ASCPT Annual Meeting
Open Forum
March 6, 2013

Contemporary Issues in Clinical Pharmacology

The FDA Office of Clinical Pharmacology Experience

Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA
Agenda

• **Introduction:** Shiew-Mei Huang, PhD

• **Model-Informed Drug Development and Regulatory Review:** Vikram Sinha, PhD
  Panel: Nitin Mehrotra, PhD, Ping Zhao, PhD

• **Development and Regulatory Evaluation of Targeted Therapies:** Michael Pacanowski, PharmD, MPH
  Panel: Issam Zineh, PharmD, MPH

• **Pediatric Drug Development:** Dionna Green, MD
  Panel: Kevin Krudys, PhD

• **Closing Remarks:** Issam Zineh, PharmD, MPH
Contemporary Issues in Clinical Pharmacology:

Introduction

Shiew-Mei Huang, PhD
Deputy Director
Office of Clinical Pharmacology
OTS, CDER, FDA
OCP Organization

- Divisions of Clinical Pharmacology 1-5
- Division of Pharmacometrics
- Genomics and Targeted Therapy
- Pediatric Team
- Mechanistic Drug Safety Team
- PBPK Program

19 Therapeutic Teams
4 Teams (including Knowledge Management)
Oncology and Non-Oncology Teams
Policy and Regulatory Science Focus
Research and Review Focus
Emerging Applications and Policy Development

→ Enhance drug development & promote regulatory innovation through applied clinical pharmacology

Office of Clinical Pharmacology Annual Report, January 2013
What Do We Do?

• Our reviewers serve as integrated members of CDER review teams and provide
  – Decision support in the review of therapeutics
  – Mechanistic based guidance in drug development

• In 2012, OCP reviewed > 2,700 IND and 900 NDA/BLA submissions
  – Increased complexity in IND and NDA/BLA reviews
  – Steady increase in pharmacometric, organ dysfunction, drug interaction evaluations [standard] and physiologically-based pharmacokinetic (PBPK), pharmacogenomics, immunogenicity, transporter and mechanistic safety reviews [new areas]
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Contemporary Issues in Clinical Pharmacology:

Model-Informed Drug Development and Regulatory Review

Vikram Sinha, Ph.D,
Director
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS, CDER, FDA
Outline

• Pharmacometrics at the FDA
• Evolution of pharmacometrics and current scope
• Future Directions
• Research Initiatives and Opportunities In the Division of Pharmacometrics
Pharmacometrics: A Quantitative Discipline at FDA

- Quantitative pharmaco-statistical analysis to answer clinical drug development, regulatory questions and influence decisions
- Influence decisions across INDs and Review continuum
- Scientists who do this work usually have background in clinical pharmacology/PKPD, biostatistics and have good judgment in the science of regulatory and drug development
FDA Pharmacometrics Evolution

Team → Staff → Division

Resources

Focus

Efforts
Multiple Points of Interactions with Sponsors

- Basic Research
- Prototype Design or Discovery
- Preclinical Development
- Clinical Development
  - Phase 1
  - Phase 2
  - Phase 3
- FDA Filing/Approval & Launch Preparation

Industry - FDA Interactions During Development
- Pre-IND Meeting
- Initial IND Submissions
- End of Phase 2a Meeting
- End of Phase 2 Meeting
- Safety Update
- Market Application Submission
- Ongoing Submission
- Pre-BLA or NDA Meeting

IND Review Phase
Application Review Phase
## Pharmacometrics: Current Scope

<table>
<thead>
<tr>
<th>Tasks</th>
<th>Decisions Influenced</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NDA Reviews</td>
<td>• Evidence of Effectiveness</td>
</tr>
<tr>
<td>• Protocols</td>
<td>• Labeling</td>
</tr>
<tr>
<td>– Dose-Finding trials</td>
<td>• Quantify benefit/risk</td>
</tr>
<tr>
<td>– Registration trials</td>
<td>– Target Patients</td>
</tr>
<tr>
<td>• QT Reviews</td>
<td>– Dose optimization</td>
</tr>
<tr>
<td>• Central QT team</td>
<td>– Dose adjustments</td>
</tr>
<tr>
<td>• EOP2A Meetings</td>
<td>• Trial design</td>
</tr>
<tr>
<td>• Disease Models</td>
<td></td>
</tr>
<tr>
<td>– Knowledge Management</td>
<td></td>
</tr>
</tbody>
</table>

*The Division has extensively published: Reviews, Commentaries and Scientific articles on its impact and influence in a collaborative manner*
# Pharmacometric - Key Decisions

<table>
<thead>
<tr>
<th>Review</th>
<th>Impact</th>
</tr>
</thead>
</table>
| Oxcarbazepine Extended-Release | • Exposure-Response (ER) as evidence to approve lower dose that did not meet statistical significance  
                            • Dosing nomogram for pediatrics                                      |
| Adalimumab                    | • ER as evidence to explore higher induction doses                      
                            • PMR issued to explore efficacy and safety of higher induction dosing regimens |
| Lixivaptan                    | • Extensive exposure/baseline Na-response analyses across two NDAs to compare efficacy between two drugs led to Complete Response |
| Truvada                       | • Adherence-response to support efficacy                                
                            • Presentation at AC meeting and impact of adherence included in the label |
| Ambien Controlled-Release     | • E-R analyses on multiple psychometric measurements led to label change in dose adjustment in female patients (will be published soon)  
                            (Note: these examples are a sample)                                    |
## Pharmacometric-Guided Pediatric Dosing Regimens

<table>
<thead>
<tr>
<th>Approaches for Dosing Regimen</th>
<th>Examples of Specific Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matching Drug Exposure in Children to Adult Exposure at Labeled-Dose</td>
<td>Busulfex® (ibusulfan) Injection, Zosyn® (piperacillin/tazobactam), Lovaquin® (levofloxacin), Videx® (didanosine), Xyzal® (levocetirizine), Digoxin Elixir, Protonix® (pantoprazole sodium), Nexium IV® (esomeprazole)</td>
</tr>
<tr>
<td>Exposure-response of biomarker or clinical endpoint data</td>
<td>Betapace® (sotalol) and Argatroban Injection® (argatroban), Trileptal® (oxcarbazepine)</td>
</tr>
<tr>
<td>Effectiveness study plus matching drug exposures</td>
<td>Celebrex® (celecoxib), Humira® (adalimumab), Illaris® (canakinumab), and Corlopam® (fenoldopam)</td>
</tr>
</tbody>
</table>


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 (submitted)
Future Directions

• The division will continue to grow both in size and scope under the current Office of Clinical Pharmacology (OCP), Office of Translational Sciences and CDER leadership.

  ➢ Key guidance within the purview of the division will be revisited and if necessary revised
  ➢ In addition to efforts to systematically implement the role of drug-disease models in the drug development process, new scientific tools such as systems pharmacology (PBPK, physiologically based pharmacodynamic models) will be assessed
  ➢ The division will look to increase its involvement in the IND phase. Specifically, develop scientific tools/approaches, collaborate with sponsors earlier in the development process thereby looking to help get important products earlier to patients
Research Initiatives and Opportunities in Pharmacometrics

- A strong collaborative environment for Reviewers, Programmer contractors and Fellows work and other divisions at the FDA
- Staff have excellent opportunities to develop their technical and scientific knowledge base and enhance their communication and decision-making skills
- Ongoing research initiatives and collaborations in the area of Huntingtons, bipolar disorder, HCV/HIV, cardiac safety and pediatrics, breast cancer, non-inferiority for anti-infectives, hepatic safety, exposure-response for biosimilars. This year, CAMD initiative will look to complete its first platform (tools, methods) in Alzheimers’ disease
- Opportunities to publish and participate in external meetings and conferences.
Acknowledgements

Contributions from the Division of Pharmacometrics, Office of Clinical Pharmacology and Review Divisions

Contacts

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Ping.Zhao@fda.hhs.gov
Vikram.Sinha@fda.hhs.gov

Division of Pharmacometrics
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
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Contemporary Issues in Clinical Pharmacology:

Development and Regulatory Evaluation of Targeted Therapies

Mike Pacanowski, PharmD, MPH
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Our Future

Targeting the Molecular Basis of Disease

Regulatory Science
Developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance

Vision
Speed innovation, improve regulatory decision-making, and get products to people in need

Focus
Innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes (e.g., trial design, biomarker qualification)
PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development

B. Advancing the Science of Meta-Analysis Methodology

C. Advancing the Use of Biomarkers and Pharmacogenetics

D. Advancing Development of Patient-Reported Outcome Assessment Tools

E. Advancing Development of Drugs for Rare Diseases

NME Genomic Data Submissions FY/CY2012

1/3 of approved NMEs contained genomic biomarker information in the original submission

Ivacaftor
Omacetaxine
Ponatanib

Vismodegib
Florbetapir
Bosutinib
Regorafenib
Cabozantinib

Efficacy/Activity
Dosing/PK
Rx/Dx

Clobazam
Deferiprone
Axitinib
Lorcaserin
Mirabegron
Teriflunomide
Tofacitinib

* Biomarker-related labeling

1QFY12
4QCY12
Targeted Therapy Successes… Ushering the Next-Generation of Drugs

- Many approved drugs target biomarker-defined subgroups of patients
- Contemporary examples have introduced major treatment advances
Seamless “Learn/Confirm” Pathway to Targeted Therapies

Investigational drugs and biomarkers → Achieve surrogate end point predictive of clinical outcome → Promising drug candidate and associated biomarker

Promising drug candidate and associated biomarker → Replicate surrogate end point → Achieve clinical outcome (regulatory standard for FDA approval)

Accelerated drug approval → Approval of biomarker → Full drug approval

## Setting the Stage for Targeted Drug Development

<table>
<thead>
<tr>
<th>Biomarker is the major pathophysiological driver of the disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited or adverse paradoxical activity of the drug is seen in a subgroup identified through in vitro or animal models (e.g., cell lines or animals)</td>
</tr>
<tr>
<td>Biomarker is the known molecular target of therapy</td>
</tr>
<tr>
<td>Preliminary evidence of harm from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of lack of activity from early phase clinical studies in patients without the biomarker</td>
</tr>
<tr>
<td>Preliminary evidence of modest benefit in an unselected population, but the drug exhibits significant toxicity</td>
</tr>
</tbody>
</table>
# Targeted Therapy Is Not a New Concept

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Label timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab Vedotin</td>
<td>Oncology</td>
<td>CD30</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Cetuximab, Panitumumab</td>
<td>Oncology</td>
<td>EGFR; KRAS</td>
<td>Pre-/Post-approval</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Oncology</td>
<td>ALK</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Exemestane, Fulvestrant, Letrozole</td>
<td>Oncology</td>
<td>ER/PR</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Oncology</td>
<td>C-Kit, PDGFR, FIP1L1</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Ivacaftor</td>
<td>Pulmonary</td>
<td>CFTR</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Lapatinib, Pertuzumab, Trastuzumab, Everolimus</td>
<td>Oncology</td>
<td>HER2</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Oncology</td>
<td>CD20 antigen</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Oncology</td>
<td>BRAF</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Hematology</td>
<td>Chromosome 5q</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Antivirals</td>
<td>CCR5</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Nilotinib, Dasatanib, Imatanib</td>
<td>Oncology</td>
<td>Ph Chromosome</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Arsenic Trioxide, Tretinoin</td>
<td>Oncology</td>
<td>PML/RARα</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>CD25/IL2</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Capecitabine, Fluorouracil</td>
<td>Oncology</td>
<td>DPD</td>
<td>Post-approval</td>
</tr>
<tr>
<td>Pimozide, Aripiprazole, Iloperidone, Tetrabenazine, Thioridazine</td>
<td>Psychiatry, Neurology</td>
<td>CYP2D6</td>
<td>Post-approval</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Analgesics</td>
<td>CYP2C9</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Psychiatry</td>
<td>CYP2C19</td>
<td>Post-approval</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Pre-approval</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Psychiatry</td>
<td>UCD</td>
<td>Post-approval</td>
</tr>
</tbody>
</table>
Comprise 12-50% of company pipelines

Mostly for internal decision-making

<10% of projects are “stratified”

Zuckerman and Milne 2012 [PMID 22378258]
## Policy and Guidance

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidance and Concept Papers</th>
</tr>
</thead>
</table>
| 2005 | Guidance on PG Data Submissions  
Concept Paper on Drug-Diagnostic Co-Development |
| 2007 | Companion Guidance on PG Data Submissions*  
Guidance on PG Tests and Genetic Tests for Heritable Markers |
| 2010 | ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards  
Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment  
Guidance on Qualification Process for Drug Development Tools |
| 2011 | Guidance on in vitro Companion Diagnostic Devices*  
Guidance on Clinical Trial Designs Employing Enrichment Designs* |
| 2013 | Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies |
| In Process | Guidance on Drug-Diagnostic Co-development |
OCP-Genomics
Strategic Priorities 2013

• Drug evaluation
  – Genetic liabilities, biomarker utility, early-phase trial design, co-development

• Policy and guidance
  – Policy gaps, implementation of new/emerging policies

• In/outreach
  – Intercenter coordination, staff training, international harmonization, human capital

• Regulatory science
  – Intra-/extramural research, new resources, knowledge management, VXDS
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Contemporary Issues in Clinical Pharmacology:

Pediatric Drug Development

Dionna Green, M.D.
Lily Mulugeta, Pharm.D.
Pediatric Clinical Pharmacology Staff
Office of Clinical Pharmacology
OTS, CDER, FDA
Successful Drivers of Pediatric Drug Research

2002
BPCA
- Renewal of pediatric incentive program
- Established process for study of off-patent drugs
- Required public dissemination of pediatric study results

2003
PREA
- Required pediatric studies of new drug products likely to be used in pediatric patients

2007
FDAAA
- Reauthorized BPCA and PREA
- Pediatric labeling requirement
- Mandated the formation of the Pediatric Review Committee (PeRC)
Pediatric Studies Conducted Under BPCA and PREA

Breakdown of FDAAA completed pediatric studies between Sept. 27, 2007 – Dec. 05, 2012

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>BPCA</th>
<th>BPCA + PREA</th>
<th>PREA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy/Safety</td>
<td>43</td>
<td>31</td>
<td>199</td>
<td>273</td>
</tr>
<tr>
<td>PK/Safety</td>
<td>9</td>
<td>36</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>PK/PD</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Safety</td>
<td>6</td>
<td>4</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>3</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>75</td>
<td>82</td>
<td>270</td>
<td>425</td>
</tr>
</tbody>
</table>

Total number of patients in completed FDAAA studies: 175,209
23,339 in BPCA studies; 32,650 in CDER PREA studies;
119,220 in CBER PREA studies (Vaccines and Blood Products)
In The Midst of Success, Challenges Remain

- **2002**
  - BPCA
    - Extended pediatric incentive program
    - Established process for studying off-patent drugs
    - Required posting of pediatric study results

- **2003**
  - PREA
    - Required pediatric studies of new drug products likely to be used in pediatric patients

- **2007**
  - FDAAA
    - Reauthorized BPCA and PREA
    - Pediatric labeling requirement
    - Mandated the formation of the Pediatric Review Committee (PeRC)

- **2012**
Challenge: Approximately 25% of pediatric trials to fail to result in a labeled indication

Breakdown of Failed Trials

- Precocious Puberty
- Diabetes
- Obesity
- Other

- Migraine
- Seizures (1-24m/o)
- Other

Pediatric studies publicly posted under FDAAA as of 2011
Challenge: Pediatric drug development lags significantly behind adult development

Of the 210 deferred pediatric studies that have reached their due date (since September 2007), the majority are still outstanding

Average time for study completion from issuance of WR by therapeutic area

Data as of Sept. 2012
Challenge: Lack of dosing information in neonates/infants

Only 1 out of the top 10 products used in the NICU is labeled for use in premature infants

Only 18 out of 161 products studied under FDAAA have PK data in pts. <1yr. of age

Data as of Dec. 2012

Building Upon Successful Legislation

2002
BPCA
• Extended pediatric incentive program
• Established process for studying off-patent drugs
• Required posting of pediatric study results

2003
PREA
• Required pediatric studies of new drug products likely to be used in pediatric patients

2007
FDAAAA
• Reauthorized BPCA and PREA
• Pediatric labeling requirement
• Mandated the formation of the Pediatric Review Committee (PeRC)

2012
FDASIA
• Makes permanent BPCA and PREA
• Places emphasis on early study planning
• Establishes timeline for submission and review of PSPs
• Highlights understudied populations
Emphasis on Early Planning of Pediatric Studies

International Harmonization Efforts
- Monthly Teleconference with EMA/PMDA/Health Canada
- Pilot Program for Parallel Review
- ICHE11 Revisions

- EMA PIP
- EOP1 meeting
- BPCA

- EOP2 meeting
- PREA PSP BPCA

- Pre-NDA meeting
- PREA BPCA
Pediatric Plans

A short paragraph stating that the Applicant plans to conduct pediatric studies (PK, safety, and/or efficacy)

Pediatric Study Plans (PSPs)

Detailed plan that must include study objectives, study design, age groups, endpoints, statistical approach, and any requests for waivers/deferrals along with supporting information

PSP Review Timeline

- Applicant required to submit PSPs
- Division must consult PeRC
- Division must meet with the applicant or provide a written response to the PSP
- Applicant must submit written agreement
- Division must confirm agreement with the applicant

EOP2 60 days 150 days 240 days 270 days

All modifications to the PSP must be reviewed by the PeRC
Pediatric Study Planning & Extrapolation Algorithm

- Is it reasonable to assume that children, when compared to adults, have a similar: (1) disease progression and (2) response to intervention?
  - [No to either]
  - [Yes to both]
    - Is it reasonable to assume similar exposure-response in pediatrics and adults?
      - [No]
      - [Yes]
        - Is the drug (or active metabolite) concentration measurable\(^{\text{c}}\) and predictive of clinical response?
          - [No]
          - [Yes]
            - Conduct:
              - (1) Adequate PK study to select dose(s) to achieve similar exposure as adults.\(^{\text{a}}\)
              - (2) Safety trials\(^{\text{b}}\) at the identified dose(s).

  - "Full extrapolation"

- "No extrapolation"

- "Partial extrapolation"

- Conduct:
  - (1) Adequate dose-ranging studies in children to establish dosing.\(^{\text{a}}\)
  - (2) Safety\(^{\text{b}}\) and efficacy\(^{\text{b}}\) trials at the identified dose(s) in children.

- "Partial extrapolation"

- Conduct:
  - (1) Adequate dose-ranging study in children to select...

Footnotes:
- a. For locally active agents.
- b. For partial extrapolation.
- c. For drugs that are extensively metabolized or have a high systemic clearance.
- d. For drugs that are not substantially cleared by extrarenal routes.
- e. When appropriate and feasible.
Pediatric Clinical Pharmacology Staff Charter

**IMPROVE PEDIATRIC DRUG DEVELOPMENT**
- Reduce unnecessary studies (via i.e., extrapolation, allometric scaling)
- Utilize quantitative tools (i.e., M&S, PBPK) to inform dose selection and trial design
- Employ innovative designs (i.e., E-R, strategic biomarkers, adaptive, enrichment, randomized withdrawal, scavenge sampling, opportunistic)

**RESEARCH, POLICY & OUTREACH**
- Conduct and circulate results of high quality scientific and regulatory research
- Develop regulatory policies and procedures to facilitate pediatric drug development
- Train individuals in regulatory science and pediatric clinical pharmacology
- Partner with stakeholders in addressing existing challenges

**KNOWLEDGE MANAGEMENT**
- Develop comprehensive database of pediatric trials
- Evaluate trial design elements across programs
- Leverage prior data to support future regulatory and scientific decision-making
Pediatric Clinical Pharmacology Staff

Office of Clinical Pharmacology
OTS/CDER/FDA

OCP = Office of Clinical Pharmacology
DCP = Division of Clinical Pharmacology
DPM = Division of Pharmacometrics
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Contemporary Issues in Clinical Pharmacology:

Closing Remarks

Issam Zineh, PharmD, MPH
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