New Paradigms in Drug Discovery: Partnerships in Genomics- and Biomarker-Enabled Drug Development, Approval and Prescribing

Michael Pacanowski, PharmD, MPH
Genomics Team Leader
OCP/OTS/CDER

Charge

• How does regulatory policy influence the use and utility of genomics-based drug development?

• What have been the effects of the Voluntary Exploratory Data Submissions (VXDS) Program? What would improve that program?

• What are the incentives for entering into partnerships…strengths, weaknesses and challenges?

• How does genomic information give strength and leverage to partnerships? What is unique about genomics than can accelerate a paradigm change?
The FDA Genomics/Personalized Medicine Universe

- Center for Tobacco Products
- Center for Veterinary Medicine (CVM)
- Center for Devices and Radiological Health (CDRH)
- Office of the Commissioner (OC)
- National Center for Toxicological Research (NCTR)
- Center for Food Safety and Applied Nutrition (CFSAN)
- Center for Drug Evaluation and Research (CDER)
- Center for Biologics Evaluation and Research (CBER)

Maternal Health and Botanical Teams

Information Technology

Medical Policy

Center Director

New Drugs

Counter-terrorism

Surveillance and Epidemiology

Translational Sciences

Management

Training and Communication

Executive Programs

Business Process Support

Regulatory Policy

Compliance
At Odds

• FDA mandate: protect and promote public health
• Tension between protection and promotion, risk aversion and innovation, regulation and flexibility

- However -

• Personalized medicine is challenging our habits of reasoning
• FDA has (arguably) been on the leading edge
Application of metabolic data to the evaluation of drugs.

A report prepared by the committee on problems of drug safety of the drug research board, National Academy of Sciences-National Research Council

C. 1970

“It is no longer possible to prescribe drugs rationally on the basis of a memorized schedule of dosages and contraindications since the same dose administered to different individuals or the same individual at different times may achieve a therapeutic, a toxic, or an inadequate effect.”
Innovation at CDER: Early Focus Areas and Programs

- VXDS
- BQ Pilot Program
- Label Updates
- GDS Guidance
Benefits of VXDS

• Share data informally without regulatory consequences
• Obtain feedback on trial designs, methodologies, data interpretation
• Gain insight into evolving regulatory processes
• Provide experience to facilitate policy development
• Discuss data elements to streamline NDA/BLA submission
• Educate FDA scientists on emerging data and innovative approaches
• Potential for synergizing with scientists from academic, diagnostic, pharma, biotech, PBM, and other settings

See Goodsaid, et al. NRDD 2011 for additional information
VXDS → NDA/BLA
NME Clinical PGx Issues – 2011

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<th>Drug</th>
<th>Approval</th>
<th>Issues</th>
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<td>Ruxolitinib</td>
<td>11/16</td>
<td>Efficacy/safety by JAK2 variant status</td>
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<td>Clobazam</td>
<td>10/24</td>
<td>Dosing for CYP2C19 status</td>
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<tr>
<td>Crizotinib</td>
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<td>Co-developed (ALK status)</td>
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<td>Ticagrelor</td>
<td>7/20</td>
<td>PD and efficacy by CYP2C19 status</td>
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<td>Indacaterol</td>
<td>7/1</td>
<td>PK by UGT1A1 status</td>
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<td>Belatacept</td>
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<td>Safety by EBV/CMV status</td>
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<td>Ezogabine</td>
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<td>PK by UGT1A1 and NAT2 status</td>
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<td>Telaprevir</td>
<td>5/23</td>
<td>Efficacy by IL28B, safety by HLA</td>
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<tr>
<td>Boceprevir</td>
<td>5/13</td>
<td>Efficacy by IL28B, safety by ITPA</td>
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<tr>
<td>Ipilimumab</td>
<td>3/25</td>
<td>PGx of safety</td>
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<td>Belimumab</td>
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<td>Efficacy by SLE biomarkers</td>
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<td>Roflumilast</td>
<td>2/28</td>
<td>Safety potential by human vs. animal genome</td>
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<td>Vliazodone</td>
<td>1/21</td>
<td>PGx of efficacy and safety</td>
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<tr>
<td>Vemurafenib</td>
<td>8/17</td>
<td>Co-developed (BRAF status)</td>
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34 NME approvals in 2011
Have We Arrived?

2008

CDER
CDRH

2011

CDER
CDRH

2012+

CDER/CDRH

XALKORI®
CRIZOTINIB

ZELBORAF™
(vemurafenib) tablets

kalydeco™
(ivacaftor) tablets
<table>
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<tr>
<th>Year</th>
<th>Guidance Title</th>
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<tr>
<td>2005</td>
<td>Guidance on PG Data Submissions</td>
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<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>Guidance on PG Tests and Genetic Tests for Heritable Markers</td>
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<td>2010</td>
<td>ICH E16 Concept Paper on PG Biomarker Qualification: Format and Data Standards</td>
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<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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<td>Guidance on in vitro Companion Diagnostic Devices</td>
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<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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http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083374.htm
Paradigm Change and the ‘Progressive Reduction of Uncertainty’

- Attrition not necessarily amenable to changes in regulatory environment
- Advantage of personalized medicine development is not less data, but rather a higher probability of success; shift to “quick win, fast fail”
- Regulatory policy has attempted to foster use of applied genomics in drug development

GWAS IL28B predicts Peg-IFN/RBV response
Dozens replicate
FDA HepC guidance
Standard analysis in RCTs
New NDAs
Partnerships

• Domains
  – Effectively develop qualified tools, surrogate biomarkers
  – Create drug safety research infrastructure
  – Comparative effectiveness

• Selected FDA partnerships
  – Consortia: C-Path PSTC, SAEC, BC
  – Academia: CERSI, CSRC
  – Government: CMS, VA, DoD, AHRQ, NIH
  – HMOs, payers: Kaiser Permanente, HealthCore

• Is precompetitive collaboration an elusive goal?
Genomic Science Agenda

• **FDA Priorities**
  – Stimulate innovation in...personalized medicine
  – Ensure FDA readiness to evaluate emerging technologies
  – Harness data through information sciences

• **CDER Needs**
  – Access to post-market data sources
  – Improve risk assessment/management strategies
  – Develop predictive models of safety and efficacy
  – Improve clinical trial design, analysis, and conduct
  – Enhance individualization of patient treatment

• **PDUFA Enhancements**
  – Expand Agency biomarker and PGx teams

http://www.fda.gov/ScienceResearch/SpecialTopics/
Summary

• FDA is committed to personalizing medicine and individualizing therapeutics
• PGx characterization part and parcel to sound drug development, Rx/Dx co-development on the rise
• Improved industry guidance and inter-center/agency communication will promote genomic applications in drug development
• Clinical implementation of genomic technologies is and will continue to be complex (cultural, logistical, informatic), partnerships necessary