# Regulatory Perspective on Integrating Pharmacogenomics into Drug Development and Regulatory Decision-Making

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Lawrence J. Lesko, Ph.D., F.C.P.
Director, Office of Clinical Pharmacology
and Biopharmaceutics
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, Maryland, USA

# What I'd Like to Do in This Presentation

- FDA's role in drug development and its focus on innovation in science
- FDA's key strategic initiatives in pharmacogenomics
- Examples of using pharmacogenomics to improve therapeutics

# FDA Mission Statement Includes Facilitating Drug Development

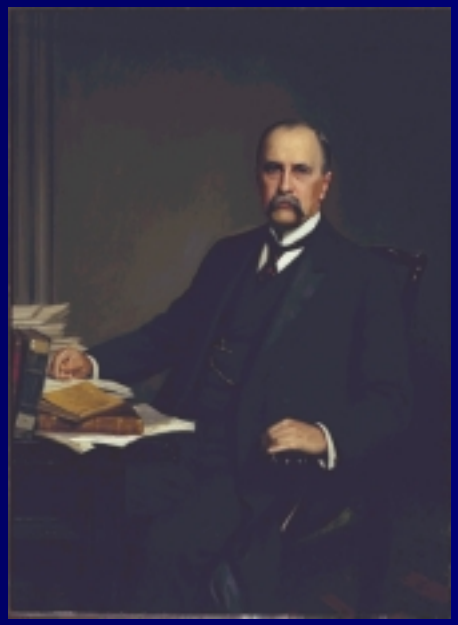
- FDA mission is to protect and advance public health.....

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

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

**Pink Sheet, February 3, 2003**

# Variability in Dose-Response is a Major Barrier to Successful Drug Development



**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"

# Why Do I Say This?

- Extremely high pre-IND failure rate of NMEs
- Less than 1 in 5 INDs for NMEs make it to NDAs
- Time from IND to market is 8-10 years
- Cost per NME is $800 million
- Multiple review cycles for most NME NDAs

For drugs completing phase 2, the failure rate in phase 3 has increased to 50% as compared to 35% a few years ago

# The Consequences of Not Predicting Failure In Late Phase Clinical Development

Late in 2003 Merck terminated phase 3 development of MK-0869 for depression and MK-767 for diabetes at a cost of $800 million dollars and exposing thousands of patients to unapproved drugs

MK-0869 = high placebo response
MK-767 = rodent toxicity

# There is a Need for Scientific Innovations to Reduce the Attrition Rate

Neither the industry or FDA really knows the root cause of late phase clinical trial failures but it is extremely important to find out

Some suspect that at least part of the problem is variability between patients caused by intrinsic and extrinsic factors

# Intrinsic and Extrinsic Factors That Influencing Dose Response

## Intrinsic Factors

- Age
- Body weight
- Gender
- Genomics
- Organ dysfunction

## Extrinsic Factors

- Normal diet
- Co-administered drugs
- Co-administered food
- Co-administered herbals
- Smoking habit

*Adapted from ICH Guideline E5: Ethnic Factors in the Acceptability of Foreign Clinical Data, 1998.*

# FDA Has a Long-Standing Interest in "Individualization Factors"

"….the appreciation of controllable sources of variability in drug action and potential injury to patients should be achieved prior to the marketing of new pharmaceutical products."

- **Peck CC, Temple RT and Collins J in JAMA, March 31, 1993**

# Case Study: Variability in Dose Response to Iressa (Gefitinib)

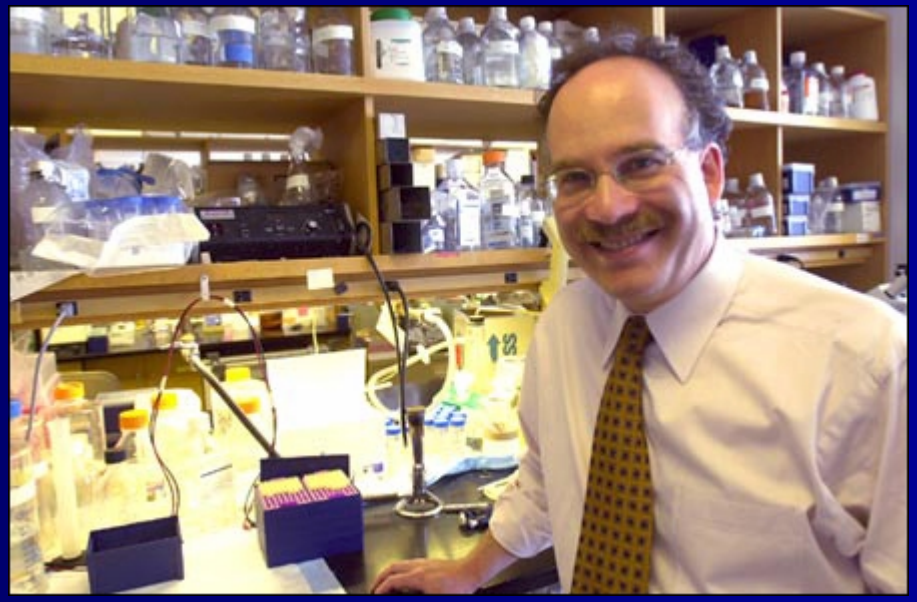
- A tyrosine kinase inhibitor that targets a tumor protein, epidermal growth factor receptor (EGFR)
- Approved for advanced non-small cell lung cancer by FDA on 5 May 2003
  - overall US response rate ~ only 1 in 10 (n = 216)
  - response rate 25-30% in Japan
  - other substantial subset differences in US
    - women and adenocarcinoma ~ 17%, men and smokers ~ 5%
    - males and females with more dramatic response (median ~ 7 mos)

# Significant Safety Concern with Iressa

- Incidence of interstitial lung disease (n = 23,000)
  - 2% in Japanese patients (approved in July 2002) and 0.3% in patients outside Japan
  - 1/3 of ILD patients died
- Consequences of exposing non-responders to Iressa are significant
- A genomic solution to the problem of variability in response to Iressa would be very beneficial
  - can genomic biomarkers identify “responders” and facilitate “individualization”

# Important Genomic Discovery: Molecular Mechanism Underlying Iressa Sensitivity

"Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non-Small Cell Lung Cancer to Gefitinib" from the laboratories of Dr. Daniel Haber, NEJM, 350 (21), May 3, 2004



# Results of Iressa Genomic Study

- Specific mutations on EGFR gene correlated with clinical response
  - deletions or amino acid substitutions around the ATP binding site of Iressa
  - increased EGFR signaling and susceptibility to inhibition
- Mutations identified in 8 of 9 responders
  - lung cancer cells with mutations are 10 times more responsive than normal cells
  - mutations much more common in tumor cells from Japanese patients
- Mutations not identified  any of 7 non-responders

# Pharmacogenomics Identifies Biomarkers for Diagnostic Tests

- Identify responders and begin treatment earlier to reduce disease progression
- Exclude nonresponders and avoid toxicity in those who do not benefit from the drug
- Lift the financial burden ($2000 per month) from patients who receive no benefit
- Enrich (stratify) clinical trials of tyrosine kinase inhibitors for other types of cancer (e.g. solid tumors, gliomas)

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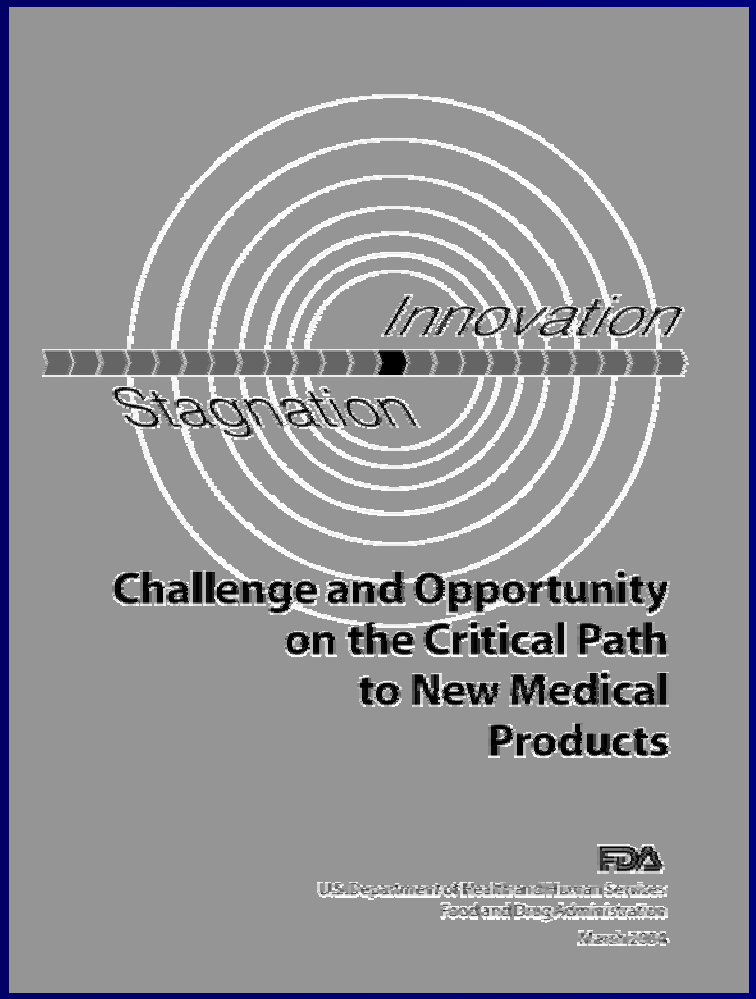
# Bringing Attention to the Problem to the "Pipeline Problem" in Drug Development




"Critical Path" Paper Calls for Academic Researchers, Product Developers, and Patient Groups To Work With FDA To Help Identify Opportunities to Modernize Tools for Speeding Approvable, Innovative Products To Improve Public Health

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

# Specific Projects to Increase Efficiency in Drug Development

- Pharmacogenomics guidances on genomic data submissions and drug/test combinations
- Biomarkers and surrogate endpoints especially the use of imaging as a guide to dose selection
- Quantitative methods of disease state progression and biosimulation to design clinical trials

# FDA's First Pharmacogenomics Guidance

- Genomic Data Submission Guidance
  - to encourage use of PG in drug development and to share these data with the FDA
  - rationale was that experience with data is needed before setting policy and standards
  - comment period closed on 3 Feb 2004 with over 30 sets of comments from industry and others
  - final guidance to issue in June-September 2004

# Created New Pathway for Voluntary Submission of Pharmacogenomics Data

- What kind of data?
  - descriptive gene expression data with no clear pathophysiological function
  - no reasonable or clear expectation that data will have impact on clinical outcome\
  - exploratory data not critical to entering patients into a clinical trial
  - data not critical to claims about efficacy, safety and/or dosing

# What Will FDA Do With Genomic Data Submissions?

- Developing MAPP for submission and review of voluntary GDS (VGDS)
  - process for industry to submit and FDA to review
- Forming an IPGRG with a new charter of responsibilities
  - review VGDS and advise review divisions
- Establishing an advisory committee for discussion of results and analysis of VGDS
  - use to recommend inclusion of genomic biomarkers in drug development

# A Brand New Pharmacogenomic Guidance Development Project

- Drug and diagnostic co-development for use as a pharmacogenomic test-guided therapy
  - Examples: Herceptin/Her-2 neu and Erbitux/EGFR
- CDER, CBER, CDRH and Office of Combination Drug Products are leading the project
- Workshop with drug and diagnostic industry and FDA scheduled for 29 July 2004 to identify issues
- Expect draft guidance in October-December 2004 and a public workshop in March-April 2005

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# Current FDA Thinking on Pharmacogenomics in New Drug Development

Information on important co-variates that can influence dose-response should be in various sections of the product label. Genotype can be an important intrinsic factor.

Understanding PG of drug response is the first step in the development of a genetic test to predict dose, risk of toxicity or the probability of efficacy

# Example of Pharmacogenomics in New Drug Development: Strattera (Atomoxetine)

- Approved by FDA in July 2003 for attention-deficit/hyperactive disorder
  - fixed dose of 0.5 mg/kg titrated up to 1.2 mg/kg
- Metabolism
  - primarily cleared by CYP2D6
  - plasma clearance was 0.35 L/hr/kg in EM and 0.03 L/hr/kg in PM (AUC ratio, PM/EM ~ 10)
- Regulatory question about safety in PM receiving recommended dose: should dosing be "individualized" based on genotype?

# Summary of Late Phase Clinical Study Results

- Assessment of adverse events in phase 3 trials without knowledge of genotype
  - post-facto stratification of subsets based on genotype
- Adverse event rate, mainly insomnia and irritability
  - 9% in PM and 6% in EM
  - 3.5% of PMs and 1.5% of EMs discontinued drug because of adverse events
  - no major differences in serious AE between PM and EM
- CYP 2D6 status mentioned 7 times in label
  - PK, AE, DDI and laboratory test sections
  - no test mandated before prescribing Strattera

# Some of the Questions That Came Up in Decision to Include CYP 2D6 in Label

- How do you define PM?
  - more than 40 alleles of CYP 2D6 with about 10 alleles having greatly decreased or null activity
  - significant variation in frequency of null alleles in different racial and ethnic groups
- How much information to include in label?
  - phenotype (PM, EM) vs. specific alleles (*2, *3, *10 etc)
- Concerns about availability, cost, quality of non-approved CYP 2D6 tests and changes in dosing based on test results

# FDA Is Looking at Approved Drugs Where Genotype is a Co-Variate

- 6-mercaptopurine
  - thiopurine methyltransferase (TPMT)
- Azathioprine
  - TPMT
- Warfarin
  - CYP 2C9
- Irinotecan
  - UGT 1A1

# FDA Advisory Committee Recommended TPMT Genotype for Label

- **6-MP approved for use in children with ALL to maintain remission**
  - dosing is major determinant of outcome
  - 6-MP widely used off-label in adults
- **Clearance varies up to 10-fold**
  - 6-MP --> 6-TG (deactivated by TPMT)
  - genetic flaw in enzyme producing gene on chromosome 6
  - 3 prevalent genotypes with range of TPMT activity (high, intermediate and low)
  - 3 different risk categories for neutropenia

# Risk of Toxicity is Associated with TPMT Genotype

- **Intermediate (1:10) and poor (1:300) receiving usual doses (50 mg/m$^2$) at risk**
  - excess 6-TG leads to severe and potentially fatal bone-marrow toxicity
    - reduce dose 50% for intermediate (controversial) and 80-90% for poor metabolizers to reduce risk (consensus)
- Tests to identify TPMT genotypes (or phenotypes) are available
- Revision of 6-MP and AZA labels underway to include pharmacogenomic information

# Let's Look at a More Recent Example: Potential to Re-Label Irinotecan

- Approved in 1996 for refractory patients with metastatic colorectal cancer
- Doses of 300-350 mg/m$^2$ every 3 weeks
- Tumor response rate of 12-15% and prolongs survival
- Causes severe diarrhea and neutropenia in 20-35% of patients
- Prevalence of fatal events ~ 5%

**Rougier et al, Lancet 352:1407-1412, 1998**
**Saltz et al, NEJM 343:905-914, 2000**

# Irinotecan Pharmacogenetics

- Irinotecan converted to SN-38 which is inactivated by UGT glucuronidation
- UGT1A1*28 is a variant allele with reduced gene expression and glucuronidation
  - homozygous UGT1A1*28 (7/7 genotype) has 2-4 fold lower glucuronidation than wild-type (6/6 genotype)
  - increased exposure to SN-38

**Ando et al, Cancer Res 60:6921-6926, 2000**
**Iyer et al, Pharmacogenomics J 2:43-47, 2002,**

# Safety Pharmacogenomics of Irinotecan

- Prevalence of grade 4 neutropenia in 59 patients was 9.5%
  - 7/7 genotype (6) → 50%
  - 6/7 genotype (24) → 12.5%
  - 6/6 genotype (29) → 0%
- Should UGT genotyping be used to identify cancer patients predisposed to severe toxicity?

**Innocenti et al, J Clin Oncology 22:1-7, 2004**

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Thank you very much for your attention

I hope that you have a successful symposium

leskol@cder.fda.gov