Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

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Center for Drug Evaluation and Research
U.S. Food and Drug Administration

EMA
8 Oct 2012
Application of metabolic data to the evaluation of drugs.

"Differences in individual ability to metabolize drugs must be considered in carrying out clinical pharmacologic studies...A universally safe drug, completely incapable of unusual or unexpected effects, is unobtainable."

NAS-NRC, CPT 1969

"It is no longer possible to prescribe drugs rationally on the basis of a memorized schedule of dosages and contraindications."

Azarnoff, JAMA 1970
Innovation at CDER: Early Focus Areas and Programs

- VXDS
- BQ Pilot Program
- Label Updates
- GDS Guidance
Present State – PG Elements of NME NDAs/BLAs FY2011

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approval</th>
<th>Issue(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crizotinib</td>
<td>8/26/11</td>
<td>Co-developed (ALK status)</td>
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<tr>
<td>Vemurafanib</td>
<td>8/17/11</td>
<td>Co-developed (BRAF status)</td>
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<tr>
<td>Ticagrelor</td>
<td>7/20/11</td>
<td>PD/efficacy by CYP2C19 status; exploratory safety</td>
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<tr>
<td>Indacaterol</td>
<td>7/1/11</td>
<td>PK by UGT1A1 status</td>
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<tr>
<td>Belatacept</td>
<td>6/15/11</td>
<td>Safety by EBV/CMV status</td>
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<tr>
<td>Ezogabine</td>
<td>6/10/11</td>
<td>PK by UGT1A1 and NAT2 status</td>
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<tr>
<td>Telaprevir</td>
<td>5/23/11</td>
<td>Efficacy by IL28B, safety by HLA</td>
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<tr>
<td>Boceprevir</td>
<td>5/13/11</td>
<td>Efficacy by IL28B, safety by ITPA</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>3/25/11</td>
<td>PGx of safety</td>
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<tr>
<td>Belimumab</td>
<td>3/9/11</td>
<td>Efficacy by SLE biomarkers</td>
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<tr>
<td>Roflumilast</td>
<td>2/28/11</td>
<td>Safety potential by human vs. animal genome</td>
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<tr>
<td>Vliazodone</td>
<td>1/21/11</td>
<td>PGx of efficacy and safety</td>
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<tr>
<td>Dabigatran</td>
<td>10/19/10</td>
<td>Differential PK/outcome by ABCB1, VKOR/2C9</td>
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34 NME approvals in FY11
## U.S. Regulatory Guidance

<table>
<thead>
<tr>
<th>Year</th>
<th>Guidance Title</th>
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<tbody>
<tr>
<td>2005</td>
<td>Guidance on PG Data Submissions</td>
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<tr>
<td></td>
<td>Concept Paper on Drug-Diagnostic Co-Development</td>
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<td>2007</td>
<td>Companion Guidance on PG Data Submissions</td>
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<td></td>
<td>Guidance on PG Tests and Genetic Tests for Heritable Markers</td>
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<tr>
<td>2010</td>
<td>ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards</td>
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<tr>
<td></td>
<td>Guidance on Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment</td>
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<td>Guidance on Qualification Process for Drug Development Tools</td>
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<td>2011</td>
<td>Guidance on Clinical PG: Premarketing Evaluation in Early Phase Clinical Studies</td>
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<tr>
<td></td>
<td>Guidance on in vitro Companion Diagnostic Devices</td>
</tr>
<tr>
<td>In Process</td>
<td>Guidance on Clinical Trial Designs Employing Enrichment Designs to Support Approval of Human Drugs and Biological Products</td>
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Rational Drug Development Successes…Ushering in the Next Generation

XALKORI® CRIZOTINIB

ZELBORAF® (vemurafenib) tablets

kalydeco® (ivacaftor) tablets

CDER

CDRH

2008

CDER

CDRH

2011

CDER/CDRH

2012+

CDER/CDRH
Problem Drugs

High variability
Disproportionality
Race effects
Outliers
No monitoring tools

Clinical PK Polymorphic metabolism/activation

Exposure/response

Efficacy Morbid/mortal indication Disease genetics

Safety Serious AEs Poor tolerability

Idiosyncrasy
FDA Guidance:
Clinical Pharmacogenomics in Early Phase Studies

• Purpose is to guide industry on when to consider how human genomic variation (specifically DNA) affects a drug’s PK, efficacy, or safety
• Provides general principles of study design, data collection, data analysis and labeling for PG studies
• Scope: Early phase clinical trials (exploratory and observational studies)
  – Not statistical considerations for later phase RCTs intended to draw conclusions from genomic subgroup effects or co-development
  – Does not address tumor genomics specifically
Background

• Uses for genomic data
  – Basis for PK/PD outliers, intersubject variability
  – Investigating molecular/mechanistic basis for lack of efficacy, AEs
  – Estimating magnitude of potential DDIs
  – Subgroup effects and enrichment

• Potential clinical outcomes
  – Select patients based on risk/benefit profile
  – Modify dosing to avoid extreme exposures
  – Intensify AE monitoring
Genetic Factors of Interest

Disease Marker

Metabolizing Enzyme

Intrinsic and Extrinsic Factors

(Un)Intended Target

Transporter

PK Variability

PD Variability

Response, efficacy, tolerability, safety

Immunologic/Idiosyncratic

Modified from Expert Opin Drug Metab Toxicol. 2008 May;4(5):529-44.
Foundational Principle: No PG without DNA

DNA in all if hypothesis
DNA in all if no hypothesis (where possible)
If not all, many (+ targeted from “cases”)
If not all, why not
DNA Collection and Storage: General considerations

- Obtain broad consent
- Collect before randomization to minimize bias
- Retain samples to allow post-approval assessment
- Document reasons for incomplete sampling
- Provide information to support sample quality and integrity, in addition to QC/QA in CSR

* Regional heterogeneity exists
Applied Clinical Evaluation: Genotyping Strategies

• Hypothesis testing: Candidate gene
  – Test well-characterized, functional variants in ADME genes or drug target
• Hypothesis-generating: ADME or genome-wide chips
  – Useful for unresolved variability in exposure and/or response
  – High rate of false-positives – confirm findings in vitro or in additional clinical studies
• Marker selection
  – Appropriate to racial/ethnic group being studied
Applied Clinical Evaluation: PG Study Design

- Retrospective genotyping
  - Subgroup analysis, meta-analysis, case-control
  - Generally exploratory; appropriate for PK and safety endpoints
- Prospective genotyping
  - Stratified randomization/intervention, enrichment (inclusion/exclusion, over-enrollment)
  - Indicated for thorough PG assessments, dose-adjusting or excluding at-risk/non-responsive subjects from early trials, evaluating stratified dosing or efficacy in late phase trials, reducing noise in DDI studies
Paradigm Change and the “Progressive Reduction of Uncertainty”

GWAS IL28B predicts Peg-IFN/RBV response

Dozens replicate

FDA HepC guidance

Standard analysis in RCTs

New NDAs

Pacanowski, Amur, Zineh. JAMA 2012. [PMID 22570460]
Seamless “Learn/Confirm” Paradigms May Provide a Path

Investigational drugs and biomarkers

Achieve surrogate end point predictive of clinical outcome

Promising drug candidate and associated biomarker

Enrichment
Prognostic
Predictive
Practical

Confirmatory Trial

Promising drug candidate and associated biomarker

Replicate surrogate end point

Achieve clinical outcome (regulatory standard for FDA approval)

Companion Diagnostic

FDA Approval

Accelerated drug approval
Approval of biomarker
Full drug approval

FDA Guidance: Companion Diagnostics

- Defines “companion diagnostic”
  - Test essential for safe and effective drug use
  - Prediction, prognosis, selection, dosing, monitoring
- Describes FDA’s policies for approval and labeling of a therapeutic/diagnostic product pair
  - Pre-market review, risk-based regulation
  - Analytical validity of tests used for critical treatment decisions to be reviewed
- Does not describe how to co-develop products
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 Methodologies

C. Advancing the Use of Biomarkers and Pharmacogenomics

D. Advancing Development of Patient-Reported Outcome (PRO) and Patient-Reported Experience Assessment Tools

E. Advancing Development of Drugs for Rare Diseases
Summary and Conclusions

• Protecting and promoting public health are equally important charges to the FDA
• The role of PG in drug development is evolving, extends beyond drug-test pairs
• Regulatory policy has attempted to foster use of applied genomics in drug development, reducing uncertainty
• Co-development and Enrichment guidances to address late-phase issues related to biomarker-based drug development
Backup
Labeling: Hierarchy of Action

- **Frequencies**
- **PK/PD effects**
- **Functional effects**
- **Altered risk/benefit**
- **Dosing and patient selection**

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<tr>
<th>INDICATIONS AND USAGE</th>
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<tr>
<td>Patient selection</td>
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<tr>
<td>DOSAGE AND ADMINISTRATION</td>
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<td>Subgroup dosing</td>
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<tr>
<th>BOXED WARNING</th>
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<tr>
<td>CONTRAINDICATIONS</td>
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<tr>
<td>WARNINGS AND PRECAUTIONS</td>
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<tr>
<td>ADVERSE REACTIONS</td>
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<tr>
<th>USE IN SPECIFIC POPULATIONS</th>
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<td>Differential safety</td>
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<tr>
<th>CLINICAL PHARMACOLOGY</th>
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<td>Impact on PK/PD</td>
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<tr>
<th>CLINICAL STUDIES</th>
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<tr>
<td>Substantial evidence of observed or neutral differences</td>
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Applied Clinical Evaluation – Additional Considerations

- Evaluate PG interactions in context of clinical covariates, particularly race/ethnicity
- PBPK modeling may provide supportive evidence
- Control multiplicity
- Evaluate test performance (e.g., PPV, NPV)
- Address bias in substudies (i.e., differences from overall population, preservation of randomization)
- Establish strength, cohesion, etc
- Replicate
- Assay
  - Establish QC materials, standards, calibrators, and validated protocols to assure continued analytical performance
  - Consult CDRH for imminent test
Summary: Review Considerations

- Is a general plan for DNA collection (for exploratory studies) indicated based on the expected metabolic/PK, efficacy, and/or safety profile?
- Should any markers be tested in all subjects?
- Should any subjects be excluded based on the potential for high exposure/toxicity?
- Should only certain subjects be included to reduce noise?
- Are a sufficient number of studies planned to support retrospective analyses?
- Will a dedicated PG study be necessary before Phase 3 (for dose selection)? Approval?
- Are the analytical methods and SAP clearly described?
Enhancing Drug Development: Prospective Maneuvers

--------- Optimize efficacy - - - Minimize risk ---------

- Restricted FIH/DDI/HV trials
- Stratified dose-finding
- Enriched/stratified trials
- Stratified dosing
- Labeling

Nonclinical

- Metabolism, transport
- Drug-target interactions
- Nonclinical safety

Phase 1

- ADME
- Intrinsic/extrinsic factors
- Safety

Phase 2

- Efficacy
- Safety
- D/R, C/R
- Intrinsic/extrinsic factors

Phase 3

Phase 4

Zineh and Pacanowski 2011 [Pharmacotherapy]
Cancer, psychiatric, and infectious disease therapeutics make up more than half of the drugs with PG labeling.

Most PG labeling is related to drug metabolism.

http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm