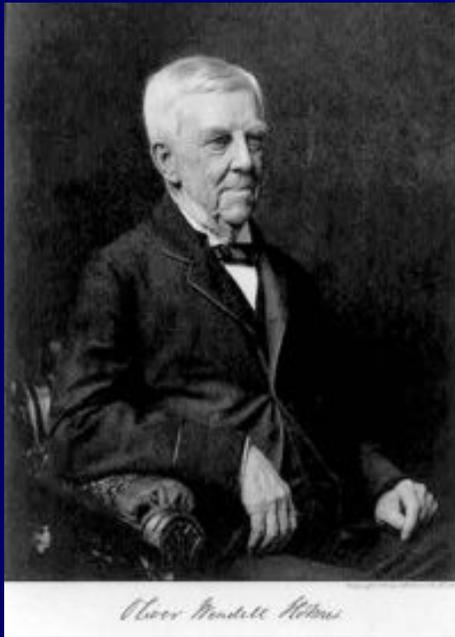


# ***Personalized Medicine: Regulatory Perspective***

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

Lawrence J. Lesko, Ph.D., FCP  
Director, Office of Clinical Pharmacology  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, Maryland, USA

# 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 -***

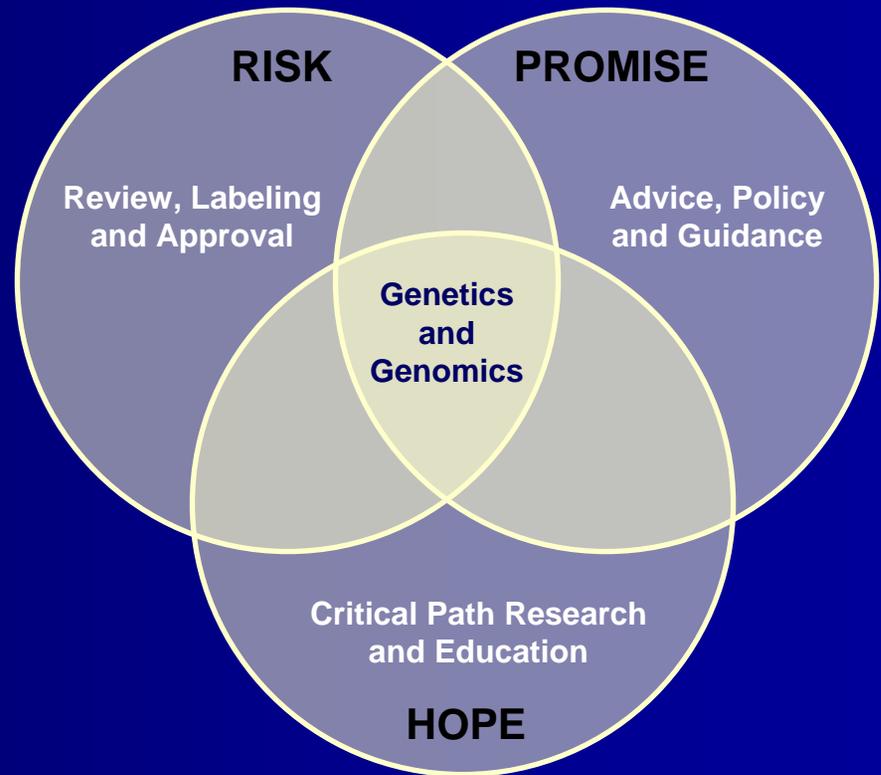
# Aspects of Personalized Medicine That Differ from Traditional Medicine

Past and Present	Example	Present and Future	Example
Diagnosis – Disease by Symptoms	High Blood Pressure – Many Causes	Diagnosis and <u>Prognosis</u> - 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**



## 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

Review,  
Labeling  
and  
Approval

# 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

## 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

Advice,  
Policy  
and  
Guidance

# New Guidances Will Bring Further Clarity and Stability

## 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 #

## TABLE OF CONTENTS

- I. Introduction
- II. Background
- III. General Strategies
- IV. In Vitro Studies
- V. Design of In Vivo Studies
- VI. Labeling Implications
- VII. Appendices and Decision Tree
- VIII. References

## Draft Preliminary Concept Paper

Not for Implementation

## Drug-Diagnostic Co-Development Concept Paper

April 2005

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



## 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

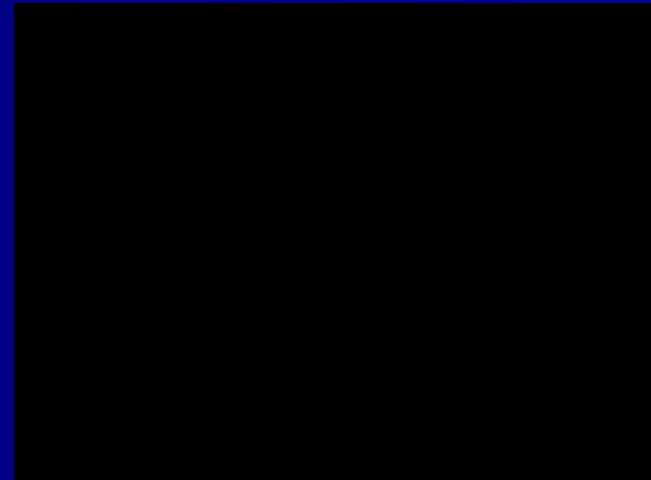
## Public-Private Partnerships ~ Industry and Other Government Agencies

- 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>



# 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>

## 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*