Personalized Medicine: Regulatory Perspective

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Context of Presentation

Physician, Poet and Writer

1809-1894

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

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

Past and Present	Example	Present and Future	Example
Diagnosis – Disease by Symptoms	High Blood Pressure – Many Causes	Diagnosis and Prognosis - Disease by Mechanisms	Breast Cancer – HER2 Gene and Oncotype Dx
Treatment Guidelines – Disease Uniformity	Non-Hodgkin's Lymphoma – Many Cancers of Immune System	Customized Guidelines – Disease Heterogeneity	Subclass of B-Cell and T-Cell – Use of Rituximab if CD-20 Positive
Patient Uniformity – One Size Fits All Dosing	Oral Warfarin Anticoagulation -- 5 mg per day	Patient Variability – Genetic-Guided Dosing	Genotypes Defined by 2C9 and VKORC1 – 0.5 to 6 mg/day
Industry Blockbuster Model	Few with Sales Between $5 – $10 Billion	Mixed Blockbuster and Mini-Buster Model	Many with Sales Between $1 -- $5 Billion
Lack of Physician and Patient Awareness	Absence of Formal Education - Access to Information	Patient Empowerment and Societal Expectations	deCode SNP Analysis, Paternity Testing Kits, Safe Drugs

Role of FDA in Supporting the Future Direction of Personalized Medicine

Protect and Promote Public Health

RISK

PROMISE

Genomics

Critical Path Research and Education

HOPE
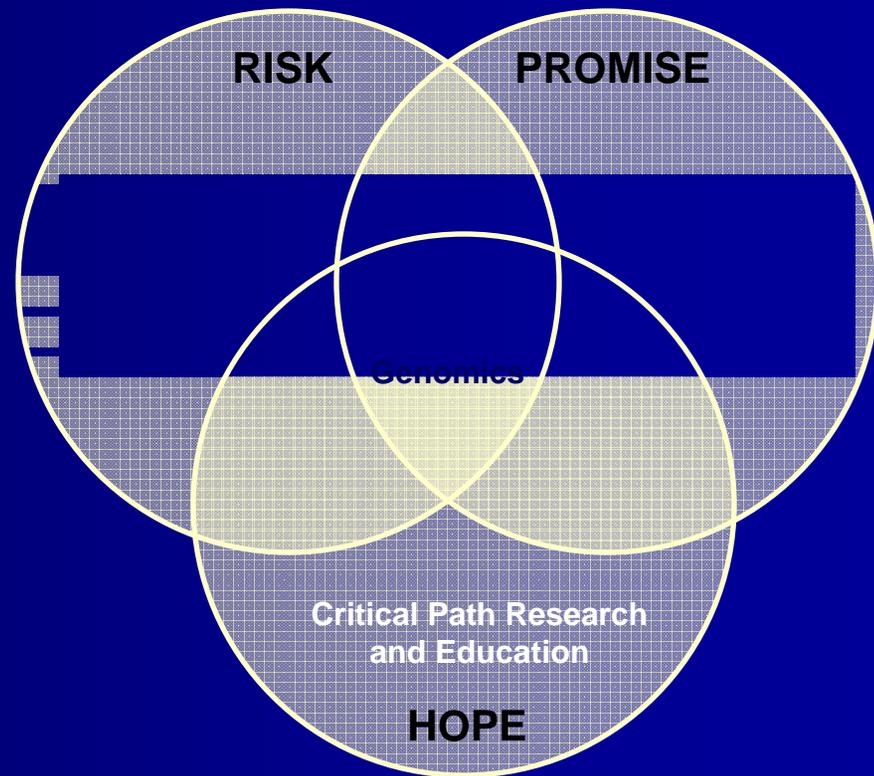
Changes Already Taking Place: What Are The Regulatory Barriers?

Drug	Test
Herceptin	HER2
Gleevec	BCR-ABL
Rituxan	CD20
Camptosar	UGT1A1
Ziagen	HLA-B5701
Selzentry	Tropism

• **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

Limitations of Drug Development Programs: Barriers and Bottlenecks

Population Level Questions

Individual Level Questions

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

Advice, Policy and Guidance

Regulatory Processes: Voluntary Genomic Data Submission Program

- 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

Valuable Spin-Offs of Voluntary Genomic Data Submissions

- 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

Advice, Policy and Guidance

Guidance for Industry

Clinical Pharmacogenetic Studies:

Study Design, Data Analysis and Recommendations for

Dosing and Labeling

Draft Guidance

This draft document is being distributed for internal purposes only

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
October 29, 2007
Clinical Pharmacology #

Draft Preliminary Concept Paper

Not for Implementation

Drug-Diagnostic Co-Development Concept Paper

April 2005

http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf

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COMING SOON

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
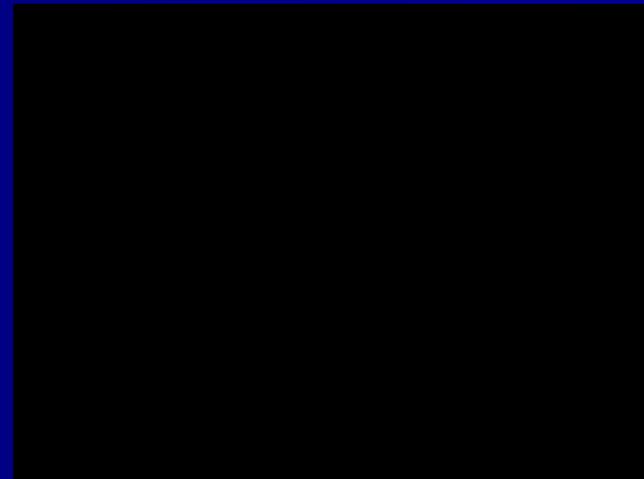
Public-Private Partnerships ~ Industry and Other Government Agencies

- 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)

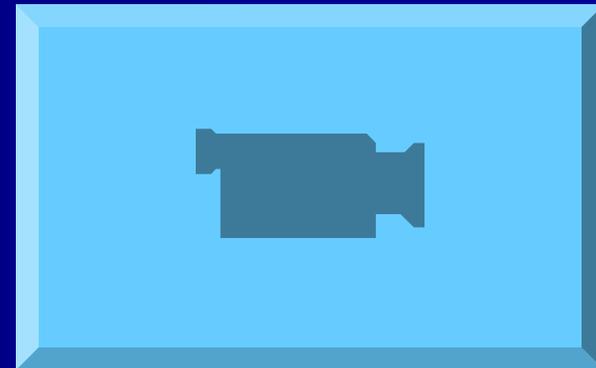** Cooperative Research and Development Agreement*

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

- FDA Patient Safety News Site on Genetic Testing:
  http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=64#6

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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*

Closing Thought: Motivational Quote From Yoda

"**Try not. DO or DO NOT. There is no try**"

Yoda to Luke Skywalker
The Empire Strikes Back