A Cost-Effective Way to De-Risk Biomarker Clinical Trials: Early Development Considerations

Ce3, Inc. and Insight Genetics, Inc.
Oncology Forum
July 15, 2015
Agenda

• Introductions
• Definitions
• Regulations
• Does your drug need a ‘test?’
• Pros and Cons
• Operational Logistics
• Selecting Partners
• Summary
Introduction: We Can Do Better

• According to CenterWatch
  – 112 oncology drugs obtained FDA approval since 2001
  – Only 14 of these drugs have a CDx assay linked to their use

• Companion Diagnostic (CDx) assays use
  – Higher response rate (80.2% - 34.0 %) compared to no assay linked (45.0% - 6.8%)
Introduction

Keeping the end in mind

- Strategy
- Planning
- Implementation
- Outcome

Effectively using CDx in early development
Introduction: An Era of Change

Dynamic Environment

Biotechs:
- Fast paced
- Nimble
- Competitive

Leveraging collaborative partnerships

Healthcare:
- Informed consumer
- Personalized medicine

Operational Considerations

Study design
Timelines
Enrollment
Cost

Regulatory
- Accelerated approval
- Breakthrough

CDx Benefits

More efficient clinical development
Faster proof of concept

High response rates

Overall lower costs
Smaller trials

The right drug to the right patient
Definitions in Context

**• Biomarker:** A molecular indicator (e.g. gene alteration) that is associated with a certain disease state and may correlate with response to therapy.

**• Diagnostic Assay:** Test used to determine presence/absence of a biomarker(s) to guide treatment decisions. Assays can be regulated under CLIA or USFDA guidelines.

  - **Research Assay:**
    - Used for testing in proof of concept studies, preclinical and early-phase clinical trials, biomarker discovery and academic/industry research projects.
    - Designed using commercially available materials
    - Testing is performed in a single laboratory.

  - **Lab Developed Test (LDT):**
    - Intended for clinical use
    - Designed, manufactured and used within a single laboratory.
    - Approved to be used for enrollment in a clinical trial (IDE).

  - **In Vitro Diagnostic/Companion Diagnostic (IVD/CDx):**
    - A subset of medical devices which are “reagents, instruments, and systems intended for use in the 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)
Diagnostics for Each Phase of Drug Development

Phase I/II
- Research
- Assay

Phase II
- Lab
- Developed
- Test

Phase II/III
- Companion Diagnostic

Decision Making and Regulatory Pathway
Definitions in Context

• **Fast Track Designation**: A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need. FDA review < 60 days.

• **Breakthrough Designation (BTD)**: A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies. FDA review < 60 days.

• **Accelerated Approval**: A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit (i.e., an intermediate clinical endpoint)
Guidance for Industry
Expedited Programs for Serious Conditions – Drugs and Biologics

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Silver Spring, MD 20993
Phone: 101-706-3400; Fax: 202-476-8714
druginfo@fdac.gov


and/or

Office of Communication, Outreach and Development
Center for Biologies Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., WO71, Room 3128
Silver Spring, MD 20993
Phone: 866-357-4769 or 240-492-7800
ocodc@fda.hhs.gov

http://www.fda.gov/Drugs/Inovations/NewDiagnosisTests/default.htm

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

May 2014
Procedural
Current FDA Regulations and Guidelines: In Vitro Diagnostics

- Final FDA Guidance on Companion Diagnostics issued August 2014
- FDA classifies diagnostic assays as **Medical Devices**
- Devices are classified as Class I, II, or III based on necessity to assure safety and effectiveness
  - Diagnostic assays used to treat oncology patients are (mostly) Class III
  - Class III medical devices are high risk and require Premarket Approval (PMA)
- Depending on potential risk, an Investigational Device Exemption (IDE) may be required **before** testing patients to enroll in a trial
Current FDA Regulations and Guidelines: In Vitro Diagnostics

- **Timeline**
  - Therapeutic and CDx should be developed contemporaneously
  - Therapeutic and CDx must be approved or cleared contemporaneously so the CDx is available for use when the therapeutic product is approved
  - 2 exemptions: New Therapeutic Products to Treat Serious or Life-Threatening Conditions; Already Approved Therapeutic Products

- **Manufacturing**
  - Devices must be manufactured in a controlled manner as per 21 CFR Part 820 (Quality System Regulation)

- **Analytical Validity**
  - How accurately does the test measure the analyte?
  - How reliably?
Current FDA Regulations and Guidelines: In Vitro Diagnostics

- **Clinical Performance**
  - How reliably does the test measure the clinical condition?

- **Labeling** (21 CFR 809.10)
  - Adequate instructions for use
  - Intended use, directions for use, warnings, limitations, interpretation of results, performance summary

- **Software/Instrument**
  - Technology platform must be FDA cleared
  - Software must be FDA cleared
  - Verification & Validation experiments
Current FDA Regulations and Guidelines: Lab Developed Tests

- Lab Developed Tests (LDTs) are manufactured and performed in a single laboratory
- FDA issued draft guidance for regulation of LDTs in October 2014
- FDA will begin requiring all LDTs go through the PMA approval process, starting with highest-risk (oncology assays)
- More info TBD when next draft guidance is released
Does Your Drug Need a Test?

- Is your drug a targeted therapeutic?
- Do early-phase studies show differential efficacy in a subset of patients?
- Has FDA mentioned looking at specific patient cohorts as a secondary endpoint?

If yes

Pros ↔ Review and Consider ↔ Cons

- Are you familiar with the operational logistics to support such a test?
PRO: Why Use a Diagnostic Assay During Early Drug Development?

- Decrease enrollment costs and shorten trial timelines by focusing on the target patient population

**Dabrafenib (Tafinlar®) GSK**

- Clinical Development: **4 years**
- Registration trial: **250 patients BRAF V600E**
- CDx: THxID BRAF assay (bioMerieux, Inc.)

**Crizotinib (Xalkori®) Pfizer**

- Clinical Development: **3 years**
- Registration trial: **82/1500 patients ALK fusion**
- CDx: ALK breakapart FISH (Abbott Molecular)
PRO: Why Use a Diagnostic Assay During Early Drug Development?

• Minimize trial failure risk
  – Identify the right patient, right treatment, right time, and right dose
    • Falconi et al. *Journal of Thoracic Oncology*. February 2014 9(2)
    • Analyzed 676 NSCLC clinical trials (Phase I-III)
    • 50% increase in successful NSCLC Phase III clinical trials using a CDx

Adapted from Olsen and Jorgensen, 2014
PRO: Why Use a Diagnostic Assay During Early Drug Development?

• Coordinate drug development and assay development timelines to ensure the validated assay is available when needed.
  – e.g. Application for Accelerated Approval or Breakthrough Designation

Breakthrough Therapy Requests as of Jun 30, 2015

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<tr>
<td>2015</td>
<td>88</td>
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– Example: Xalkori® (crizotinib, Pfizer)
  • Accelerated Approval for ALK positive NSCLC patients: August 2011
  • Breakthrough Therapy for ROS1 positive NSCLC patients: April 2015
CON: Why to Not Use a Diagnostic in Early Drug Development?

- Need to know biomarker or conduct research-based biomarker discovery studies
- Need to determine which patient population and indication the drug will be developed for
- Assay takes time to develop, coordination of timelines is key
- Additional party to coordinate during the clinical trial
- Additional investment in early development phase
Key Players in CDx Approval

- Biopharma
- Diagnostic Developer
- Platform Company
- Contract Manufacturer
- Clinical CRO
- Central Testing Lab
- Dx Regulatory
- Rx Regulatory
- Statistical Support
- FDA Approval
Research Article

Practical Guidance for Implementing Predictive Biomarkers into Early Phase Clinical Studies

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The recent U.S. Food and Drug Administration (FDA) coapprvals of several therapeutic compounds and their companion diagnostic devices (FDA News Release, 2011, 2013) to identify patients who would benefit from treatment have led to considerable interest in incorporating predictive biomarkers in clinical studies. Yet, the translation of predictive biomarkers poses unique technical, logistic, and regulatory challenges that need to be addressed by a multidisciplinary team including discovery scientists, clinicians, biomarker experts, regulatory personnel, and assay developers. These issues can be placed into four broad categories: sample collection, assay validation, sample analysis, and regulatory requirements. In this paper, we provide a primer for drug development teams who are eager to implement a predictive patient segmentation marker into an early clinical trial in a way that facilitates subsequent development of a companion diagnostic. Using examples of nucleic acid-based assays, we briefly review common issues encountered when translating a biomarker to the clinic but focus primarily on key practical issues that should be considered by clinical teams when planning to use a biomarker to balance arms of a study or to determine eligibility for a clinical study.

1. Introduction
At many biopharmaceutical companies, predictive biomarker assays are developed and validated either internally or externally with partner companies with expertise in molecules for a clinical studies.

2. Sample Collection Considerations
2.1. Sample Collection Method. After the identification of the biomarker and the source tissue from which the predictive biomarker will be assayed, the next-most important
Operational Considerations

Seamless Execution

- Timelines
- Feasibility & Site Selection
- Study Documents
- Study Manual
- Training
- Screening & Enrollment
- Tracking & Reconciliation
- Integration of Data
- Sample Analysis

- Collection
- Handling
- Processing
- Storing
- Shipping
- Retention

- Time
- Temperature
- Quantity

Sample Collection
Study Manual
Training
Screening & Enrollment
Tracking & Reconciliation
Integration of Data
Sample Analysis

Study Documents
Table 2: Predictive biomarker checklist.

Team formation
- Form team; include representatives from assay development, clinical therapeutic area, program management, regulatory affairs and clinical statistics
- Establish regular team meetings

Sample collection considerations
- Determine source tissue for biomarker analysis
- Minimize amount of specimen required; use non-invasive techniques if possible
- Allow 1-3 months if sample collection method does not exist
- Train personnel at clinical site, if needed; create visual aids for training
- Retain extra specimens for potential bridging studies
- If utilizing a bridging strategy, initiate sample stability studies
- If using FFPE specimens, establish minimum percent tumor specification
- Select clinical sites with licensed pathologist able to mark slides and perform macrodissection
- Collect extra sections before and after sections being analyzed for H&E staining
- Perform sample collection experiment to qualify each clinical site, if necessary

Assay considerations
- Clearly define and document assay intended use, how positive and negative calls are made and how results determine patient eligibility
- Select assay technology platform, consider assay output, establish clear requirements
- Develop validation strategy, validating each sample type or collection method
- Allow several months to complete vendor agreement
- Allow time for vendor qualification, if new vendor
- Obtain clinical specimens for analytical validation and decision-point threshold
- Allow 1-6 months for assay development for a CTA; at least 24 months for a IVD

Sample analysis considerations
- Document anticipated turn around time from patients’ perspective
- Don’t include any specimen that may be collected in the future
Selecting Partners

• Nimble infrastructure
  – Similar philosophy
  – Flexible and responsive
  – High-touch
• Niche provider
  – Early development focus
  – Oncology
• Resources to support:
  – Attention to detail
  – Enhanced communications
  – Contingency planning
  – Timely coordination
# Does Your Drug Need a Test?

1. Is your drug a targeted therapeutic?
2. Do early-phase studies show differential efficacy in a subset of patients?
3. Has FDA mentioned looking at specific patient cohorts as a secondary endpoint?
4. Are you familiar with the operational logistics to support such a test?

<table>
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| **It’s Required!**  
FDA requires identification of patients with a companion diagnostic if the therapeutic is safe/effective in a subset of patients. |
| **Get Educated!**  
Companion Diagnostics are a Class III Medical Device and require separate FDA Pre-Market Approval (PMA). Parallel development of Drug and Diagnostic |
| **Shorten Timelines!**  
Enrichment of target populations with a Lab Developed Test (LDT) allows for rapid accrual of statistical power. |
| **Start Early!**  
Development of the diagnostic commercial strategy must be aligned with the pharmaceutical brand strategy- start as early as Pre-clinical, ensuring test development aligns with drug approval. |
| **Get Coordinated!**  
The IVD companion diagnostic device and therapeutic product should be approved or cleared *contemporaneously* to ensure drug approval is not delayed. Integration of clinical trial and CDx activities |
| **Decrease Risk!**  
Deploying a sound Regulatory strategy and enrolling the right patient population mitigates risk throughout the clinical trial process. |
Q&A

Thank you for your time!

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