Start With the End in Mind – A Diagnostic Company’s Perspective on Companion Diagnostic Development

Paul Docherty PhD
Relationship Management
Disclaimer

• This presentation contains my personal views and research and does not necessarily reflect the policies or endorsement of Hologic Inc.

• This presentation contains forward-looking information that involves risks and uncertainties, including statements that are based upon assumptions made by market research which are subject to known and unknown risks and uncertainties that could cause actual results to differ materially from those anticipated.
Hologic Overview

• Established, stable company
  • Develop, manufacture and sell diagnostic kits and systems
  • 5,500 employees across 15 countries
  • $2.8 billion annual revenue

• Proven track record
  • 73 FDA approved/cleared products on the market
  • >80 million diagnostic tests per year

• Global footprint
  • Three ISO13485 certified manufacturing facilities
  • Products sold in 111 countries

>30 years experience as Contract Research Organisation
Preferred Supplier, Sole Provider, Partnership – Pharma & Biotech
Hologic Overview

• **Biomarker Services**
  - RUO
    - DNA and RNA Extraction / Genomic analysis / Data analysis and Bioinformatics
  - CLINICAL
    - Biomarker discovery & validation / Assay development & validation / Regulatory compliant processing

• **Companion diagnostic services**
  - Concept and feasibility
  - Product development
  - Product validation
  - Regulatory approval
  - Manufacturing
  - Sales and Support

Hologic provides its CDx and Dx development service through its Tepnel brand
“Traditional” Companion Diagnostic Development Workflow

Pre-Clinical

Phase I

Phase II

Phase III

Launch

Biomarker Discovery and Verification

Companion Diagnostic Development

Concept and Feasibility

Product Development

Analytical and Clinical Validation

Regulatory
“Traditional” Companion Diagnostic Development Workflow

Pre-Clinical Phase I Phase II Phase III Launch

Biomarker Discovery and Verification

Concept and feasibility Product Development Analytical and Clinical Validation Regulatory

Companion Diagnostic Development
Our Companion Diagnostic Development Service

- Concept and Feasibility
- Product Definition and Planning
- Development and Verification
- Validation and Launch Prep
- Post Market Support

LDT | + | +++ | +++ | + | +++
---|---|----|----|---|----
CE  | + | ++  | ++  | + | ++
FDA | +++| +++ | +++ | +++| +++
## Timelines

<table>
<thead>
<tr>
<th>Approval Process</th>
<th>Number of Products on the Market</th>
<th>Examples</th>
<th>Development Times</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDT</td>
<td>LDT</td>
<td>Multiple</td>
<td>1-6 months</td>
</tr>
<tr>
<td>CE</td>
<td>CE-Mark</td>
<td>54</td>
<td>APTIMA® HPV and PROGENSA® PCA3</td>
</tr>
<tr>
<td>FDA</td>
<td>510k</td>
<td>29</td>
<td>APTIMA® Combo 2</td>
</tr>
<tr>
<td>FDA</td>
<td>PMA</td>
<td>8</td>
<td>Aptima HPV 16 18/45 genotype assay</td>
</tr>
</tbody>
</table>
Our Companion Diagnostic Development Service

Concept and Feasibility → Product Definition and Planning → Development and Verification → Validation and Launch Prep → Post Market Support

LDT
+++ + + +

CE
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FDA
+++ +++ +++ +++
The Reality
Our Companion Diagnostic Development Service

Concept and Feasibility

Product definition and Planning

Development and Verification

Validation and Launch Prep

Post Market Support

Decisions that are made here

End up here

LDT

+++ + ++ + ++

CE

+++ ++ +++

FDA

+++ +++ ++++

+ + + + +
Our Companion Diagnostic Development Service

Concept and Feasibility
Concept and Feasibility

- Driven by Pharma and Dx company - multiple stop/go’s before design control
- When should I engage with a Dx partner and regulatory authorities?
- The sooner the better:
  - Biomarker discovery and proof of concept studies (Study Design, Lab work and Bioinformatics)
  - R&D assay development
  - Platform/technology choice
  - Legal agreements and IP searches
  - Regulatory assessment of clinical trial design
  - Market research
  - Risk analysis
  - **Define Product Requirements** – this feeds directly into the product design
Biomarker to Clinical Test?

Inherited variation in the PA


Comparison of three methods for genotyping the

Comparison of the Third Wave Invader Human Papillomavirus (HPV)
Assay and the Digene HPV Hybrid Capture 2 Assay for
Detection of High-Risk HPV DNA

Linnea M. Baudhuin*, W. Edward Highsmith, Jennifer Skierka, Leonard Holtegaard,
Brenda E. Moore, Dennis J. O’Kane

C. C. Ginocchio, D. Barth, and F. Zhang

Submitted 2 June 2014; accepted in final form 23 July 2014

100s Biomarkers in Regular Clinical Use
Why do Biomarkers not make Clinical Tests?

Limited understanding of the product development process

- Workflow
- Development time and cost
- Platform choice
- Validation requirements
- Regulatory
- Reimbursement issues

Issues with CDx development

- Heterogeneous diseases
- Lack of end point
- Issues with Doctor’s
- Issues with payers

True Discovery

- Fail during Product Development
- Unsuitable for Clinical Use
- Poor Clinical Performance

False Discovery

- Poor Study Design
- Failed Validation
- Results not reproducible
- Not genuine biomarkers
Product Requirements

- Key to the success of a CDx development product – multi stage process
- As much information as possible is required - as early as possible
- Gathered from multiple sources and stakeholders by both Pharma and Dx companies
Product Requirements

User
- Hardware Platform
- Assay Technology
- Intended Use
- Specimen Type
- Specimen Stability
- Specimen Collection Device
- Specimen Transport Device
- Specimen Volume
- Specimen Dilution
- External Controls
- Internal Controls
- Calibrators
- Specimen Processing
- Reagent Use
- Software Platform
- Throughput
- Turnaround time
- Hands on time
- Interference performance
- Cross reaction performance
- Regulatory requirements
- Proposed workflow

Business
- Inhibition performance
- Kit vs Centralised
- Analytical Performance
- LOD
- Specificity
- Sensitivity
- Range of Quantification
- Precision
- Clinical Performance
- NPV/PPV
- Testing numbers
- Kit format
- Kit size
- Kit shelf life
- Kit storage
- Kit shipping conditions
- Operator Expertise
- Pricing
- Language requirements
- Instructions for Use
- Package Insert
- Labelling

Regulatory

Intended Use
Product Requirements

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Regulatory

Intended Use
Our Companion Diagnostic Development Service

- Concept and Feasibility
- Product Definition and Planning
Project Plan and Schedule

• High level project plan covering the whole development process
• Identifies processes, deliverables, milestones and timelines
• Product Scope (from Product Requirements)
• Project Team and Responsibilities
• Supplemented by individual plans from each functional area:
Extended Team Structure
Design Control

- Design Control is a formal documentation procedure applied to product development
- It is an FDA requirement for medical devices
- Runs alongside and throughout the product development process
Design Outputs

- Specify how the product will be tested during Verification and Validation
- Design Verification: Did you design the device right? Outputs = Inputs?
- Design Validation: Did you design the right device?
Design Control

- Design Control is a formal documentation procedure applied to product development.
- It is an FDA requirement for medical devices.
- Runs alongside and throughout the product development process.

![Diagram of Design Control process]

Requirements → Design Input (What?) → Design Process → Design Outputs (How?) → Verification → Design Review → Validation → Product
Design and Stage Reviews

Design Reviews:

• Formal technical reviews conducted by Core Team and an independent technical experts (Pharma and/or Dx)
• Ensure design inputs are addressed by outputs to meet design requirements
• Move project to next stage

Stage Reviews:

• Gate meeting to make business decision on continuation of the project.
• Review progress against Project Plan and Schedule
• Go/Kill/Hold/Recycle
Cost of Correcting a Requirements Error

Repeat Design – Pre Market Bridging Studies – Post Market Bridging Studies
Our Companion Diagnostic Development Service

- Concept and Feasibility
- Product Definition and Planning
- Development and Verification
Development and Verification

- Implementation of product design and the systems required to manufacture them
- Verification testing to ensure all components of the product are ready for validation
  - QC method development and verification
  - Manufacturing
  - Regulatory preparation
  - Clinical Trial preparation
Our Companion Diagnostic Development Service

- Concept and Feasibility
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Validation and Regulatory Submission

• **Analytical Validation**
  – Carried out prior to clinical validation
  – Demonstrate the fitness of the assay (e.g. repeatability, reproducibility)

• **Clinical Validation**
  – Clinical utility of both the CDx test and the drug
  – Store samples that are consented for use in bridging studies
  – The sooner you engage with a Dx partner the sooner we can look at the your trial design

• **Regulatory Submission**
  – Regulatory guidance is required throughout the entire product development process
  – Timelines and requirements vary depending on factors including; 510k/PMA/CE, US/ex-US
HOLOGIC

May 25, 2012 Approval Letter

October 3, 200

Assay

October

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
K132251
K091053

B. Purpose for Submission:

This is a new 510k chain reaction (RT PCR) instrument with discrimination of human papilloma virus (HPV-1, HPV-2, HPV-31, HPV-33) from normal nucleic acid. The HPV is performed on the MagNA Pure Total Nucleic Acid System (bioMérieux) and the AmpliGen (Salmonech) amplification genes.

E. Applicant:
Dear Dr. Maderazo:

ProGeni:

ARNEC
AUGUST 17
ProCode: O

D. Type of Test:
A multiplexed reverse transcriptase PCR diagnostic test intended for the quantitation of the MTHFR mutation.

C. Measurement:
Human 5,10-methylenetetrahydrofolate reductase (MTHFR)

B. Purpose:
New diagnostic test

A. 510(k) Number:
k100496

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY

A. 510(k) Number:
k1232

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION DECISION SUMMARY

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the PROGENSA® PCA3 Assay. This device is indicated for:...
Our Companion Diagnostic Development Service

- Concept and Feasibility
- Product Definition and Planning
- Development and Verification
- Validation and Launch Prep
- Post Market Support
Post Approval

- cGMP full scale IVD manufacturing production lots
- Post Launch Surveillance
- Marketing
- Manuals and IFU
- Technical Support
- Customer Support
- Reimbursement
- Bridging studies
Case Study 1

Pharma company - developed assay to be ‘turned into’ a CDx product
- Prepared budget and timings for PMA route
- Up to 24 months and ‘several million’ USD
Case Study 1

Biomarker

PMA?
Detailed discussions – necessary?

- Regulatory brief prepared
- Initial conversations and meeting with FDA on clients behalf

New Route/Solution:

HUD
<12 months and <200k USD
Case Study 2

- Project assessed the suitability of five assays developed by pharma company for development into a companion diagnostic test
  - DNA extraction assay
  - Four mutation detection assays
- Following tech transfer all assays were evaluated using both FFPE and cell line material
Case Study 2

- Project assessed the suitability of five assays developed by our client for development into a companion diagnostic test
  - DNA extraction assay
  - Four mutation detection assays
- Following tech transfer all assays were evaluated using both FFPE and cell line material
  - The mutation detection assays exhibited a number of issues which would render them ineffective for use as a clinical assay
## Case Study – Pharma Client

<table>
<thead>
<tr>
<th>Recommended Changes</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidated assays to run at a single set of conditions + platform change</td>
<td>Simpler validation</td>
</tr>
<tr>
<td></td>
<td>Decrease cost</td>
</tr>
<tr>
<td></td>
<td>Availability of Dx platform</td>
</tr>
<tr>
<td>Changed DNA QC methodology from qPCR based method to OD</td>
<td>Simpler validation</td>
</tr>
<tr>
<td></td>
<td>Decrease cost</td>
</tr>
<tr>
<td>Fluorescent dye change - the fluorescent dye used in the assays was only available</td>
<td>Risk reduction</td>
</tr>
<tr>
<td>from a single manufacturer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No initial dye calibration</td>
</tr>
</tbody>
</table>

![Process Flow Diagram](image-url)
Case Study 3

Public-private collaborative project into early Rheumatoid Arthritis

RA is one of the most common autoimmune diseases in the world characterized by pain and fatigue. Typically these problems mean that daily life is more difficult for RA patients leading to massive health economic implications.

Goals:
• Identify the key predictors of clinical response and remission in RA patients
• Identify those individuals at high risk of developing RA.
Case Study 3

Public-private collaborative project into early Rheumatoid Arthritis

Pilot phase – improved communication; increased yields/TAT; amended SOPs

Transcriptomics studies ~18 months
  • Clinical trial study - 5 iterative stages
  • Vaccine – 1 stage

Future Stage – Use identified signature to develop clinical test
Start with the End in Mind….