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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"

A treatment with a 10% advantage over a comparator could still be the wrong drug for many people. And a drug with a severe side effect may be the best treatment for people who are not at risk for that problem.

Janet Woodcock

Our ongoing assessment of the drug and medical product safety system has affirmed that it is essential that our processes and scientific methods keep pace with the rapid evolution of science, technology and the health care system.

Andrew C von Eschenbach
Commissioner, Food and Drug Administration
January 30, 2007


- 35 submissions received
- 25 sponsor meetings held (2 bilateral with EMEA)
- Cancer (multiple types)
- Alzheimer's Disease
- Hypertension
- Hypoglycemia
- Depression
- Obesity
- Rheumatoid Arthritis

Required Submissions

Critical Path Opportunities

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into 21st century
- Developing Products to Address Urgent Public Health Needs
- Specific At-Risk Populations--Pediatrics

March 2006

Guidance for Industry
Pharmacoepidemiologic Data Submissions

Voluntary Submissions
FDA Critical Path Initiatives: Opportunities in Drug Development, Regulatory Review & Clinical Practice

VGDS Recent Discussion Examples

- Biomarker selection
- Novel clinical trial design
- Labeling language
- Others

Drug-Test Co-Development Process: Formal Industry - FDA Interactions

Preclinical Development

Drug Development

Device/Test Development

VGDS Recent Discussion Examples

- Biomarker selection
- Novel clinical trial design
- Labeling language
- Others

Biomarker Qualification

- Develop conceptual framework
  Reach general consensus on amount/type of data needed for various uses - FDA guidance
- Develop consortia for qualification of specific biomarkers
  - OBQI (Oncology Biomarker Qualification Initiative)
  - Predictive Safety Test Consortium
  - The Biomarkers Consortium
  - Serious Adverse Events Consortium
- Exploratory Biomarker Qualification Process Pilot

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

- Metabolism, transport, drug-interaction info key to benefit/risk assessment
- Integrated approach (in vitro and in vivo) may reduce number of unnecessary studies and optimize knowledge

Shiew-Mei Huang, PhD, AAPS Annual meeting, Hot Topic Discussion, November 14, 2007, San Diego, CA
**What's New?**

- In vitro models to determine whether in vivo evaluation is needed
  - CYP inhibition (additional CYPs)
  - CYP induction
  - Transporter-based interactions
- Classification of inhibitors, substrates
- Others

**DNA based biomarkers of enzyme activities considered as valid biomarkers**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Model drugs</th>
<th>Outcome measures</th>
<th>Study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>Warfarin</td>
<td>Maintenance dose</td>
<td>Patients with *2 and *3 maintained with lower doses and took longer time to reach stable dosing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time to reach stable dosing</td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Proton pump inhibitors</td>
<td>Plasma levels</td>
<td>Higher in FM (20mg) higher dose (40 mg) showed no difference</td>
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<tr>
<td></td>
<td></td>
<td>Gastric pH</td>
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<td></td>
<td></td>
<td>Gastroesophageal reflux</td>
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<tr>
<td></td>
<td></td>
<td>Disease cure rate</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Atomoxetine</td>
<td>Pharmacokinetic measure</td>
<td>FM higher AUC (10-fold)</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Urine output</td>
<td>Grade 3 neutropenia</td>
<td>UGT1A1 3/7 and 6/7 more frequent than 6/6</td>
</tr>
<tr>
<td>TPMT</td>
<td>6-MP</td>
<td>Dose-limiting hematopoietic toxicity</td>
<td>More in TPMT deficiency or heterozygosity</td>
</tr>
</tbody>
</table>

**Key Opportunity for Improving Outcomes**

- Overview
- Background Information
- Tables of Substrates, Inhibitors and Inducers
- CYP Enzymes
- In vitro
- In vivo
- Examples of in vivo Substrates, Inhibitor, and Inducers for Specific CYP Enzymes
- Classification of Inhibitors
- Classification of Substrates
- P-gp Transporters
- Major Human Transporters
- Possible Models for Decision-Making
- CYP-Based Drug-Drug Interaction Studies
- P-gp-Based Drug-Drug Interaction Studies
- Regulatory Guidance and Manual for Policies and Procedures
- Publications
- Presentations
- Advisory Committee Meetings

**Figure 1. Decision tree to determine whether an investigational drug is an inhibitor for P-gp and whether an in vivo drug interaction study with a P-gp substrate is needed**

- Bi-directional transport assay
- Net flux 1 with conc of drug
- Net flux 2 with conc of drug
- Poor or non-inhibitor
- [I]/IC50 (or Ki) > 0.1
- [I]/IC50 (or Ki) < 0.1

**FDA Internet**

- Drug Development and Drug Interactions

Launched in May 2006

- More frequent updates - tables, models for decision-making, etc
**Irinotecan (Camptosar®)**

**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).

**Warfarin (Coumadin®)**

**Effect of CYP2C9 genotype on Warfarin Maintenance Dose**

- N=185, median time = 543 days (14-4032 days)
- [+1*1: 69%, +1*2: 15%, +1*3: 2%, +2*2: 10%, +2*3: 1.6%, +3*3: 2.7%]

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

**Warfarin**

- CYP1A1
- CYP1A2
- CYP1AC
- CYP3A4
- CYP2C9

- Vitamin K oxidase
- Reduced Vitamin K
- Hypofunctional F, II, VII, IX, X
- Functional F, II, VII, IX, X
- Protein C, S, Z

- From Brian Gage; http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_02_02-Huang.ppt
- Other relevant slides: http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_Slide-Index.htm, http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4194S1_R2_Busse.ppt

- Shiew-Mei Huang, PhD, AAPS Annual meeting, Hot Topic Discussion, November 14, 2007, San Diego, CA
FDA Critical Path Initiatives: Opportunities in Drug Development, Regulatory Review & Clinical Practice

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

- Within a CYP2C9 genotypes, further differentiation among VKORC1 genotypes

Predicting the Warfarin Stable Dose

- Age, Gender, Drugs, BW, Race, Diet
- Others

FDA Approves Updated Warfarin (Coumadin) Prescribing Information

New Genetic Information May Help Providers Improve Initial Dosing Estimates of the Anticoagulant for Individual Patients

The labeling change highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. Testing may help optimize the use of warfarin and lower the risk of bleeding.

FDA Clears Genetic Lab Test for Warfarin Sensitivity

The U.S. Food and Drug Administration today cleared for marketing a new genetic test that will help physicians assess whether a patient may be especially sensitive to the blood-thinning drug warfarin (Coumadin), which is used to prevent potentially fatal blood clots in blood vessels. One-third of patients receiving warfarin metabolize it quite differently than expected and experience a higher risk of bleeding. Research has shown that some of the unexpected response to warfarin depends on variants of two genes, CYP2C9 and VKORC1. The Nanosphere Verigene Warfarin Metabolism Nucleic Acid Test detects some variants of both genes.

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PDUFA IV Negotiated Deliverables - Responsibility of Office of Biostatistics

- Three guidances with substantial scientific and biostatistical content
  - Non-Inferiority study design and analysis
  - Adaptive Clinical Trial Designs
  - Multiple endpoints in clinical trials
- Consensus building - possible guidance
  - Missing data in clinical trials

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March 2006

Pharmacometric analysis


Model-based analysis

- Trileptal case

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<tr>
<th>Adults</th>
<th>Adjunctive</th>
<th>Monotherapy</th>
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<tbody>
<tr>
<td></td>
<td>Clinical trials</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Children (4-16 years of age)</td>
<td>Clinical trial</td>
<td>‘Model Based Bridging’ approach proposed by FDA</td>
</tr>
</tbody>
</table>

FDA’s proactive model-based analysis alleviated the need to conduct additional clinical trial for the approval of Trileptal monotherapy in pediatrics

FDA/Sponsor pursued approaches to best utilize knowledge from the positive trials to assess if monotherapy in pediatrics can be approved without new controlled trials

< AAPS Journal 2005 >

Parkinson’s Disease - Model Based Approach

Single point will not differentiate ”symptomatic” vs. ”protective” effects

Unified Parkinson Disease Rating Scale (UPDRS) -- The UPDRS is a rating tool to follow the longitudinal course of Parkinson’s Disease. It is made up of the 1) Mentation, Behavior, and Mood; 2) Motor and 3) Motor sections. These are evaluated by interview. 199 represents the worst (total) disability, 0 -- no disability.


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Summary

Identified Critical Path opportunities can enhance drug development, regulatory review and clinical practice [safe and effective use of medical products in individual patients]

Collaborative efforts are required/ongoing
- knowledge and data-sharing
- standard toolkit development
- guidance development
- others

Acknowledgement

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Drug Interaction WG

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Shirley Murphy
Robert Powell

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S Buckman, S-M Huang, S Murphy, Clin Pharmacol & Ther, 81(2): 141-144, Feb 2007 (figure 1; adapted from figure supplied courtesy of RM Long, NIH)

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