Agilent Dako

Agilent CDx

Success and Challenges in Pre-Market Registration and Approval of Companion Diagnostic in Global Markets

Xiaolei Xu, Ph.D.
Director of Global Regulatory Affairs
Companion Diagnostics
Agilent Technologies, Inc.

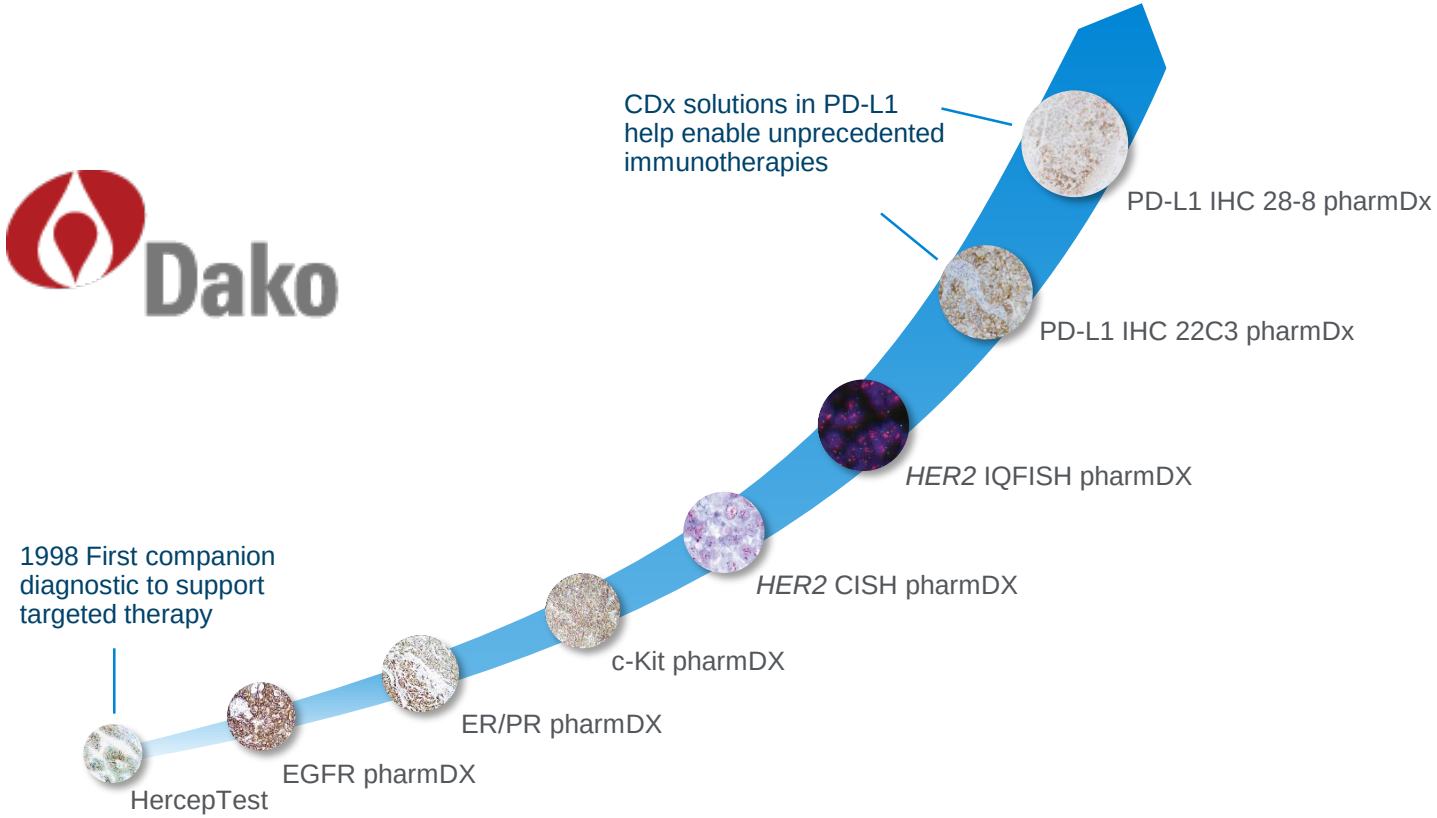
Agilent

Agilent Companion Diagnostics (CDx) started with the Dako branded HercepTest

Agilent Dako

Celebrating 20 years of companion diagnostic assay development since launching the first CDx, HercepTest, in 1998

We have a proven legacy developing diagnostics that support groundbreaking therapies, from HercepTest to PD-L1, everywhere in between, and beyond.



US FDA Guidance and **Companion Diagnostics (CDx)**

Agilent Dako

Companion Diagnostic (FDA guidance)

An *IVD companion diagnostic device* is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. (device include reagent, instrumentation, software)

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

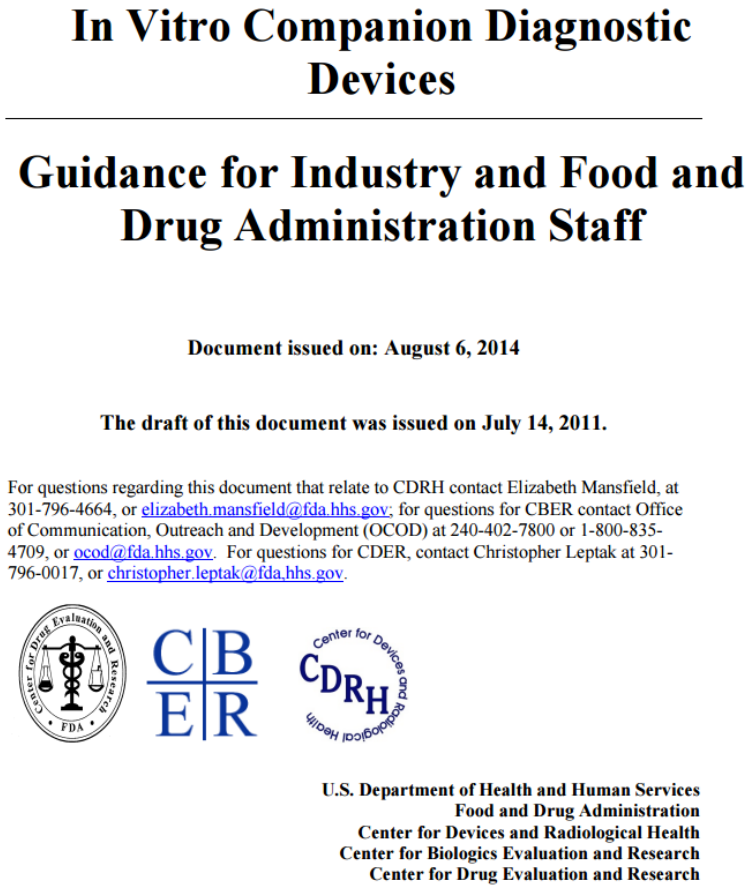
The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product.

Drug approval will depend on the Device approval and vice versa

History of Companion Diagnostics (CDx)

Agilent Dako

- FDA first published a draft guidance on IVD CDx back in 2011, with final guidance issued in August 6, 2014 to layout the frame work of CDx
- Guidance described “what” but not “how”
- FDA recognized the need to describe the processes both IVD and pharma companies should take in co-development process
- Collaboration between CDER, CBER and CDRH



In Vitro Companion Diagnostic Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on: August 6, 2014

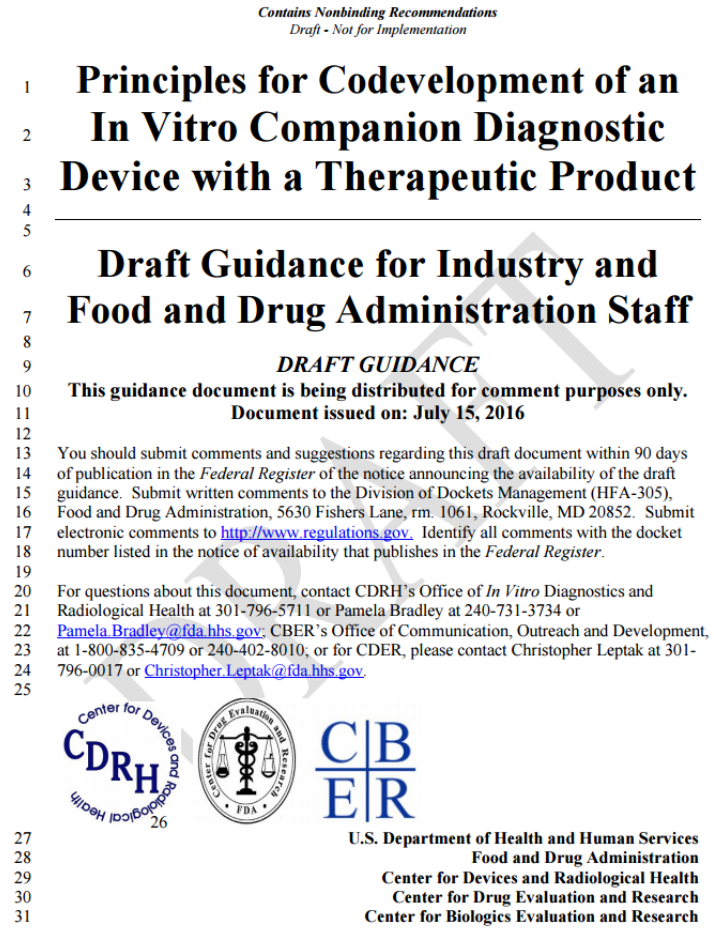
The draft of this document was issued on July 14, 2011.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; 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. For questions for CDER, contact Christopher Leptak at 301-796-0017, or 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

Draft Co-development guidance

- Draft guidance on co-development of an IVD and Rx issued July 15, 2016
- Important guidance for both IVD *AND* pharma (CDRH, CDER and CBER)
- Good reference document to describe processes encountered in most co-development partnership
- Represents a culmination of experiences and enables partners and FDA to have same reference point



Contains Nonbinding Recommendations
Draft - Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: July 15, 2016

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact CDRH's Office of *In Vitro* Diagnostics and Radiological Health at 301-796-5711 or Pamela Bradley at 240-731-3734 or Pamela.Bradley@fda.hhs.gov; CBER's Office of Communication, Outreach and Development, at 1-800-835-4709 or 240-402-8010; or for CDER, please contact Christopher Leptak at 301-796-0017 or Christopher.Leptak@fda.hhs.gov.

26

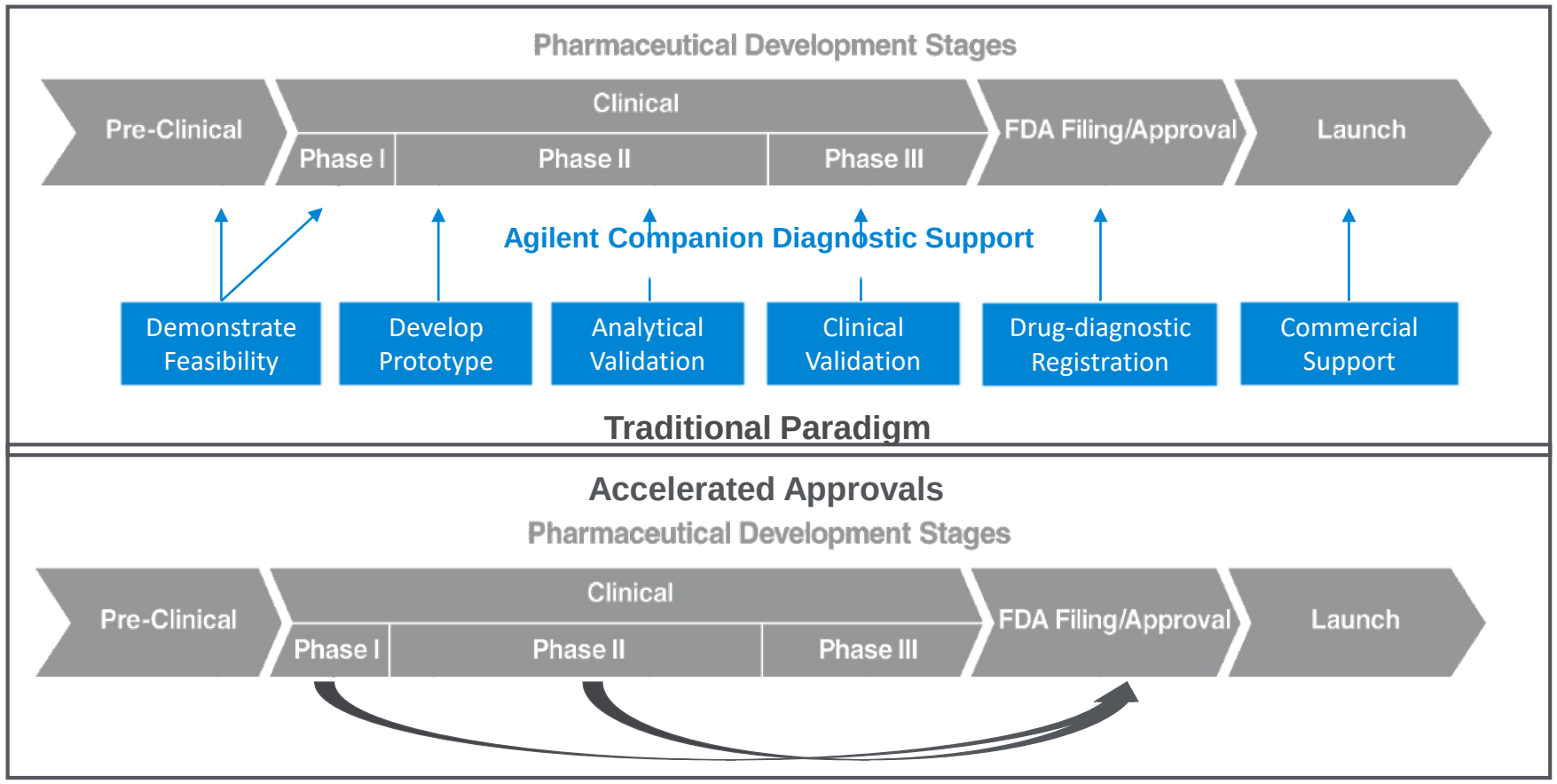
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research

Ensuring Co-development Alignment

Agilent Dako

Example: Accelerated Drug Approval

Fully align drug-diagnostic co-development to enable timely and cost effective commercialization



Challenges in Development and Registration

Agilent Dako

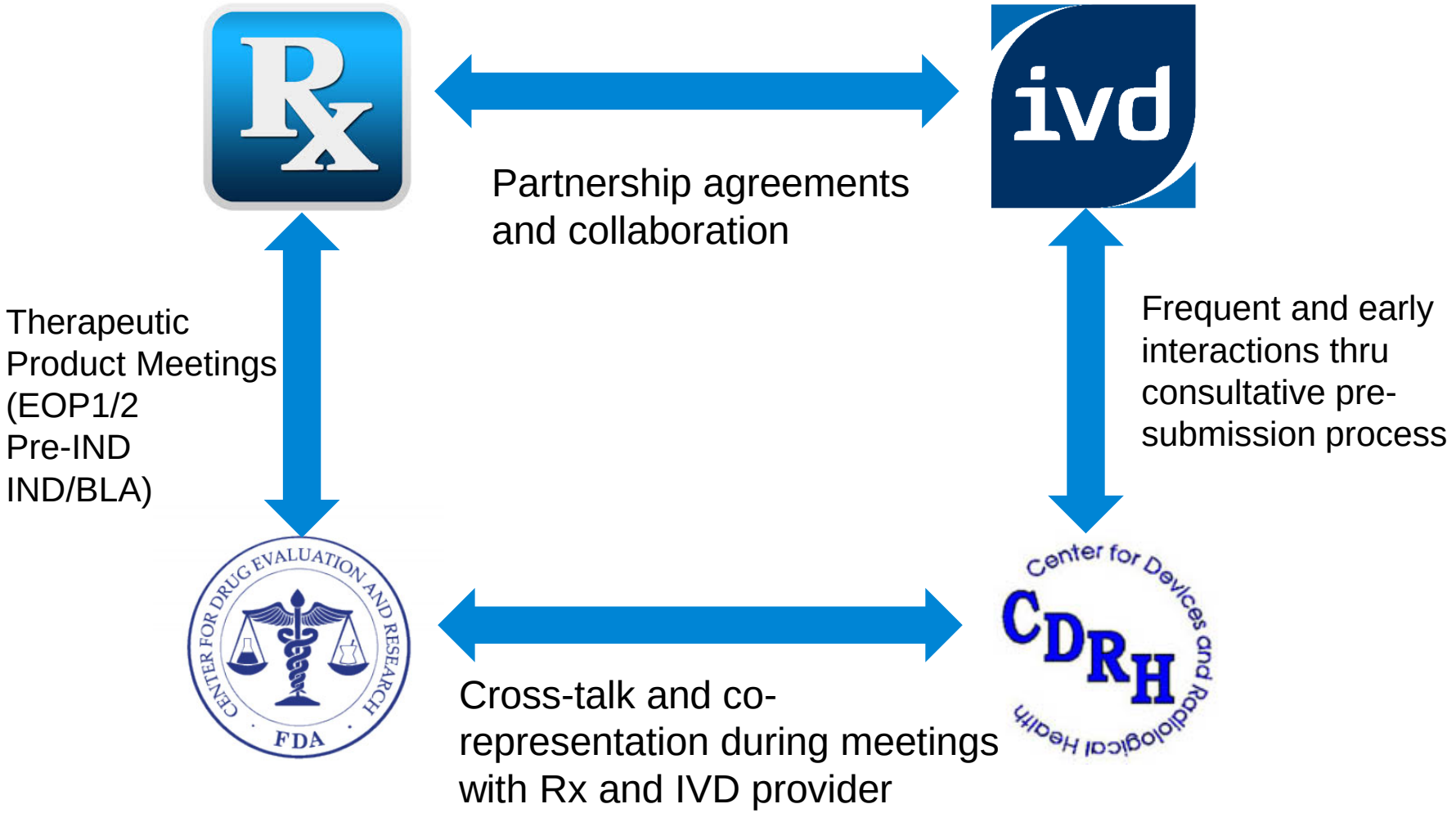
- Accelerated pharma development timeline
- Pharma often come to Dx developer after the start of clinical trial
  - Often using a prototype assay (CTA) in early phases, Re-testing/Bridging study strategy
  - Not enough samples saved for cutoff evaluation
  - Not enough samples available for Re-testing/Bridging study (within stability window)
  - Not enough time to develop and finish IVD assay verification/validation
    Pharma does not always recognize the development time for Dx can be 6 to 12 months for V&V
- Pre-analytical factors not included in the assay validation

- Expansion of indications:
  - Different scoring methods and cut offs
  - Multiple cut offs need to be developed
  - Difference in study design to demonstrate clinical utility and claims, the needs for CDx/Complementary not know until the end of therapeutic review

- ROW/ex-US product requirement not included in planning

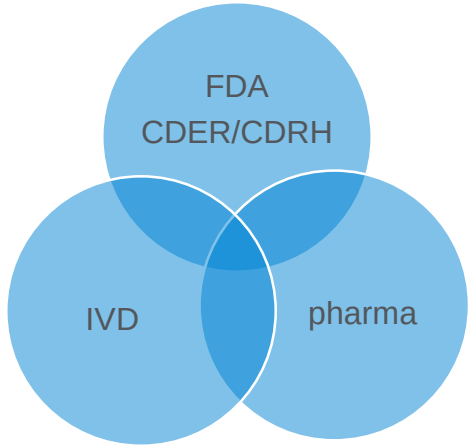
Interactions between Rx,Dx and FDA during co-development and approval process

Agilent Dako



Interactive collaborations with FDA

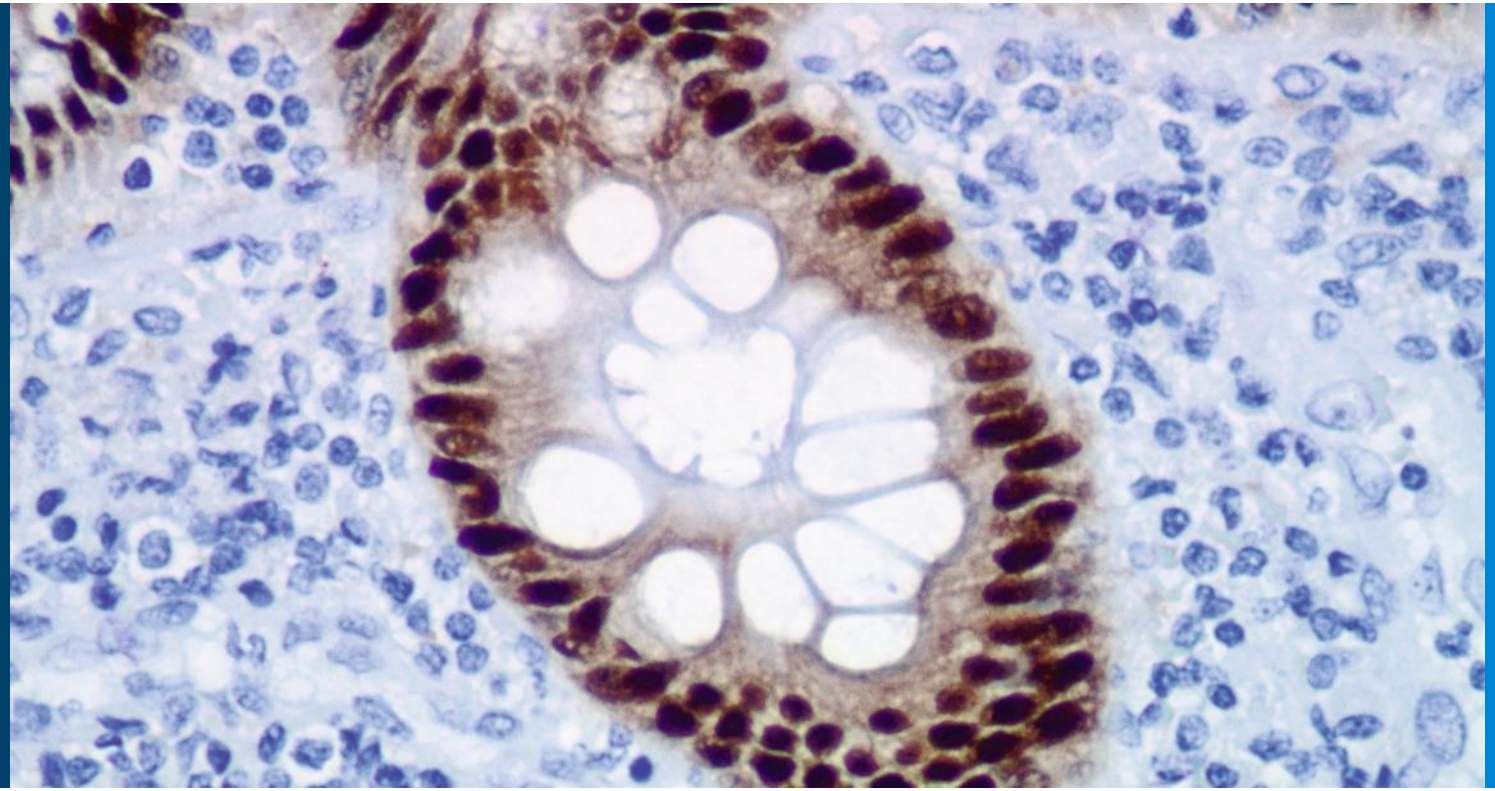
- Early introduction of both CDx/Rx programs to both CDER & CDRH
  - Understand the biomarker early
  - Form Dx and Rx partner early in the process
  - Share regulatory correspondence between pharma and Dx developer especially related to clinical development strategy



- Frequent use of pre-submission process: strategy, protocols, SAP/analysis plans
  - Leverage existing/approved validation, propose smarter validation approaches
- Cross-center interactions & participation in meetings (4-ways)
- FDA listening and collaborative when met with challenges
- CDRH and Dako worked to ensure contemporaneous approval
- Post approval commitment
- Both CDRH and Dako committed to quick TAT on review issues/questions

Agilent Dako

CDx Regulatory Considerations in Global Markets



Agilent

Challenges

Agilent Dako

- Lack of CDx Co-approval process
  - No CDx concept, but in general CDx is considered highest risk (i.e. Class III)
  - Rx and Dx are on different review paths, create significant challenges to align on co-approval of Rx and CDx (both indications and cut offs)

- Country of Origin approval is required in many ROW (Rest of World) Countries
  - Required to use US approved or EU CE marked IFUs
  - Operational challenge to manage inventory to meet both US/EU and ROW needs

- When adding new indications/new scoring methods/new cut offs
  - Required new submission
  - Change application
  - Rolling submission not allowed

Japan CDx Regulatory Considerations

Agilent Dako

- **CDx**
  - Likely considered as class III IVD (high risk product)
  - Approval by MHLW
  - Provide product QMS file and product technical file prepared according to Guide to the Japanese Revised Pharmaceutical Affairs Law
- **Technical Guidance on Companion Diagnostic agents and Related Pharmaceutical Products by PMDA (Pharmaceuticals and Medical Devices Agency)**

  Ihatsu no. 1224029

  December 24, 2013

  Provide the guidance on Clinical studies during development of pharmaceutical products related to companion diagnostic agents.

  Points to notes include:
  - Handling of biomarker-negative
  - The need for prospective confirmatory clinical studies
  - Evaluation of Clinical significance of companion diagnostic agents
  - Studies to evaluate the concordance of companion diagnostic agents

- **Experiences:**
  - PMDA is interested in US FDA filing strategy (Rx and CDx) although FDA approval is not required
  - Expect co-submission and co-approval of Rx and CDx (CDx submission maybe within one month of Rx submission)
  - Representation of Japanese patients
  - Central testing can be done outside of Japan
  - Consultation with PMDA highly recommended, especially clinical consultation
  - Prepare to provide data (i.e. case report form) from central testing lab(s) to support clinical data audit
  - Apply for reimbursement approval

Korea CDx Regulatory Considerations

Agilent Dako

- Regulatory Classification: Class III IVD
- Anticipated timeframe for registration approval: ~ 3 months for submission preparation and 6 months for agency review
- In general no additional testing required if submission is based on approved PMA
- Anticipated timeframe for approval of Korean reimbursement: HTA – 30 days(existing) or 140 days(New); HIRA Reimbursement application – approximately 150 days
- Require KGMP certification

Case Study: PD-L1 IHC 22C3 Pharm Dx

Agilent Dako

- CDx for Keytruda (Merck and Co.)
- In US: currently Approved for 4 Indications as CDx for Keytruda
  - Non-Small Cell Lung Cancer (NSCLC)
  - Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
  - Cervical Cancer
  - Urothelial Carcinoma
- Currently registered/approved in over 80 countries including all major markets
  - Goal: align with Keytruda approval in each country
- Experiences:
  - Closely managed cross function teams (CDx/Rx regulatory, Commercial/Marketing, R&D, Project management, CDx operations….)
  - Interaction with Agencies (jointly with Rx)
  - Exploring novel regulatory pathways
    - Bundling submission
    - Requesting interactive reviews
    - Take advantage of pre-submission consultation where possible
    - Education and alignment to addressing co-approval

Agilent CDx

Thank you and Questions

Xiaolei Xu, Ph.D.
xiaolei.xu@agilent.com

Companion Diagnostics
Agilent Technologies, Inc.