Personalized Medicine: Regulatory Perspective

President’s Council of Advisors on Science and Technology
Washington, D.C.
January 8, 2008

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Context of Presentation

“The great thing in this world is not so much where we stand, as in what direction we are moving”

Physician, Poet and Writer
1809-1894
Rationale: Variability in Drug Response ~
Adverse Events and Absence of Benefit

“If it were not for the great variability among individuals, medicine might have well been a science and not an art”

Sir William Osler (1849 – 1919)
The Father of Modern Medicine

“One important characteristic of biology is its diversity, its variation. It’s why personalized medicine is so important”

Dr. Andy Kessler (1958 -)
Author and Hedge Fund Manager
Government Can and Should Lead the Way: Initiatives Including Genomic Biomarkers

Personalized Health Care Initiative of HHS Secretary Michael Leavitt (2007)
http://www.hhs.gov/myhealthcare/

Critical Path Initiative of FDA Acting Director of CDER Janet Woodcock (2005)
http://www.hhs.gov/myhealthcare/
Genomic Biomarkers Are the Foundation of Personalized Medicine

- We look for *variability* in drug response for every molecule and the source of that variability

- Biomarkers are typically in the causal pathway of disease pathology or drug pharmacology

- *Qualification* of biomarkers refers to the extent of information needed to understand its clinical utility

- *Qualification* is for a specific intended use that informs a regulatory and/or medical decision
Categories of Personalized Medicine

- Diagnostic test used to select (potential for benefit) or avoid (potential for harm) a drug
- Diagnostic test used to select an optimal initial and/or maintenance dose of drug
- Biomarker discovered during drug development to inform subsequent clinical trial design

Rigorous qualification and regulatory oversight is mandatory in the first two categories, and highly desirable in the third category; implications of false + and false -.
## Aspects of Personalized Medicine That Differ from Traditional Medicine

<table>
<thead>
<tr>
<th>Past and Present</th>
<th>Example</th>
<th>Present and Future</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis – Disease by Symptoms</td>
<td>High Blood Pressure – Many Causes</td>
<td>Diagnosis and Prognosis - Disease by Mechanisms</td>
<td>Breast Cancer – HER2 Gene and Oncotype Dx</td>
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<td>Patient Uniformity – One Size Fits All Dosing</td>
<td>Oral Warfarin Anticoagulation -- 5 mg per day</td>
<td>Patient Variability – Genetic-Guided Dosing</td>
<td>Genotypes Defined by 2C9 and VKORC1 – 0.5 to 6 mg/day</td>
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<tr>
<td>Industry Blockbuster Model</td>
<td>Few with Sales Between $5 – $10 Billion</td>
<td>Mixed Blockbuster and Mini-Buster Model</td>
<td>Many with Sales Between $1 -- $5 Billion</td>
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Role of FDA in Supporting the Future Direction of Personalized Medicine

Protect and Promote Public Health
Changes Already Taking Place: What Are The Regulatory Barriers?

- There is no regulatory backlog of targeted therapies
- FDA is re-labeling “older drugs” with genetic information
- There are specific areas needing greater clarity
  - drug side – level of evidence
  - device side – CLIA vs. PMA
  - format/language in labels
  - potential future incentives
  - too early to “write rules”? 
  - incentives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Test</th>
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<tr>
<td>Herceptin</td>
<td>HER2</td>
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<td>Gleevec</td>
<td>BCR-ABL</td>
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<td>Rituxan</td>
<td>CD20</td>
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<td>Camptosar</td>
<td>UGT1A1</td>
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<td>Ziagen</td>
<td>HLA-B5701</td>
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<td>Selzentry</td>
<td>Tropism</td>
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Limitations of Drug Development Programs: Barriers and Bottlenecks

Important Questions Related to Public Health
-- RCT for evidence of efficacy in described population
-- Treatment effects often small
-- Many patients do not benefit
-- Observational data for safety are empirical and descriptive
-- Hard to predict outcomes in clinical practice

Important Questions Related to Clinical Practice
-- Genomic biomarker discovery, and selection for use in clinical trials
-- Frequency of gene variant
-- Prevalence in subsets
-- Magnitude of benefit or risk in representative cohorts
-- Collecting appropriate samples and generating evidence
Established to encourage exploratory genomic studies and reduce fear sharing with FDA

Intended to foster industry-regulatory exchanges and for all to become more knowledgeable

Serve as a bedrock for creating relevant policies and useful guidances ~ PDS Guidance (2005) and Appendix on Standardization of Data Submission

Successful for the most part – approximately 40+ submissions – with increasing quality and utility
Companion guidance to the GDS guidance provides recommendations for *standardization of genomic data submission*

- Learning experiences from VGDS submissions and meetings led to a *Biomarker Qualification Process*

- VGDS became more sophisticated and opportunistic and reduced the tension between exploratory and required genomic data

- Provided unique “training” in contemporary –omics technologies for reviewers and medical officers
New Guidances Will Bring Further Clarity and Stability

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Draft Preliminary Concept Paper
Not for Implementation
Drug-Diagnostic Co-Development Concept Paper
April 2005

Additional Guidances Planned for 2008-2010

- **End-of-Phase 2A Guidance** ~ discuss clinical trial design using D/R, PK/PD, modeling and simulation, statistical model selection and appropriate genomic issues

- **Adaptive Trial Guidance** ~ discuss clinical trial methodology allowing for design modifications after patient have been enrolled in the protocol

- **Enrichment Trial Guidance** ~ discuss how trials can be designed to decrease heterogeneity in patients by enriching based on gene variants
Industry consortia such as Predictive Safety Testing Consortium ~ 16 members sharing data and cross-validation of biomarkers (Renal Toxicity Biomarker)

Serious Adverse Event Consortium to collectively identify genetic biomarkers to predict individuals who are at risk (Stevens-Johnson Syndrome)

CRADA* with Pharsight to build a data warehouse and informatics infrastructure for building drug-disease models (Parkinson’s Disease Progression)

FDA-NCI-CMS Oncology Biomarker Qualification Consortium (FDG-PET in Non-Hodgkin's Lymphoma)

* Cooperative Research and Development Agreement
Collaborative Web-Based Learning Programs

- AMA/FDA Practicing Physician Training in Pharmacogenomics: http://ama.learn.com
- ACCP/FDA Medical and Graduate Student Training in PGx: http://www.accp1.org/~user/index.html
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Challenges: Clinical Utility ~ We Need to More Clearly Define the Evidence and How to Get It

- What clinical trial data are necessary to document the value of diagnostic test to predict benefit (include patients) or harm (excludes patients)?
- What clinical study designs are acceptable (prospective RCT, observational cohort, retrospective) to provide such evidence ~ especially for safety predictor tests
- How are the data expected to be different when the question is one about optimal dosing ~ use of biomarkers vs. clinical outcomes?
- To what extent can modeling and clinical trial simulation be used as evidence of biomarker qualification?
Challenges: Greater Clarity Surrounding the Path Forward on Regulation of Diagnostic Tests

- Finalize the Guidance on In Vitro Multi-Variate Index Assays (IVDMIA) ~ what will be regulated, complexity classification and the regulatory process
- Finalize the Guidance on Drug/Test Co-Development with a focus on principles of review and labeling
- Sorting out the overlap between CMS CLIA oversight and FDA regulations
- Get greater understanding of the clinical validity and utility of “home brew” (in-house) tests and what future gaps in oversight needed to be addressed
- Boils down to having high quality analytical and clinical validation, and evidence to back up specific claims
“Try not. DO or DO NOT. There is no try”

Yoda to Luke Skywalker
The Empire Strikes Back