The Role of Clinical Pharmacology in Risk-Benefit Assessment of New Drugs

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Office of Clinical Pharmacology
OTS, CDER, FDA
NME approvals
US, EU and Japan

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FDA and Regulatory Science

- Adaptive licensing (MIT Center for Biomedical Innovation report)
- Analysis of FDA review division performance (Tufts Center for the Study of Drug Development)
- Development of biosimilars
- Nine papers from the FDA

http://www.nature.com/clpt/journal/v91/n3/index.html
FDA on Innovation

Our job is to enable innovation – but without sacrificing our high standards for ensuring safe, effective and high quality products

Margaret Hamburg, NEHI conference on Bridging the Innovation Gap, Boston, April 26, 2012
Question-Based Review (QBR)¹

• What clinical situations alter the exposure-response of the drug and can we ensure safety and efficacy in intended patient population by adjustment of the dosing regimen?

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Impact of Extrinsic Factors

- What *extrinsic factors* (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response?
- What is the impact of any differences in exposure on response?

![Figure 1. Impact of other drugs on Vilazodone PK](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf)
Impact of Intrinsic Factors

• What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and
• What is the impact of any differences in exposure on efficacy or safety responses?

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022567s000lbl.pdf
Question-Based Review (QBR)

- What is the systemic exposure-response relationship of the drug for safety/efficacy?
Clinical Pharmacology Development Plan

Pre-IND ➔ Phase 1 ➔ Phase 2 ➔ Phase 3 ➔ NDA

1st in Man PK/PD dose escalation

Mass Balance

Food Effects

PK/PD in patient population

DDI

Hepatic Impairment

Renal Impairment

Bio Equivalence

Metabolism/Transport

CYP 450 Screening

Analytical Methods

Pharmacogenomics

QTc

PMR/PMC

Courtesy: Atik Rahman
Some products may require additional disciplines such as microbiology and virology.
Safety-Related Labeling Changes
(changes made Oct 2002-Aug 2005, n=2645 label changes for 1601 NDA/BLA entries)

Clopidogrel**
Simvastatin*

Black Box Warnings
Warnings
Precautions
Contraindications
Adverse Reactions
1. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, according to SLC01B1 rs4149056 Genotype (c.521T>C)
2. Association replicated in another 40 mg group
Electronic prescription for simvastatin

- **80 mg daily**
  - FDA recommends against 80 mg dose unless patient has tolerated > 12 mo (unless normal CK and no myalgias)

- **40 mg daily**
  - FDA recommends against 40 mg dose if the patient is also using any of these: amiodarone,amlodipine,ranolazine

- **20 mg daily**
  - FDA recommends against 20 mg dose if the patient is also using any of these: verapamil,diltiazem

**TT**
- Proceed based upon clinic

**TC**
- WARNING: genetic testing indicates this patient is at increased risk of myopathy with 40 mg simvastatin
- OR (at 80 mg) 4.5
- Lower dose
  - 20 mg simvastatin + monitor serial CK (Consider lipid clinic)

**CC**
- OR (at 80 mg) 20
- Alternative statin
  - Choice #1
  - Choice #2
  - Choice #3

PREDICT (Pharmacogenomics Resource for Enhanced Decisions in Clinical Care and Treatment) decision support algorithm for simvastatin.

Algorithm activated by provider selection of any simvastatin dose during the process of electronic prescribing at Vanderbilt University Medical Center. CK, creatine kinase.
Selected transporters for endogenous compounds and xenobiotics, expressed on the sinusoidal and canalicular membranes of human hepatocytes.

BSEP, bile salt export pump; MATE1, multidrug and toxin extrusion protein 1; MRP, Multiple drug resistance protein; OAT, organic anion transporter; OCT, organic cation transporter; OSTa-OSTb, heteromeric organic solute transporter.

Application of PBPK - Pravastatin -

**Plasma**

- PSinf
- OATP1B1
- PSbile
- MRP2
- PSeff

**Liver**

- OATP1B1
- MRP2

**Sensitivity Analysis**

- : × 3
- : × 1
- : × 1/3

**Courtesies of Dr. Yuichi Sugiyama**

Watanabe T, et al, JPET, 328:652, 2009
Inherited polymorphisms related to statin pharmacokinetics and endocytosis of LDL particles by the LDL receptor are common in the general population and influence individual patient response to statin therapy.

- 6989 Europeans
- 20 mg vs placebo

Chronology of Clopidogrel-CYP2C19 Pharmacogenetic Studies

- CYP1A metabolism (1994)
- CYP3A metabolism (1994)
- PLAVIX Approved
- All CYP metabolism
- HULOT PD
- 1997
- 2003
- 2005
- 2006
- 2007
- 2008
- 2009

- PK (AM; N=4)
- PD (N=28)
- Outcomes (N=10)

Modified from Pacanowski, M. ACC.11, April 3, 2011
Roles in Clopidogrel Activity of Proteins with Known Genetic Polymorphisms

A Pharmacokinetic Response

<table>
<thead>
<tr>
<th>Gene</th>
<th>Percent Difference in AUC₀₋ₜ</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-32.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-6.8</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-15.7</td>
<td>0.03</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>5.6</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>11.2</td>
<td>0.45</td>
</tr>
</tbody>
</table>

B Pharmacodynamic Response

<table>
<thead>
<tr>
<th>Gene</th>
<th>Absolute Difference in ∆MPA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-9.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-0.6</td>
<td>0.86</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-5.7</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>7.5</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>0.5</td>
<td>0.90</td>
</tr>
</tbody>
</table>

CYP2C19 and Clopidogrel

Composite Clinical Outcome*

Carriers

Non-Carriers

Active Metabolite AUC

Carriers: with at least one variant alleles, *2, 3, 4, 5, 8 (IM+PM);
Outcome: a composite of death from cardiovascular causes, myocardial infarction, or stroke

Another study also examined MDR1

March 2010 Relabeling

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

• Effectiveness of Plavix depends on activation ... by .... CYP2C19
• Poor metabolizers ..... exhibit higher cardiovascular event rates following ... acute coronary syndrome (ACS). or ... percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
• Tests are available to identify .. CYP2C19 genotype ...
• Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

WARNINGS AND PRECAUTIONS

• Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole)

Drugs at the FDA (Plavix, “HIGHLIGHTS”)
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/
Algorithm for suggested clinical actions based on CYP2C19 genotype when considering treatment with clopidogrel for ACS patients undergoing PCI (ACS/PCI).

ACS: acute coronary syndrome; PCI: percutaneous coronary intervention;

UM: ultrarapid metabolizer; EM: extensive metabolizer; IM: intermediate metabolizer; PM: poor metabolizer

May 2013 online: doi:10.1038/clpt.2013.105
### Examples of FDA Labeling with Pharmacogenetic-Related Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene</th>
<th>Context</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>HLA-B</td>
<td>Boxed warning that patients with the HLA-B*5701 allele are at increased risk for hypersensitivity to abacavir. Genetic screening is recommended before starting abacavir.</td>
</tr>
<tr>
<td>Azathioprine and 6-mercaptopurine</td>
<td>TPMT</td>
<td>Description of increased risk for myelotoxicity with conventional azathioprine or 6-mercaptopurine doses in patients with a nonfunctional TPMT allele in the clinical pharmacology section. Consideration of TPMT genetic testing is recommended.</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>CYP2D6</td>
<td>Warning that dose adjustment may be necessary in CYP2D6 poor metabolizers to avoid adverse drug effects.</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>DPD</td>
<td>Warning about an increased risk for severe toxicity (e.g. diarrhea, stomatitis, neutropenia, and neurotoxicity) in patients with dihydropyrimidine dehydrogenase deficiency.</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B</td>
<td>Boxed warning of increased risk for serious dermatologic reactions (e.g. toxic epidermal necrolysis, Stevens-Johnson syndrome) in patients with the HLA-B<em>1502 variant. Patients from genetically at-risk regions (e.g. Southeast Asia) should be screened for the HLA-B</em>1502 allele prior to starting carbamazepine.</td>
</tr>
<tr>
<td>Cetuximab and Panitumumab</td>
<td>EGRF, KRAS</td>
<td>These drugs are indicated for EGRF-expressing colorectal cancer and may be ineffective in patients whose tumors have a KRAS mutation in codon 12 or 13.</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Warning about greater conversion to morphine and higher than expected morphine concentrations in patients who are ultra-rapid metabolorizers secondary to the CYP2D6<em>2x</em>2 genotype. These individuals are at increased risk for symptoms of overdose (e.g. extreme sleepiness, confusion, respiratory depression) with conventional doses of codeine.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>Boxed warning of possible reduced drug effectiveness in CYP2C19 poor metabolizers with 2 loss-of-function alleles.</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK</td>
<td>Confirmation of the lymphoma kinase (ALK)-positive mutation is required using an FDA-approved test prior to drug use. A clinical trial to explore responses in ALK-negative patients is being conducted post-marketing.</td>
</tr>
</tbody>
</table>

Disease-drug-trial models are mathematical representations of the time course of biomarker-clinical outcomes, placebo effects, drug’s pharmacologic effects and trial execution characteristics for both the desired and undesired responses, and across experiments.
Annualized Relapse Rates and Dose

Fingolimod (Gilenya) for multiple sclerosis (0.5 mg daily)

The similarity in effectiveness of 0.5 and 1.25 mg doses suggests that a lower dose might be as effective. The clinical findings of concern, bradycardia, liver enzyme elevation, macular edema, are clearly dose-related.

→ Postmarketing commitment to evaluate a lower dose, 0.25 mg

## Citalopram and QT

<table>
<thead>
<tr>
<th>Citalopram Dose</th>
<th>Increase in QT Interval (ms)</th>
<th>90% Confidence Interval (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg/day</td>
<td>8.5</td>
<td>(6.2, 10.8)</td>
</tr>
<tr>
<td>60 mg/day</td>
<td>18.5</td>
<td>(16.0, 21.0)</td>
</tr>
<tr>
<td>40 mg/day</td>
<td>12.6*</td>
<td>(10.9, 14.3)*</td>
</tr>
</tbody>
</table>

*Estimate based on the relationship between blood citalopram and QT interval.

Citalopram labeling changed in August 2011 and March 2012 to include warnings about the potential QT internal prolongation and Torsade de Pointes

- Citalopram should not be dosed more than 40 mg/day
- CYP2C19 PM and patients taking CYP2C19 inhibitors-dose be capped at 20 mg/day

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Systems Biology in Drug Regulatory Research to Advance the Science of Drug Safety

- Prediction of Clinical Adverse Drug Reactions before they have been observed
- Identification of Patient subgroups particularly susceptible to ADRs
- Systems Pharmacology based mechanism to strengthen potential ADR signal

Courtesy: Darrell Abernethy
Interaction map showing $n$ number of drugs, $k$ number of proteins, $m$ number of pathways, and $h$ number of adverse drug reactions (ADRs).
Abbreviation: GI, gastrointestinal
Applications of Physiologically-Based Pharmacokinetic Modeling (PBPK)


Utility of PBPK incorporated in clinical pharmacology guidance documents
Application of PBPK Modeling

The degree of complexity of the PBPK model can vary according to the need.

Huang, S-M, PBPK as a Tool in Regulatory Review. Biopharm Drug Disp, 2012


Regulatory Submissions with PBPK Data

Area of applications in the 33 PBPK submissions in IND/NDA received by FDA’s Office of Clinical Pharmacology from 2008-12

Huang, Abernethy, Wang, Zhao, Zineh, J Pharm Sci September 2013
Regulatory Submissions with PBPK Data (2)

Number of PBPK applications contained in the IND/NDA submissions or developed by FDA’s Office of Clinical Pharmacology reviewers from 2008 to 2012.
Fesoterodine (CYP2D6 & CYP3A)

<table>
<thead>
<tr>
<th>PM + Keto (n=6)</th>
<th>PM (n=8)</th>
<th>EM + Keto (n=11)</th>
<th>EM (n=11)</th>
</tr>
</thead>
</table>


<table>
<thead>
<tr>
<th>AUCR of 5-HMT</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM with/without ketoconazole</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>PM with/without ketoconazole</td>
<td>2.5</td>
<td>3.3</td>
</tr>
<tr>
<td>PM / EM</td>
<td>2.3</td>
<td>1.6</td>
</tr>
<tr>
<td>PM with ketoconazole / EM without ketoconazole</td>
<td>5.7</td>
<td>5.4</td>
</tr>
<tr>
<td>EM with/without fluconazole</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>PM with/without fluconazole</td>
<td>-</td>
<td>1.5</td>
</tr>
<tr>
<td>PM with fluconazole/EM without fluconazole</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

Vieria, MLT, et al, ASCPT Annual Meeting, National Harbor, MD, March 2012; manuscript in preparation
Fesoterodine Labeling

• “The recommended starting dose is 4 mg once daily...the dose may be increased to **8 mg**...”

• “…the recommended fesoterodine daily dose should **not exceed 4 mg** when taken with a potent CYP3A inhibitor, such as ketoconazole, itraconazole and clarithromycin…”

• “…there is no clinically relevant effect of moderate CYP3A inhibitors on the pharmacokinetics of fesoterodine…”

FDA labeling-Toviaz (fesoterodine fumarate) for oral administration. August 2012.

[Link to FDA labeling](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022030s009lbl.pdf)
Consequences of Renal Impairment on Drug Disposition

- Decreased hepatic uptake and metabolism:
  - OATP, CYPs, and NATs downregulation
- Increased biliary excretion (possible):
  - Upregulation of efflux transporter (P-gp)
- Increased bioavailability:
  - Downregulation of CYPs
  - Downregulation of efflux transporters (P-gp, MRP)
- Decreased renal excretion:
  - Decreased glomerular filtration
  - Decreased tubular secretion
- Accumulation of uremic toxins

→ Affects both metabolism and transport

Table 1. Comparative systemic exposure and corresponding starting (and maintenance) dose recommendation in subgroups with various renal impairment (Data compiled from the FDA drugs@fda website (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/))

<table>
<thead>
<tr>
<th>ADME a</th>
<th>Renal Function (mL/min) b</th>
<th>Fold-Change in exposure (AUC)</th>
<th>Initial Dose</th>
<th>Daily Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>paliperidone</td>
<td>fe=60%</td>
<td>Clcr &gt; 80 Clcr 50-80 Clcr 10-50 Clcr 10-50</td>
<td>1-fold(control) 1.5-fold (mild) 2.6-fold (moderate) 4.8-fold (severe)</td>
<td>6 mg 3 mg 1.5 mg 1.5 mg</td>
</tr>
<tr>
<td>telbivudine</td>
<td>fe=40%</td>
<td>Clcr &gt; 50 Clcr 30-49 Clcr &lt;30 ESRD</td>
<td>1-fold (control) 1.9-fold (moderate) 3.4-fold (severe) 7-fold (ESRD)</td>
<td>10-20 mg 10-20 mg 5 mg</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>fe=6%  F=20%</td>
<td>Clcr &gt; 80 d Clcr &gt;30 Clcr &gt;30 Clcr &lt;30</td>
<td>1-fold (control) 1-fold (mild) 1-fold (moderate) 3-fold (severe)</td>
<td>10-20 mg 10-20 mg 5 mg</td>
</tr>
<tr>
<td>telithromycin</td>
<td>fe=13%  F=57%</td>
<td>Clcr &lt;30 Clcr&lt;30 f</td>
<td>1-fold (control) 1.9-fold (severe) 4-5 fold (severe) e</td>
<td>800 mg QD 600 mg QD 400 mg QD</td>
</tr>
</tbody>
</table>

1 fe: fraction of an oral dose excreted unchanged in the urine; F= % absolute oral bioavailability
2 Estimated by the Cockcroft-Gault equation
3: not recommended in Clcr<10
4: in mL/min/1.73M²
5: patients also taking ketoconazole
6: patients also with hepatic impairment

Renal Impairment & Drugs with Major Hepatic Elimination

<table>
<thead>
<tr>
<th>Compound (% CL by kidney)</th>
<th>Observed AUCR (Severe/Normal)</th>
<th>PBPKa Predicted AUCR (severe/Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil (&lt;1%)</td>
<td>2.0b</td>
<td>2.2</td>
</tr>
<tr>
<td>Repaglinide (&lt;1%)</td>
<td>SD: 2.7 MD: 3.0c</td>
<td>SD: 2.5 MD: 2.3</td>
</tr>
<tr>
<td>Telithromycin (~20%)</td>
<td>1.9d</td>
<td>1.6</td>
</tr>
</tbody>
</table>


Repaglinide

\[ \text{CL}_H = \text{CL}_{\text{CYP2C8}} + \text{CL}_{\text{CYP3A}} \]

\( \cdot \sim 38 \, \text{L/h} (\geq 99\% \text{ CL}) \)

\( \cdot \) CYP3A4:CYP2C8 50%:50%

\( \cdot \) CL\text{uptake} mainly by OATP1B1

\[ \text{Hepatocytes} \]

\[ \text{Sinusoid} \]

\[ \text{Free drug} \]

\[ \text{CL}_{\text{int, met}} \]

\[ \text{Hepatocytes} \]

\[ \text{CL}_R < 1\% \text{ CL} \]

<table>
<thead>
<tr>
<th>Assumption on ( \text{PS}_{\text{inf,OATP1B1}} )</th>
<th>Repaglinide AUC Ratio in Severe Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Observed</strong></td>
<td><strong>Single dose</strong></td>
</tr>
<tr>
<td>Predicted</td>
<td>2.7</td>
</tr>
<tr>
<td>Predicted</td>
<td>No change</td>
</tr>
<tr>
<td>Predicted</td>
<td>▼ 52%</td>
</tr>
</tbody>
</table>


\( \rightarrow \) Hepatic uptake (OATP) is likely to be affected by renal impairment

International Transporter Consortium

- First workshop in October 2008; whitepaper published in NRDD, March 2010 (Giacomini et al)
- Second workshop in March 2012
- Whitepapers in July 2013 CPT
- Expand to include other regulatory agencies

Huang S-M, Zhang L, Giacomini K, Clin Pharmacol Ther 2010
**Red**: Critical transporter proteins to evaluate prospectively

**Green**: Additional ones to evaluate prospectively

**Yellow**: Retrospective evaluation

**Blue**: Additional transporters


In Vitro Model (OATP1B1/1B3 Inhibitors)

- Is the \( IC_{50} \) of the NME \( \leq 10 \) times \( unbound \ C_{\text{max}} \)?
  - Yes
    - Is the AUC or \( C_{\text{max}} \) of statin (for example, rosuvastatin, pravastatin, pitavastatin) predicted to increase > 2-fold in presence of the NME using extrapolation (for example, \( R \) value > 2)?
      - Yes
        - Clinical DDI study with sensitive substrate (for example, rosuvastatin, pravastatin, pitavastatin)
      - No
        - Clinical study may not be needed
    - No
      - NME probably not an in vivo inhibitor of OATP

Development of a Drug Transporter Database: UCSF-FDA TransPortal

Kari M. Morrissey, Chris Wen, Susan J. Johns, Shiew-Mei Huang, Lei Zhang, Kathleen M. Giacomini

1 Department of Bioengineering and Therapeutic Sciences and 2 Pharmaceutical Chemistry, University of California, San Francisco, CA
2 Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

ABSTRACT

Drug transporters are key determinants of absorption, distribution and elimination of many drugs and appear to play important roles in therapeutic and adverse drug effects. Though a large body of data are available on drug transporters, there are few databases that inform drug developers, regulatory agencies and academic scientists about transporters important in drug action and disposition. We have selected 31 drug transporters from the ATP-Binding Cassette (ABC) and Solute Carrier (SLC) transporter superfamilies and compiled primary literature from their expression levels, subcellular localization, inhibitors, substrates and clinical drug-drug interactions. This project is supported by the FDA Critical Path to build a public drug transporter database to serve as a central resource for information needed by the scientific community on important drug transporters.

DATABASE SCREENSHOTS

Drug Transporters in Selected Organs & Direction of Transport

Blood-Brain Barrier

Liver

Small Intestine

Kidney

Expression Data

Kidney - RNA-Sequencing

Kidney - Quantitative PCR

REFERENCES

2. Nishimura M, Naito S. Drug Metab Pharmocokinet. 2006 Dec;21(6):527-77

http://bts.ucsf.edu/fdatransporter/


Clin Pharmacol Ther, Nov 2012
FDA Expedites Drug Review

Fast Track
• Codified in 2007. facilitate the development and expedite the review of drugs to treat serious or life-threatening diseases that will fill an unmet medical need (AIDS, Alzheimer’s disease, cancer, epilepsy, diabetes)
• Early and frequent communications; “rolling review”

Priority Review
• PDUFA 1992; two-tiered system (priority and standard).
• Major advancement in treatment

Accelerated Approval
• Created in 1992; for drugs that treat serious or life-threatening diseases that will fill an unmet medical need, based on a surrogate endpoint

Flexible Clinical Development Program
• Approval of drugs for serious diseases without satisfactory alternatives on the basis of non-traditional clinical trial designs

Breakthrough Therapies
• New tools under FDASIA - drugs for serious and life-threatening disease and preliminary clinical evidence shows the drug may offer substantial improvement over existing therapies
FY2012 Innovative Drug Approvals

Thirty-Five (35) New Molecular Entities approved in FY 2012
• 77% approved on the first cycle
• 97% met PDUFA goal date
• 75% first approved in the US
• include nine (9) for orphan diseases (see below)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Approval Date</th>
<th>Indication</th>
<th>Orphan Drug</th>
<th>Approved First in U.S.</th>
<th>Approved 1st Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERWINAZE (asparaginase erwinia chrysanthemi)</td>
<td>11/18/11</td>
<td>For patients with acute lymphoblastic leukemia (ALL) and allergy to E. coli-derived asparaginase and pegasparagase chemotherapy drugs</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>JAKAFI (ruxolitinib)</td>
<td>11/16/11</td>
<td>For the bone marrow disease myelofibrosis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>KALYDECO (ivacaftor)</td>
<td>11/31/11</td>
<td>For cystic fibrosis patients with G551D mutation</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>VORAXAZE (glucarpidase)</td>
<td>1/17/12</td>
<td>To treat toxic methotrexate concentrations in plasma of patients receiving chemotherapy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>BOSULIF (bosutinib)</td>
<td>9/4/12</td>
<td>For chronic myelogenous leukemia (cml)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>EIEIYSO (taliglucerase alfa)</td>
<td>5/1/12</td>
<td>For type-1 gaucher disease, a rare genetic disorder</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FERRIPROX (deferiprone)</td>
<td>10/14/11</td>
<td>For iron overload in patients with thalassemia (a genetic disorder causing anemia)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>KYPROLIS (carfilzomib)</td>
<td>7/20/12</td>
<td>For multiple myeloma</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ONFI (clobazam)</td>
<td>10/21/11</td>
<td>For seizures associated with Lennox-Gastaux syndrome</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

[Link to the FDA report](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM330859.pdf)
Summary

• During drug development, a range of doses needs to be evaluated and the exposure-response relationships be assessed to make informed benefit-risk evaluation.

• Once a safe and effective population dose (doses) has been defined, individual patient doses can be adjusted based on patient-specific factors (genetics, organ functions, concomitant medications)
• Advancement in clinical pharmacology and quantitative modeling and simulation have resulted in increasing use of more mechanistic, model-based approaches in the determination of the “right” dose for patients (including those with rare diseases) with multiple patient factors in drug development

• Collaborations is key to future success
Office of Clinical Pharmacology (OCP)/OTS

FDA White Oak

Bldg 51—Where OCP resides
References

FDA Drug Development and Drug Interactions Website;

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Clinical Pharmacology Guidance for industry:
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