Translational Pharmacogenomics: The FDA Experience

Mike Pacanowski, Pharm.D., M.P.H.
Genomics Group
Office of Clinical Pharmacology
U.S. Food and Drug Administration
The views expressed are those of the speaker and do not necessarily reflect the official policy of the FDA. No official endorsement is intended or should be inferred.
Agenda

• Overview of Genomics at FDA

• Voluntary eXploratory Data Submission and Biomarker Qualification

• Regulatory activities

• Scientific challenges
U.S. Food and Drug Administration

Center for Tobacco Products

Center for Devices and Radiological Health (CDRH)

Center for Food Safety and Applied Nutrition (CFSAN)

Center for Drug Evaluation and Research (CDER)

Center for Veterinary Medicine (CVM)

Office of the Commissioner (OC)

National Center for Toxicological Research (NCTR)

Center for Biologics Evaluation and Research (CBER)

Maternal Health and Botanical Teams

Compliance

Information Technology

Medical Policy

Center Director

Regulatory Policy

New Drugs

Translational Sciences

Management

Counter-terrorism

Surveillance and Epidemiology

Pharmaceutical Sciences

Executive Programs

Business Process Support

Training and Communication
The Genomics Group

Issam Zineh, PharmD, MPH
Associate Director

Federico Goodsaid, PhD
Associate Director for Operations

Li Zhang, MD, PhD
(statistics, genetics)
Reproductive/ Urinary
Gastrointestinal
Neurology
Psychiatry

Shashi Amur, PhD
(molecular biology, technology)
Antiinfectives/ Antivirals
Special Pathogens
Transplant
Anesthesia/ Analgesia/ Rheum

Mike Pacanowski, PharmD, MPH
(clinical, epidemiology)
Cardiovascular/ Renal
Hematology
Metabolic/ Endocrine
Pulmonary

Rosane Charlab Orbach, PhD
(molecular biology)
Drug Oncology

Christian Grimstein, PhD
(gene therapy)
Biologics/ Biologic Oncology

Padmaja Mummaneni, PhD
(molecular biology)
Program Support
The Common Mission of Regulatory Agencies Worldwide: Translational Medicine

1. Health protection: keeping “bad” medical products off the market – *classic regulatory mandate*

2. Health promotion: facilitate getting “good” medical products to patients ASAP – *utilize modern science and innovations*

3. Public education: consolidate scientific thinking and share knowledge – *professional obligation to improve the enterprise*

Our Environment

- High rates of attrition
- Mostly related to efficacy, lots of toxicology and clinical safety issues

Kola and Landis, NRDD 2004 [PMID 15286737]
FDA as a hub and catalyst for public-private partnerships

VXDS
Biomarkers Consortium (FNIH)
Preclinical and clinical
Predictive Safety Testing
Consortium (C-Path, Industry)
Pharmacogenomics,
proteomics, metabolomics
Cardiac Safety Research

5th Workshop in a Series on Pharmacogenomics
Generating and Weighing Evidence in Drug Development and Regulatory Decision Making
February 2-4, 2010
Marriott Bethesda North Hotel and Conference Center
Bethesda, MD, USA
Molecularly-Targeted Therapy and Attrition

Walker et al 2009 [PMID 19008887]
Optimizing Drug Knowledge

Demographics  Exposure  Diet  Compliance  Genetics

Unaccounted Variability (%)

Knowledge of B/R

Time
VXDS and BQP
What is VXDS?

• A way to share information with the FDA
• Captures exploratory pharmacogenomic (or other) investigations otherwise not submitted to IND/NDA
• “Safe harbor” benefits industry and FDA by providing a means to ensure that regulatory scientists are familiar with and prepared to evaluate future submissions
• Content areas
  – Genetic loci or gene expression profiles being explored
  – Test systems and techniques being employed
  – Applying pharmacogenomic tests to drug development
  – Transmitting, storing, and processing large, complex data sets
  – Developing bioinformatics software
35 initial face-to-face meetings (~5-10 per year)

Most clinically oriented

All therapeutic areas (multiple cardio-renal and oncology)
What Are the Incentives for Companies to Use the VXDS Program?

• Opportunity for early, informal peer-review and feedback
• Flexibility in review and meeting process
• Insight into current FDA thinking about exploratory biomarkers may assist in strategic decisions
• Time- and cost-savings by familiarizing both parties early with novel exploratory biomarker approaches
• Opportunity to impact FDA’s thinking and help build consensus around standards, policies and guidances
Exploratory Biomarkers
*(VXDS Meetings)*

Qualified Biomarkers
*(Biomarker Qualification Process)*

*Regulatory Applications*
What is Biomarker Qualification?

- **Definition:** Qualification is a conclusion that within the stated context of use, the results of patient assessment with a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory decision-making.

- **Regulatory implication:** Once qualified, drug developers will be able to use the biomarker in the qualified context in IND and NDA/BLA submissions without requesting that the relevant CDER review group reconsider and reconfirm the suitability of the biomarker.
Why Do We Need It… How Do We Achieve It?

**Purpose**

- To capture consensus on the value of biomarkers
- To encourage the development of new biomarkers
- To develop an efficient process for qualifying biomarkers

**Process**

- Formal Process proposed in 2009
- Approved by the CDER Senior Management Team
- Draft Guidance expected in Q2 2010
Regulatory Activities
Natural experiments, *in silico* / *in vitro* / *in vivo* modeling

→ *Anticipate untoward effects*

PK/PD heterogeneity, outliers

→ *Optimize dosing*

Prodrugs, response heterogeneity

→ *Identify (non)responders*

Idiosyncratic/ immunologic reactions

→ *Exclude toxic responders*

<table>
<thead>
<tr>
<th>Nonclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
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</thead>
<tbody>
<tr>
<td>Metabolism, transport</td>
<td>Dose-ranging</td>
<td>Dose-response</td>
<td>Efficacy</td>
<td>Efficacy</td>
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<tr>
<td>Nonclinical safety</td>
<td>ADME</td>
<td>Intrinsic/extrinsic factors</td>
<td>Safety</td>
<td>Safety</td>
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<tr>
<td></td>
<td>Intrinsic/extrinsic factors</td>
<td></td>
<td>D/R, C/R relationship</td>
<td>D/R, C/R relationship</td>
</tr>
<tr>
<td></td>
<td>Safety</td>
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</tbody>
</table>
What Do GG Reviewers Do?

Enhance product development by:

Minimizing likelihood for imperfect data (IND)
&
Analyzing and interpreting data in regulatory submissions (NDA, BLA)
What Do GG Reviewers Do?

1. Consider all products of the genome

   Systems biology approaches

<table>
<thead>
<tr>
<th>Genome</th>
<th>Transcriptome</th>
<th>Proteome</th>
<th>Metabolome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA</td>
<td>mRNA</td>
<td>Proteins</td>
<td>Metabolites</td>
</tr>
<tr>
<td>Genotyping assays</td>
<td>Microarray</td>
<td>QRT–PCR</td>
<td>LC–MS/MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MALDI–MS/MS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2D gels–MS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NMR</td>
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<td></td>
<td></td>
<td></td>
<td>GC–MS</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LC–MS</td>
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<td></td>
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<td>FT–IR</td>
</tr>
</tbody>
</table>

2. Consider all genomes

   Polymorphism
   - a In proteins that affect drug availability to tumour
   - b In proteins that affect tumour drug sensitivity
   - c In proteins that affect toxicity

What Do GG Reviewers Do?

3. Integrative biology


4. Constructive pharmacology

What Do GG Reviewers Do?

5. Translational analyses

Elevated B2MG

**Progressive Disease**

- OR
  - AND
    - 12q tri
  - 17 del
    - AND
      - Low cCD20
      - Not 12q tri

Multi-Disciplinary Review Team

- Project manager
  - Sponsors
    - INDs, Protocols
    - Meeting Packages
    - Advice letters
    - NDAs

- Chemistry
- Statistical
- Medical
- Preclinical Pharm/Tox
- Clinical Pharmacology

Decisions influenced:
- Trial design?
- Dose-optimized?
- Labeling appropriate?
- Acceptable risk/benefit?
- Post-marketing studies?
- Safe & effective?
AN INTEGRATED GENOMICS, PHARMACOMETRICS AND CLINICAL PHARMACOLOGY REVIEW PROCESS

CONTENTS

PURPOSE
BACKGROUND
REFERENCES
DEFINITIONS
POLICY
RESPONSIBILITIES
PROCEDURES
EFFECTIVE DATE

Attachment A – OCP Scoping Meeting Form

PURPOSE

- This MAPP establishes a review process for genomics, pharmacometrics and clinical pharmacology, referred to as the Integrated Review Process (IRP), for the evaluation of new drug applications and biological license applications for NMEs and applications or supplements for Pediatric indications in the Office of Clinical Pharmacology (OCP).

- The guiding principle is that reviewers from Divisions of Clinical Pharmacology, Genomics and Pharmacometrics work collaboratively on OCP reviews.
IND and NDA/BLA Review Growth

<table>
<thead>
<tr>
<th>Year</th>
<th>IND</th>
<th>NDA</th>
<th>BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>37</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>2009</td>
<td>92</td>
<td>36</td>
<td>16</td>
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</tbody>
</table>
Best Practices in Genomics Reviews

Define key issues for review

- Biomarker claim in labeling?
- Genomic biomarker data submitted?
- Known biomarkers for disease or related drugs?
- PK/PD profile
  - Exposure/response relationship, race effects, variability, outliers, substrate for polymorphic DME, prodrug, significant drug interactions?
- Efficacy and safety profile
  - Non-response rate, serious AEs, race effects?
- Biomarker relationships with PK/ PD/ efficacy/ safety?
# Approved Drugs with PGx in Label

<table>
<thead>
<tr>
<th>Drug</th>
<th>Marker</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>TPMT</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>CYP2D6</td>
<td>Neurologic</td>
</tr>
<tr>
<td>Codeine</td>
<td>CYP2D6</td>
<td>Opioid toxicity</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>UGT1A1</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19</td>
<td>Failure</td>
</tr>
<tr>
<td>Warfarin</td>
<td>CYP2C9</td>
<td>Dose/INR/Bleeding</td>
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<tr>
<td><strong>Mechanistic/Pharmacodynamic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetux/ panitumumab</td>
<td>KRAS</td>
<td>Failure</td>
</tr>
<tr>
<td>Abacavir</td>
<td>HLA B*5701</td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA B*1502</td>
<td>SJS/TEN</td>
</tr>
<tr>
<td>Warfarin</td>
<td>VKORC1</td>
<td>Dose/INR/Bleeding</td>
</tr>
</tbody>
</table>
Recent Label Updates: Common Themes

• Frequent and/or severe clinical events
• Accurately able to define phenotype
• Highly replicated
• Large effect sizes
• Understanding of disease pathology and drug target; biological plausibility
• Clinical validation in prospective studies
• Actionable recommendation
Scientific Challenges
Pharmacogenetics Review Issues

- Retrospective vs. prospective
- Efficacy vs. safety
- Agnostic vs. hypothesis-driven
- Clinical validity + epidemiological strength
  - Stats and magnitude
  - Replication
  - Biological gradient
  - Biologically plausible
  - Supported by analogy and cohesion
- Additional experimental evidence
Race/Ethnicity as an Added Dimension

<table>
<thead>
<tr>
<th>Therapeutic area</th>
<th>Drug products: generic (brand) names</th>
<th>Ethnicity information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiorenal</td>
<td>Isosorbide dinitrate–hydralazine (BiDil)</td>
<td>Indicated for self-identified blacks</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II antagonists and ACE inhibitors</td>
<td>Smaller effects in blacks&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Rosuvastatin (Crestor)</td>
<td>Lower dose for Asians</td>
</tr>
<tr>
<td>Hematology</td>
<td>Warfarin (Coumadin)</td>
<td>Lower dose for Asians</td>
</tr>
<tr>
<td>Neuropharmacological</td>
<td>Carbamazepine (Tegretol)</td>
<td>Box warning for Asians with variant alleles of HLA-B&lt;sup&gt;*1502&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Huang and Temple 2008 [PMID 18714314]
Maximizing the Explanatory Power of Genetics

• Heterogeneity in drug response, exposure, or AEs by race and/or study country are not uncommon
  – Differences in prevalence of important gene variants
  – Trial designs
  – Eligibility criteria
  – Patient characteristics
  – Differences in SOC or background treatment

• Particularly relevant in global research
### Reported Safety PGx Relationships

<table>
<thead>
<tr>
<th>Drug</th>
<th>Safety Issue</th>
<th>Biomarker</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Hepatotoxicity</td>
<td>NAT2, CYP2E1</td>
</tr>
<tr>
<td>Lumiracoxib</td>
<td>Hepatotoxicity</td>
<td>HLA-DQA1*0102</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Hepatotoxicity</td>
<td>HLA-B*5701</td>
</tr>
<tr>
<td>Amox/clav</td>
<td>Hepatotoxicity</td>
<td>HLA-DRB1*1501</td>
</tr>
<tr>
<td>Lapatanib</td>
<td>Hepatotoxicity</td>
<td>HLA-DQA1*0201</td>
</tr>
<tr>
<td>Ximelagatran</td>
<td>Hepatotoxicity</td>
<td>HLA-DRB1*0701</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Hepatotoxicity</td>
<td>HLA-A*3303</td>
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<tr>
<td>Tranilast</td>
<td>Hyperbilirubinemia</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Azathioprine/6-MP</td>
<td>Neutropenia</td>
<td>TPMT</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Neutropenia</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Agranulocytosis</td>
<td>HLA-DRB5*0201</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Skin reactions</td>
<td>HLA-B*5801</td>
</tr>
<tr>
<td>Contraceptives</td>
<td>Thrombosis</td>
<td>F5</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>PRCA</td>
<td>HLA-DRB1*9</td>
</tr>
</tbody>
</table>

### How do you acquire sufficient data to verify PGx relationships in diverse patient populations?
Working to Fill Science Gaps

Medco Announces Research Collaboration with FDA Focused on Personalized Medicine

Mon Aug 18, 2008 4:00pm EDT
Active CRADAs

- Co-development (Novartis)
- Reference database exploration tool (Ingenuity)
- Standards, data integration, and applications for analyzing heterogeneous datasets (Lilly)
- Software tool to optimize clinical study design (GSK/Adaptive Pharmacogenomics)
Enhance regulatory decision making

Utilize opportunities presented by science

Improve patient care

Expedite medical product development process

Collaboration is Key

FDA

NIH/Academia

Industry

HMOs

PARTNERING

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)
The Horizon

- 1000 Genomes: sequencing replaces GWAS
- DNA banking becomes standard procedure for clinical trials
- eMR-linked Biobanks: Kaiser Permanente, Vanderbilt and Marshfield biobanks, Coriell CPMC
- Consortia: Duke CSRC, SAEC, C-Path/ PTSC, PGRN, DILIGEN, EUDRAGENE, eMERGE, Alliance Against SCD
- Clinical uptake of (pharmaco)genetic testing
Summary and Conclusions

• FDA at the forefront of advancing genomic sciences

• Pharmacogenetic data increasingly entering the regulatory stream

• Many kinks in the system, barriers (hurdles) to translation remain