In Vitro Companion Diagnostics: Considerations for Regulatory Affairs Professionals

Allison Nance
Executive Director, Regulatory Affairs
Celgene Corporation USA

TOPRA NJ Event – 25 September 2012
What is an in vitro companion diagnostic device?

Let’s start by defining a biomarker:

“A biomarker is a characteristic that is objectively measured as an indicator of normal or pathogenic processes or pharmacologic response to therapies”

Biomarker tests have been used for years in drug development

- To identify disease targets and elucidate cellular pathways and biological processes in discovery
- To accelerate clinical trials through patient selection

Biomarker tests have also facilitated the practice of medicine

- Use of lab tests to confirm a differential diagnosis made on the basis of clinical assessment, as well as management of therapy
What is an in vitro companion diagnostic device?

So when does a biomarker test rise to the level of an in vitro companion diagnostic device?

- When the therapeutic product *depends on* the use of the test for its safe and effective use
- In other words, the IVD companion diagnostic device provides information that is *essential* for the safe and effective use of a corresponding therapy

Prognostic

→ Provides information on the likely course of the cancer disease in an untreated individual

Predictive

→ Pretreatment measurement to identify subpopulations of patients who are most likely to respond to a given therapy

Pharmaco-dynamic

→ Dynamic assessment showing response in a patient following treatment

Surrogate Endpoint

→ Expected to predict clinical outcome of a patient

*IVD companion diagnostics tend to be predictive biomarkers to select patients for a particular drug*
What is an in vitro companion diagnostic device?

IVD companion diagnostic devices which function as predictive biomarkers are generally based on:

- inherited genetics
- genetics of a tumor
- viral genotype
### Classic examples of predictive biomarkers

<table>
<thead>
<tr>
<th><strong>Novartis tyrosine kinase inhibitor</strong></th>
<th><strong>Ph chromosome karyotyping test (CML)</strong></th>
<th><strong>Predictive biomarkers to select patients who are likely to respond to Gleevec</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>targeted therapy used in first line treatment for Philadelphia chromosome (Ph)-positive chronic myeloid leukemia, patients with unresectable and/or metastatic malignant gastrointestinal stromal tumors…</td>
<td>FDA-approved in vitro companion diagnostic device - c-Kit pharmDx immunohistochemistry kit by Dako (mGIST)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Genentech’s targeted anti-HER2</strong></th>
<th><strong>FDA-approved in vitro companion diagnostic device</strong> to detect HER2 protein overexpression and HER2 gene amplification (Dako HercepTest)</th>
<th><strong>Predictive biomarker to select patients who are likely to respond to Herceptin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>antibody therapy for patients with breast cancer or metastatic gastric cancer whose tumors overexpress the HER2 protein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pfizer drug indicated, in combination with other antiretroviral agents, in adult patients infected with only CCR5-tropic HIV-1. Selzentry selectively binds to the CD4 T cell CCR-5 cell surface co-receptor, which blocks HIV from entering the cell.</strong></th>
<th><strong>CCR-5 tropism testing assay</strong></th>
<th><strong>Predictive biomarker to select patients appropriate for use of Selzentry</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Benefits of an in vitro companion diagnostic device

Allows for selection of only a subset of patients who are likely to respond to treatment

“Treatment of the right patient at the right time”

In vitro companion diagnostic devices are the foundation of a Personalized Medicine approach

- Personalized medicine is a medical model which emphasizes the customization of healthcare, in which decisions are tailored to the characteristic of each patient
Traditional treatment paradigm

“One size fits all” approach

Responders

Non-responders

Adverse Drug Event
New treatment paradigm

“Personalized medicine” approach
Global need for personalized medicine

Personalized medicine can address a number of challenges our societies face today...

The world population is increasing in size

The world population exceeded 7 billion in 2012

Source: US Census Bureau
Global need for personalized medicine

The rise in chronic disease in this growing and aging population has had a remarkable impact on healthcare costs.

*Projections
Global need for personalized medicine

- Amid finite resources, something has got to give...
  - An estimated 90% of drugs are effective in 30 - 50% of patients
  - Up to 40% of all global drug spending is wasted on ineffective drugs

- Industry would prefer to streamline clinical development and achieve better response rates for its therapies
  - The biggest failure rate occurs in phase 3, after significant investment has been made (45 candidates in phase 3 failed last year)
  - Response rates are still quite poor in part due to the treatment of patients as if they are a genetically homogenous population

“We treat the majority for the benefit of the uncharacterized minority”
Rich Simon, Chief, Biometric Research Branch, NCI
Global need for personalized medicine

- Physicians want to move away from the trial and error approach to the treatment of patients

Patients are demanding safe, more effective drugs

Source: Adapted from Pao and Hutchinson, Nature Medicine 2012
Considerations for regulatory professionals

Key aspects

- Regulation of in vitro companion diagnostic device
- Integrated drug-device development plan
- Impact on clinical development
- Sample acquisition
- Appreciation of different business models
Considerations for regulatory professionals

Regulation of in vitro companion diagnostic device

- In vitro companion diagnostic devices are the most highly regulated diagnostics and are considered medical devices.

- FDA has oversight of in vitro companion diagnostic devices as use with a therapeutic raises important concerns about the safety and effectiveness of both the device and the therapeutic.

- FDA generally considers these class III, significant risk devices as an error could have a serious consequence for the patient in either unnecessarily treating or denying treatment, based upon the erroneous test result.

- In order to definitively determine the diagnostic categorization and classification, need to consult with CDRH.

<table>
<thead>
<tr>
<th>Biomarker Sample</th>
<th>Assay Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, peptides, amino acid sequences</td>
<td>ELISA, IHC, mass spectrometry, GC/MS</td>
</tr>
<tr>
<td>DNA, RNA, nucleic acids</td>
<td>Microarray, PCR, FISH, SNP, CNV, sequencing</td>
</tr>
<tr>
<td>Cells and cellular structures</td>
<td>Flow cytometry</td>
</tr>
</tbody>
</table>
Considerations for regulatory professionals

Regulation of in vitro companion diagnostic device

- If FDA determines the test is an in vitro companion diagnostic device, an IDE application will be required to permit collection of data to support a submission. The data collected should demonstrate the device is safe, useful, and reliable around the threshold.

- Contemporaneous filing of a pre-market application, appropriate for the device classification, along with the drug application is generally required, as labeling for both the drug and diagnostic is associated.

<table>
<thead>
<tr>
<th>Type of application</th>
<th>Class I</th>
<th>Class II</th>
<th>Class III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target review time</td>
<td>Registration</td>
<td>90 days</td>
<td>180 days</td>
</tr>
</tbody>
</table>

- Dr. Pazdur/FDA has three principles for review:
  1. Is the diagnostic essential for the use of the drug?
  2. Use of the diagnostic will be placed in the context of existing therapies
  3. Efficacy trumps all, so if drug is superior to all available therapies, question why one would need the diagnostic
## Considerations for regulatory professionals

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidance on PG Data Submissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>Concept Paper on Drug-Diagnostic Co-Development</td>
</tr>
<tr>
<td>2007</td>
<td>Companion Guidance on PG Data Submissions</td>
</tr>
<tr>
<td></td>
<td>Guidance on PG Tests and Genetic Tests for Heritable Markers</td>
</tr>
<tr>
<td>2010</td>
<td>ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards</td>
</tr>
<tr>
<td></td>
<td>Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment</td>
</tr>
<tr>
<td></td>
<td>Guidance on the Qualification Process for Drug Development Tools</td>
</tr>
<tr>
<td>2011</td>
<td>Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies</td>
</tr>
<tr>
<td></td>
<td>Guidance on in vitro Companion Diagnostic Devices</td>
</tr>
<tr>
<td>2012</td>
<td>Guidance on Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications</td>
</tr>
<tr>
<td>In Process</td>
<td>Guidance on Clinical Trial Designs Employing Enrichment Designs to Support Approval of Human Drugs and Biological Products</td>
</tr>
</tbody>
</table>
Considerations for regulatory professionals

- Integrated drug-device development plan

- An integrated plan requires exceptional coordination
- Partner early in R&D and plan on 3 months for contract negotiations
  - If needed, delink “research collaboration” and “commercial” agreements to expedite matters
- Advanced submission of IDE could prevent clinical trial delays
- Assay validation (reliability in clinical samples) & clinical validation (capacity to make a clinical distinction) are dependent upon samples from clinical development
- Consider modular review of PMA application: analytical, manufacturing, and clinical performance submitted in modules
Considerations for regulatory professionals

Impact on clinical development

Stratification using genomic information can allow smaller numbers of participants and increase statistical power for establishing effectiveness and reducing morbidity.

Targeted Design

All Subjects → Test all subjects and only enroll and randomize marker + subjects → Marker +

Therapy

Standard of Care

Limitations of a targeted design approach

- Marker+ patients shown to do better on treatment than standard therapy, but can’t tell if the treatment is also better than the standard in marker- patients (i.e. not a predictive marker)
- Labeling is restricted to a ‘selection’ claim as opposed to ‘prediction’
- FDA may mandate evaluation of marker- population either prior to or post approval (Xalkori)
Considerations for regulatory professionals

Impact on clinical development

- Preferred study, in principle, is the **biomarker-based prospective design**
  - True ‘predictive’ claim as generates data on the effect of the drug versus standard therapy in both the marker+ and - patients
  - Complex 4-arm study, but should at least study in early development
  - Control needed otherwise can’t tell if marker+ patients would have done better than marker- regardless of treatment (i.e. it’s a prognostic marker)

**Biomarker-based Prospective Design**

- **All subjects**
- Test all subjects and randomization is stratified by marker

**Therapy**

- **Marker +**
- **Standard of Care**

- **Marker -**
- **Therapy**

- **Standard of Care**
Considerations for regulatory professionals

Impact on clinical development

- Another viable option is the **non-targeted design**
  - Evaluates the effect of the therapy in all subjects and evaluation of marker effect is evaluated *post hoc* using banked or retrospective samples

Non-Targeted Design

- Test all subjects (possibly after trial), randomization is not stratified by marker status
- All Subjects
- Therapy
- Standard of Care

Agility in incorporation of new data in the development plans – necessary in an era of dramatically evolving science
Considerations for regulatory professionals

- **Impact on clinical development**

  - **Take into account device characteristics**
    - Adequate assay validation (6-12 months)
    - Clear definition of threshold

- **Discordance** – could be a testing problem or, in the case of cancer, could be heterogeneity in the tumor
Considerations for regulatory professionals

- Sample acquisition
  - Highly recommend a sample acquisition plan to ensure sufficient number of samples, appropriate handling, and quality of samples (e.g. damage during routine fixation)
  - Develop an adequate Informed Consent to carry you through diagnostic evaluation (even if post hoc)
  - Decide on who will keep the inventory (internal or external contractor) and ensure adequate storage conditions
  - Ensure easy access to inventory (tracking software)
  - Be mindful of processing time
  - Who will be responsible for integration and interpretation of results
Considerations for regulatory professionals

- Appreciation of different business models

  - Two industries have business models that are completely misaligned

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Description</th>
<th>Regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro diagnostic manufacturer</td>
<td>Analyte specific reagent</td>
<td>Intended for use in a diagnostic application</td>
<td>FDA (generally Class I devices)</td>
</tr>
<tr>
<td></td>
<td>Lab-developed test</td>
<td>Service – test developed by a single lab for use in that lab</td>
<td>CMS (through CLIA)</td>
</tr>
<tr>
<td></td>
<td>In vitro diagnostic</td>
<td>Low-cost, generally single-use kit</td>
<td>FDA (OIVD)</td>
</tr>
<tr>
<td>Drug manufacturer</td>
<td>Prescription drug</td>
<td>High cost treatment that garners long term access to market</td>
<td>FDA (CDER/CBER)</td>
</tr>
</tbody>
</table>

- Very different commercial incentives
  - If a small diagnostic revenue stream is projected, up front development costs and project expenses will be a challenge
  - Generally don’t understand other’s business or how to effectively work together
Considerations for regulatory professionals

Appreciation of different business models

Two partnership models are possible

• **In-house diagnostic units**
  - Novartis and Roche are among those with internal diagnostic divisions, aim to align R&D activities between both branches early on
  - Up to 60% of Roche’s pipeline drugs could come paired with an in vitro companion diagnostic device

• **Formation of partnerships with external companies**
  - Companies like AstraZeneca and Celgene are very interested in integrating molecular diagnostics in drug development and achieve this through the formation of strategic alliances with independent diagnostic companies, which allows for collaborations early in development

Manage the program, not your partner…leverage core competencies and communication is key
Identify the appropriate and relevant use of biomarkers/diagnostics in development

Deliver the biomarker/diagnostic strategic plan

Functional Representation
- Translational Development
- Clinical Development
- Regulatory Affairs
- Legal/IP
- Business Development
- Commercial
Recent in vitro companion diagnostic device success stories

<table>
<thead>
<tr>
<th>Genentech drug indicated for treatment of late-stage (metastatic) or unresectable melanoma patients with a mutated BRAF gene, as detected by an FDA-approved test</th>
<th>Roche Molecular Diagnostics Cobas 4800 BRAF V600 Mutation Test is intended for the detection of the BRAF V600E mutation, using real-time polymerase chain reaction technology, to be used as an aid in selecting patients for vemurafenib treatment</th>
<th>Drug received priority review and was approved by FDA months ahead of its goal date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer drug indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer that is anaplastic lymphoma kinase-positive as detected by an FDA-approved test</td>
<td>Abbott Molecular Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the ALK gene via fluorescence in situ hybridization to aid in identifying those patients eligible for treatment with Xalkori (crizotinib)</td>
<td>Drug was approved by FDA ahead of its goal date under the accelerated approval program</td>
</tr>
</tbody>
</table>
**Recent in vitro companion diagnostic device success stories**

<table>
<thead>
<tr>
<th>Device</th>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vertex drug</strong></td>
<td>Indicated for the treatment of a rare form of cystic fibrosis in patients ages 6 years and older who have the specific G551D mutation in the cystic fibrosis transmembrane regulator gene.</td>
<td>Drug label indicates that use of an FDA-cleared CF mutation test should be used to detect the presence of the G551D mutation if the patient’s genotype is unknown.</td>
</tr>
<tr>
<td><strong>ImClone drug</strong></td>
<td>Drug indication expanded to be used in combination with FOLFIRI for first-line treatment of patients with K-ras mutation-negative (wild-type), EGFR-expressing metastatic colorectal cancer as determined by an FDA-approved test.</td>
<td>Drug received priority review and was approved by FDA in three months.</td>
</tr>
<tr>
<td><strong>QIAGEN Therascreen KRAS RGQ PCR Kit</strong></td>
<td>Uses a real-time polymerase chain reaction assay to detect 7 different mutations of the K-ras gene in a tumor specimen. Diagnostic is intended to weed out the 40% of colorectal patients who have a K-ras gene mutation that makes them unresponsive to Erbitux.</td>
<td>Evaluated through retrospective analyses of tumor samples from one pivotal and two supportive studies and showed no benefit or potential harm in patients with the K-ras mutation.</td>
</tr>
</tbody>
</table>
Pharma industry commitment

Progress in developing the science of personalized medicine

Starting to Develop
- Metabolics
- Respiratory
- Virology

In Some Programs
- CV
- CNS
- Immunology

In Most Programs
- Oncology

Discovery strategy includes biomarker and/or targeted therapy: 100%

Require all compounds in development to have associated biomarker: 30%

Companies with established strategic partnerships related to PM: 81%

Trials that collect DNA samples from clinical trial participants: 50%

Source: Adapted from Tufts Center for the Study of Drug Development
Next steps

• **Refinement of FDA policy and requirements**
  - Better understanding of FDA expectations – final guidance soon
  - FDA efforts in early stages and the regulatory construct is still ambiguous
  - Room for industry, academia, advocacy to refine FDA thinking

• **Clearer guidance on management and enforcement of LDT versus IVD**
  - FDA exercises enforcement discretion on LDTs and don’t have the resources to ensure compliance
  - FDA recently convened a meeting on the oversight of diagnostic tests made by labs ranging from the big players to small, individual operations

• **Better transparency on how CDER/CBER and CDRH will interact**
Next steps

• Keeping up on the science
  ▪ Continual advancements in technology and research to define the genetic component of diseases
  ▪ Development of analytical tools to better interpret the data

• Novel thinking in the development of cancer therapies
  ▪ As diagnosis is becoming less about the tissue where the tumor is found, and more about the characteristics of the tumor, there could be a fundamental shift in how targeted therapies are tested in humans
  ▪ Dr. Pazdur/FDA does not see a dilemma and foresees an indication such as “for the treatment of tumors that over-express [a certain histological subtype]…”

• Global harmonization
In summary

• The rise of chronic disease in an aging population amid finite resources increases the demand for innovative therapies

• The “one size fits all” approach to drug development no longer works as we learn more about disease on a molecular level

• Use of new predictive safety and efficacy biomarkers can lead us down the path of personalized medicine, which has the potential for considerable benefit to patients and societies

• There are considerable challenges in achieving this approach, and regulatory professionals must support development teams to drive this evolution and engage health authorities to influence future policy

It is more important to know what sort of person has a disease than to know what sort of disease a person has.

Hippocrates, 460-370 B.C.
Smithsonian to create its first major exhibit on the human genome – coming summer 2013!

- Marks the 10th anniversary of sequencing the human genome and commemorates the 60th anniversary of Drs. Watson and Crick’s discovery of DNA’s double helix
- Areas of the 2,500 sq ft exhibit hall devoted to scientific education, ancestry, and personalized medicine

Renderings shown here are early designs and may be altered throughout the course of exhibition development.