# Translation of Pharmacogenomics and Pharmacogenetics: A Regulatory Perspective

Session VII: Integration of Pharmacogenomics and Pharmacogenetics into Drug Development and Clinical Practice

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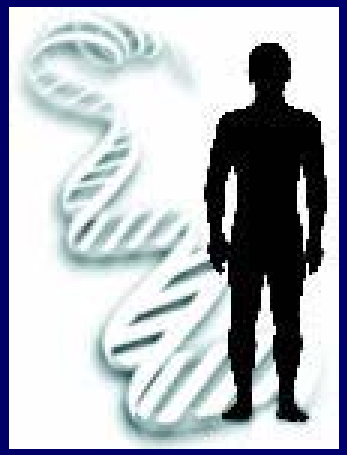
# Translation of PGx: How Can Regulatory Agencies Help Drive It?

"Change is inevitable, except from vending machines"

*Woody Allen*

# Change is Opportunity – Change is Good for Public Health



Pharmacogenetics and pharmacogenomics are expected to play an important role in the development of better medicines for ***populations*** and targeted therapies with improved benefit/risk ratios for ***individuals***

How Long?


How Fast?

# Translation – Bench To Bedside
# The Hard Part

*A process by which genomic or genetic information coded in disease pathophysiology or treatment response directs drug development and changes medical practice.*

- Identify molecular targets
- Measure biological effects
- Understand causation of outcomes
- Diagnosis and prognosis of disease
- Predict response, lack of response or toxicity

# Expanding the FDA's Mission: Lots of Rhetoric…..

- It's mission is to protect and advance public health.....

  "…..by helping to speed innovations that make medicines and foods more effective, safer and more affordable."

*** Pink Sheet, February 3, 2003**

**Improving Innovation in Medical Technology: Beyond 2002**

Move from changing behavior to changing minds

# …..To a Call for Action: FDA's Commitment to Work With Industry


- New *development* tools are needed to improve the predictability of drug development, lower the cost of research by helping industry identify product failures earlier and identify successful candidates more quickly

*www.fda.gov/oc/initiatives/criticalpath/whitepaper.htm*.

# Thesis of Critical Path: There Has Been a Failure of Predictability

"For all that modern science has to offer, developing new medicines is still very much an art – in which hunches, intuition and luck play a critical role."

*Peter J. Pitts*

# Humans Are Unique Individuals and Naturally Have Unique Genomes

Sir William Osler
1892

The Practice of Medicine

"If it were not for the great variability among individuals, medicine might as well be a science and not an art"

# Even Today, Modern Medicine Is Still An Art With Much Uncertainty

Should I take a statin for high cholesterol? Will it help me?

Number needed to treat:

70 previously well middle-aged men with high cholesterol, will take over 200,000 statin pills, over the course of several years to prevent one fatal, or no-fatal, heart attack.

# Trends in Medical Practice Are Bringing the Bench Closer to the Bedside

- Protocol-driven medicine
  - Brings research to the bedside via clinical trials used by FDA to approve drugs for <u>populations</u>
- Evidence based medicine ~ *how it is*
  - Use of current best evidence and protocol-driven medicine to make decisions about <u>individuals</u>
- Personalized medicine ~ *how it should be*
  - Extension of protocol- and evidence-based medicine to include genomic and other biomarkers (imaging) to guide decisions on drug choice and dose selection for <u>individuals</u>

# Lessons from Iressa: Protocol-Driven Medicine Is Still Rather Primitive

- Iressa failed to show a survival benefit in overall population (n = 1692) with lung cancer (5.6 mo vs 5.1 mo for placebo)

1. Incomplete understanding of biology: clinical trials treat diseases not biological hypotheses
2. Response rate is imperfect surrogate for survival (8.2% for Iressa vs 8.9% for Tarceva – erlotinib)
3. Unresolved or inappropriate dose selection (250 mg vs 500 mg) and schedule selection
4. Failure to identify subsets most likely to response (survival benefit in Asians, 9.5 mo vs 5.5 mo on placebo)

# Evidence-Based Medicine Seeks the Truth

*Step* 1. Convert the need for information into an answerable question

*Step 2.* Develop the best evidence with which to answer the question

*Step 3.* Critically appraise the evidence for validity, impact and applicability

*Step 4.* Integrate the critical appraisal with drug development and clinical expertise and with patient's unique biology

# Step 1 - Applied to Iressa: Convert the Need for Information Into an Answerable Question

ROCKVILLE, Md., March 4, 2005. FDA's Oncologic Drugs Advisory Committee said that AstraZeneca's **Iressa ®** confirmatory trial showed a lack of overall survival benefit in the NSCLC setting

SOUTH SAN FRANCISCO, Calif., March 7, 2005. ViroLogic Inc. announced today that it had entered into an agreement with AstraZeneca to conduct a cancer biomarker study with application to Iressa ®, AstraZeneca's selective epidermal growth factor receptor kinase inhibitor. ViroLogic, utilizing its proprietary eTag(TM) assays will test tumor samples from lung cancer patients treated with Iressa ***to evaluate the utility of these assays in targeting patients who would most likely benefit from Iressa.***

## Number of PGx Biomarkers and Clinical Endpoints Is Unlimited….Validation Process Will Not be Simple But Critical

"For every complex problem, there is a simple solution and it is almost always dead wrong"

*H.L. Mencken*

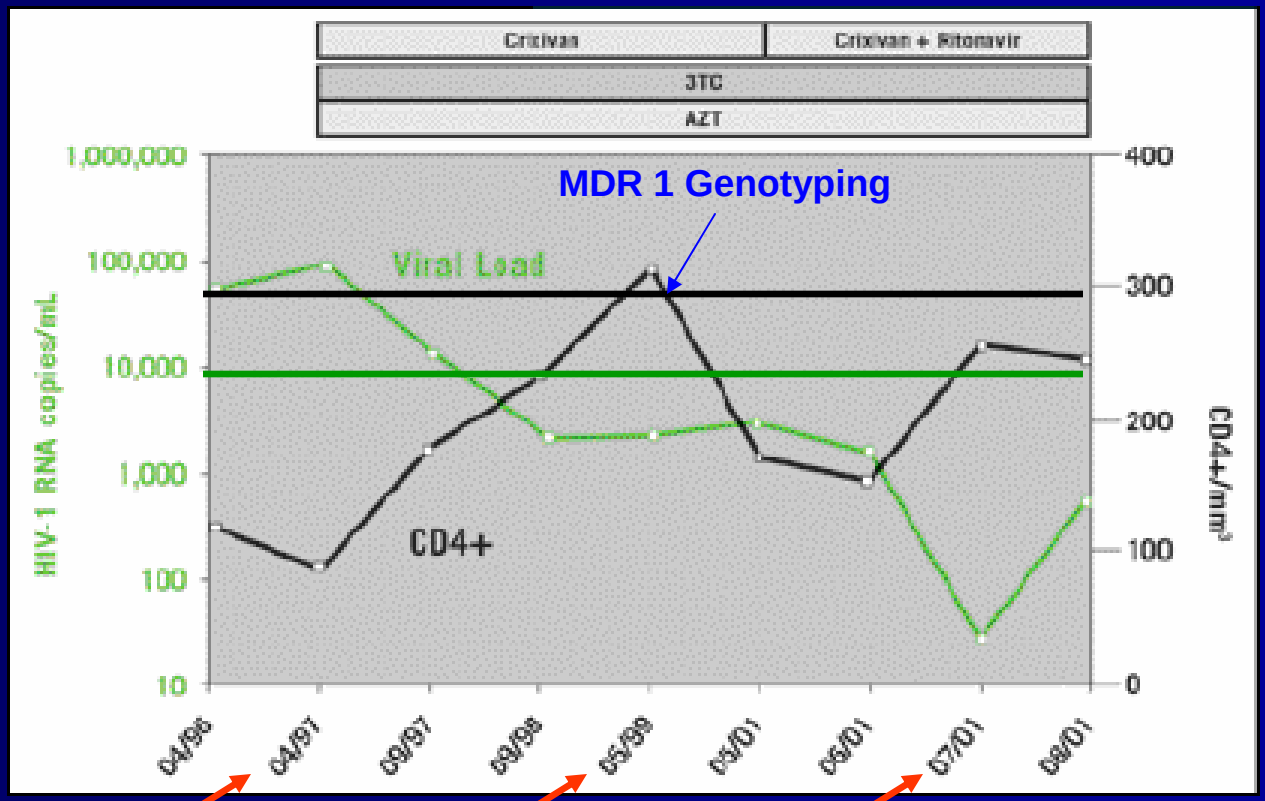
# The End of the Story: What Can Personalized Medicine Do For Patients?

## Jim's Story: Dealing with AIDS

Jim found out he was HIV+ in April 1996. A year later he started an *AZT, 3TC and indinavir* regimen. In May 1999, Jim's viral load and CD4 began to take a turn for the worse. Jim's doctor looked at *indinavir* blood levels, and found them to be low. He checked Jim's MDR1 genotype and found Jim had a homozygous allele resulting in rapid clearance of indinavir. *Ritonavir* was added to boost Jim's regimen. By July 2001, Jim's therapy failed again. His doctor ordered a drug resistance test. The test showed-cross resistance to *indinavir, ritonavir* and high resistance to *3TC*. These drugs were stopped and Jim received AZT, *Viread and lamivudine*.

*Real case history adapted from www.virologic.com with modifications*

# Jim's Treatment Chart



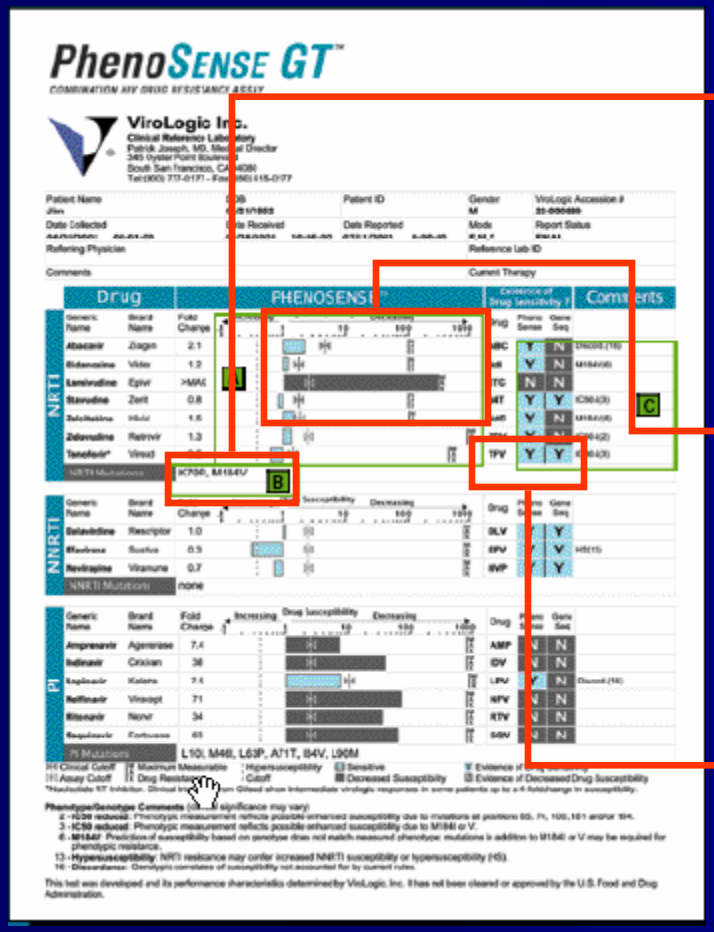

Started antivirals

Losing control

Antivirals failing

Resistance testing

# Resistance Testing Report Form: Understand Failures and Treatment Options




Genotype: mutations in virus that confer drug resistance in one or more drugs or drug classes

Phenotype: color and length of horizontal bar indicates actual resistance to individual drugs

Resistance assessment: predicts whether or not a drug or drugs will work against patient's virus

Adapted from http://www.virologic.com

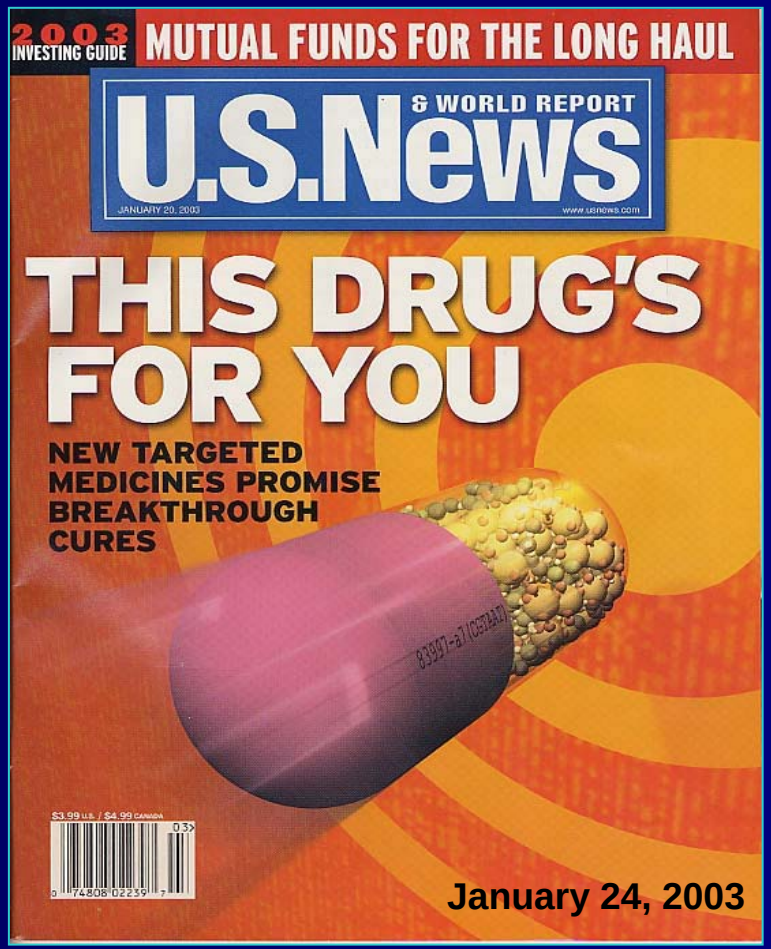
# So What Does All This Mean? Translation of PG is Complex But It Is Here Today!

Predictive, prognostic and response biomarkers: HIV-1 RNA, CD4, Blood levels, and viral genotype

***Personalized Medicine***

1. Reliance on relevant biomarkers
2. Genomics as an adjunct tool
3. Available diagnostic tests
4. Clinical expertise to interpret data
5. Selecting best drug for individual patient

# Increasing Number of Targeted Treatments: Halfway Towards Personalized Medicine




HIV viral genotype ~
NRTI selection
Hepatitis viral genotype ~
PEG-Interferon
HER2 neu ~
Herceptin
BRC-ABL translocation ~
Gleevec
HER1 ~
Erbitux
EGFR positivity ~
Tarceva

# Has Big PhRMA Taken Pharmacogenomics Seriously?

"Dr. Fishman also is changing how Novartis selects diseases to study. Traditionally, it and other big companies have decided by calculating the size of the potential market. He thinks Novartis has a better chance of increasing sales and curing people if it goes after *illnesses whose genetic makeup it has the best chance of deciphering, and diseases for which few treatments are available*."

"Most drugs today are tested on large groups of patients suffering from a common illness. But Dr. Fishman believes that many diseases, such as hypertension and diabetes, can be divided into subgroups. So Novartis has begun conducting more specific drug trials in smaller groups of patients, which Dr. Fishman says has the added benefit of saving money and time."

*From Wall Street Journal, January 25, 2005*

# Has FDA Taken Pharmacogenomics Seriously?

"Clinical trials of drugs and diagnostics using pharmacogenomics will deviate from standard empirical clinical trial model."

"Learning about differences in response to treatment is not so easy and requires that we do subset analysis."

"I think there's a change in the air. That change is a growing recognition that there could be important differences between people, and trying to identify those differences and target treatments to the people most likely to benefit may be desirable."

*Dr. Robert Temple, FDA, at Workshop on PGx and Co-Development, April 11, 2005*

What steps is FDA taking to speed innovation in PGx?

Has there been successes?

Why should anybody care?

# Guidances for Industry in Critical Areas of PGx

- Genomic Data Submission
  - Proposed new classification of biomarkers
  - Decision trees for voluntary and required submissions
- Drug Metabolizing Enzyme Genotyping Systems
  - Supports classification these systems into Class II and identifies issues related to a 510(k) premarket notification
- Instrumentation for Clinical Multiple Test Systems
  - Supports classification of instrumentation for clinical multiplex test systems into Class II (special controls)
- Drug and Test Co-Development
  - Analytical and clinical validation of a genomic assay
  - Evidence of clinical utility and labeling of drug and device

# Preparing Today to Address PGx Drug and/or Test Development Tomorrow

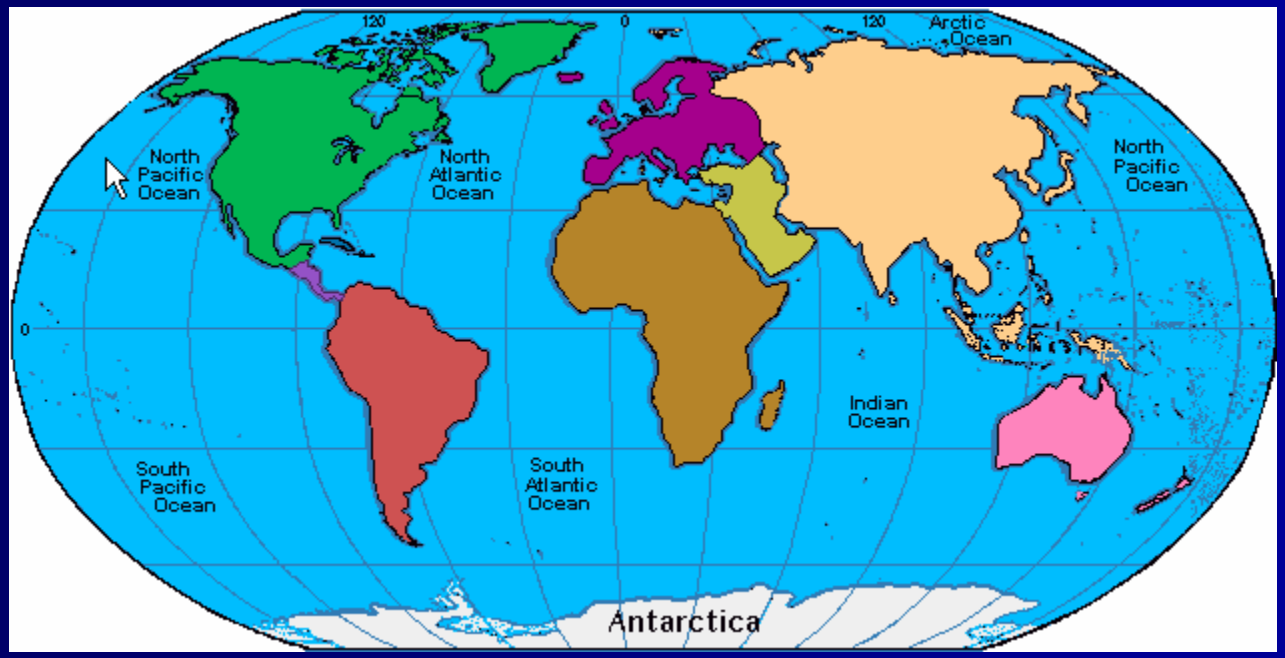
- SOPs
  - Processing and reviewing VGDS
  - Management of the IPRG
- IPRG
  - Consult to review divisions on INDs and NDAs
  - Offer educational programs throughout CDER
  - Develop research consortia to address the process and standards for biomarker validation

# Outreach: Organizational Role and Bringing Stakeholders Together

- FDA-PhRMA-BIO-PWG workshops in May 2002, November 2003, July 2004 and April 2005
  - Publicly discuss and vetted issues of uncertainty surrounding PGx
- Numerous “partnerships” – consortia, cooperative agreements
  - Bringing trade associations, individual companies, NIH and academic centers of excellence together to improve standardization in PGx, discuss ways to apply it in drug development and to validate biomarkers

# Globalization of Drug Development

**North America - Europe - Asia**




*The type of information needed to support a regulatory filing needs to be clear, and where feasible, harmonized between national drug and device regulatory authorities*

# International Activities

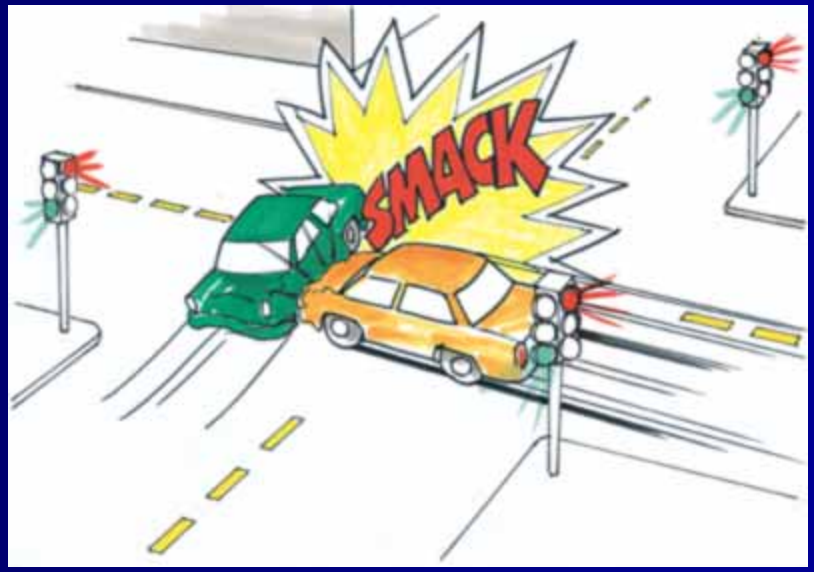
- Creating alignment between FDA, EMEA and MHLW leading to harmonization
  - Input into draft business plan for PGx as an ICH topic
  - Conducting joint VGDS meetings with EMEA under FDA-EMEA bilateral agreement
- Working with CIOMS and OECD to assist in development of PGx policies for non-ICH regions

# PGx Can Improve Previously Approved Drugs

- Process of reviewing the evidence provided by PGx to update package inserts
- Completed relabeling of 6MP and AZA to include new information on TPMT pharmacogenetics
- Negotiating relabeling of irinotecan to add UGT pharmacogenetic information
- Conducting prospective study to address the question of clinical utility of CYP2C9 testing for warfarin

# FDA: At the Crossroads of the Translational Process – Bridge the Gap Between Bench and Bedside

Industry: Drive to create more effective drugs and better risk/benefit




Medicine: Standard of Care of making sure medicines work for all patients

FDA is uniquely positioned to complement the work of industry and the needs of medicine by facilitating drug development while protecting public health

# Summary: Translation of PGx From Bench to Bedside is a Continuum

- New drug development process has already benefited from PGx
- Greater benefits can be expected from applications involving drug-diagnostic test co-development
- Changes in medical practice will be evolutionary and proportional to the extent of indecision treatment choices
- Major upheaval in the existing health care system needed to take full advantage of PGx
- When translation is successful this can lead to immense benefit to patients…….and profits

# Conclusion

Translation of PGx from bench to bedside…..it's the right time, it's the right thing

There have been successes…..and there have been failures.

And, it will not be easy

“Ease is relative to the experience of the doer”

*- Sir Winston Churchill*

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