sponsors developing drugs within a therapeutic group for the same mutation (e.g. the 4<sup>th</sup> EGFR inhibitor to market) using an approved CDx are generally required to submit a supplemental PMA for clinical performance

# Group labeling expands on a concept introduced in previous guidance



## In Vitro Companion Diagnostic Devices

### Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or [elizabeth.mansfield@fda.hhs.gov](mailto:elizabeth.mansfield@fda.hhs.gov); for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 240-402-7800 or 1-800-835-4709, or [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov). For questions for CDER, contact Christopher Leptak at 301-796-0017, or [christopher.leptak@fda.hhs.gov](mailto:christopher.leptak@fda.hhs.gov).



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Devices and Radiological Health  
Center for Biologics Evaluation and Research  
Center for Drug Evaluation and Research

- In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, **the intended use/indications for use should name the therapeutic class rather than each specific product in the class**

# Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products



## Overview

Describes an approach and specific conditions where device sponsors may request broader labeling for CDx to include multiple drugs in the same therapeutic group

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Developing and  
Labeling *In vitro*  
Companion Diagnostic  
Devices for a Specific  
Group of Oncology  
Therapeutic Products

Guidance for Industry

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

April 2020  
Procedural

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## Example

### Original CDx indication

*“identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with **Erlotinib.**”*

### New CDx indication with the group labeling claim

*“identifying patients with NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and are suitable for treatment with a **tyrosine kinase inhibitor approved by FDA for that indication.**”*

## List of cleared or approved CDx with group labeling claim

- [https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group\\_Labeling](https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools#Group_Labeling)

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# Drug Development for Rare Molecular Subsets



## Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease Guidance for Industry



- Rare Molecular Subsets
- Single tumor type



- Group variants
- expect similar response



- Drug approved if clinical trial successful



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

October 2018  
Clinical Pharmacology

Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease  
10/12/18

# Application of Guidance: GILOTRIF (afatinib) Label



## NDA 201292, Supplement # 14

| Label Section | Was                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Is now                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|---------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section 1     | <p>GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have <b>epidermal growth factor receptor (EGFR) <u>exon 19 deletions or exon 21 (L858R) substitution mutations</u></b> as detected by an FDA-approved test [see Clinical Studies (14.1)].</p> <p><u>Limitation of Use:</u> The safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations [see Clinical Studies (14.1)].</p> <p><i>therascreen EGFR PGQ PCR kit , for GILOTRIF (afatinib): Exon 19 deletions, L858R, L861Q, G719X, S768I</i></p> | <p>GILOTRIF is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have <b><u>non-resistant</u> epidermal growth factor receptor (EGFR) mutations</b> as detected by an FDA-approved test [see Clinical Pharmacology (12.1) and Clinical Studies (14.1)].</p> <p><u>Limitation of Use:</u> The safety and efficacy of GILOTRIF have not been established in patients whose tumors have <b>resistant</b> EGFR mutations [see Clinical Studies (14.1)].</p> |

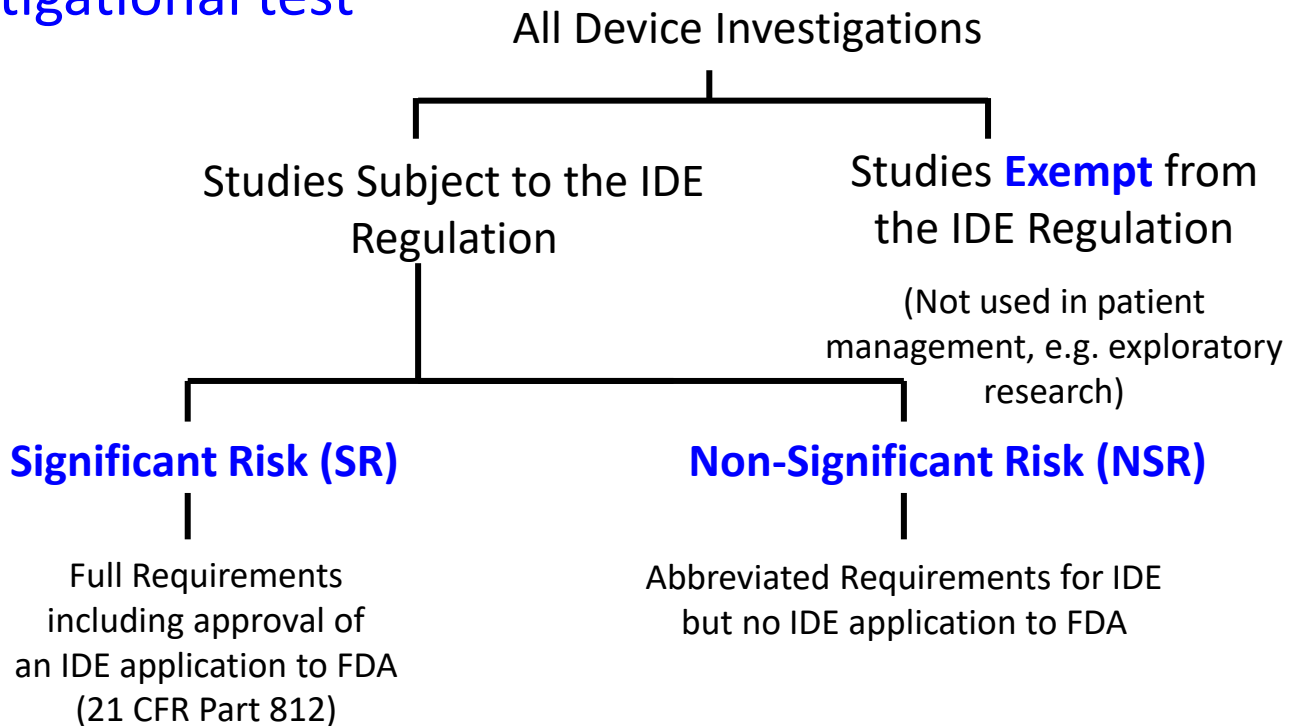
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# When Biomarkers are used for patient selection in clinical trials



- An Investigational test



# Use of the investigational test in the trial is Non-Significant risk



- If the trial is enrolling patients who have **incurable solid tumors** (non-curable locally advanced or metastatic disease in solid tumors) or **relapsed or refractory hematologic malignancies** associated with unfavorable long-term overall survival

# “Curative” solid tumor or hematologic malignancies associated with favorable long-term overall survival

Determine whether the investigational IVD proposed in the trial is **significant risk (SR)** by evaluating whether:

- The results from the IVD device will cause some **study subjects to forgo/delay an alternative treatment known to be effective**
- Incorrect results from the IVD device will cause some study subjects to be exposed to excessive toxicities associated with an investigational drug
- Is it likely, based on existing knowledge about the relationship between the biomarker and the investigational drug, that incorrect results from the investigational IVD would present a potential for serious risk to study subjects.
- The use of the investigational IVD requires invasive sampling that is not part of standard of care.

# Two guidances

## References:

- i. Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry  
<https://www.fda.gov/media/112605/download>
- ii. Investigational IVDs Used in Clinical Investigations of Therapeutic Products: Draft Guidance for Industry, Food and Drug Administration Staff, Sponsors, and Institutional Review Boards <https://www.fda.gov/media/109464/download>

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# CDx challenges



- Approval of a Therapeutic Product without an Approved or Cleared IVD Companion Diagnostic Device (CDx guidance: Page 9)
  - *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 .....*
- LDTs used in clinical practice vs. approved CDx
- Rare biomarkers & NSR trials: several local tests may be (several clinical trial assay(s) or CTAs) used for enrollment

# Oncology Diagnostics Pilot

- Oncology Dx Pilot Guidance
  - <https://www.fda.gov/media/169616/download>
  - Voluntary pilot program for certain Center for Drug Evaluation and Research (CDER)-regulated oncology drug products used with certain in vitro diagnostic tests

# Oncology Diagnostics Pilot

- To provide greater transparency regarding performance characteristics that certain tests for oncology biomarkers should meet.
- Support better and more consistent performance of certain LDTs used to identify patients for treatment with certain oncology drug products
- 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.

## Oncology Dx Pilot

- On its website, the FDA has provided a series of templates that oncology drug product sponsors, when requested by the agency, can use to facilitate the provision of performance characteristic information on the CTAs used in their clinical trials.
- If FDA approves an oncology drug product enrolled in this pilot program, at the time of drug product approval, FDA will publicly post the recommended performance characteristics on the CDRH website for tests used to identify patients for treatment with that drug product.

# Oncology Dx Pilot



## Scope

- Pilot program 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) ; 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

# Conclusion

- Precision Oncology is critical to many drug development programs
- Rapidly evolving Biomarker landscape for drug development
- Collaboration with OCE/CDER/CBER/CDRH

Questions:  
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