Companion Diagnostics and Codevelopment Update

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FDA and Personalized Medicine

- "The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies."
  - Hamburg, M. and Collins, F., "The Path to Personalized Medicine," 363 N. Engl. J. Med. 301-304 (July 22, 2010).
- Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development (October 2013)

Companion Diagnostics

- Defined as being essential for the safe and effective use of a corresponding therapeutic product
- Companion diagnostic
  - Performance characteristics critical
  - It matters which test you use
- Draft Guidance for Industry and Food and Drug Administration Staff - In Vitro Companion Diagnostic Devices—July 2011

Codevelopment

- Development of companion diagnostics together with therapeutics
- Recognized as essential to the success of personalized medicine.
- Allow for more efficient studies with smaller patient population
- Leading to more focused therapies that offer better outcomes, less toxicity, and fewer treatment delays.

Business Issues

- Therapeutic product sponsors are responsible for assuring that a companion diagnostic device will be brought forward
- Device sponsor responsible for submission, performance, compliance with device regulations

Companion Diagnostic Policy

- Requires contemporaneous approval of a test when that test is essential for safe and effective use of a therapeutic product
- CoDx requirement
  - Decision made by drug review division
  - Device center provides insight
- Labeling
  - Therapeutic label refer to “FDA approved Test”
  - Device label name the drug

Therapeutic Product Labeling (Example)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XALKORI® safely and effectively. See full prescribing information for XALKORI.

XALKORI® (crizotinib) Capsules, oral
Initial U.S. Approval: August 2011

----------INDICATIONS AND USAGE----------
XALKORI is a kinase inhibitor indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. (1) This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

Companion Diagnostic Labeling (Example)

INTENDED USE

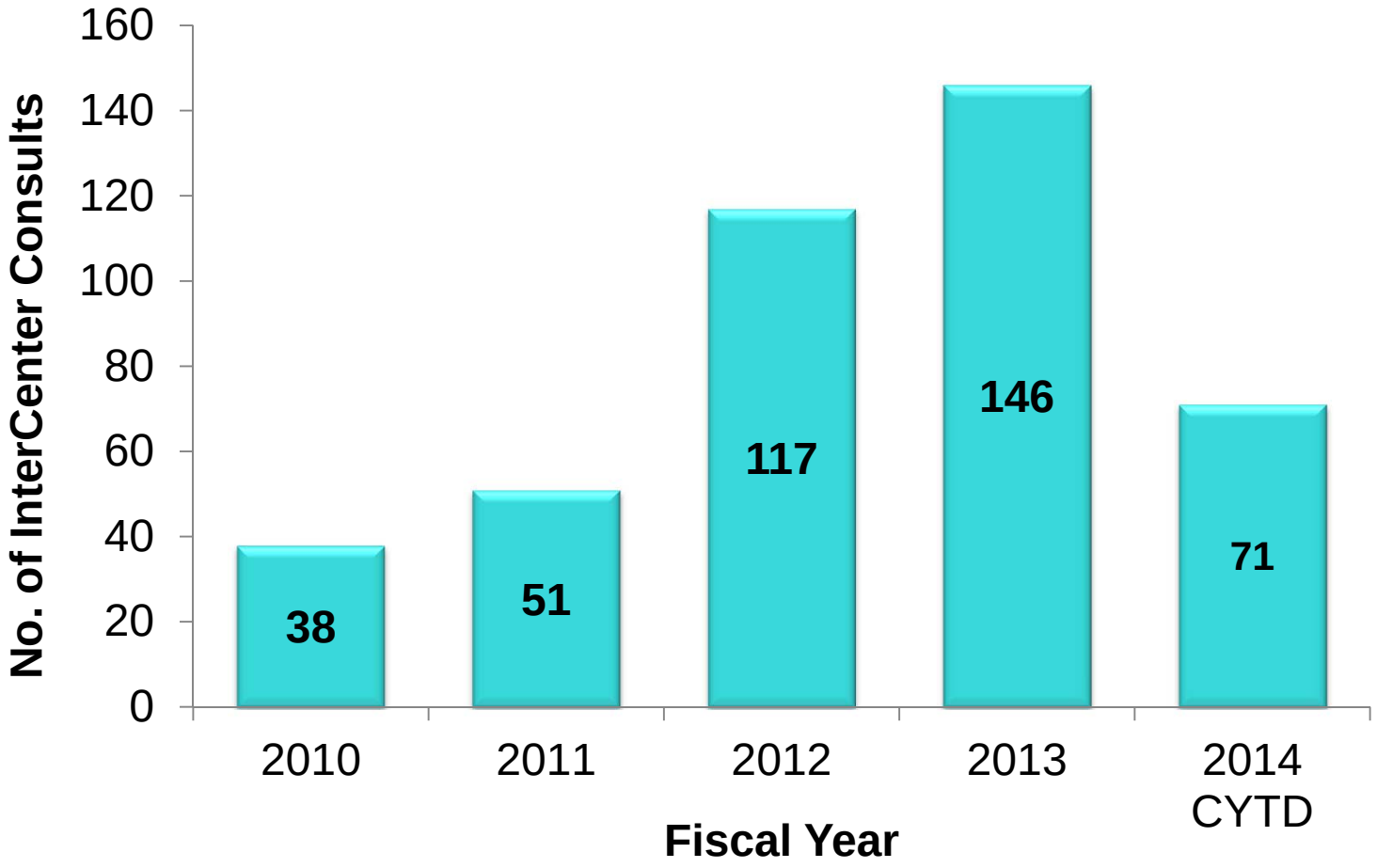
The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization (FISH) in formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue specimens to aid in identifying those patients eligible for treatment with XALKORI® (crizotinib).

The test is for prescription use only.

Current Status

- To date: 19 different approved drug/diagnostic combinations
  - Many are HER-2 specific
  - Others are novel agents/new tests
  - www.fda.gov/companiondiagnostics for a current list

Increase in InterCenter CoDx Consults



Advances in Intercenter Policies & Communications

- Essential to work together early and often
- Different Centers have different laws, regulations, cultures, and needs
- Process becoming established as “normal”:
  - Inviting each Center to (almost) all internal and sponsor meetings
  - Centers work on labeling together
  - Centers coordinate joint PR

Additional Intercenter Advances

- Creating agreed-to ways of working together
- Recognizing each Center's role in process
  - Including limitations
- Creating streamlined regulatory communication methods
  - Different centers use different systems to archive, track submissions
- Increasing recognition of status of tests in INDs
- Regular internal interactions on broader scope

Lessons Learned from Companion Dx Approvals

- No two development programs are the same
- We should use all possible regulatory mechanisms to create pathways that work
- Early determination of CoDx need is better for codevelopment
  - But we can handle variations

Lessons Learned from Companion Dx Approvals

- Bridging from CTA to IVD is not easy
  - Save samples, consider covariates, avoid bias
- Accelerated drug approval does not significantly change when companion Dx needed
- Modular PMA process for Dx highly preferred over traditional
- Drug and Dx sponsors should carefully define expectations for each other

Relevant Guidance

- In Vitro Companion Diagnostic Devices
  - Published 2011, still draft
- Principles of Codevelopment
  - Draft guidance in internal review
- Investigational IVD Devices Used in Therapeutic Product Studies
  - Draft guidance in internal review
- Clinical Trial Designs Employing Enrichment Strategies
  - Draft guidance published December 2012
    - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf

Codevelopment (Draft) Guidance

- Guidance drafted by CBER, CDER, CDRH; in internal review
- Guidance will:
  - describe points to consider in both therapeutic and diagnostic development programs
  - describe FDA preferences for certain elements
  - not prescribe any particular development pathway

Investigational Requirements for Companion Diagnostics

- Most companion diagnostics will not have been already approved with the same intended use
- Therefore, most will be investigational within the context of the therapeutic trial
- Subject to the Investigational Device Exemption (IDE) regulation 21 CFR Part 812
- Draft guidance forthcoming: Investigational IVD Devices Used in Therapeutic Product Studies

Investigational Application

- If test use considered investigational and "significant risk"
  - Sponsor must submit an IDE application
  - Sponsor can be pharma, biotech, device
    - Whoever will be responsible for use of IVD in the trial
  - Sufficient information to mitigate risks of test use, other IDE requirements
  - Discourage filing device info in IND

Marketing Submissions for CoDx

- Most companion diagnostics will require a PMA (risk of incorrect result)
- CDRH prefers modular PMA approach
  - Can begin review early
  - If timed correctly, clinical module coincides with NDA filing
  - Increases chances of contemporaneous approvals
- Device review, in practice, follows therapeutic review timeline
  - Accelerated approvals and fast tracks require a lot of CDRH planning and resources

Summary

- Still developing internal and external policies related to CoDx
- FDA has built systems of interaction to accommodate information exchange
- Actively working to evolve the codevelopment model
  - looking forward to new technologies
  - a better model through multiplex testing that will test all possibilities at once
- Encourage early interaction of sponsors with FDA through pre-submission process.

Questions?

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