Agilent CDx

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

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

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)**

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)

- FDA first published a draft guidance on IVD CDx back in 2011, with final guidance issued in August 6, 2014 to layout the framework of CDx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
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- Draft guidance on co-development of an IVD and Rx issued July 15, 2016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
Ensuring Co-development Alignment
Example: Accelerated Drug Approval
Fully align drug-diagnostic co-development to enable timely and cost effective commercialization

Pharmaceutical Development Stages
Pre-Clinical | Clinical | FDA Filing/Approval | Launch
Pre-Clinical Phase I | Clinical Phase II | Phase III | FDA Filing/Approval | Launch

Agilent Companion Diagnostic Support
Demonstrate Feasibility | Develop Prototype | Analytical Validation | Clinical Validation | Drug-diagnostic Registration | Commercial Support

Traditional Paradigm
Accelerated Approvals
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Companion Diagnostics Forum – September 14, 2018
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Challenges in Development and Registration

• 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

Partnership agreements and collaboration

Therapeutic Product Meetings (EOP1/2 Pre-IND IND/BLA)

Cross-talk and co-representation during meetings with Rx and IVD provider

Frequent and early interactions thru consultative pre-submission process
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
CDx Regulatory Considerations in Global Markets
Challenges

- 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

- **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

- 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

- 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
Thank you and Questions

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