AMDM 2017 FOCUS MEETING

STRATEGIES FOR DRUG APPROVALS WITH NO SIMULTANEOUS CDX APPROVAL

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Outline

- **Companion Diagnostics (CDx)**
  - Definition & Examples
- **“Follow-on” CDx**
- **Complementary Diagnostics**
- **What is not a CDx**
- **Some examples of no simultaneous approvals and Post Market Commitments (PMCs)**

Guidances

- Developed by CDRH, CDER, and CBER

- **"In Vitro Companion Diagnostic Devices"**
  - Defined companion diagnostic (abbreviated as CoDx or CDx)
  - Described regulatory requirements (e.g., co-approval, labeling)
  - Finalized August 2014
- **"Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product"**
  - Draft guidance published on July 15, 2016
  - Public comments submitted to the docket considered in finalization of the guidance
  - Describes best-practices in co-development

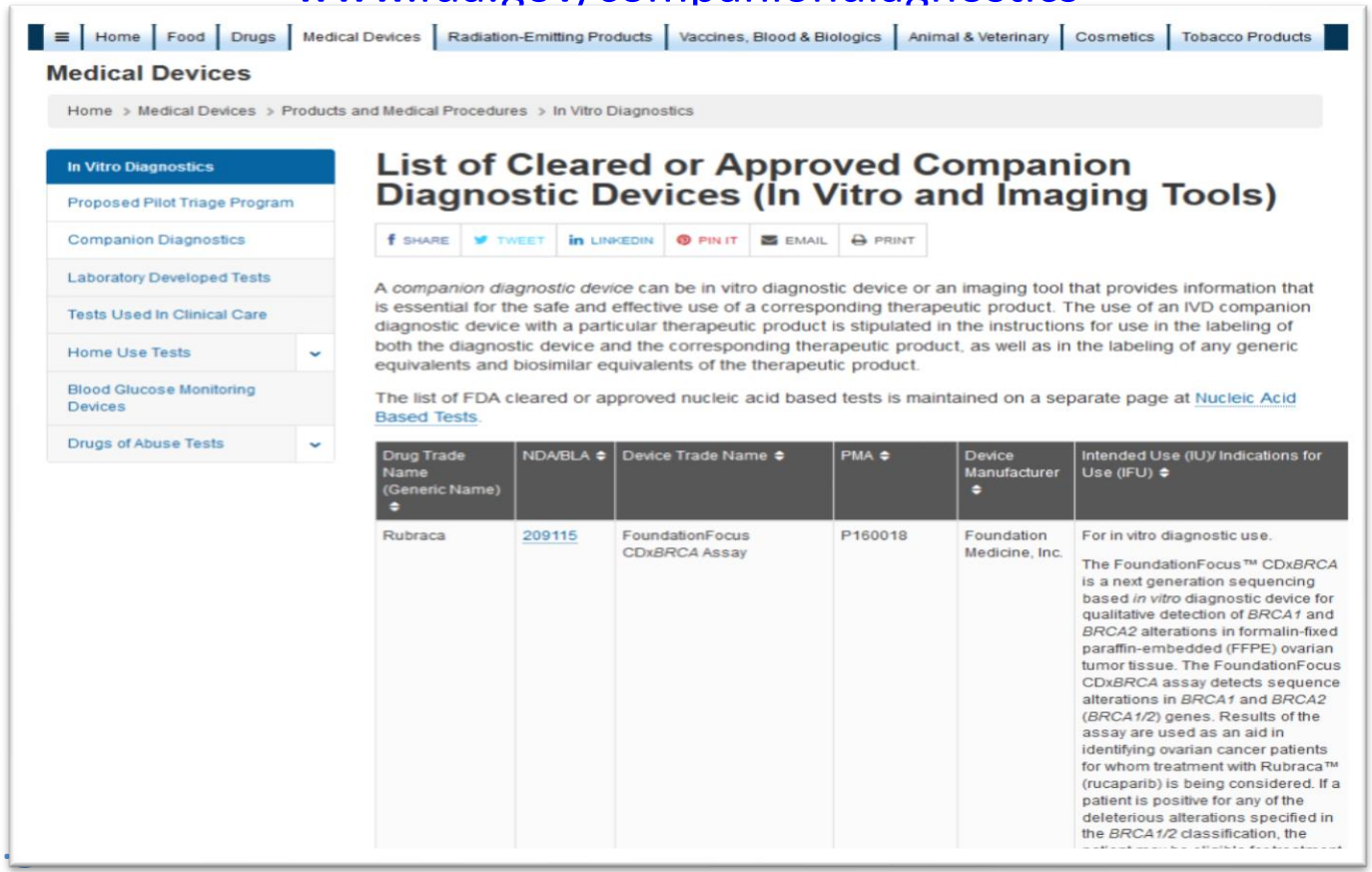
Companion Diagnostics

- The success of personalized medicine depends on having accurate, reproducible and clinically useful companion diagnostic tests to identify patients who can benefit from targeted therapies.

- A **companion diagnostic** is an IVD that provides information that is **essential** for the safe and effective use of a corresponding therapeutic product

FDA Approved Companion Diagnostics

www.fda.gov/companiondiagnostics



Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Medical Devices

Home > Medical Devices > Products and Medical Procedures > In Vitro Diagnostics

- In Vitro Diagnostics
- Proposed Pilot Triage Program
- Companion Diagnostics
- Laboratory Developed Tests
- Tests Used In Clinical Care
- Home Use Tests
- Blood Glucose Monitoring Devices
- Drugs of Abuse Tests

List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)

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A *companion diagnostic device* can be in vitro diagnostic device or an imaging tool that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the labeling of any generic equivalents and biosimilar equivalents of the therapeutic product.

The list of FDA cleared or approved nucleic acid based tests is maintained on a separate page at Nucleic Acid Based Tests.

Drug Trade Name (Generic Name)	NDA/BLA	Device Trade Name	PMA	Device Manufacturer	Intended Use (IU)/ Indications for Use (IFU)
Rubraca	209115	FoundationFocus CDx*BRCA* Assay	P160018	Foundation Medicine, Inc.	For in vitro diagnostic use. The FoundationFocus™ CDx*BRCA* is a next generation sequencing based *in vitro* diagnostic device for qualitative detection of *BRCA1* and *BRCA2* alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. The FoundationFocus CDx*BRCA* assay detects sequence alterations in *BRCA1* and *BRCA2* (*BRCA1/2*) genes. Results of the assay are used as an aid in identifying ovarian cancer patients for whom treatment with Rubraca™ (rucaparib) is being considered. If a patient is positive for any of the deleterious alterations specified in the *BRCA1/2* classification, the

www.fda.

Many successful CDx examples

	Companion Diagnostics in Oncology
41	Approved IVD Companion Diagnostic-Therapeutic Product Pairs
30	Approved IVD Companion Diagnostics
18	Approved Cancer Therapeutic Products
16	Molecular markers ALK, BRCA1, BRCA2, BRAF, C-KIT, EGFR, FLT3, HER-2/NEU, IDH2, KIT, KRAS, NRAS, PDGFRB, PD-L1, ROS1, 17p deletion

www.fda.gov/companiondiagnostics

	Intended Use (excerpts)
FoundationFocus™ CDxBRCA 1st NGS CDx	Next generation sequencing based in vitro diagnostic device for qualitative detection of BRCA1 and BRCA2 alterations in formalin-fixed paraffin-embedded (FFPE) ovarian tumor tissue. Results of the assay are used as an aid in identifying ovarian cancer patients for whom treatment with Rubraca™ (rucaparib) is being considered.
Oncomine™ Dx Target Test 1st NGS test for multiple CDx indications	Qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in ROS1 from RNA isolated from formalin- fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC) using the Ion PGM™ Dx System. Aid in selecting NSCLC patients for treatment with Tafinlar, Iressa, and Xalkori.
Praxis™ Extended RAS Panel 1st CDx based on negative mutation status	Qualitative in vitro diagnostic test using targeted high throughput parallel sequencing for the detection of 56 specific mutations in RAS genes [KRAS (exons 2, 3, and 4) and NRAS (exons 2, 3, and 4)] in DNA extracted from formalin-fixed, paraffin-embedded (FFPE) colorectal cancer (CRC) tissue samples. Aid in the identification of patients with colorectal cancer for treatment with Vectibix® (panitumumab) based on a no mutation detected test result.

Considerations for CDx Development

- Therapeutic product sponsors are responsible for assuring that a companion diagnostic (CDx) device will be brought forward
- Device sponsors are responsible for CDx submission, performance, compliance with device regulations
- Therapeutic product and CDx sponsors should carefully define expectations for each other

Companion Diagnostic

- Definition: essential for the safe and effective use of a corresponding therapeutic product; "essential" determined by CDER/CBER
- Safety and efficacy of the therapeutic evaluated in population defined by the CDx
- Therapeutic product's label (Indications and Usage section) specifies use of FDA approved CDx. Test name is also referred in the Clinical Studies section of the therapeutic product label
- Expectation for contemporaneous approval of CDx with approval of therapeutic product so an FDA-approved CDx is available for use
- FDA has experience with several kinds of applications: IVD manufacturers, LDTs, HDEs, Follow-ons

"Follow-On" CDx

- Seeks the same therapeutic indication in its intended use, as in the intended use of a FDA-approved CDx
- "Follow-on" CDx should consistently and accurately select the same intended use patient population as the originally-approved companion diagnostic devices for the indicated therapeutic drug
- "Follow-on" CDx should demonstrate the same or comparable level of analytical and clinical performance for specific mutations as in the originally-approved CDx

"Follow-On" CDx : Review Considerations

- Dx test not used in registrational trial
- Method comparison - Procured clinical sample set representing the intended use population
  - Each enrolled sample will be tested by "Follow-On" CDx once and by Comparator CDx twice
  - Agreement between Follow-On" CDx and Comparator CDx is comparable to the agreement between two replicates of Comparator CDx

Emerging Paradigm – Complementary Diagnostics

- A **complementary diagnostic** is an IVD that identifies a biomarker-defined subset of patients with a different benefit-risk profile than the broader population for which a therapeutic product is indicated
- It is not a prerequisite for receiving the therapeutic product
- Information (including name is) included in "Clinical Studies" section of drug label

Complementary Dx Approval Examples

	Intended Use (excerpts)
PD-L1 IHC 28-8 pharmDx	PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC may be associated with enhanced survival from OPDIVO ® (nivolumab).
PD-L1 IHC 28-8 pharmDx	Positive PD-L1 status as determined by PD-L1 IHC 28-8 pharmDx in melanoma is correlated with the magnitude of the treatment effect on progression-free survival from OPDIVO®.
Ventana PD-L1(SP142) CDX ASSAY	PD-L1 expression in ≥ 5% IC determined by VENTANA PD-L1 (SP142) Assay in urothelial carcinoma tissue is associated with increased objective response rate (ORR) in a non-randomized study of TECENTRIQ™ (atezolizumab).

What is (generally) not a CDx?

- Tests that are medically established and collectively recognized as necessary for the diagnostic work-up of a patient:
  - Hereditary tests that are part of the diagnosis (e.g., CF testing for Kalydeco, DMD for Exondys 51)
  - Exception: when there may be multiple methods that will yield highly discordant results (e.g., diagnostic sub-classification)
- Clinical laboratory tests that are commonly used and well understood biochemical assays (e.g., serum creatinine)
- Histological features without testing are conclusive for diagnosis (e.g., CD30 IHC & brentuximab for Hodgkin lymphoma)
- Tests used as surrogate endpoints for drug safety and efficacy

Approval of a Therapeutic Product without an Approved or Cleared CDx - From the CDx guidance

- New Therapeutic Products to treat Serious or Life-Threatening Conditions for which no satisfactory alternative treatment exists
- Already Approved Therapeutic Products - addressing a serious safety issue.

If 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

FDA Approves New ROS1 Indication for Xalkori With Post-Marketing CDx Commitment - March 11, 2016

- The agency approved the new indication with a post-marketing commitment for Pfizer to develop a companion diagnostic in the future. This may be an opportunity for Pfizer to bring to market a next-generation sequencing-based universal CDx, a tool that multiple drug and diagnostics firms are working on developing recognizing that the rapid pace of genomic research has already made the one-drug, one-biomarker, one-test paradigm obsolete.

FDA approved Thermo Fisher Scientific's Oncomine™ Dx - June 22, 2017

- as the first NGS-based companion diagnostic that screens tumor samples against panels of biomarkers to identify patients who may respond to one of three different treatments for non-small cell lung cancer (NSCLC).
- high-throughput, parallel-sequencing technology to screen tumor samples for 23 NSCLC genes, to identify patients with EGFR L858R mutation & Exon 19 deletions, BRAF V600E mutations, ROS1 fusions who may be eligible for therapy

FDA granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature - May 23, 2017

- Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment

Keytruda approval with Post Marketing Commitment (PMC)

- to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based in vitro diagnostic device, and a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are mismatch repair deficient.

Complementary Dx
PMCs fulfilled

- PD-L1 IHC 28-8 pharmDx : Fulfillment of a post market commitment to support complementary diagnostics for the treatment of patients with nivolumab in squamous cell carcinoma of head and neck (SCCHN) and urothelial carcinoma (UC) respectively

Summary

- If the use of an IVD companion diagnostic device is essential for the safe and effective use of a therapeutic product, an approved or cleared IVD companion diagnostic device should be available for use once the therapeutic product is approved.
- In most circumstances, an IVD companion diagnostic device and its corresponding therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling

Summary

…. continued

- FDA may decide that it is appropriate to approve a therapeutic product even though an IVD companion diagnostic device is not approved or cleared contemporaneously
  - New Therapeutic Products to Treat Serious or Life-Threatening Conditions
  - Already Approved Therapeutic Products – labeling revisions to address a safety issue

Thank You!

Additional questions, inquiries …
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