Precision Medicine: The New Normal

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This presentation reflects the views of the speaker and should not be construed to represent FDA’s policies.
Thank You!

Genomics and Targeted Therapy Group Staff/Fellows/Affiliates/Alumni
• Christian Grimstein, Rosane Charlab Orbach, Padmaja Mummaneni, Jeff Kraft, Sarah Dorff, Anu Ramamoorthy, Bart Rogers, Bob Schuck, Kate Drozda, Jilian Sun, Oluseyi Adeniyi, Spencer, Todd
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Office of New Drugs
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• Marni Hall*, David Graham, J.R. Williams*, Judy Staffa†

Center for Drug Evaluation and Research
• Janet Woodcock, Bob Temple, Bob Guidos, Rich Moscicki*

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• Liz Mansfield*, Bob Becker, David Litwack, Pam Bradley, et al.

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• John Wagner, Deanna Kroetz, Sarah Robertson, Naoto Uemura, Mark Dresser, Valentina Shakhnovich, Nina Isoherranen, Chris Austin, Sharon Terry
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* Former position; † At FDA in a different organization than is listed
A personal vision of the future...

Genomic information will be universally accessible and portable
Patient care and clinical research will be more seamless, and mechanistically-driven
Real-time synthesis of evidence from patient experience will support clinical decision-making
Realizing the Vision

• In post-approval therapeutic optimization...
  – Access to reliable “next-generation” technologies in the clinic
  – Health record infrastructure to absorb dense information
  – Common data architecture for pooling and analysis across platforms

• In new drug development...
  – Knowledge and exploitation of molecular pathology/pharmacology
  – High-throughput exploration to resolve response variability
  – Robust biomarker to detect drug effects
The “Virtuous Circle” of FDA’s Genomics and Targeted Therapy Group

Promote the rational application of biomarkers to support the targeted development and use of drugs through regulatory review, policy development, and research.
Agenda

• Optimizing benefits and risks of marketed drugs

• Proactive management of the investigational pipeline

• Building a regulatory science toolkit
Agenda

- Optimizing benefits and risks of marketed drugs
- Proactive management of the investigational pipeline
- Building a regulatory science toolkit
Effectiveness of clopidogrel dose escalation to normalize active metabolite exposure and antiplatelet effects in CYP2C19 poor metabolizers
Genetic Determinants of Response to Clopidogrel and Cardiovascular Events

Tabassome Simon, M.D., Ph.D., Céline Verstuyt, Pharm.D., Ph.D., Murielle Mary-Krause, Ph.D., Lina Quteineh, M.D., Elodie Drouet, M.Sc., Nicolas Méneveau, M.D., P. Gabriel Steg, M.D., Ph.D., Jean Ferrières, M.D., Nicolas Danchin, M.D., Ph.D., and Laurent Becquemont, M.D., Ph.D., for the French Registry of Acute ST-Elevation and Non–ST-Elevation Myocardial Infarction (FAST-MI) Investigators

Cytochrome P-450 Polymorphisms and Response to Clopidogrel


Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study

Jean-Philippe Collet, Jean-Sébastien Huot, Anna Penq, Eric Villard, Jean-Baptiste Estève, Johanne Silvain, Laurent Payot, Delphine Brugier, Guillaume Cylja, Farzin Beygui, Gilbert Bensimon, Christian Fünke-Buentano, Gilles Montalescot
WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE

The effectiveness of Plavix results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]. Plavix at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed “CYP2C19 poor metabolizers”). Tests are available to identify patients who are CYP2C19 poor metabolizers [see Clinical Pharmacology (12.5)]. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.
### Other Selected Post-Marketing Labeling Revisions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism Enzyme</th>
<th>Adverse Effect</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>POLG</td>
<td>Liver failure</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Codeine/Tramadol</td>
<td>CYP2D6</td>
<td>Respiratory depression</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Pimozide</td>
<td>CYP2D6</td>
<td>Sudden death</td>
<td>Dose cap/slow titration</td>
</tr>
<tr>
<td>Citalopram</td>
<td>CYP2C19</td>
<td>QT prolongation</td>
<td>Dose cap</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-B<em>1502, HLA-A</em>3101</td>
<td>Severe skin reactions</td>
<td>Warnings</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>SLCO1B1</td>
<td>PK difference</td>
<td>Treat as usual</td>
</tr>
</tbody>
</table>
Factors Guiding the Strength of Prescribing and Testing Recommendations

- Population-level utility
- Evidence quality
- Evidence gaps
- Generalizability

Context
- Outcome severity
- Predictive value
- Available therapies
- Test accessibility

Uncertainty
- Test everyone
- Test a targeted, at-risk subset
- Test at a certain threshold
- Silent / clinical judgement

Testing approaches
• **Actionable biomarker:** labeling includes a specific prescribing recommendation that is included in one of the following label sections: 1) Boxed Warning, 2) Indications and Usage, 3) Dosage and Administration, 4) Contraindications, or 4) Warnings and Precautions.

• Biomarkers may be any genomic biomarker or other selected protein biomarker that are used for patient selection.
Agenda

• Optimizing benefits and risks for marketed drugs

• Proactive management of the investigational pipeline

• Building a regulatory science toolkit
# Uses of Genomics in Drug Development

<table>
<thead>
<tr>
<th>Preemptive</th>
<th>Retrospective</th>
<th>Prospective</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Validate targets for drug development&lt;br&gt;• Predict drug toxicities&lt;br&gt;• Define target population</td>
<td>• Explain variable responses to drug&lt;br&gt;• Identify (non-)responders or patients with adverse reactions&lt;br&gt;• Identify risk for serious drug interactions</td>
<td>• Predict drug exposure&lt;br&gt;• Minimize noise&lt;br&gt;• Identify patients at risk for disease or event&lt;br&gt;• Select patients likely to respond to drug</td>
</tr>
</tbody>
</table>
A Tale of Two Drugs

Lead compound
Proof of concept
NDA
Biomarker discovery
Pivotal trial
Approval
Clinical trial (safety)
Pivotal trial
Accelerated approval
Withdrawal
NDA PMA

~22 years

Lead compound
Biomarker identification
Proof of concept in marker +
Pivotal trial in marker + IVO test
Accelerated approval
Approval
Clinical trial (safety/ activity)
LDT CTA
Pre-IDE/IDE
NDA Rolling PMA
Confirmatory trial

~8 years
Feb 26, 2017; selected examples
* Approved companion or complementary dx
† Not “essential”
## Innovations in Drug Development

### Selected Examples

<table>
<thead>
<tr>
<th>Disease/mechanism</th>
<th>Drug(s)</th>
<th>Indicated subset in FDA-approved labeling</th>
<th>Low-frequency molecular alteration(s) within disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC/ EGFR inhibitor</td>
<td>Erlotinib</td>
<td>EGFR exon 19 deletions or exon 21 L858R substitution</td>
<td>Additional EGFR mutations including L861Q, G719A/C/S, and T790M</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Afatinib</td>
<td>Non-resistant EGFR mutations</td>
<td></td>
</tr>
<tr>
<td>Melanoma/BRAF inhibitor</td>
<td>Vermurafenib</td>
<td><strong>BRAF V600E mutation</strong></td>
<td><strong>BRAF V600K/D/R</strong></td>
</tr>
<tr>
<td></td>
<td>Dabrafenib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma/MEK inhibitor</td>
<td>Trametinib</td>
<td><strong>BRAF V600E/K mutations</strong></td>
<td><strong>BRAF V600D/R</strong></td>
</tr>
<tr>
<td>Ovarian cancer/PARP inhibitor</td>
<td>Olaparib</td>
<td>Deleterious or suspected deleterious germline <strong>BRCA mutations</strong></td>
<td>Most individual <strong>BRCA1</strong> and <strong>BRCA2</strong> mutations occur at low frequency in ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>Rucaparib</td>
<td>Deleterious germline and/or somatic <strong>BRCA mutations</strong></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer/EGFR inhibitor</td>
<td>Cetuximab</td>
<td><strong>KRAS wildtype (not RAS mutations)</strong></td>
<td>Low-frequency <strong>KRAS</strong> mutations outside of exon 2, other <strong>RAS family mutations</strong></td>
</tr>
<tr>
<td></td>
<td>Panitumumab</td>
<td><strong>KRAS wildtype (exon 2) (not RAS mutations)</strong></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis/CFTR potentiator</td>
<td>Ivacaftor</td>
<td><strong>CFTR mutations that are responsive to ivacaftor based on clinical and/or in vitro assay data</strong></td>
<td></td>
</tr>
<tr>
<td>Duchenne muscular dystrophy/exon skipper</td>
<td>Eteplirsen</td>
<td><strong>DMD exon 51 skipping amenable</strong></td>
<td>All individual mutations occur at low frequencies</td>
</tr>
</tbody>
</table>

Schuck, et al. CPT 2018
Precision Drug Development Practices: Cardiometabolic Disorders

...Phase 2 or 3 development programs for cardiac and metabolic diseases

31% ...of drug targets (n=86) have a genetic association supporting the corresponding indication

47% ...of clinical trial protocols (n=155), covering 66 programs, have exploratory aims to study genomic biomarkers

...clinical trial protocols use genomic biomarkers prospectively in
  • Patient selection
  • Patient stratification
  • Subgroup hypothesis testing

O. Adeniyi
Agenda

• Optimizing benefits and risks of marketed drugs

• Proactive management of the investigational pipeline

• Building a regulatory science toolkit
Summary

• Diverse data streams and resource are required to inform decision-making

• Investigational and new drugs have benefitted from precision medicine principles

• Medicine (clinical pharmacology) is an art, information is a medium
FDA U.S. FOOD & DRUG ADMINISTRATION
## Post-Marketing Commitments and Requirements

<table>
<thead>
<tr>
<th>Validation</th>
<th></th>
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<tbody>
<tr>
<td>Clopidogrel</td>
<td>CYP2C19 effects on PK/PD</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CD86 effects on immune-related AEs</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>CYP450 genotype effects on outcomes</td>
</tr>
<tr>
<td>Belinostat</td>
<td>Safety and PK by UGT genotype</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Discovery</th>
<th></th>
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<tbody>
<tr>
<td>Telaprevir</td>
<td>Exploratory GWAS for skin reactions</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>DNA banking for agranulocytosis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>DNA banking for HSTCL</td>
</tr>
<tr>
<td>Agalsidase alfa</td>
<td>Mutation effects on renal disease</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>DNA banking for skin reactions</td>
</tr>
</tbody>
</table>
Synthetic Oligonucleotides and Other Genetically Targeted Therapies

DNA

RNA

Protein

CRISPR/Cas9

Antisense (mipomersen)
Splice-altering (eteplirsen, nusinersen)
siRNA
microRNA
mRNA replacement

Aptamers (pegatinib)
CpG/TLR
Investigational New Drug and Marketing Application Review Issues

- What biomarkers/genetic factors need to be prospectively assessed?
  - (*disease, target, pathway, disposition*)

- Are biomarker/genomic studies needed to resolve variability in exposure or response?
  - (*variability, race effects; certain AEs*)

- Do genetic studies indicate a potential for target-based toxicities?
  - (*genetic epidemiology of drug target or pathway*)

- Is the target population appropriate?
  - (*molecular diversity, marker-negatives*)

- Is review of the investigational or to-be-marketed in vitro diagnostic needed?
  - (*enrichment/stratification; codevelopment*)

- Are different dosing or patient selection recommendations needed on the basis of differences in exposure or response across biomarker subgroups?