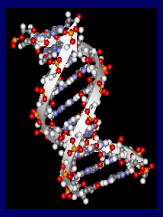
NCDEU 46th Annual Meeting
Boca Raton, Florida, June 15, 2006

Can Pharmacogenomics Help in Psychiatric Drug Development?



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Office of Clinical Pharmacology & Biopharmaceutics
CDER, FDA
shiewmei.huang@fda.hhs.gov

1

Traditional Inefficiency in Drug Development

- Only 8% IND's for NME's reached the market (worse than the historical success rate, 14%)
- Estimated cost per NME about $.8 – 1.7 billion

→a drug entering Phase 1 trials in 2000 was not more likely to reach the market than one entering Phase 1 trials in 1985

<http://www.fda.gov/oc/initiatives/criticalpath/>
< http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

2

Developing better drugs, faster, hinges on "new science"
-- biomedical research into the cause of disease; nanotechnology; bioinformatics to capture and synthesize health data, and biological/micro assembly methods

Janet Woodcock
April, 2006, "Transforming American Healthcare: Pathways to Change"

With genetic testing, developers will have a much clearer set of data with far more compelling results that insurers will be unable to ignore and that will cut overall costs

February 2006, "Biotechnology Healthcare"

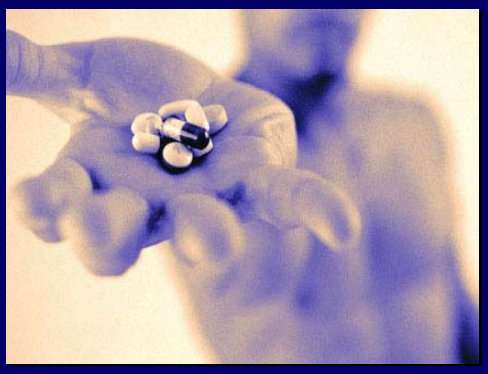
3

20th Century Medicine:

One Size (or Dose) Fits All

4

21st Century Medicine:



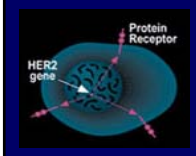
Is This Drug (Dose) For You ?

5

Trastuzumab
(Herceptin®)

6

Trastuzumab (Herceptin®)



In a normal breast tissue cell, the Her-2 gene is expressing cell surface receptor required for normal cell growth.

In certain types of breast cancers, the Her-2 gene is over-expressing this cell surface receptor, contributing to cancerous cell growth. (~30% of breast cancers)

Herceptin (trastuzumab) is an antibody that blocks the cell surface receptor and thereby prevents further growth. As a result, disease progression is slowed down.

7

Trastuzumab (Herceptin®)

INDICATIONS & USAGE

indicated for..metastatic breast cancer whose tumor overexpress the HER2 protein…..

.. Patients whose tumor evaluated with an assay validated to predict HER2

http://www.fda.gov/cder/foi/label/2005/009218s101lbl.pdf

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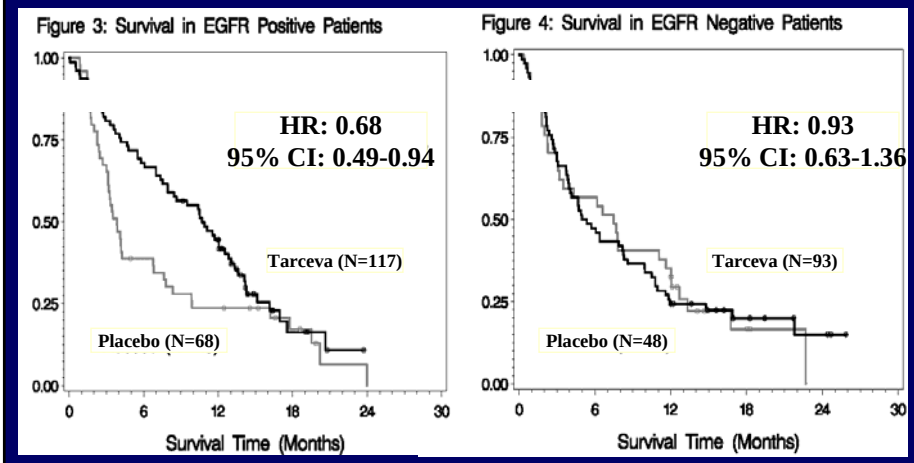
Erlotinib (Tarceva®)- NSCLC



- Survival benefit in overall population
- Survival benefit correlates with EGFR status
- Approximately 50% of patients are EGFR positive

<http://www.fda.gov/cder/foi/label/2005/021743s003lbl.pdf/>

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DNA based biomarkers of enzyme activities considered as valid biomarkers

Enzyme	Model drugs	Outcome measures	Study results
CYP2C9	Warfarin	Maintenance dose Time to reach stable dosing	Patients with *2 and *3 maintai with lower doses and took longe time to reach stable dosing
CYP2C19	Proton pump inhibitors	Plasma levels Gastric pH Gastroesophageal reflux disease cure rate	Higher in PM (20mg) Higher dose (40 mg) showed no difference
CYP2D6	Atomoxetine	Pharmacokinetic measure	PM higher AUC (10-fold)
UGT1A1	Irinotecan	Grade ¾ neutropenia	UGT1A1 7/7and 6/7 more frequ than 6/6
TPMT	6-MP	Dose-limiting hematopoietic toxicity	More in TPMT deficiency or heterozygosity

<Huang, S-M, Goodsaid, F, Rahman, A, Frueh, F, and Lesko LJ, application of Pharmacogenomics in Clinical Pharmacology, *Toxicology Mechanisms and Methods*, 2006;16:89-99>

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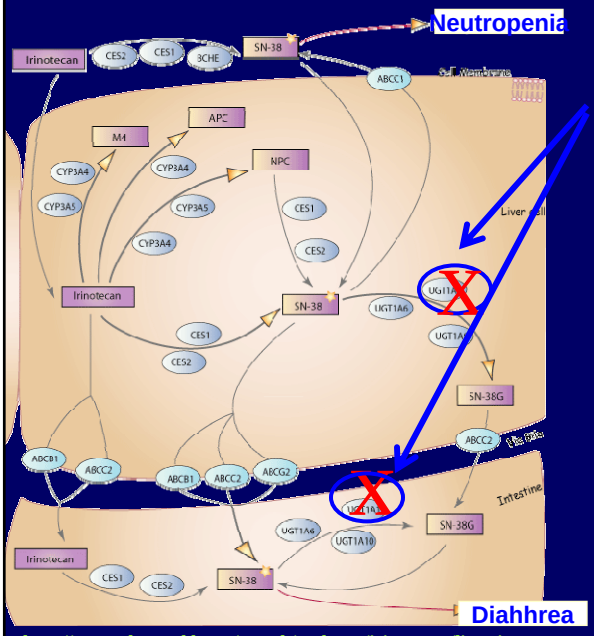
Irinotecan (Camptosar ®)

Irinotecan (Camptosar ®)

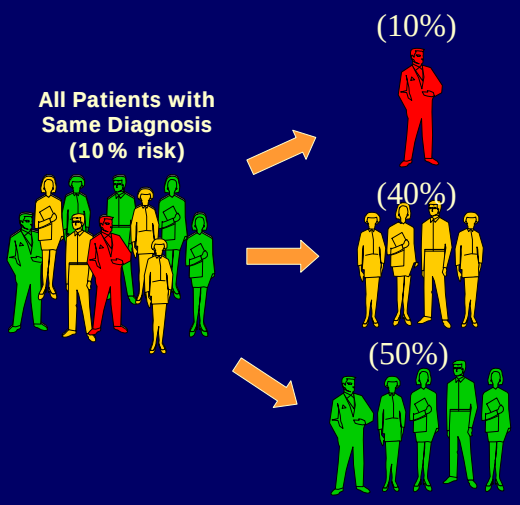


<http://www.pharmgkb.org/search/pathway/irinotecan/liver.jsp>

The UGT1A1*28 allele is common (30%) in Caucasians and is associated with a significant decrease in UGT1A1 activity.

Carriers of UGT1A1*28 when treated with irinotecan can experience AEs

Potential of UGT1A1 Testing to Guide Irinotecan Treatment



PGx profile for *high risk (50 %):* treat with alternative drug or dose (7 / 7 genotype)

PGx Profile for *moderate risk (12.5 %):* treat with alternative drug or dose (7 / 6 genotype)

PGx Profile for *low risk (0 %):* treat with conventional dose (6 / 6 genotype)

<Data taken from Innocenti et al, Clin Pharmacol Ther (2004)>

*CAMPTOSAR (irinotecan) [Dosage & Administration] When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele (See CLINICAL PHARMACOLOGY and WARNINGS).*

FDA NEWS

THE FOOD AND DRUG ADMINISTRATION / AN AGENCY OF THE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICE

FOR IMMEDIATE RELEASE
P05-53
August 22, 2005

Media Inquiries: Julie Zawisza 301-827-6242
Consumer Inquiries: 888-INFO-FDA

FDA CLEARS GENETIC TEST THAT ADVANCES PERSONALIZED MEDICINE
Test Helps Determine Safety of Drug Therapy

Today, FDA cleared for marketing a new blood test that will help doctors make personalized drug treatment decisions for some patients. The Invader UGT1A1 Molecular Assay detects variations in a gene that affects how certain drugs are broken down and cleared by the body. Doctors can use this information to help determine the right drug dosage for individual patients, and minimize harmful drug reactions.

"This test represents the power of DNA-based testing to provide individualized medical care," said Daniel Schultz, MD, Director of FDA's Center for Devices and Radiological Health. "These technologies can significantly improve patient management and reduce the risk of ineffective or even harmful drug therapy by telling doctors how to individualize drug dosing."

< http://www.fda.gov/cder/foi/label/2005/020571s024,027,028lbl.pdf >

Warfarin

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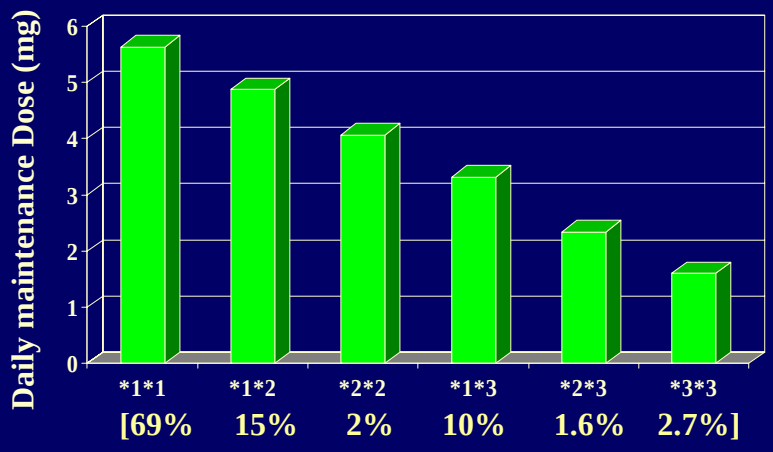
Effect of CYP2C9 genotype on Warfarin Maintenance Dose



N=185, median time= 543 days (14-4032 days)

< Adapted from Higashi MK et al, JAMA 2002; 287:1690>

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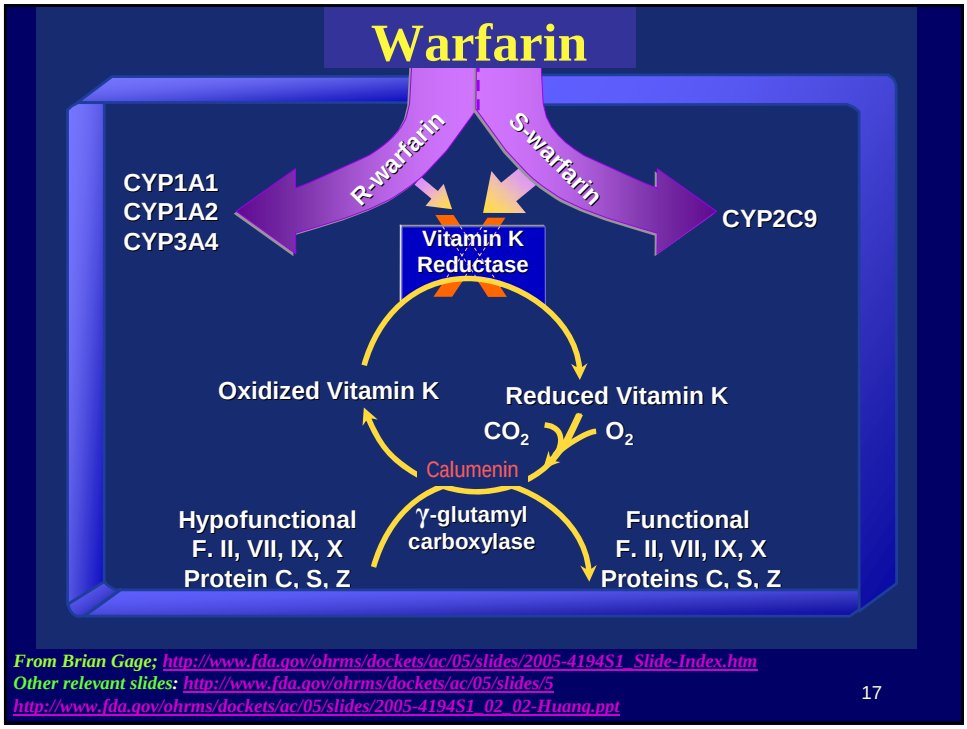

From Brian Gage; http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm
Other relevant slides: http://www.fda.gov/ohrms/dockets/ac/05/slides/5
http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_02_02-Huang.ppt

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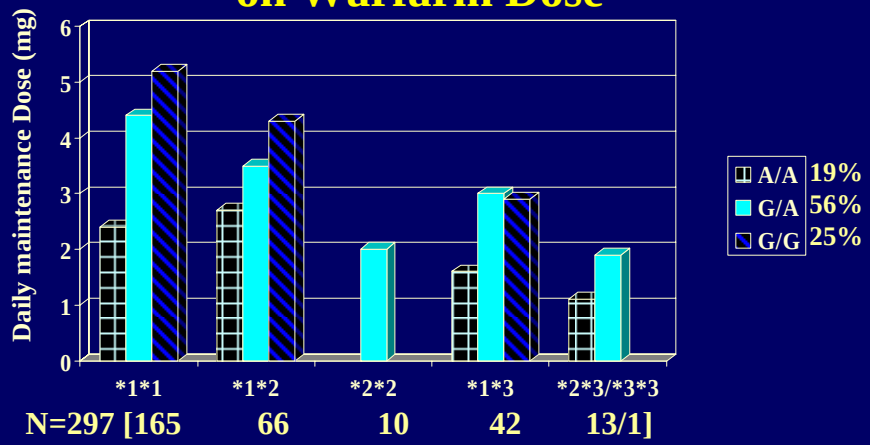
Effect of CYP2C9 (*1, 2, 3) and VKORC1 (-1639G>A) on Warfarin Dose



N=297 [165 66 10 42 13/1]

→ Within a CYP2C9 genotypes, further differentiation among VKORC1 genotypes

< Adapted from Sconce et al, Blood, October 2005>

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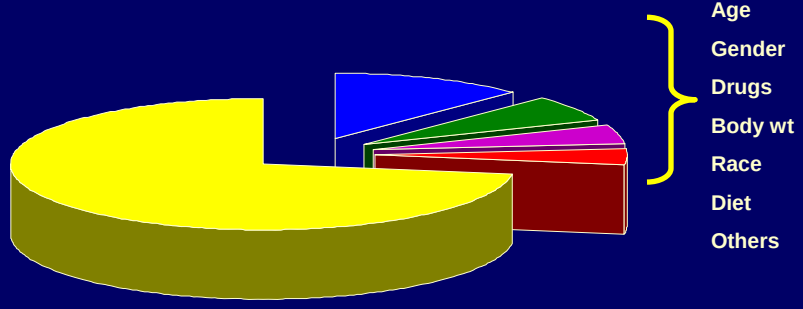
Predicting the Warfarin Stable Dose



What about CYP2C9 genotype?

<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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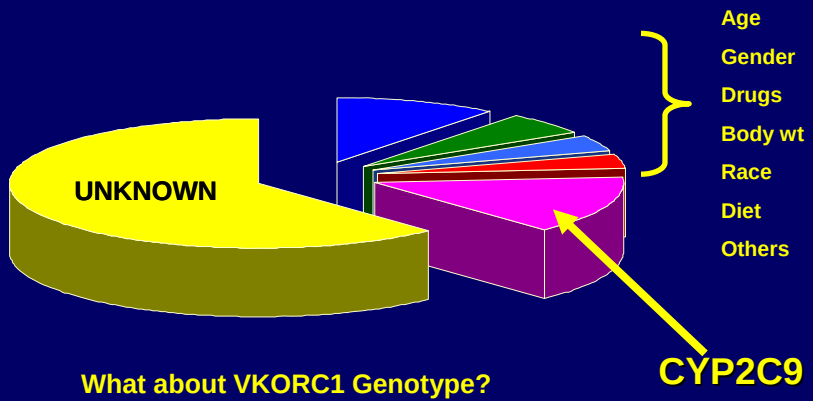
Predicting the Warfarin Stable Dose by adding CYP2C9 genotype



What about VKORC1 Genotype?

<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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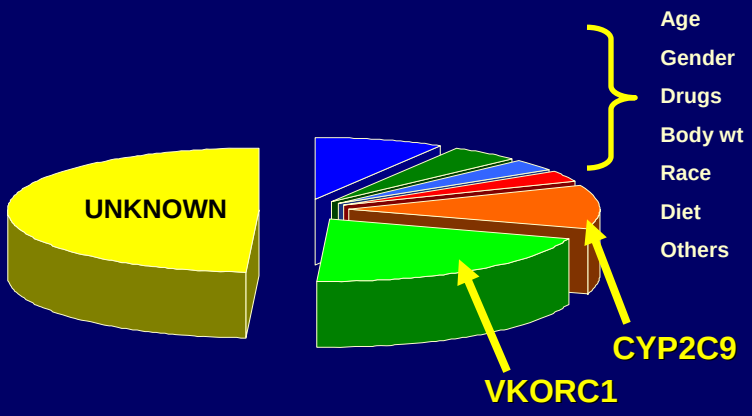
CYP2C9 and VKORC1 on Warfarin Stable Dose



<Modified from Caldwell M., CPSC Advisory Committee Meeting, November 14, 2005>
http://www.fda.gov/ohrms/dockets/ac/05/slides/8>

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Advisory Committee Recommendations:

Does the committee agree that sufficient mechanistic and clinical evidence exists to support the recommendation

- to use lower doses of warfarin for patients with genetic variations in CYP2C9 that lead to reduced activities?

10 YES, 0 NO

- to use lower doses of warfarin for patients with genetic variations in VKORC1 that lead to reduced VKORC1 activities?

10 YES, 0 NO

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Warfarin Meeting
June 14, 2006

C-Path Warfarin Summit Meeting in Bethesda, MD
To discuss specific elements of clinical trial design

- **Which dosing algorithms to evaluate**
- **What SNPs to measure**
- **How data will be analyzed**
- **What information allow for specific genotype-based recommendations**
- **Sharing data and possible eduacational campaigns**

<http://www.c-path.org/>

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Atomoxetine
(Strattera ®)

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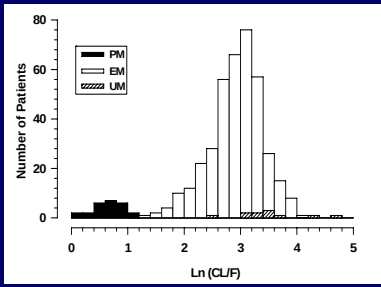
Strattera (atomoxetine)



Witcher et al. 2001. Population Pharmacokinetic Analysis of Atomoxetine in Pediatric Patients.

Between EM and PM of CYP2D6

No differences:

- **serious adverse events (SAE)**
- **discontinuation due to AE**

Difference:

- **common AE**

Melissa Stutts, ORA presentation, October 2004
From http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera_Approv.pdf
http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera_medr_P1.pdf
http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera_biopharmr_P1.pdf

25

Strattera (atomoxetine)

Issue on QT prolongation

- ***"The direct effect model analysis showed a negligible slope (0.0027) between plasma concentration and QT prolongation. It predicts that more than 6-fold difference in Cmax between UM and PM groups will have 4 msec difference in QTc (375 vs 379 msec). This change is not considered clinically important."***

http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera_biopharmr_P1.pdf

26

Strattera (atomoxetine)

Issue on QT prolongation

- *"few, if any, PM patients dosed with the newly recommended dose will reach plasma levels exceeding 2500ng/ml where QT signal was observed" "only a minimal increase in QT interval duration associated with a substantial increase in serum atomoxetine concentrations"*

http://www.fda.gov/cder/foi/nda/2002/21-411_Strattera_medr_P1.pdf

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Strattera (atomoxetine)

Labeling

- *no mention of QT effect*

- *Laboratory Tests* **: Laboratory tests are available to identify CYP2D6 PMs** ***…….higher blood levels in PMs lead to higher rate of some adverse effects of STRATTERA.***

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Strattera (atomoxetine)

Labeling

Adverse Reactions (in percent, child and adolescent trials)

	EM	PM
Discontinued treatment	5	7
Decreased appetite	16	23
Insomnia	7	13
Sedation	2	4
Depression	2	6
Tremor	1	4
Early morning awakening	1	3
Pruritus	1	2
Mydriasis	1	2

< Data compiled from PDR entry for STRATTERA™ (Lilly) (atomoxetine HCl) labeling>

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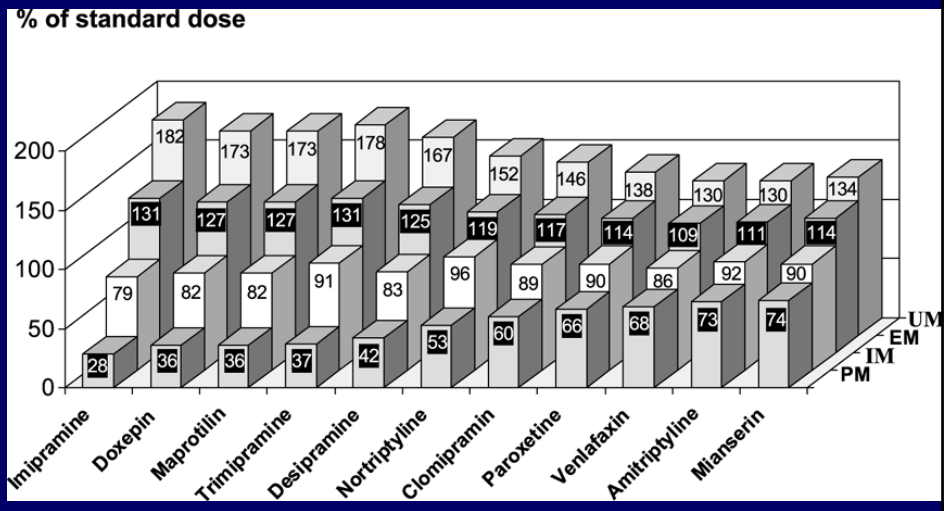

<Roots, I et al, Drub Meta Review 2004 Oct;36(3-4):617-38>

30

Genes Evaluated for effects on Effectiveness and Side Effects

Antidepressant responses

- 5-HTT
- 5-HT2A
- 5-HT6
- G-protein
- Beta-adrenergic receptor
- TPH
- ACE
- Dopamine 2 receptor
- Dopamine 4 receptor
- Interleukin-1 beta
- nNOS
- P-glycoprotein

Antipsychotic responses

- DR1
- DR2
- DR3
- DR4
- 5-HT2A
- 5-HT2C
- 5-HT3A
- 5-HT3B
- 5-HT5
- 5-HT6
- H1

< Steimer W, et al, "Pharmacogenomics of drug targets in psychoactive drug therapy", in "Pharmacogenomics and Proteomics" eds, Wong, Linder, Valdes, AACC Press, 2006

31

Variation in the Gene Encoding the Serotonin 2A Receptor Is Associated with Outcome of Antidepressant Treatment

Francis J. McMahon* Silvia Buervenich* Dennis Charney, Robert Lipsky, A. John Rush, Alexander F. Wilson, Alexa J. M. Sorant, George J. Papanicolaou, Gonzalo Laje, Maurizio Fava, Madhukar H. Trivedi,5 Stephen R. Wisniewski, and Husseini Manji

→ these new genetic data make a compelling case for a key role of *HTR2A* in the mechanism of antidepressant action

- 18% decrease in absolute risk of non-response
  - this polymorphism 6x higher in Whites than Blacks
- no association with serotonin transporter polymorphisms
- metabolizing genes not examined in this part of investigation

<McMahon, et al, Am J Hum Genet, May 2006: 804-14; http://www.journals.uchicago.edu/AJHG/journal/issues/v78n5/43135/43135.web.pdf>

32

Polymorphic Variations in GSTM1, GSTT1 Pgp, CYP2D6, CYP3A5, and Dopamine D2 and D3 Receptors and Their Association with Tardive Dyskinesia in Severe Mental Illness

Jose de Leon, Margaret T Susce, Run-Mei Pan, Walter Koch, and Peter Wedlund

→ **Ser9Gly Dopamine D3 receptor polymorphism and GSTM1 absence were related to tardive dyskinesia**

CYP2D6 and CYP3A5 absence potential for significant associations

<Jose de Leon et al, J Clinical Psychopharmacology, 2005, 25(5): 448>

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Pharmacogenomics - Voluntary genomic data submission-

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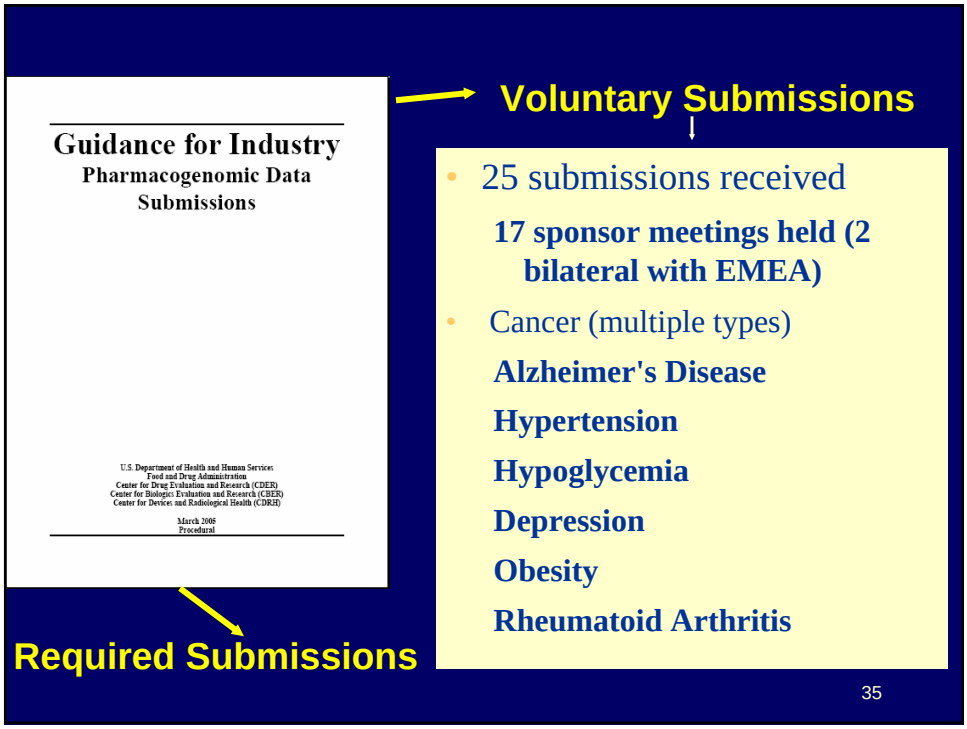
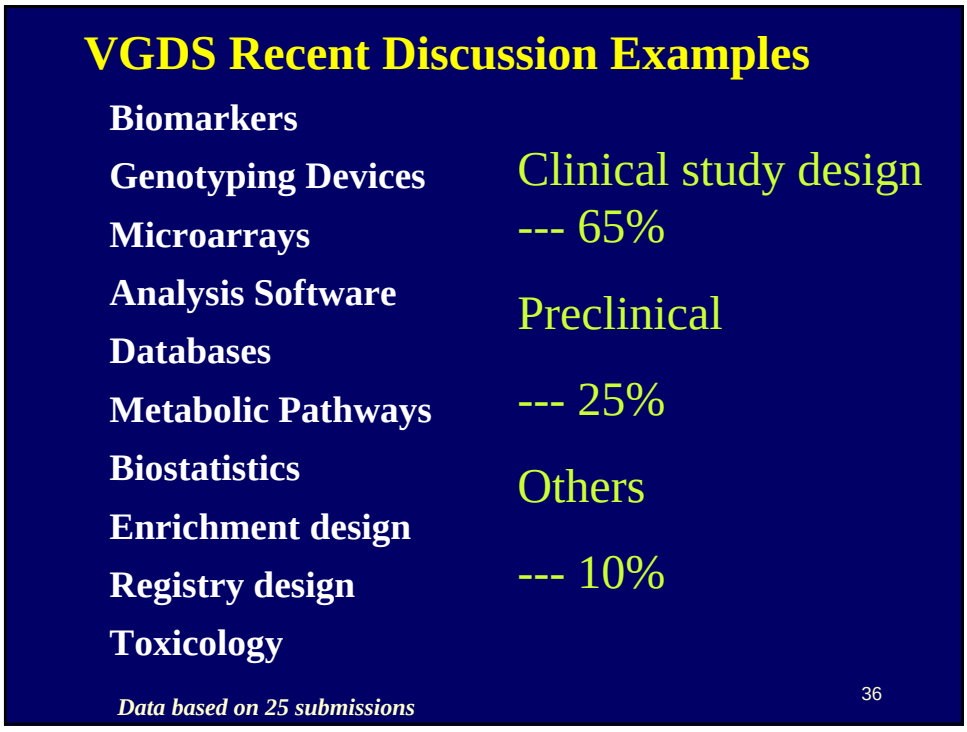
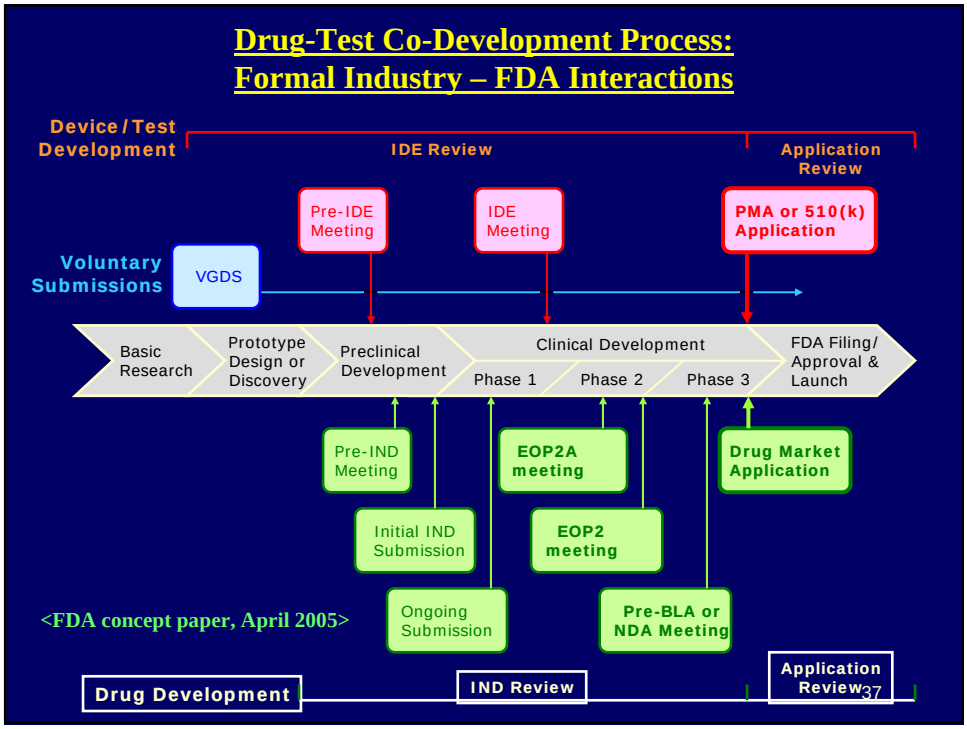
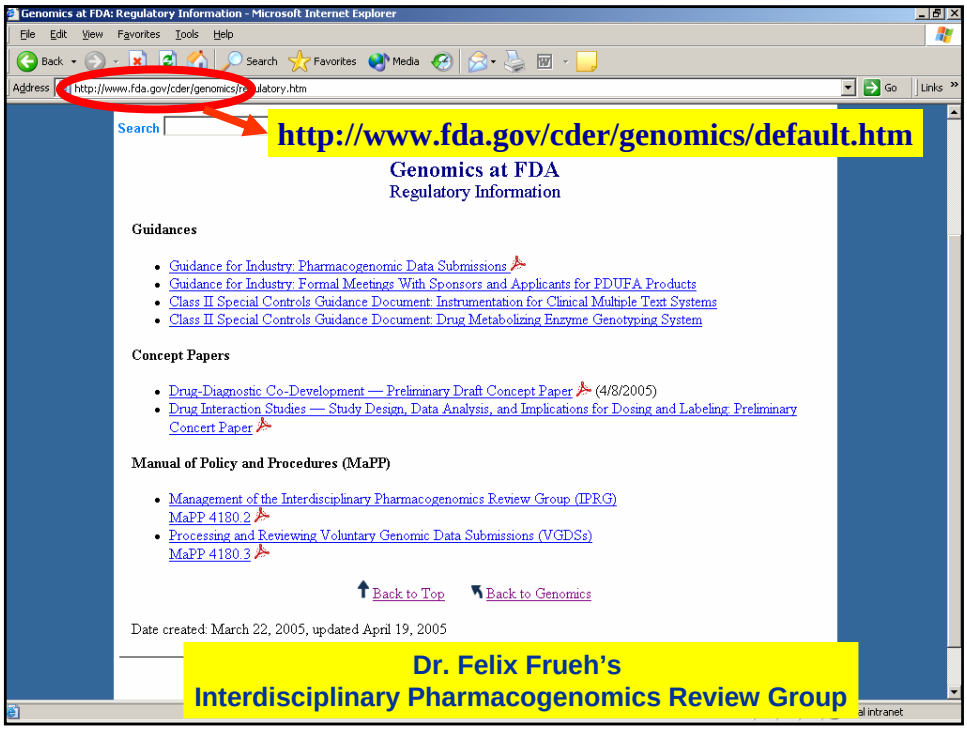

Guidance for Industry
Pharmacogenomic Data Submissions
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
March 2005
Procedural
Voluntary Submissions
25 submissions received
17 sponsor meetings held (2 bilateral with EMEA)
Cancer (multiple types)
Alzheimer's Disease
Hypertension
Hypoglycemia
Depression
Obesity
Rheumatoid Arthritis
Required Submissions
35


VGDS Recent Discussion Examples
Biomarkers
Genotyping Devices
Microarrays
Analysis Software
Databases
Metabolic Pathways
Biostatistics
Enrichment design
Registry design
Toxicology
Clinical study design --- 65%
Preclinical --- 25%
Others --- 10%
Data based on 25 submissions
36


Drug-Test Co-Development Process:
Formal Industry – FDA Interactions
Device / Test Development
IDE Review
Application Review
Pre-IDE Meeting
IDE Meeting
PMA or 510(k) Application
Voluntary Submissions
VGDS
Basic Research
Prototype Design or Discovery
Preclinical Development
Clinical Development
Phase 1
Phase 2
Phase 3
FDA Filing/ Approval & Launch
Pre-IND Meeting
EOP2A meeting
Drug Market Application
Initial IND Submission
EOP2 meeting
Ongoing Submission
Pre-BLA or NDA Meeting
<FDA concept paper, April 2005>
Drug Development
IND Review
Application Review
37


Genomics at FDA: Regulatory Information - Microsoft Internet Explorer
http://www.fda.gov/cder/genomics/default.htm
Genomics at FDA
Regulatory Information
Guidances
Guidance for Industry: Pharmacogenomic Data Submissions
Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products
Class II Special Controls Guidance Document: Instrumentation for Clinical Multiple Test Systems
Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System
Concept Papers
Drug-Diagnostic Co-Development — Preliminary Draft Concept Paper (4/8/2005)
Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling: Preliminary Concept Paper
Manual of Policy and Procedures (MaPP)
Management of the Interdisciplinary Pharmacogenomics Review Group (IPRG) MaPP 4180.2
Processing and Reviewing Voluntary Genomic Data Submissions (VGDSs) MaPP 4180.3
Back to Top
Back to Genomics
Date created: March 22, 2005, updated April 19, 2005
Dr. Felix Frueh's
Interdisciplinary Pharmacogenomics Review Group

Summary

- Pharmacogenomics has been increasingly incorporated in drug development
- Psychiatry is one area where pharmacogenomics can have great impact in targeted drug development and can provide useful tools to identify patients at risk or non-response
- FDA encourages early communications (e.g., EOP2A meeting, voluntary genomic submission, guidances)

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Acknowledgement

Lawrence J Lesko
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Federico Goodsaid
OCP Pharmacogenomics WG
OCP Pharmacogenomics Group

Tom Laughren
Ramana Uppoor
Ray Baweja
Sally Yasuda
Mehul Mehta

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References

- **FDA website, http://www.fda.gov/cder/genomics/default.htm**
- **Huang, S-M, Goodsaid, F, Rahman, A, Frueh, F, and Lesko LJ, application of Pharmacogenomics in Clinical Pharmacology, *Toxicology Mechanisms and Methods,* 2006;16:89-99.**
- **Huang, S.-M., and Lesko, L. J. Application of Pharmacogenomics in Clinical Pharmacology—in Volume I: Molecular Medicine, Correlation between genes, diseases and biopharmaceuticals. In *"Modern Biopharmaceuticals- Design, Development and Optimization"* Knablein, Jorg, and Muller, R H, Eds.; Wiley: VCH, (2005): 49–70.**
- **Andersson T, Flockhart DA, Goldstein DB, Huang SM, Kroetz DL, Milos PM, Ratain MJ, Thummel K, Drug-metabolizing enzymes: evidence for clinical utility of pharmacogenomic tests. *Clin Pharmacol Ther*. 2005 Dec;78(6):559-81.**
- **Frueh FW, Goodsaid F, Rudman A, Huang S-M, Lesko LJ, The Need for Education in Pharmacogenomics: a regulatory perspective. P*harmacogenomics Journal.* 2005;5(4):218-20.**
- **Huang S-M, Lesko LJ, Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions — what have we learned? *J Clin Pharmacol.* 2004; 44:559-569**

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Additional Labeling Examples

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Azathioprine

Laboratory Tests:
TPMT Testing: **It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are *TPMT*2, TPMT*3A and TPMT*3C*. Patients with two non-functional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. …**

<July 2005, Imuran labeling; http://www.fda.gov/cder/foi/label/2005/016324s030,017391s013lbl.pdf> 43

Thioridazine

CONTRAINDICATIONS

… elevated levels of thioridazine would be expected to augment the prolongation of the QTc interval associated with thioridazine and may *increase the risk of serious, potentially fatal, cardiac arrhythmias, such as torsade de pointes-type arrhythmias*. …. Therefore, thioridazine is contraindicated …. in patients, comprising about 7% of the normal population, who are known to have a *genetic defect* leading to *reduced levels of activity of P450 2D6* (see WARNINGS and PRECAUTIONS).

<July 2003, PDR labeling> 44