## Genomic Medicine: Regulatory Science Perspective

House of Lords Inquiry on Genomic Medicine Visit Lawton Chiles International House June 6, 2008

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#### Century-Old Challenge: Identifying Causes of Variability in Medicine



"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



(AND NAKED MICE) WILL REBOOT YOUR DOCTOR



Andy Kessler

"One important characteristic of biology is its diversity, its *variation*. It's why personalized medicine is so important"

Dr. Andy Kessler NY Times Best Selling Author (2005)

## What I Will Address in My Presentation

Why genomic applications are important to to new drug development

- How genomic knowledge can be used to improve previously approved drugs
- What are the challenges and solutions to further enabling genomics

#### **Conceptual Foundation for Policies in Genomic Medicine and Pharmacogenomics**

#### Personalized Health Care Initiative of HHS Secretary Michael Leavitt (2007)

http://www.hhs.gov/myhealthcare/





Challenge and Opportunity on the Critical Path to New Medical Products Critical Path Initiative of FDA Director of CDER Janet Woodcock (2005)

http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf

#### Genomic Medicine Is A Component of Personalized Health Care

Science of using genomic biomarkers as diagnostic tests to target therapies

- 1. Total patient populations are "<u>stratified</u>" into subgroups based on similar test results
- 2. Subgroups of patients follow different treatment strategies with "probabilities" for outcomes

### Personalized Health Care Doesn't Have to Be Based Only on Genomic Biomarkers

#### Are These Cases of Personalized Medicine?



#### Pharmacogenomics: Component of Genomic Medicine

- Science of using inherited variations in genes that influence drug selection, drug exposure (PK) and/or drug action (PD)
- Genomic biomarkers: measurable DNA or RNA characteristics in human, tumor or virus samples that are indicators of
  - Normal biologic processes
  - Pathogenic processes
  - Response to drugs

Source: Adapted from ICH E15 Guideline on Definitions and Coding, January 2008

## Genomics: Understanding Heterogeneity in Disease Biology and Drug Response



### Once the Symptoms and Diagnosis Is Complete

Physicians have basically two decisions to make when treating patients:

1. Selecting the right drug

2. Choosing the right dose



### **Consequences of Empirical, Not Mechanistic, Approach to Medicine**



Non-Responders with Unacceptable Toxicity (10%) – Avoid drug

Modest Non-Responders with moderate AE (60%) – adjust dose or consider alternative drug

Good Responders (30%) – Use drug at usual or standard doses; mild AEs likely

## Fundamental Paradox: Develop Drugs for Populations But Treat Individual Patients



Sources: Spear, Trends in Medicine 2001: 7(5), and Aspinall, ACMG Presentation March 13, 2008 National Vital Statistics Reports 2005: 53 (17) – US data from 2001

## THE WALL STREET JOURNAL.

Heightened Media Challenges

As of 9:30 a.m. EST Friday, February 29, 2008

# FDA to Increase Warnings and Advisories on Side Effects

Wall Street Journal, Feb 29, 2008

"Consumers will know we are the case. The Agency's goal is to find out which consumers benefit the most from a particular drug and which ones should avoid it, rather than pulling drugs off the market. This notion is becoming more of a reality with increased use of genetic testing."

Dr. Janet Woodcock, Director Center for Drug Evaluation and Research Food and Drug Administration

## Consequences to Studying Drugs in Total Populations

Improve Productivity of New Drug Development



- Success rates of phase 3 trials is 56%
- Attrition in 1/2 of cases is due to lack of efficacy-
- 1/3 of failure rate is lack of differentiation
- Formula for success = signal/noise x square root of sample size

# How Can We Do Better? How Can We Increase Benefit or Decrease Risk?



"We can't solve problems by using the same kind of thinking we used when we created them"

"Insanity is doing the same thing over and over again and expecting different results"

Albert Einstein (1879 – 1955)

#### Five Biggest Obstacles to Genomic Medicine and Pharmacogenomics



Adapted from survey conducted by Dr. Mollie Roth, Diaceutics, April 2008

Do You Agree That The Regulatory Framework Affects the Adoption of Genomic Medicine and Pharmacogenomics?



Adapted from survey conducted by Dr. Mollie Roth, Diaceutics, April 2008

### FDA Has Invested Resources in Three Broad Areas



Protect and Promote Public Health



#### Knowledge of Disease Biology and Drug Pharmacology Is Key Prerequisite



Source: Gage and Eby, Pharmacogenomics J, 2004

## **Re-Labeling Previously Approved Products With Genomic Medicine**

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Drug	Test		
Trastuzumab	HER2 Receptor Positive		
Imatinib	C-Kit (CD117) Positive		
Rituximab	CD20 Positive B-Cell NHL		
Cetuximab	EGFR Expression +		
Erlotinib	EGFR Expression +		
Maraviroc	CCR5-Tropic HIV-1 Positive		

Efficacy: Test Required

#### Safety: Test Recommended

Drug	Test		
6-MP	TPMT Genotyping		
Camptosar	UGT1A1 Genotyping		
Warfarin	2C9, VKORC1 Genotyping		
Ziagen	HLA-B5701 Variants		
CBZ	HLA-B1502 Variants		
Atomoxetine	2D6 Genotyping		

# What Other Genomic Biomarker Can Reduce AEs by 50% and Save \$900 Per Person?



FDA Label for Warfarin Changed August 2007 to Mention P-genomic Testing in Initial Dosing

"This marks the first time such pharmacogenetic information has been included in a widely used drug....

This means personalized medicine is no longer an abstract concept, but has moved into the mainstream, where it is recognized as a factor in a product used by millions of Americans every day."

 Lawrence J. Lesko, Ph.D., F.C.P Director, Clinical Pharmacology Division FDA

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Sources: Health News Daily, August 17, 2007.

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Source: Medco Health Solutions, 2007

## And Then Lead to Actionable Decisions: Warfarin Dosing Algorithms



#### http://www.warfarindosing.org

	CYP2C9				
VKORC1	*1*1 *1*2	*1*3	*2*2 *2*3	*3*3	TL C` ge
BB	5 mg†	4 mg	2.5 mg	1 mg	cc Ag
AB	4 mg†	2.5 mg	2 mg	1 mg	1. He
AA	3 mg†	2.5 mg	2 mg	0.5 mg	SL
Approximate time to max. effect for a given dosage regimen	5-7 days	10-14 days	14-21 days	28+ days	1.

Dose adjustments for SYP2C9\*1\*1 or CYP2C9\*1\*2 enotypes ONLY (yellow olumn)

Age ≥ 65 years old - subtract 1.0 mg

Height ≤ 155 cm (5'1") subtract 1.0 mg

Height ≥ 175 cm (5'9") - add I.0 mg

#### Challenge: Encouraging the Industry to Explore Genomic Biomarkers

#### Guidance for Industry Pharmacogenomic Data Submissions

Additional argies are available from

Office of Training and Communication Distant of Drug Information, HFD240 Center for Drug Evaluation and Research Food and Drug Administration Solio Enheren Lane Rockville, MD 20257 (Tel) 301 427 4573 http://hows.file.gov/date/guidanceIndex.htm

andbr

Office of Communication, Training and Manifacturers Assistance, HTM-40 Center for Biologies Evaluation and Racords Food and Drug Administration 1401 Bocknille Dias, Bocknille, MD 20323-1448 http://www.fba.gov/dow/guidelines.htm. (Tel) Votee.htmmaties System at 800435-4709 or 501427-1800

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) Center for Devices and Radiological Health (CDRH)

November 2003

www.fda.gov/CDER/guidance/5900dft.doc

• Need to build trust that genomics would not be used prematurely

 Need to learn from each other about potential applications

• Need to standardize collection, storage and reporting of data

New VOLUNTARY GENOMIC DATA SUBMISSION pathway as a building block for expansion of genomics into the drug development process

#### Providing Advice Within the VGDS Program

- Approximately 45-50 voluntary submissions from 12-15 different companies
- Provided shared access to experiments related to
  - Gene mapping and sequencing
  - Genome wide association studies
  - Population genetics
  - New biomarkers
  - Innovative clinical trial designs
  - New "omics"
- Program expanded to collaboration and shared VGDS meetings with EMEA and PDMA

### Developing Policies Based on Experience Gained With The VGDS Program

#### Biomarker qualification pilot process

- Provide more rapid "validation" of biomarkers with a defined context for use ("fitness for purpose")
- Address uncertainties related to sensitivity and specificity of biomarker "tests"
- Compare performance ("predictability") and incremental value to established reference test
- Case study: preclinical nephrotoxicity biomarkers
  - Multiple data sources from industry consortium
  - Review conducted by multidisciplinary review team
  - Sign-off of "validation" package at CDER Director level
  - Joint review with EMEA

#### Guidance Development Is a Continuous Process to Provide a Regulatory Framework

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#### **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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http://www.fda.gov/cder/genomics/default.htm

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#### Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels

Pharmacogenomic information is contained in about ten percent of labels for drugs approved by the FDA. A significant increase of labels containing such information has been observed over the last decade. In order to provide a reference for genomic biomarkers in labels of FDA-approved drug products, we created the table shown below. Genomic biomarkers can play an important role in identifying responders and non-responders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. In the context of drug labels, these genomic biomarkers can be classified on the basis of their specific use, for example:

- · Clinical response and differentiation,
- Risk identification,
- · Dose selection guidance,
- · Susceptibility, resistance and differential disease diagnosis,
- Polymorphic drug targets.

http://www.fda.gov/cder/genomics/genomic\_biomarkers\_table.htm

### Education Is One Of The Obstacles That Is Holding Back Genomic Medicine



Adapted from survey conducted by Dr. Mollie Roth, Diaceutics, April 2008

#### Collaborative Web-Based Learning Programs and Literature

- AMA/FDA Practicing Physician Training in Pharmacogenomics: <u>http://ama.learn.com</u>
- ACCP/FDA Medical and Graduate Student Training in PGx:

http://www.accp1.org/~user/index. html

 FDA Patient Safety News Site on Genetic Testing: <u>http://www.accessdata.fda.gov/scr</u> <u>ipts/cdrh/cfdocs/psn/transcript.</u> <u>cfm?show=64#6</u>

#### Personalized health care report 2008: Warfarin and genetic testing

Twenty-one percent of patients who receive anticoagulant therapy experience either major or minor bleeding events. Knowing a patient's genotype may aid in initial warfarin dosing.

http://www.amaassn.org/ama1/pub/upload/mm/464/ warfarin\_brochure.pdf



#### **Map of Regulatory Genomic Activities**



#### Rational Prescribing Based on Genomic Medicine



Rudolph Buchheim (1820-1879) Founder of Translational Medicine "Fortunately a surgeon who uses the wrong side of the scalpel cuts his or her own fingers and not the patients.....

.....if the same applied to drugs they would have been investigated very carefully a long time ago"

Beitrage zur Arzneimittellehre, 1849

## Let Us Apply Genomic Medicine and Pharmacogenomics To Change Their Lives



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