Strategies for Companion Diagnostic Development in a Pharmaceutical R&D Setting

John C Bloom, VMD, PhD
Executive Director
Diagnostic and Experimental Medicine
Eli Lilly & Company

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Definitions

Targeted Therapeutics
Drug therapy directed towards a specific patient population as identified by a diagnostic (e.g. Herceptin, Gleevec)

Biomarkers
Any measurable endpoint useful in understanding disease and/or the treatment of disease (e.g. BP, body temperature, cholesterol level)

- **Valid Biomarker**
  A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic pharmacologic or clinical significance of the results

Diagnostics
A test that identifies biomarker(s) and is sold either as an FDA approved kit, also called an IVD (In Vitro Diagnostic), or for research use only as an ASR (Analyte Specific Reagent) also called “Home Brew”

- **Disease Diagnostics**
  Diagnostic(s) applicable to diagnosing or providing prognosis for a disease, not limited to a particular drug therapy

- **“Companion” Diagnostics**
  Diagnostic(s) tied to a drug therapy via the drug label (e.g. Herceptest)
FDA Guidance on Drug-Diagnostic Co-Development

Concept paper currently under review that is anticipated to be published this year and address in detail the issues involved in drug and *in vitro* diagnostic co-development:

- co-development process
- industry-FDA interactions
- analytical validation
- clinical validation
- clinical utility
ASSUMPTIONS THAT DEFINE THE STRATEGY
(Guiding Principles)

1. Overarching priority: *use diagnostics to optimize the value of Lilly drugs in the marketplace*
   - Critical to Lilly’s corporate strategy: *improve outcomes for individual patients*
   - “Stand-alone” business value of diagnostics is limited, compared with new drugs

2. Range of assay-driven technologies and commercialization needs requires multiple, and often novel, partnerships

3. Indication/opportunity for a value-added diagnostic can occur at any point of the drug development/commercialization chain

4. The diagnostic registration process is regulatory-driven and well-defined

5. Factors critical to successful diagnostic development include:
   - *Freedom to operate through enabling IP and regulatory strategies*
   - *Effective strategic partnership development and management*
   - *Access to human specimens*
   - *Organizational effectiveness with functional expertise/alignment*
DIAGNOSTICS ENABLE LILLY’S CORPORATE STRATEGY

Improve individual patient outcomes through tailoring: *right drug, right patient, right time, right dose*

One size fits all  |  Targeted Therapy

Tailoring

*assess spectrum of patient response to therapy; stratify patient population; optimize benefit/risk; improve patient outcomes*

**2006 Objective:** Improve understanding of diagnostics industry and potential impact of ongoing shifts to a tailored therapeutic approach in the global healthcare market and develop Lilly’s diagnostic strategy to support the launch of selected products.
Biomarker Strategy Drives Diagnostic Development

Novel assay related to disease state
CSF A beta (Alzheimer’s Dis)

Novel application of currently available assays
P1NP (osteoporosis) Platelet Aggregation (thrombosis)

Novel assay related to drug target
Molec targets in tumor (eg survivin)

Sponsor’s needs in this area could include:
- Routine applications of established diagnostics
- Novel applications of registered diagnostics
- Development and registration of a candidate-specific diagnostic
1. Defined by portfolio needs

2. Drive internal investment and partnership development strategies

- **Immunohistochemical assays**
  Particularly relevant to targeted cancer agents

- **Pharmacogenomic assays**
  DNA-based polymorphism analysis for patient stratification

- **Serum/plasma immunoassays for circulating proteins**
  Most relevant for biomarkers where rapid, “near-patient” analysis is required to drive therapy

- **Imaging assays**
  Particularly for hard-to-access tissues, i.e., brain, tumor
Diagnostic registration is regulated by the FDA’s Center for Devices and Radiologic Health (CDRH), and is driven by a risk-based classification of the end product.

The main differences between classes are the levels of controls required, and the length/expense of the registration process.

The final designation of the product determines how a product will be labeled and marketed.

- **Product class**
  - RUO/IUO
  - ASR
  - Class I
  - Class II
  - Class III

- **FDA premarketing requirements**
  - Very limited (RUO label)
  - Limited (Labeling, quality requirements, sales restriction)

- **In vitro diagnostics**
  - 510k
  - PMA

Must be labeled “not for clinical use” (Cannot market assay for clinical applications)
An Idealized Diagnostic Development Timeline (IHC used as prototype)

Pre-Clinical Development

**Phase 1**
- Development Phase 1
- Decision 1: Is DX candidate feasible in current format?

Phase appropriate biomarker development

Decision 2: Does DX candidate provide clinically relevant information?

- Analyte-specific reagent (ASR)
  - 6-12 mos $200-500,000 (assumes method in place)

Phase 2

- 12-24 mos $1-2,000,000 (depends on amount of development work required)

**Post Launch**
- Registration/Launch
- Post Launch

- Evaluate utility of biomarker in clinical trial context
- Develop validated biomarker assay for clinical trial support (internal decision-making use)

6-12 mos $20-40,000
Alternate DX Development Scenarios

Because DX needs may arise at any point in the drug development process, the idealized timeline will not always be possible.

Having ready access to clinical trial samples is the key resource to allow accelerated registration of the diagnostic.
Stage-critical factors for diagnostic development

At interim analysis, has the biomarker shown sufficient promise to warrant diagnostic development?

Has a partner been identified who can commercialize the diagnostic?

Have IP considerations been addressed?

Is clinical trial powered to identify biomarker effect?

Is the ICD written in a manner to allow use of collected samples for IVD development?

Have timelines been aligned?

Have sufficient samples been stored/banked to provide material for diagnostic submission support?
DX Development Requires a Virtual R&D Capability

Most Pharma Cos have:

- some dx discovery experience
- limited dx development experience
- no dx commercialization experience (ie, reimbursement)

Primary focus to date has been fee-for-service arrangements with a wide range of companies – from small biotech to large diagnostic firms.

Partnership with multiple vendors and alliances ensures access to range of required capabilities and experience across the value chain. Potential working arrangements with diagnostics partners may include:

- Fee-for-service transactions
- “Pay-as-you-go” agreement
- Broader alliances (e.g. proprietary kit)
- Combination of the above
Understanding this difference in strategic focus of partners is critical to meeting sponsor’s needs.

- **DX Development**
  - Biomarker Disc.
  - Assay Dev.
  - Assay Validation
  - IVD Dev.
  - IVD Validation
  - IVD Approval

- **Commercialization**

**Spectrum of Partnerships**

- **Academic/Gov/Res Institutions**
- **Biomarker Discovery Companies**
- **Small/Niche Diagnostic Companies**
- **Med/Large Diagnostic Companies**
Scenario 1:
Public domain protein identified as potential biomarker

Scenario 2:
Public domain protein identified as potential biomarker

Scenario 3:
Previously-unknown target identified as potential biomarker

Commercially available (RUO) kit identified to measure protein *
Sponsor develops assay to measure protein (often with CRO using commercial reagents ) *
Sponsor develops assay to measure target

Assay applied to clinical trial samples and utility identified *
Assay applied to clinical trial samples by CRO and utility identified *

* = opportunity for sponsor IP?

The end goal of obtaining IP is to allow widespread availability of the DX assay at the time of launch
For biomarkers where commercially available assays/reagents are used, assessment of “freedom to operate” as early as Candidate Selection is essential.

- Define existing patent protection around target, reagents and kits.
- Defines downstream options for reagent licensing, platform changes, patent expirations, etc.

For assays developed in conjunction with a CRO, maintaining sponsor’s freedom to operate when establishing contracts is critical.

- Preserve flexibility for sponsor to transfer assays or change vendors as needed for commercialization.
- Oversight of this is often a challenge for sponsors

IP may be required for a diagnostic partner business case and “freedom to operate”.

*Understanding partner’s requirements is critical!*
Experience in Dx Development at Lilly: Examples that Define the Principles

P1NP

- amino-terminal propeptide of type 1 procollagen
- marker of osteoblastic (anabolic) activity in patients with osteoporosis
- potential diagnostic for compliance in patients treated with teriparatide
- collaborated with two partners to ensure access:
  1. specialized Dx co to develop 510K-approved polyclonal RIA
  2. large Dx co to develop more precise dual MoAb automated electrochemiluminescent assay adapted to globally-accessible platform (*freedom to apply to CT limited by patent restriction*)

**STRATEGY**: partner to develop latter with former as backup
Experience in Dx Development at Lilly: Examples that Define the Principles, con’t

Platelet aggregation
• Dx for clopidogrel and prasugrel-induced platelet inhibition (ADP receptor blockade).
• partnered with Accumetrics
• late phase development opportunity driven by emerging PD profile of prasugrel vs. clopidogrel
• Lilly provided clinical context to assess performance, refine assay and validate

Protein C Assay for Sepsis
• marker to predict severity of disease and monitor response to Xigris
• partnered with Biosite to develop and validate
• another late stage development opportunity
The Use of the VerifyNow P2Y12 Point-of-Care Device to Monitor Platelet Function Across a Range of P2Y₁₂ Inhibition Levels Following Prasugrel and Clopidogrel Administration


*Daiichi Sankyo Company, Limited and **Eli Lilly and Company

Study funded by Daiichi Sankyo Company, Limited and Eli Lilly and Company

Experience in Dx Development at Lilly: 
*Examples that Define the Principles, con’t*

Markers for Alzheimer’s Disease Diagnosis and Progression

- **Neurochemistry**: CSF A beta, Tau proteins; plasma A beta
- **Imaging**: brain plaque burden, function, atrophy
- Constellation of partnerships/collaborations (ADNI): incl other pharma, large and small Dx cos, universities, government (NIH)
- Several IP, technical and global regulatory challenges and opportunities
Alzheimer’s Disease Neuroimaging Initiative (ADNI)
Public-Private Partnership

Foundation for the National Institutes of Health

National Institute on Aging

ADNI

Industry Partners
- Merck
- Pfizer
- Eli Lilly
- Bristol-Myers Squibb
- Novartis
- AstraZeneca
- Innogenetics

Philanthropic Partners
- Alzheimer’s Association
- Alzheimer’s Drug Discovery Foundation

Academic Partners
- Mayo-ADCS – Clinical Coordinators
- UCSD – Loni Site
- UCLA – Grant PI Mike Weiner
Experience in Dx Development at Lilly: *Examples that Define the Principles, con’t*

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Experience in Dx Development at Lilly: 
*Examples that Define the Principles, con’t*

**KRAS Genetic Mutation**

- Predicts efficacy for anti-EGFR agents (Erbitux)
- Unique business development strategy with multiple Dx partners and shared risk
- Lack of FDA guidance complicated freedom to operate—restriction on off-label testing
Functional Support for DX Development in an R&D Setting

Framework for the cross-functional integration required to support process
Lilly Diagnostic Core Team
(and contributors)

John C. Bloom, VMD, PhD,  Executive Sponsor
Brian Edmonds, PhD     Chair, Global External Research & Development

Members:

John T Brandt, MD  Diagnostic and Experimental Medicine
Leeann Chambers  Global Regulatory Affairs
Christine M Gathers  Global Regulatory Affairs
Paul J Gaylo, JD  LRL Law
Blake C Salisbury  Global Business Development
Jayne Talbot  Diagnostic Experimental Medicine

Additional contributions by Thomas Daly, MD, Cleveland Clinic
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