Companion Diagnostic Development Transactions Webinar

December 15, 2014

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Preliminaries

Introductions

- **Christopher Jowett** is the Global Head of Companion Diagnostics for Abbott Molecular. He was appointed to his current role in April 2012. Previously, he served as GM Commercial Operations - U.S. & Canada for Abbott Molecular, where he was responsible for Sales & Marketing for more than 450 molecular products in the areas of Infectious Disease, Genetics, and Oncology.

- **Pamela Swatkowski** is Director of Regulatory Affairs at Abbott Molecular, responsible for strategic regulatory programs including companion diagnostics, oncology and infectious disease product regulatory and business development support, product lifecycle management, and global product registration for the molecular diagnostics product line.

- **Sue McGown**, Principal of McGown & Associates, provides business development consulting services to biotechnology and pharmaceutical companies. She has led overall corporate business development departments on a temporary basis and provided project-specific services including strategic planning, opportunity assessment, and contract negotiations.

- **Bruce Manheim** is a Partner at WilmerHale and represents life science companies on a wide array of FDA and regulatory matters, including life cycle management strategies for pharmaceuticals, and valuation and diligence on life science transactions.

- **Steven Barrett** is a Partner at WilmerHale and Co-Chair of the firm’s Technology Transactions and Licensing Practice Group. He advises a variety of life sciences and technology companies regarding the structuring, negotiation and drafting of agreements for a broad range of technology transactions.
Preliminaries

- Agenda
  - One-hour webinar
  - Presentation topics:
    - What is a Companion Diagnostic?
    - Development Considerations
    - Regulatory Considerations
    - Business Development Considerations
    - Contract Considerations
    - Q&A
1. What is a Companion Diagnostic?

Definitions

“**Personalized Medicine**” is defined as the customization of healthcare where medical decisions are tailored to the individual patient based on their susceptibility to disease or response to a particular treatment.

**Personalized medicine** primarily involves testing for genetic or other factors that reflect risk for disease / disease characteristics specific to that patient. Testing may involve information from one or more diagnostic tests to characterize the - appropriateness of a specific treatment for a specific patient.
What is a Companion Diagnostic?

“Diagnostics” is defined as the use of clinical tests to inform clinical decision making. The area includes both tests conducted on specimens from the body (i.e., in vitro diagnostics) and imaging tests (e.g., in vivo diagnostics), for the purpose of disease prediction, screening, diagnosis, treatment selection, prognosis and monitoring.

Molecular diagnostics, and other advanced technologies, have fueled the development of Companion Diagnostics (CDx) – tests that ensure the right treatment is given to the right patient at the right time.

“Companion Diagnostics” are defined as test that is used as a “companion” to inform prescription or dosing of the drug based on test results (i.e., the patient would receive the test prior to a treatment decision to ensure that is appropriate for that particular patient, or the test could be used to monitor drug response and alter dose). A test that provides information that is essential for the safe and effective use of a corresponding therapeutic product.
What is a Companion Diagnostic?

Targeted therapies and companion diagnostics are two pillars of personalized medicine. Integration of companion diagnostics into clinical practice requires several parties to work collaboratively, including test and treatment manufacturers, regulators, payers, clinicians and patients.

“Biomarker” is defined as a biological property or substance(s) that is: (a) a sign of a normal or abnormal process, or of a condition or disease and (b) used to determine how patients respond to treatments.

“Reagent” is defined as a chemical substance (other than the specimen) used in conducting a diagnostic test/assay.

“Analyte” is defined as a substance measured by a diagnostic test, for instance, a specific mutation or blood chemistry component.
What is a Companion Diagnostic?

“In Vitro Diagnostic (IVD) Test” is defined as a diagnostic test that is conducted outside of the body on specimens such as blood or tissue.

IVD is also a regulatory designation of approved/cleared tests that include a broad array of laboratory tests.

“Test System” is defined as an FDA cleared or approved IVD test package that includes all of the reagents, software, and instruments as necessary to obtain test results (excluding the patient specimen/sample) and a protocol with instructions for using the test kit.

2. Development Considerations

• **Identify/Define the Immediate Needs and Priorities**
  – Where is the therapy in the development process defines the most immediate needs and critical path to keep the therapeutic development on track
  – Agree on CDx requirements for supporting therapeutic clinical utility
  – This sets expectations, provides team focus, starts the project on the right path…

• **Keep Big Picture in mind (Product Vision)**
  – Incorporate process for addressing Life Cycle initiatives
  – Incorporate language addressing potential project scope changes
  – This allows for flexibility without having to renegotiate a new agreement

• **Outline process for handling “What if” scenarios. For example…**
  – Alternate regulatory and commercial strategies if an accelerated approval is requested/sought
  – Identify factors that could affect patient accrual rates for clinical studies
Development Considerations

• Use planned commercial *in vitro* diagnostic product in drug pivotal study
  – Investigational Use Only product should be approved for study via an Investigation Device Exemption (IDE) application

• Make every effort to avoid a “bridging” strategy
  – May have multiple Lab Developed Tests that were used in a pivotal studies
  – If a bridging study is required, gain agreement with agency on what test will be used as the comparator, and what the agency will accept as truth

• Team meetings with partner on weekly basis to maintain project status visibility
  – Allows for identified critical concerns to be addressed immediately

• Combined meetings with all regulatory agencies is important for alignment and agreement as early in the process as possible
**Development Considerations**

**FDA CDx Approvals Include 19 Tests for 12 Therapeutics**

- As per the FDA definition, there are 19 CDx products currently on the market, Source: fda.gov
- For now, the predominant model of CDx development is 1 drug – several diagnostics rather than 1 drug – 1 Dx or even several drugs – 1 Dx
- Targeting biomarkers is quickly becoming the standard requirement for new drug development programs
- Approximately 90 Companion Diagnostic agreements have been publically announced in the past 3 yrs.

[Diagram showing FDA-approved CDx Tests per Drug]

**Total: 19 CDx Tests for 12 Therapeutics**
3. Regulatory Considerations: Navigating the Evolving Regulatory Environment

Co-developed companion diagnostics are generally

- Review of diagnostic by CDRH or CBER
- Review of drug by CDER or CBER
- Diagnostic information in the drug submission
  - Clinical development section
- All diagnostic devices are classified based on risk
  - Intended use of the device
  - Risk/consequences of a false result

Medical Device products are likely to be Class III (PMA)
Components of an FDA IVD Product *PMA Requires Manufacturer to Prove Entire “System” is Safe and Effective*

A “System” is Required to Generate a Test Result

- Specimen Preparation
- Reaction Preparation
- Amplification and Detection
- Data Processing
- Result Reporting

Software Analysis Package
A Common Understanding of CDx Requirements to Support Clinical Utility of Therapy is Critical…

Identify / define the immediate needs and priorities

• Where the therapy is in the development process normally defines the most immediate needs and critical path to keep the therapeutic development on track
• Agree on CDx requirements for supporting therapy clinical utility
• This sets expectations, provides team focus, starts the project on the right path…

Keep big picture in mind (Product Vision)

• Incorporate process for addressing Life Cycle initiatives
• Incorporate language addressing potential project scope changes
  – This allows for flexibility without having to renegotiate a new agreement

Outline process for handling “What if” scenarios

For example…

• Alternate regulatory and commercial strategies if an accelerated approval is requested/sought
• Identify factors that could affect patient accrual rates for clinical studies
Ideally, the Diagnostic and Therapeutic Development Should Occur in Tandem…

Drug Development Pathway

Basic Research → Prototype Design or Discovery → Preclinical Development → Clinical Development → FDA Filing and Approval → Launch

Device Development Pathway

Basic Research → Feasibility Analysis → Analytical Verification → Clinical Validation → Qualification of Biomarker → FDA Filing and Approval → Launch

It Appears Seamless

For therapeutic, Phase 3 is predicated on Phase 2 data (by indication, by dose, by population)

For diagnostic, Phase 3 device is predicated on Phase 2 data (by indication, by device design, by population)
But in Pharma R&D Today, it is Rare That the Same Diagnostic Assay is Used Throughout the Development Process…

Research and Discovery Capabilities (Biomarker Partners)
Service Capabilities (Lab Partners)
Commercialization Capabilities (IVD Partners)

The registration device is used for Clinical Validation (Phase 3/pivotal study) and predicated on device used in prior studies.

Research Use Only (RUO)
Investigational Use Only (IUO)
Investigational Device Exemption (IDE)

Lab Developed Test?
Same technology as planned IVD?
Easily transferable to an IVD partner?
July 31, 2014, FDA issued final guidance for Companion Diagnostics

Final guidance, In Vitro Companion Diagnostic Devices:

Final guidance, In Vitro Companion Diagnostic Devices

• Defines IVD companion diagnostic device
• Emphasizes the need for FDA oversight of IVD companion diagnostics
• Intent, in most cases, for simultaneous clearance/approval of IVD companion diagnostics and therapeutic
• 2011 comments on the draft guidance included several recommendations, which were incorporated into the guidance, including refining the definition of an IVD companion diagnostics as “essential” to the therapeutic to avoid inclusion of other diagnostics and increased flexibility in the use of investigational submissions
Regulatory Considerations: Conclusions

Incorporating the planned commercial diagnostic early facilitates program success.

The coordination of the two regulatory pathways, by FDA and industry, allows for the development of efficient methods to ensure the safety, effectiveness, and quality of combination products.

Clinical development studies are complex and conducted worldwide.

U.S. FDA has made it very clear that if a device is required for patient selection prior to therapeutic treatment or for adjustment an approved test must be available.
4. BD Considerations

Basic Quid Pro Quo in Typical Deal

- Rx company gets commitment from Dx company to develop the CDx pursuant to a joint R&D plan and to make the CDx commercially available
- Dx company gets commitment from Rx company to fund development and gets to keep proceeds of commercialization of CDx product
BD Considerations

Initial vetting of prospective partnership

- **From Rx company’s perspective, does Dx company have**
  - Relevant platform technology, demonstrated expertise
  - Installed base; Global reach for relevant pt populations
  - Cost-competitive offering
  - Ability to meet Rx timelines

- **From Dx company’s perspective, does CDx**
  - Represent attractive market opportunity
  - Leverage installed base, platform, disease-relevant expertise
  - Have reasonable probability of reaching the market
  - Rx combination have appropriate timeline expectations

**Intangibles: Partner “chemistry” & motivation**
BD Considerations

Business Models: Big Picture

Risk

Low

High

Low

High

Reward (not necessarily ROI)

Rx

Dx
**BD Considerations**

**Rx business model is high risk**

- **Discover/Develop**
  - $2.6B to Market \(^{(1)}\)
  - 10-to-15 yrs. to Market \(^{(2)}\)
  - P(approval) 7-15% from Ph I \(^{(3)}\)
  - 2 in 10 generate revenues \(\geq\) R&D Costs \(^{(2)}\)

- **Revenue:**
  - Milestones
  - Royalties
  - Rx sales

- **Product:**
  - Rx
  - Responder hypothesis

- **Partner:**
  - Dev’t & commercialization
  - Specialized capabilities

**Source:**
2. “2013 Profile Biopharmaceutical Research Industry”
BD Considerations

Dx business model tends to be diversified

Diagnostic Platform

- Low dev’t cost (Est. ≤1% of Rx)
- Shorter timelines to market
- Leverage Diagnostic “Platform” across Patients
- Multiple sources of revenue

Partner:
- For test sites/centers
- For CDx

Product revenue:
- CDx
- Tests, kits, hardware, reagents
## BD Considerations

### Negotiation considerations

**Rx Company**

- **Intellectual Property:**
  - Owns Rx IP
  - May have relevant CDx IP
  - Requires FTO as it relates to Rx

**Dx Company**

- **Intellectual property:**
  - Owns CDx platform
  - Desires to build on Dx portfolio

**Nature of Products (Rx and CDx) drive regulatory requirements**

- **Rx:** Rx partnerships can heighten sensitivity to certain provisions
- **Dx:** Hospital, Central lab(s) may be relevant for testing sites, accessing patient populations, etc.

- **Rx:** Dx – wants commitment for specialized services (i.e. to market CDx)
- **Dx:** Rx – marketing “commitment” may be viewed as costly

**Emphasizes importance of non-blocking licenses for Rx; Dx company to leverage for other product offerings**

**Factors into Termination for Both:** Limit exposure in event of development delays, failure, etc.

**Requires mutual understanding, coordination and transparency**

**Wants transparency, reliable estimates, cost containment**

**Wants costs covered and flexibility in the event of overages**
5. Contract Considerations

- R&D Program costs
  - Rx company wants predictability in costs, performance of plan and flexibility to modify plan as needed based on concurrent development of therapeutic (including termination if appropriate)
  - Dx company wants committed funding to pay for development resources and opportunity to complete development and commercialize CDx product
Contract Considerations

- **Diligence**
  - Rx company, in a perfect world, wants Dx company to commit to make the CDx commercially available for as long as the Rx company commercializes its therapeutic product in every country where Rx company commercializes
  - Dx company concerned about circumstances in which continued commercialization of the CDx product is or becomes uneconomic
Contract Considerations

- Diligence Mechanisms
  - General diligence standard
  - Detailed definition of deliverables and timelines
  - If arrangement is non-exclusive, how does Rx company incent Dx company to appropriately prioritize the CDx in furtherance of Rx company’s competitive and commercial goals?
  - Back-up license or alternative distribution of CDx if Dx company ceases to perform?
  - Other remedies?
  - Challenge: Formulating balanced contractual mechanisms that protect the deal’s basic *quid pro quo*
Contract Considerations

- Intellectual Property
  - Cross-licensing to facilitate each party’s product typical (i.e., Rx company grants license to Dx company to develop/commercialize CDx product and Dx company grants license to Rx company to develop/commercialize Rx product)
  - Scope of licenses may exclude background IP
  - Dx company will typically withhold licensing of IP that is specific to its platform
Contract Considerations

- Third party IP
  - Parties do not necessarily have full visibility into what IP may surface
  - Dx company fears that license/infringement costs could be calculated based on Rx product economics
  - Rx company does not want to pay for IP specific to Dx company platform or for costs that increase as CDx product sales increase (since Dx company keeps proceeds of CDx product sales)
  - Dx company also is typically unwilling to comply with common Rx licensing terms (reporting CDx net sales, royalties on CDx product, licensor audit rights, etc.)
Contract Considerations

- Termination
  - Often Dx company will seek a termination fee if Rx company elects not to proceed, in order to protect its opportunity cost/resources investment and profit opportunity
  - Dx company does not want a fee-for-services model
  - Rx company will generally seek flexibility to discontinue development if it is ceasing to progress its therapeutic product, without paying large fees
  - In some circumstances, a staged-project approach may help to bridge competing priorities
6. Q&A