Pharmacogenomic Biomarkers in FDA Drug Labels

Robert Schuck, Pharm.D., Ph.D.
Genomics and Targeted Therapy
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
Food and Drug Administration
Outline

- Genomics at FDA
- Targeted therapies and companion diagnostics
  - Definitions
  - Labeling principles
  - Cross-labeling example
- Current and future landscape of pharmacogenomic drug labeling
- Emerging challenges
Problem Statement

Doctors are men who prescribe medicines of which they know little, to cure diseases of which they know less, in human beings of whom they know nothing.

Voltaire (1694 – 1778)
Pharmacogenomics Improves Our Understanding

*Doctors are men who prescribe:*

- medicines of which they know **little**, – provides additional information to assess the risk benefit profile
- to cure diseases of which they know **less**, - improves the precision with which we diagnose diseases
- in human beings of whom they know **nothing**, – prescribe drugs based on genotype (germline and/or somatic) and other genomic or proteomic biomarkers (in addition to patient factors)

- **All of this is conveyed in product labeling**
Office of Clinical Pharmacology - Genomics and Targeted Therapy Review Perspective
History of Genomics at FDA

2002

FDA commits to PGx

Integrated IND/NDA/BLA drug review

PDUFA V: industry invests in biomarkers and PGx

FDA-DIA PGx Workshop → “Safe harbor” concept

Clinical PGx in early-phase trials guidance

Companion Dx and enrichment guidances

Inception of VGDS (later VXDS); PGDS guidance

BQ Program

Drug-diagnostic co-approvals

Present
How do Genomic Factors Impact Drugs?

Intrinsic and Extrinsic Factors

- Disease Marker
- Metabolizing Enzyme
- Transporter

PK Variability

PD Variability

Response, efficacy, tolerability, safety

(Un)Intended Target

Immunologic/Idiosyncratic

Modified from Expert Opin Drug Metab Toxicol. 2008 May;4(5):529-44.
Improving Net Clinical Benefit Through Targeted Therapeutics

- Targeted therapies demonstrated benefits in specific subgroups of patients → optimizing efficacy further shifts risk-benefit
- May address an unmet medical need or be more effective than current standard of care treatments
- Drugs may have substantial benefits in targeted subsets
Definitions

Targeted Therapy
Drug that exerts its activity and benefit by modulating biological processes through interaction with a specific molecular target.

OR

Drug proposed to have a treatment effect in a subset of patients.

OR

Drug for which knowledge of patient “status” can inform individualized treatment decisions.

Companion Diagnostic

• Medical device, often an in vitro device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product
  – Most likely to respond
  – Increased risk of AE
  – Monitor response
## Targeted Therapy/Companion Diagnostic Co-Approvals in Oncology

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer/ Mechanism</th>
<th>Indicated Subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>NSCLC/ EGFR inhibitor</td>
<td>EGFR exon 19 deletions or exon 21 L858R substitution</td>
</tr>
<tr>
<td>Afatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Melanoma/ BRAF inhibitor</td>
<td>BRAF V600E mutation</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trametinib</td>
<td>Melanoma/ MEK inhibitor</td>
<td>BRAF V600E/K mutations</td>
</tr>
<tr>
<td>Panitumumab*</td>
<td>CRC/ EGFR inhibitor</td>
<td>KRAS wild-type (non-12/13)</td>
</tr>
<tr>
<td>Cetuximab*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Narrowing of indication and companion diagnostic approval occurred post-marketing
Product Labeling – General Concepts

- Medical product labeling must provide adequate information about the product and its use
- FDA requires product labeling to be balanced, scientifically accurate and not misleading
  - Clear instructions must be communicated to healthcare practitioners for drug prescribing and/or administration
- Personalized medicines and targeted therapies that may only be safe and effective in particular sub-populations must be labeled accordingly
  - May be addressed in numerous ways
Pharmacogenomic Labeling: Hierarchy of Action

INDICATIONS AND USAGE
Patient selection

DOSAGE AND ADMINISTRATION
Subgroup dosing

BOXED WARNING, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS, USE IN SPECIFIC POPULATIONS
Differential safety

CLINICAL PHARMACOLOGY
Impact on PK/PD

CLINICAL STUDIES
Substantial evidence of observed differences
Cross-Labeling with Companion Diagnostics

- In cases where a therapeutic product is approved together with a companion diagnostic device, the labeling of the two products must be consistent.

- In cases where a companion diagnostic is developed for use with an already approved therapeutic product, it may be necessary to update the therapeutic product’s labeling with appropriate test-related information.
  - When such information is essential to the safe and effective use of the product.
Example – Targeted Therapy (afatinib)

INDICATIONS AND USAGE

GILOTRIF is a kinase inhibitor indicated for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test (1).

Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations (1).
Example – Companion Diagnostic

Intended Use

The therascreen EGFR RGQ PCR Kit is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the epidermal growth factor receptor (EGFR) gene in DNA derived from formalin-fixed paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tumor tissue. The test is intended to be used to select patients with NSCLC for whom GILOTRIF™ (afatinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated. Safety and efficacy of GILOTRIF (afatinib) have not been established in the patients whose tumors have L861Q, G719X, S768I, exon 20 insertions, and T790M mutations, which are also detected by the therascreen EGFR RGQ PCR Kit.
## 14 CLINICAL STUDIES

Non-small Cell Lung Cancer (NSCLC)

Table 4: Objective Tumor Responses in GILOTRIF-Treated Patients Based on Investigator Assessment in the "Other" (Uncommon) EGFR Mutation Subgroup

<table>
<thead>
<tr>
<th>EGFR Mutations</th>
<th>Number of GILOTRIF-Treated Patients</th>
<th>Number of Patients with Partial Responses</th>
<th>Duration of Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>L858R and T790M</td>
<td>5</td>
<td>1</td>
<td>6.9 months</td>
</tr>
<tr>
<td>L858R and S768I</td>
<td>2</td>
<td>1</td>
<td>12.4+ months</td>
</tr>
<tr>
<td>S768I</td>
<td>1</td>
<td>1</td>
<td>16.5+ months</td>
</tr>
<tr>
<td>G719X</td>
<td>3</td>
<td>1</td>
<td>9.6 months</td>
</tr>
</tbody>
</table>

+ Censored observation
Pharmacogenomics and Immunogenicity

- Hemophilia B caused by mutations in \textit{F9} gene
- Treated with recombinant FIX
- Some patients develop immune response resulting in drug neutralizing antibodies called inhibitors

The Next Generation of Medicine Is Upon Us
“The Gap” Is Narrowing
Pharmacogenomic Labeling Principles

• Labeling should include PGx information to:
  – Inform prescribers about the impact (or lack of impact) of genotype on phenotype
  – Indicate whether a genomic test is available
    • If so, indicate whether testing should be considered, is recommended, or is necessary

• If applicable, a “Pharmacogenomics” subsection (12.5) should be included in the CLINICAL PHARMACOLOGY Section
  – Include clinically relevant data or information on the effect of genetic variation on drug therapy
Potentially Applicable PGx information

- Information on allele frequencies
- Description of functional effects of genomic variants
- Dosing and patient selection based on genotype
  - May be applicable to biologics in cases of a gene-dose effect
- Description of pharmacogenomic studies that provided evidence of genetically-based differences in drug benefit or risk
  - Targeted therapies, immunogenicity
PGx Biomarkers in Labeling – Current Landscape

- **169 gene-drug pairs**
  - 141 drugs, 45 biomarkers
  - 47% metabolism/transport
  - 30% target/pathway
  - 23% immunologic/other safety

- **76 actionable**
  - Others descriptive of study design feature or presence/absence of gene-drug interaction

• 15 gene-drug pairs
  -12 drugs, 8 unique biomarkers
  • 75% target/pathway
  • 25% safety
## Current Biologic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Therapeutic Area</th>
<th>Biomarker</th>
<th>Type</th>
<th>Label Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ado-Trastuzumab</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Emtansine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Cetuximab (2)</td>
<td>Oncology</td>
<td>KRAS</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Denileukin Diftitox</td>
<td>Oncology</td>
<td>IL2RA</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Oncology</td>
<td>MS4A1</td>
<td>Target/Pathway</td>
<td>Clinical Studies</td>
</tr>
<tr>
<td>Panitumumab (1)</td>
<td>Oncology</td>
<td>EGFR</td>
<td>Target/Pathway</td>
<td>Clinical Studies</td>
</tr>
<tr>
<td>Panitumumab (2)</td>
<td>Oncology</td>
<td>KRAS</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>Rheumatology</td>
<td>G6PD</td>
<td>Safety</td>
<td>Contraindication-</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Rasburicase (1)</td>
<td>Oncology</td>
<td>G6PD</td>
<td>Safety</td>
<td>Box Warning</td>
</tr>
<tr>
<td>Rasburicase (2)</td>
<td>Oncology</td>
<td>CYB5R1-4</td>
<td>Safety</td>
<td>Warnings &amp; Precautions</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Oncology</td>
<td>MS4A1</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Tositumomab</td>
<td>Oncology</td>
<td>MS4A1</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Oncology</td>
<td>ERBB2</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>Endocrinology</td>
<td>LDLR</td>
<td>Target/Pathway</td>
<td>Indications &amp; Usage</td>
</tr>
</tbody>
</table>
Targeted Therapies – Moving Beyond Oncology

Novel biomarkers for asthma stratification and personalized therapy

de Jong et al. Arthritis Research & Therapy 2014, 16:110
http://arthritis-research.com/content/16/3/110

Moving towards personalized medicine in rheumatoid arthritis

Tamara D de Jong¹, Saskia Vosslamber¹ and Cornelis L Verweij¹,²

See related research by Dennis et al, http://arthritis-research.com/content/16/2/R90
Emerging Challenges in Pharmacogenomic Labeling

- Next-Gen Sequencing
- RNA-Seq
- Rare Diseases
  - Rare Subsets
  - Rare Mutations
Summary

- Pharmacogenomics can improve our understanding of drugs, diseases, and patients
  - Product labeling must accurately convey pharmacogenomic information
  - Accurate cross labeling with companion diagnostics
- Targeted (targeted biologic) therapies are rapidly entering the market
  - Most examples of pharmacogenomics in biologic drug labeling are related to patient selection and safety issues
- Big data and rare diseases present challenges to pharmacogenomic labeling for both small and large molecule drugs
Additional Resources

FDA Guidance for Industry: Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements


FDA Guidance for Industry: Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling


Table of Pharmacogenomic Biomarkers in Drug Labeling:

- [http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm](http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)
Questions???

Guidance for Industry

Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-301), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document, contact (CDER) Lawrence Lesko at 301-796-1565 or Sheri-Mae Hung at 301-796-1541, or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 301-827-1800, or Changting Handelschild at 301-827-3947, or (CDRH) Frances Kalush at 301-796-3408.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2011
Clinical Pharmacology