Evolution of Precision Medicines from a Regulatory Perspective

ASCPT Annual Meeting
March 15, 2019

Mike Pacanowski
Office of Clinical Pharmacology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
A Brief History of Medicines
Past, Present, and Future of Precision Medicine

Managing response variability

Targeting genetic drivers of disease

Modifying the genome

Present
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.
# Notable CDER Approvals 2018
(Total Novel Drug N=59)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Disease or Condition</th>
<th>Biomarker</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patisiran*, Inotersen*</td>
<td>Polyneuropathy of hereditary transthyretin-mediated amyloidosis</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Tezacaftor* + ivacaftor</td>
<td>Cystic fibrosis</td>
<td>Responsive CFTR variant</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Migalastat*</td>
<td>Fabry disease</td>
<td>Amenable GLA variant</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Ivosidenib*</td>
<td>Relapsed or refractory AML</td>
<td>Susceptible IDH1 mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Binimetinib*, encorafenib*</td>
<td>Metastatic melanoma</td>
<td>BRAF V600E/K mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Dacomitinib*</td>
<td>Metastatic NSCLC</td>
<td>EGFR exon 19 deletion or L858R</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Larotrectinib*</td>
<td>Solid tumors</td>
<td>NTRK gene fusion</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Gileritinib*</td>
<td>Relapsed or refractory AML</td>
<td>FLT3 mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Lorlatinib*</td>
<td>Metastatic NSCLC</td>
<td>ALK gene rearrangement</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Talazoparib*</td>
<td>Advanced or metastatic breast cancer</td>
<td>Germline BRCA mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Afatinib</td>
<td>Metastatic NSCLC</td>
<td>Non-resistant EGFR mutation</td>
<td>Patient Selection</td>
</tr>
<tr>
<td>Amifampridine*</td>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>NAT2 genotype</td>
<td>Dosing</td>
</tr>
<tr>
<td>6-MP/TG/AZA</td>
<td>ALL/acute nonlymphocytic leukemia</td>
<td>TPMT/NUDT15 genotype</td>
<td>Dosing</td>
</tr>
<tr>
<td>Avatrombopag*</td>
<td>Thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure</td>
<td>FVL</td>
<td>Warning</td>
</tr>
<tr>
<td>Lofexidene*</td>
<td>Opioid withdrawal symptoms</td>
<td>CYP2D6 genotype</td>
<td>Informational</td>
</tr>
<tr>
<td>Elagolix*</td>
<td>Severe pain associated with endometriosis</td>
<td>SLCO1B1 genotype</td>
<td>Informational</td>
</tr>
</tbody>
</table>

* New molecular entity
Managing Response Variability
Managing Response Variability

For more information see: Guidance for Industry - Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling
Guidance for Industry
Pharmacogenomic Data Submissions

U.S. Department of Health and Human Services
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2005

Guidance for Industry and FDA Staff
Pharmacogenetic Tests and Genetic Tests for Heritable Markers

Document issued on June 30, 2007

The draft of this guidance was issued on February 5, 2006

U.S. Department of Health and Human Services
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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

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)
January 2015

Clinical Pharmacology
Clinical Medical

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

1. PURPOSE AND SCOPE

This staff manual guide (SMG) provides procedures for FDA staff when a new drug product is submitted for approval. It is primarily intended as a guide to the development and implementation of regulatory policies and procedures for the review of new drug applications. The intent of this guide is to ensure that the review and approval process is consistent, transparent, and responsive to the needs of stakeholders. This guide is not intended for use by the public or industry when making submissions to the Agency.

The SMG is applicable to new products and drugs of biological products. It should be noted that the content and format of this guide have been approved by the Assistant Commissioner for Policy and Planning, and that the present impact products reviewed in more than one Center within the Agency.

This SMG does not apply to any non-prescription processes for drug products or to any non-prescription processes for drug products or to any new drug prod...
Characterizing Genetic Effects on Response Post-Approval

- Ivosidenib was approved for the treatment of relapsed or refractory AML with a susceptible IDH1 mutation
- Patients with more co-occurring mutations tended to have lower response rates

Characterize the long-term safety of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG120-C-001, A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation. Include data from approximately 205 patients with relapsed or refractory AML.

Include in the final study report the exploratory subgroup analyses and corresponding subject level data related to pre- and post-treatment cytogenetics, specific IDH1 mutations, and mutation analyses for other genes as obtained under the trial protocol.
Incorporating Pharmacogenomic Markers into Prescribing Recommendations in the Post-Marketing Setting

**Time to Inclusion of PGx Information in Labeling**
(Selected Examples)
Incremental Enhancements to Improve Benefit-Risk

Inherited NUDT15 Variant Is a Genetic Determinant of Mercaptopurine Intolerance in Children With Acute Lymphoblastic Leukemia

Jan J. Yang, Wendy Landier, Wenjian Yang, Changfeng Liu, Lindsey Hegenmuller, Cheng Cheng, Dingqing Pei, Tianjun Chen, Kristine K. Crews, Nancy Kornegay, F. Leevine Wong, William E. Evans, Ching-Hsun Pei, Sunita Bhatia, and Mary V. Belling

<table>
<thead>
<tr>
<th>Genetic Risk Score</th>
<th>0</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>569</td>
<td>40</td>
<td>27</td>
<td>44</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Median (%)</td>
<td>67.7</td>
<td>70.0</td>
<td>65.1</td>
<td>41.5</td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>25th percentile (%)</td>
<td>70.8</td>
<td>54.4</td>
<td>48.8</td>
<td>31.6</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>75th percentile (%)</td>
<td>96.7</td>
<td>90.7</td>
<td>87.1</td>
<td>48.6</td>
<td>9.7</td>
<td></td>
</tr>
</tbody>
</table>

P = 3.2 x 10^-6

MP Dose Intensity (μg/kg/day)

TPMT  NUDT15

WT WT HET WT HET HET HOM for either
2.2 Dosage in Patients with TPMT and/or NUDT15 Deficiency
Consider testing for TPMT and NUDT15 deficiency in patients who experience severe bone marrow toxicities or repeated episodes of myelosuppression [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.5)].

*Homozygous deficiency in either TPMT or NUDT15*
Patients with homozygous deficiency of either enzyme typically require 10% or less of the standard PURIXAN dosage. Reduce initial dosage in patients who are known to have homozygous TPMT or NUDT15 deficiency.

*Heterozygous deficiency in TPMT and/or NUDT15*
Reduce the PURIXAN dosage based on tolerability. Most patients with heterozygous TPMT or NUDT15 deficiency tolerate recommended mercaptopurine doses, but some require dose reduction based on toxicities. Patients who are heterozygous for both TPMT and NUDT15 may require more substantial dosage reductions.

5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
The most consistent, dose-related toxicity of PURIXAN is bone marrow suppression, manifested by anemia, leukopenia, thrombocytopenia, or any combination of these. Monitor CBC and adjust the dose of PURIXAN for severe neutropenia and thrombocytopenia.

Evaluate patients with repeated severe myelosuppression for thiopurine S-methyltransferase (TPMT) or nucleotide diphosphatase (NUDT15) deficiency. TPMT genotyping or phenotyping (red blood cell TPMT activity) and NUDT15 genotyping can identify patients who have reduced activity of these enzymes. Patients with homozygous TPMT or NUDT15 deficiency require substantial dosage reductions of PURIXAN [see Dosage and Administration (2.2) and Clinical Pharmacology (12.5)].
Pharmacogenetic Testing

Goals: Reliable tests, resources to support clinical validation and interpretation of results
Genetically Targeted Therapies
Molecular Enrichment Approaches

Evaluate a single molecular alteration
Evaluate each alteration in separate trials
Group similar alterations for single trial
Enroll all patients with clinical disease

Highly enriched trial design
- Highly targeted drug
- Minimal molecular heterogeneity in disease

Less enriched trial design
- Less targeted drug
- All or most molecular alterations expected to respond
Migalastat

• Fabry disease is a rare X-linked disease caused by hundreds of different mutations in the gene encoding alpha-galactosidase A (aGalA), GLA

• Migalastat is a small molecule chaperone that binds aGalA, allowing it to traffic to lysosomes to break down glycosphingolipids

• Patients with “amenable” variants, based on in vitro response in a HEK-293 cell system, were enrolled in clinical trials

→ Indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data
Migalastat

- Are the consequences of individual mutations sufficiently well understood?
- Dose the in vitro assay directly measure the function of the human protein affected by the disease?
- Is the drug’s mechanism well-understood and consistent with the mechanism of disease?
- Are clinical data from both drug-responsive and -nonresponsive mutations available?
- Has the assay been formally validated?
- Are raw instrument data available so that results can be recreated?

Tissue Agnostic Drug Development

• Traditional cancer drug development paradigm
  – Based on tumor type, e.g.,
    • Previously untreated pancreatic cancer
    • HCC after previous sorafenib treatment
  – Based on a biomarker within a tumor type, e.g.,
    • HER-2 positive breast or gastric cancer
    • RAS wild-type colorectal cancer

Lemery, et al. NEJM 2017
Larotrectinib

- Tropomyosin receptor kinase inhibitor
- Antitumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions
- Efficacy based on data from patients with NTRK1/2/3 gene fusions enrolled in three single-arm trials
- Indicated for adults and children with solid tumors that have NTRK gene fusion (without known acquired resistance mutation), are metastatic/nonresectable, have no alternative

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>N</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcoma</td>
<td>11</td>
<td>91%</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>12</td>
<td>83%</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>7</td>
<td>100%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>100%</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>75%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
<td>50%</td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
<td>25%</td>
</tr>
<tr>
<td>GIST</td>
<td>3</td>
<td>100%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>SD, NE</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
<td>SD</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>PD</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
<td>SD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fusion Partner</th>
<th>N</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV6-NTRK3</td>
<td>25</td>
<td>84%</td>
</tr>
<tr>
<td>TPM3-NTRK1</td>
<td>9</td>
<td>56%</td>
</tr>
<tr>
<td>LMNA-NTRK1</td>
<td>5</td>
<td>40%</td>
</tr>
<tr>
<td>Inferred ETV6-NTRK3</td>
<td>3</td>
<td>100%</td>
</tr>
<tr>
<td>IRF2BP2-NTRK1</td>
<td>2</td>
<td>CR, PR</td>
</tr>
<tr>
<td>SQSTM1-NTRK1</td>
<td>2</td>
<td>PR, PR</td>
</tr>
<tr>
<td>PDE4DIP-NTRK1</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>PPL-NTRK1</td>
<td>1</td>
<td>CR</td>
</tr>
<tr>
<td>STRN-NTRK2</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>TPM4-NTRK3</td>
<td>1</td>
<td>CR</td>
</tr>
<tr>
<td>TPR-NTRK1</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>TRIM63-NTRK1</td>
<td>1</td>
<td>PR</td>
</tr>
<tr>
<td>CTRC-NTRK1</td>
<td>1</td>
<td>SD</td>
</tr>
<tr>
<td>GON4L-NTRK1</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>PLEKHA6-NTRK1</td>
<td>1</td>
<td>SD</td>
</tr>
<tr>
<td>GON4L-NTRK1</td>
<td>1</td>
<td>NE</td>
</tr>
<tr>
<td>PLEKHA6-NTRK1</td>
<td>1</td>
<td>SD</td>
</tr>
</tbody>
</table>
Considerations for Tissue Agnostic Drug Development

• Establishment of indication-defining biomarkers

• Differences in mutations and resistance mechanisms across cancers
  – BRAF and MEK inhibitors in BRAF V600 colorectal cancer

• Design of clinical trials
  – Available therapies, unmet medical need, magnitude of benefit, size of patient population

• Companion diagnostic development

Genetically Targeted Technologies/Therapies

- CRISPR/Cas9
- Antisense (mipomersen, inotersen)
  - Splice-altering (eteplirsen, nusinersen)
  - siRNA (patisiran)
- microRNA
- mRNA replacement
- Aptamers (pegaptinib)
- CpG/TLR
History of Oligo IND/NDA Submissions and NDA Approvals

- 1992: 1st ASO submissions
- 1995: 1st siRNA submission
- 1996: 1st CpG submission
- 1998: 1st aptamer
- 2004: 1st antagomir
- 2010: pegaptanib approval
- 2013: mipomersen approval
- 2016: eteplirsen approval
- 2017: volanesorsen, nusinersen, patisiran, inotersen

Courtesy of Xuan Chi (OND, DCRP) and PTCC Oligonucleotide Subcommittee 2018
Synthetic Oligonucleotides

Unique Challenges

- Nonclinical pharmacology
  - Animal toxicology – target may not be conserved
  - PK – primate models to estimate exposure and dosage
- Clinical pharmacology
  - Organ impairment – renally cleared, some hepatically targeted
  - Drug interactions – endo/exonuclease metabolism, limited interaction potential
  - QT – unlikely to interact with HERG
  - Immunogenicity – recognized as non-self, anti-drug antibodies can develop
- Safety
  - Thrombocytopenia (consistent, moderate vs. severe, sporadic)
  - Immune-mediated AEs
A tailormade drug developed in record time may save girl from fatal brain disease

By Jocelyn Kaiser | Oct. 19, 2018, 9:00 PM

For years, a Colorado couple searched for an explanation for why their bright, active little girl was having increasing trouble walking, speaking, and seeing. In December 2016, Julia Vitarello and Alek Makovec learned that 6-year-old Mila Makovec almost certainly had Batten disease, an inherited and fatal neurodegenerative disorder. Now, in a stunning illustration of personalized genomic medicine, Mila is receiving a drug tailored to her particular disease-causing DNA mutation—and it appears to have halted the condition's progression.

Today at the annual meeting of The American Society of Human Genetics in San Diego, California, researchers told the story of how in less than a year, they went from sequencing Mila's genome to giving her a synthetic RNA molecule that helps her cells ignore her genetic flaw and make a needed protein. The same steps could help some other patients with diseases caused by unique mutations in a single gene, they said.

The Future
Gene therapy
  RNAi
  Precision medicines
  Regenerative medicine

Artificial intelligence
  Machine learning
  Modeling and simulation
  Systems
  Data lakes

Interventions

Measurements
  Omics
  Wearables
  Surrogates
  PROs

Complex, innovative trials
  EHRs
  Telemedicine

Analytics

Collection
Summary

• Technological advancements have facilitated the translation of pharmacogenetics and paved the way for development of targeted therapies

• FDA has communicated via guidance to industry current thinking on emerging technologies and continues adapting to the changing landscape

• Further understanding genomic and other mechanisms of disease will give rise to an increasing number of complex and personalized treatment modalities