FDA/Johns Hopkins University/PhRMA Educational Workshop
Drug Metabolizing Enzymes and Pharmacogennmic Testing-
September 13-14, 2003
Rockville, MD

Regulatory Issues in Genotyping Metabolizing Enzymes- *CDER* Perspective

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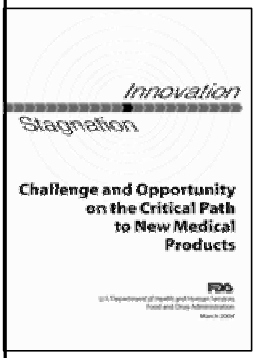
Traditional Inefficiency in Drug Development

- **Extremely high pre-IND failure rate**
- **Less than 1 in 5 IND's for NME's = NDA's**
- **Estimated cost per NME about $800 million**
- **Time from IND to market around 8-10 years**
- **Multiple review cycles for most NME NDA's**

Is this a systemic problem?
Is this the best that can be done?
What is needed?

<Lesko, L, Pharmaceutical Sciences World Conference, Japan, May 18, 2004>



The product development problems we are seeing today can be addressed, …… generation of …….. predictive tools.

The new tools ….. such as bioinformatics, *genomics*, imaging technologies, and materials science.

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

Clinical Pharmacology and Biopharmaceutics Review

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Extrinsic factors

Environmental

Medical Practice/ Regulatory

Smoking/Diet

Drug-drug interaction

Intrinsic factors

Gender

Genetics

Race

Age

Organ Dysfunction

Disease

Pregnancy

Lactation

Adapted from ICH E5, 1998: http://www.fda.gov/cder/guidance/2293fnl.pdf

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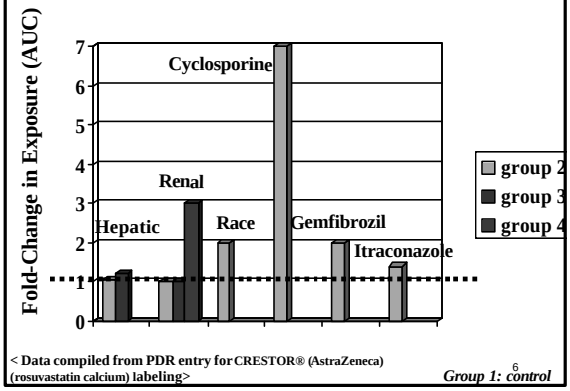

< Data compiled from PDR entry for CRESTOR® (AstraZeneca) (rosuvastatin calcium) labeling>

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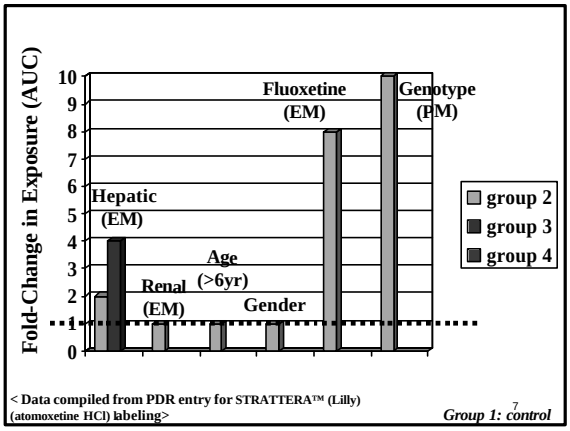
Group 1: control



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

Group 1: control

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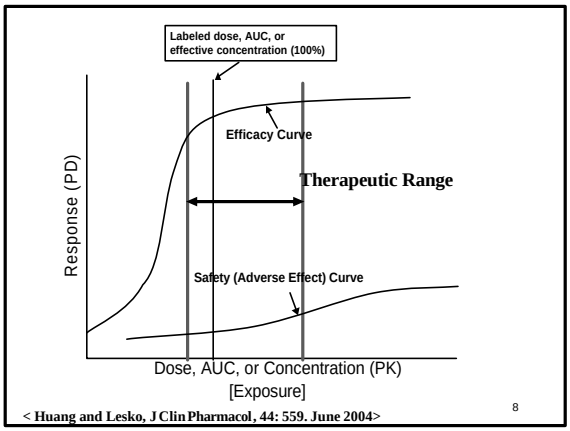

< Huang and Lesko, J Clin Pharmacol, 44: 559. June 2004>

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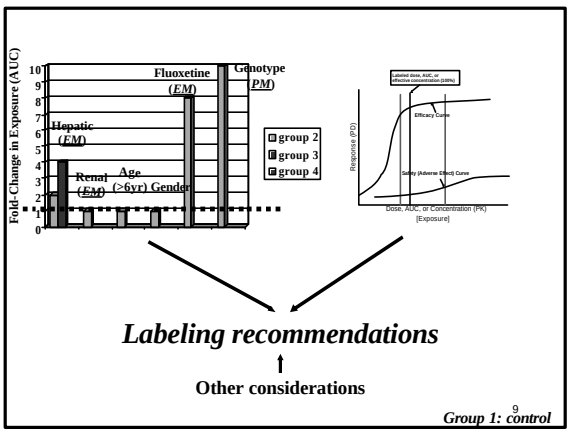

Group 1: control

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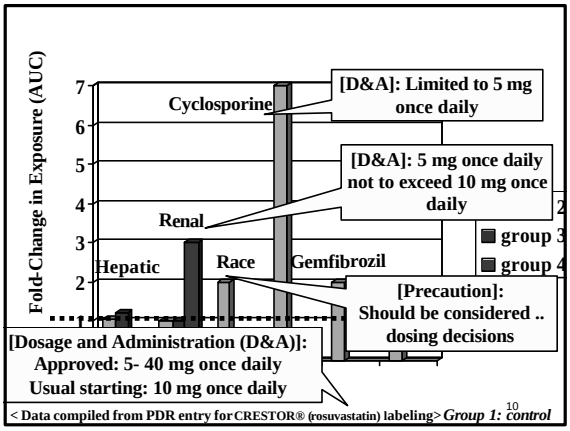
Shiew-Mei Huang, FDA/Johns Hopkins/PhRMA Workshop on "Drug Metabolizing Enzymes and Pharmacogenomics Testing, September 13, 2004, Rockville, MD



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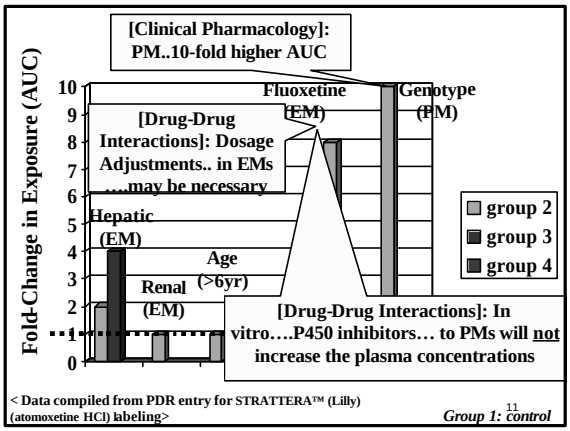

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Atomoxetine Labeling

• ***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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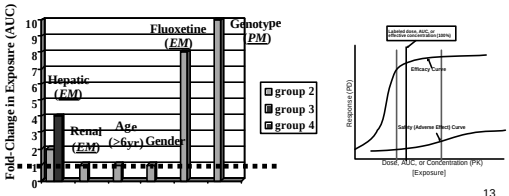
What <u>Pharmacogenomic Testing data</u> are needed when generating these initial PK data (or clinical data) that eventually support the labeling (or future labeling) for drugs metabolized by polymorphically distributed enzymes?



Group 1: control

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Issues

- **Are designations of EM and PM inadequate?**
  - ***do we need UM and IM?***

CYP2D6

EM	***with 1 wild type *1***	***1*1, *1*2,…*1*5, *1*10, *1*17…**
PM	***with two null alleles***	***3*3, *3*5, *4*6,…**
		***3-8, *11-16, ……**
IM?	***with two reduced alleles or one reduced, one null***	***10*10, *17*17, *4*17,…**
UM?	***with *2xN***	***1*2xN**

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Issues (2)

- **Are designations of EM and PM inadequate?**
  - ***do we need UM and IM?***
- **What data to support genotype-phenotype correlation?**
- **How could these designations be improved?**
- **What are the definitions of EM and PM for all enzymes?**
  - ***"PM" applicable to all enzymes? CYP2C9?***

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Issues (3)

• **What alleles need to be assessed before declaring a specific genotypes?**

- Can we extrapolate data from one ethnic/race group to the other?

CYP2C9

	Caucasian	*Asian*	*African American*	*Hispanic*
***2**	**8-19**	**0**	**3.2**	**12**
***3**	**3.3-16**	**1.1-3.3**	**1.3**	**3.4**
***5**	**--**	**--**	**0.2-1.7**	**0-0.5**
***6**	**--**	**--**	**0.6-1.5**	**----**

< Data from Xie HG, et al, Advanced Drug Delivery Reviews 54 (2002) and references therein>

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Issues (4)

•**What information (PM, EM/others and specific alleles) is to be included in the drug label?**

• **To what extent should the test be commercially available?**

• **Why should the test be approved by the FDA to be in the labeling?**

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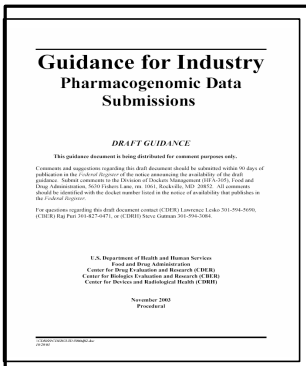

Guidance for Industry
Pharmacogenomic Data Submissions

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Lawrence Lesko 301-594-5650, (CBER) Raj Puri 301-827-0471, or (CDRH) Steve Gutman 301-594-3084.

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
Procedural

Known *valid biomarker*

…..CYP2D6 and TPMT (thiopurine methyltransferase)

< Guidance for Industry: Pharmacogenomic Data Submission:; >
< http://www.fda.gov/cder/guidance/index.htm procedural (draft), November 2003; >

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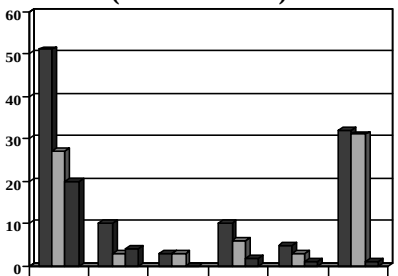
IND/NDA Reviews (70 submissions)



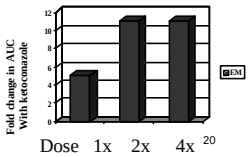
	2D6	2C19	2C9	3A	1A2	Others
Total	51	10	3	10	5	32
Genotyping	27	3	3	6	3	31
Phenotyping	20	4	0	2	1	1

Others: P -gp, transferase & others

<Chou W, Huang, S-M, Sahajwalla C, Lesko, LJ, presented at the ASCPT meeting, April 2003>

Case 1
Drug A (NDA)

- *metabolized by CYP3A/CYP2D6*
- *PM 2-3 fold higher AUC than EM (high variability)*
  - *PM/EM determination*
    - *earlier studies: *3, *4*
    - *later studies: *3, *4, *5, *6, *10, *16, (*17)*
- *possible reduced CYP2D6 contribution at higher doses*



Case 1 (2)
Drug A

- **Based on PK and clinical data: the sponsor *suggested no special dosing requirement for PM***
- ***How critical is the accuracy in the PM and EM designation in evaluating these data?***
  - *Alleles analyzed are limited and differ among studies*
  - *Data analysis grouped based on EM and PM only*
  - *Labeling mentions and makes recommendations based only EM and PM*

Case 2
Drug B (IND)

- ***Metabolized by CYP2C9***
- **the sponsor is conducting a drug interaction study with a CYP2C9 inhibitor, fluconazole**
- **Planning on retrospective CYP2C9 genotyping to identify impact on exposure of Drug B with fluconazole**
- ***What alleles should be assessed in this study? Would the analysis of *2,*3,*5 (reduced activity), or *6 (null; but rare) appropriate?***

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Case 3
Drug C (IND)

- ***Inhibits CYP2C19 and CYP3A***
- **the sponsor is conducting a drug interaction study with a CYP2C19/CYP3A substrate, nelfinavir**
- **Planning on retrospective CYP2C19 genotyping to identify impact on exposure of nelfinavir with drug C**
- ***What alleles should be assessed in this study? Would the analysis of *2 and *3 appropriate?***

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Today's discussion on metabolic biomarkers

- **Known valid biomarkers**
  - **CYP2D6, CYP2C9, CYP2C19**
- **Probable valid biomarkers**
  - **UGT1A1**
- **Exploratory biomarkers**
  - **ABCB1; CYP3A4/5**
  - **Others**

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Special Considerations for Individual Metabolic Biomarkers
Chair: S.-M. Huang, FDA

CYP2D6	D. Flockhart	Indiana Univ.
CYP2C9	P. Milos	Pfizer
CYP2C19	T. Andersson	AstraZeneca
UGT1A1	Mark Ratain	Univ. Chicago
CYP3A4/5	K. Thummel	Univ. Washington
P-gp and other transporters	D. Kroetz	UCSF
Haplotype Mapping of ADME Genes	D. Goldstein	UC, London

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Discussion

- **In vitro - in vivo correlation**
- **Genotype- phenotype correlation**
- **What alleles to measure?**
- **Haplotypes?**

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Acknowledgement

OCPB Pharmacogenomics Working Group and OCPB reviewers (case examples)

A Bhattaram F Frueh S-M Huang
M-J Kim I Lee L Lesko
A Rahman K Roy A Rudman
H Sun J Wei S Yasuda
L Zhang S Nallani J Collins
P Hinderling

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