DRUG INFORMATION ASSOCIATION

42nd Annual Meeting

FDA-EMEA Joint Session on Emerging Therapies and Technologies

Philadelphia 2006

U.S. Food and Drug Administration

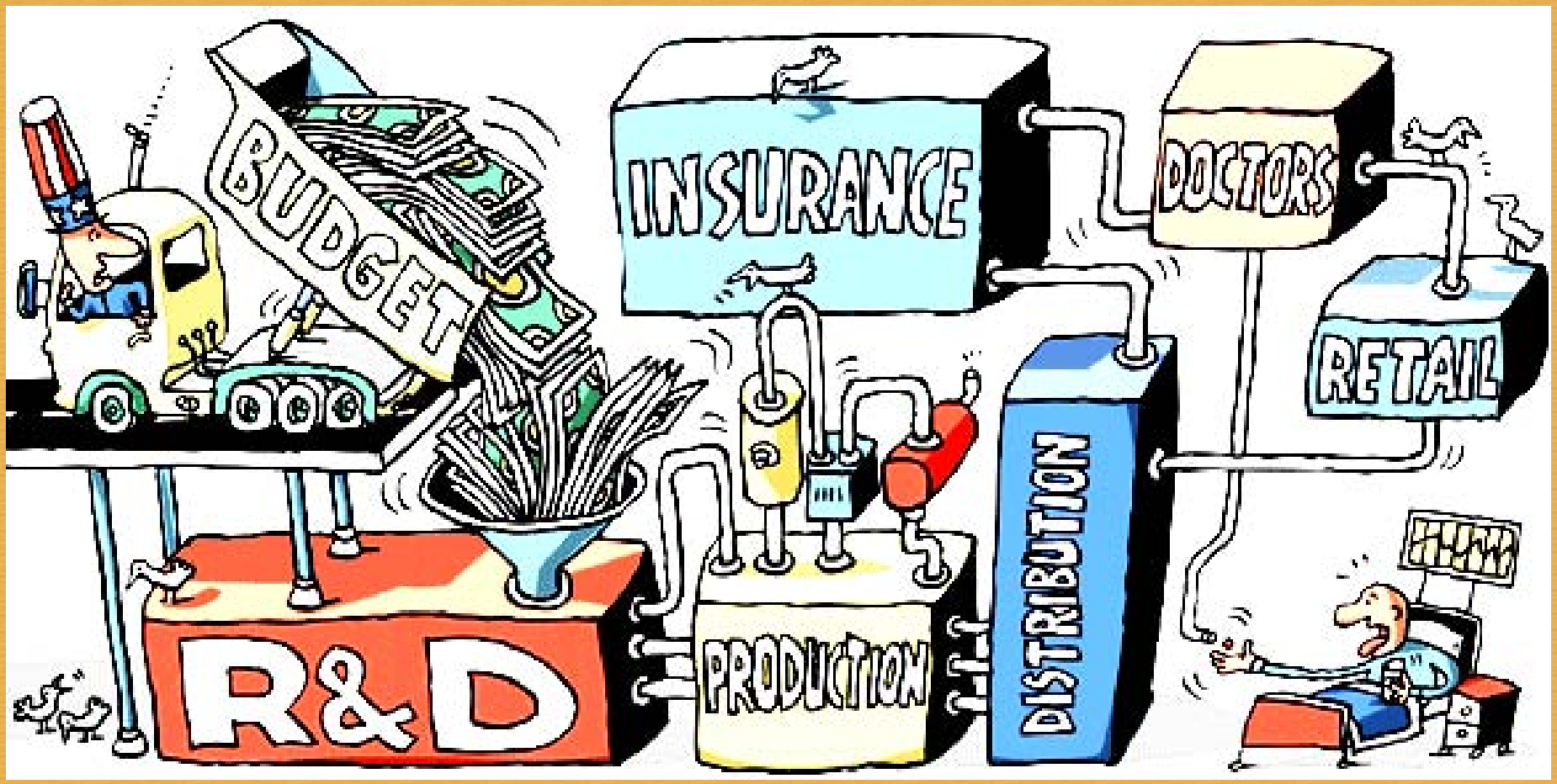
European Commission

European Medicines Agency

Agenda

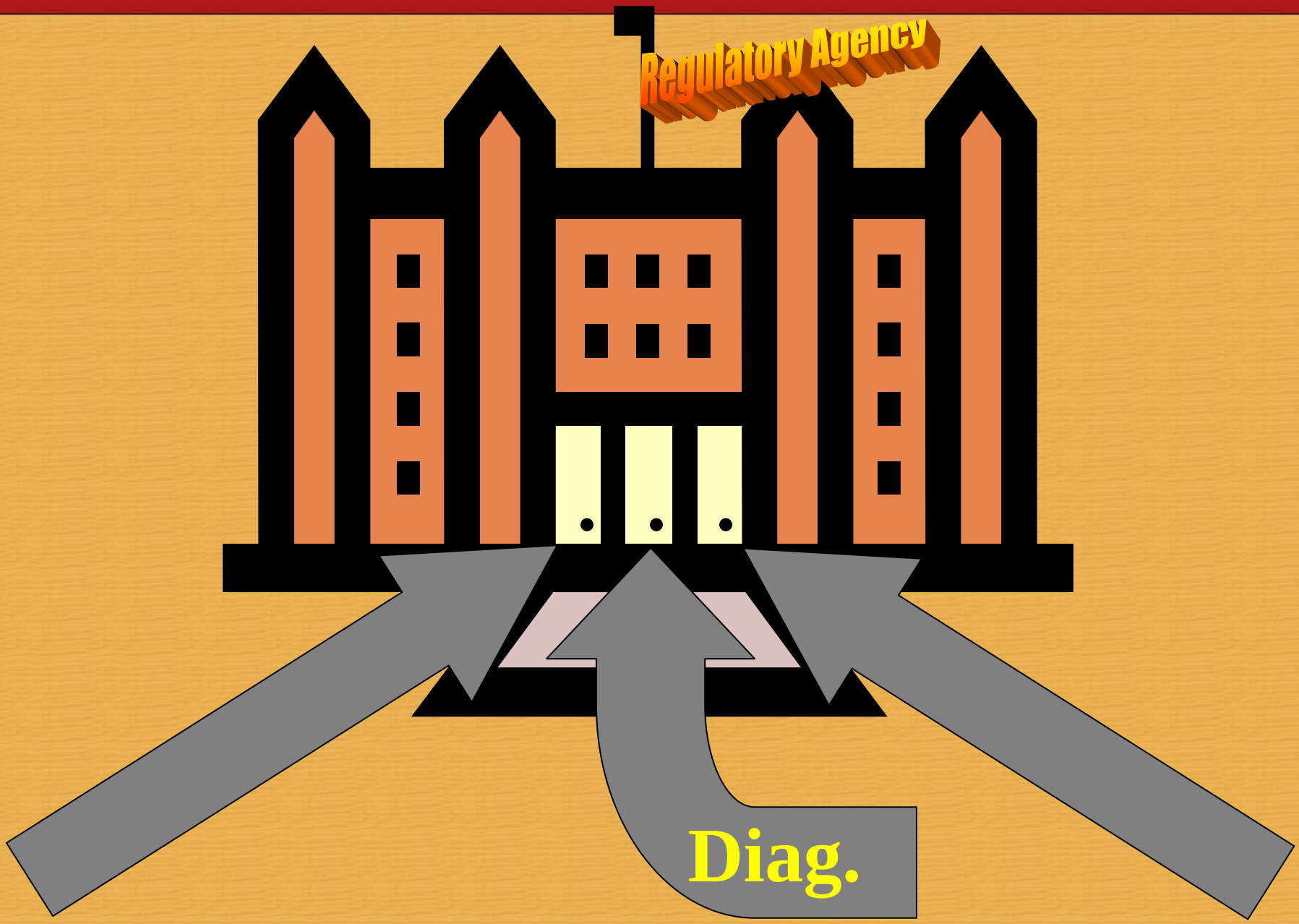
- ***Introduction:*** **Regulation vs. Innovation: can we encourage innovation through regulation? (10‘). *Federico Goodsaid, USFDA***
- **EMEA activities for emerging therapies and technologies (15‘). *Marisa Papaluca-Amati, EMEA***
- **Joint USFDA-EU Pharmacogenetics Initiatives (15‘). *Federico Goodsaid, USFDA***
- **Joint USFDA-EU Initiatives on Gene and Cell Therapy (20‘). *Klaus Cichutek, EMEA***
- **Panel discussion (25‘)**
  - ***Next Steps in Joint Pharmacogenomics Initiatives (Eric Abadie and Federico Goodsaid)***
  - ***Next Steps in Gene Therapy (Klaus Cichutek and Marisa Papaluca-Amati)***
- **Questions from the floor**
- **Concluding remarks (5‘): *Federico Goodsaid***

Drug Development 2006



Regulation vs. Innovation: *can we encourage innovation through regulation?*

- **Reguspeak (1984-George Orwell)**
  - **"It was intended that when Newspeak had been adopted once and for all and the Oldspeak forgotten, a heretical thought … should be literally unthinkable, at least so far as thought is dependent on words."**
  - **"Its vocabulary was so constructed as to give exact and often very subtle expression to every meaning that a Party member could properly wish to express, while excluding all other meanings and also the possibility of arriving at them by indirect methods."**
  - **"This was done partly by the invention of new words, but chiefly by eliminating undesirable words and by stripping such words as remained of unorthodox meanings."**


Regulatory Agency
Diag.


Regulatory Agency
Solutions

Innovation @ FDA

- **The Critical Path**
- **Pharmacogenomic Guidance**
- **Pharmacogenomic Biomarkers in the Context of Drug Labels**

Critical Path Opportunities List

U.S. Department of Health and Human Services
Food and Drug Administration

March 2006

Pharmacogenomic Guidance

Submitting data to an:	IND	New (Unapproved) NDA, BLA, or Supplement	Previously Approved NDA or BLA
Known Valid Biomarker	Must be submitted, pursuant to 21 CFR 312.23 (a) (8), (9), (10) (iv) or (11).	Must be submitted, pursuant to 21 CFR 314.50 and 601.2. See section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Probable Valid Biomarker	Does not need to be submitted if not used by the sponsor in decision making. *The FDA welcomes voluntary submission of such data in a VGDS.*	The FDA recommends submission, using algorithm in section IV.B. of the guidance.	Must be submitted pursuant to 21 CFR 314.81 in annual report and should be submitted pursuant to § 601.12 as synopses or abbreviated reports.
Exploratory or Research Pharmacogenomic Data	*The FDA welcomes voluntary submission of such data in a VGDS.*	The FDA recommends submission, using algorithm in section IV.B. of the guidance. *The FDA welcomes voluntary submission of such data in a VGDS.*	*The FDA welcomes voluntary submission of such data in a VGDS.*

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Pharmacogenomic Biomarkers in the Context of Drug Labels

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Labeling Regulations: WMD

"If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, *the labeling shall describe the evidence and identify specific tests needed for selection and monitoring of patients who need the drug."*

- 21 CFR 201.57

Pharmacogenomic Information in Drug Labels

Brand Name (generic name)	Labeling Section	Labeling Statement
HERCEPTIN® (trastuzumab) August 2002	INDICATIONS AND USAGE	HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS : HER2 Testing and CLINICAL STUDIES : HER2 Detection).
Purinethol (6-Mercapto-purine) July 2004	WARNINGS DOSAGE and ADMINISTRATIONS	Individuals who are homozygous for an inherited defect in the TPMT (thiopurine-S-methyltransferase) gene may be unusually sensitive to the myelosuppressive effects of mercaptopurine and prone to developing rapid bone marrow suppression following the initiation of treatment. …….. (see DOSAGE AND ADMINITRATION). Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe PURINETHOL toxicity from conventional doses of mercaptopurine and generally require substantial dose reduction. The optimal starting dose for homozygous deficient patients has not been established (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS sections)

Turning the Table Around

Table of Known Biomarkers in the Context of Approved Drug Labels
Updated April 2006

Biomarker	*Label Context*			*Other Drugs Associated with this Biomarker*	*References*
	Representative Label	**Test***	**Drug**		
C-KIT expression	**Gastrointestinal stromal tumor *c-Kit* expression** "*In vitro*, imatinib inhibits proliferation and induces apoptosis in gastro-intestinal stromal tumor (GIST) cells, which express an activating c-kit mutation." "Gleevec is also indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)."	**3**	Imatinib mesylate		PMID: 12851888; PMID: 16226710 PMID: 16294026
CYP2C19 Variants	**CYP2C19 Variants (Poor Metabolizers-PM and Extensive Metabolizers-EM) with genetic defect leads to change in drug exposure.** "*In vivo* studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUCτ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous	**3**	Voriconazole	Omeprazole[1] Pantoprazole[2] Esomeprazole[3] diazepam[4] Nelfinavir[5] Rabeprazole[6]	PMID: 12867215 PMID: 11866669

Comment [m1]: "Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P450 system (eg, cyclosporine, disulfiram, benzodiazepines). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with PRILOSEC."

Comment [m2]: "The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic ...

Comment [m3]: "The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in t...

Comment [m4]: "The metabolism of diazepam is primarily hepatic and involves demethylation (involving primarily CYP2C19 and CYP3A4) and 3-hydroxylation (involving primarily CYP3A4), followed by glucuronidation. The marked inter-individual variability in the clearance of diazepam reported in t...

Comment [m5]: "In vitro, multiple cytochrome P-450 enzymes including CYP3A and CYP2C19 are responsible for metabolism of nelfinavir. CYP2C19 may decrease nelfinavir plasma concentrations and reduce its therapeutic effect. Nelfinavir is metabolized by CYP3A and CYP2C19. Coadministrat...

Comment [m6]: "In a clinical study in Japan evaluating rabeprazole in patients categorized by CYP2C19 genotype (n=6 per genotype category), gastric acid suppression was higher in poor metabolizers as compared to extensive metabolizers."

Turning the Table Around: *Label Context*

	extensive metabolizer counterparts."				
CYP2C19 Variants with alternate Context	**CYP2C19 Variants, drug exposure interactions and metabolism-** Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes. Studies have shown that lansoprazole does not have clinically significant interactions with other drugs metabolized by the cytochrome P450 system. Because of the small magnitude and the direction of the effect on theophylline clearance, this interaction is unlikely to be of clinical concern. Nonetheless, individual patients may require additional titration of their theophylline dosage when lansoprazole is started or stopped to ensure clinically effective blood levels	3	Lansoprazole	Amoxicillin,Clarithromycin, Lansoprazole;[7] Lansoprazole and Naproxen[8] Proguanil+Atovaquone[9] Delavirdine[10]	PMID: 12680476 PMID: 12495367 PMID: 12809821; PMID: 16413249; PMID: 16413245 PMID: 15871633; PMID: 15496214 PMID: 14664653
CYP2C9 Variants	**CYP2C9 Variants PM and EM genotypes and drug exposure**; "Patients who are known or suspected to be P450 2C9 poor metabolizers based on a previous history should be administered celecoxib with caution as they may have abnormally high plasma levels due to reduced metabolic clearance."	Primary Context		Warfarin[11]	PMID: 16118328 PMID: 15637526 PMID: 15714076 PMID: 15037866 PMID: 14558433
CYP2C9 Variants with alternate Context	**CYP2C9 variants, metabolism and drug interactions-** "Fenofibrate is weak inhibitors of CYP2C19 and CYP2A6, and mild-to-moderate inhibitors of CYP2C9 at therapeutic concentrations."	Secondary Context		Bosentan;[12] Fluvastatin[13]	PMID: 12481201 PMID: 9515185 PMID: 16132947
CYP2D6 Variants	**CYP2D6 PM and EM Variants and drug exposure and risk-** "population, who are known to have a genetic defect leading to reduced levels of activity of P450 2D6. Fluoxetine, like other agents that are metabolized by P450IID6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble "poor metabolizers." Therapy with medications that are predominantly metabolized by	3	Fluoxetine HCL	Fluoxetine HCL and Olanzapine;[14] Cevimeline hydrochloride;[15] Tolterodine;[16] Terbinafine;[17] Tramadol +	PMID: 16472103 PMID: 16384813; PMID: 15063083; PMID: 16271013 PMID: 16236141 PMID: 15828850 PMID: 15492763 PMID: 15037866 PMID: 14639062

Comment [m7]: "PREVACID is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes."

Comment [m8]: "Lansoprazole is metabolized through the cytochrome P450 system, specifically through the CYP3A and CYP2C19 isozymes."

Comment [m9]: "Proguanil is metabolized to cycloguanil (primarily via CYP2C19) and 4-chlorophenylbiguanide. Proguanil is metabolized primarily by CYP2C19. Potential pharmacokinetic interactions with other substrates or inhibitors of this pathway are unknown."

Comment [m10]: "Delavirdine is an inhibitor of CYP3A isoform and other CYP isoforms to a lesser extent including CYP2C9, CYP2D6, and CYP2C19."

Comment [m11]: "The cytochrome P- 450 isozymes involved in the metabolism of warfarin include 2C9, 2C19, 2C8, 2C18, 1A2, and 3A4. 2C9 is likely to be the principal form of huma..."

Comment [m12]: "Bosentan is an inducer of CYP2C9 and CYP3A4 and possibly also of CYP2C19. Co-administration of such combinations o..."

Comment [m13]: "In vitro data indicate that fluvastatin metabolism involves multiple Cytochrome P450 (CYP) isozymes. CYP2C9 is one me..."

Comment [m14]: "Direct glucuronidation and CYP450-mediated oxidation are the primary metabolic pathways for olanzapine. In vitro studi..."

Comment [m15]: "ISOZYMES CYP2D6 AND CYP3A3/4 ARE RESPONSIBLE FOR THE METABOLISM OF CEVIMELINE. ..."

Comment [m16]: "The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) ..."

Comment [m17]: "In vivo studies have shown that terbinafine is an inhibitor of the CYP450 2D6 isozyme."

Logic of a Predictive Safety Testing Consortium