Changes in the Drug Development and Regulatory Landscape: Focus on Biomarkers

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Disclaimers

• Views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

• I do not have any financial disclosures regarding pharmaceutical drug products
Overview

• Changes in the landscape

• Novel uses of biomarkers in regulatory approvals – some examples

• What we’re facing: IND and NDA workload

• Biomarkers – the “BEST” approach

• Biomarker qualification: pathways

• BQP: the steps to validation
Changes in drug and drug regulatory landscape

**Changing drug development program targets**
- Focus on rarer diseases - fewer programs targeting common, chronic diseases
- Common disease programs targeting subsets, poorly responsive subsets
- More drug programs targeting molecular disease “subsets”
- Changing nosology – tissue agnostic indication

**Changing platforms**
- More biologicals vs small molecules
- Novel platforms (e.g., antisense oligonucleotides)
- Increase in cellular / regenerative medicine, gene therapy approaches

**Changing development approaches**
- Use of “real world evidence” to support drug effectiveness, broaden labels
- Accelerating tools for drug development
- Use of mobile technologies in trials (and RWD)
- Innovations in trial design and analysis

**Changing regulatory review and advice**
- Rising use of “fast track” and accelerated approval pathways
- Changing CDER application review approaches: interdisciplinary reviews, streamlined reviews
- Pilot posting study reports
- Accelerating availability of guidances

**Changing role of the patient**
- Patient at “center” of drug development: “patient-focused drug development”
- Use of mobile technologies to collect patient-based observations

- CDER will continue to conduct thorough, scientific, data-driven reviews and decisions
- Ongoing (but expanding) collaboration with stakeholders (patients and caregivers, academia, industry, other regulators) to meet unmet medical needs
Changes in drug and drug regulatory landscape

**Changing drug development program targets**
- Focus on *rarer* diseases - fewer programs targeting common, chronic diseases
- Common disease programs targeting *subsets*, poorly responsive subsets
- More drug programs targeting *molecular disease “subsets”*
- Changing nosology – *tissue agnostic* indication

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**BUT...what’s not changing....**
- CDER will continue to conduct thorough, scientific, data-driven reviews and decisions
- Ongoing (but expanding) collaboration with stakeholders (patients and caregivers, academia, industry, other regulators) to meet unmet medical needs
Effect of ivacaftor on lung function in patients with cystic fibrosis in a responsive mutation

Mutations causing decrease in CFTR transporter function

Patients with a functional loss mutation (G551D) treated with ivacaftor vs pbo

Mutations causing absence of CFTR transporter protein

From S Rowe et al NEJM 2005
Using *in vitro* data to expand indicated use of ivacaftor in cystic fibrosis

**In vitro sweat chloride assay** – testing drug effect on Cl⁻ transport in cell line expressing different CF mutations

Previously studied responsive mutation

- E193K
- G551S*
- F1052V
- R117H*, S1251N*, D1152H*
- S549N*, G1069R
- G178R*, D579G*
- G1349D*, K1060T
- S945L*
- G551D*, S1255P*, R74W, A1067T
- R1070W*, D110H, R347H*, D1270N
- G1244E*, P67L*, D110E, R352Q*
- E56K, S549R*
- F508del* and other mutations#

Mutations showing response – increase in chloride transport

Specific mutations added to labeled indication

Not indicated

From Ivacaftor prescribing information
Changing definition of disease: tissue agnostic approval

Changing program targets

- Increasing focus on rare diseases, fewer large programs targeting chronic disease
- Targeted therapies — targeting molecular “subsets”
- Changing nosology — tissue agnostic indication

Traditional development paradigm

- Based on tumor type, e.g.,
  - Previously untreated pancreatic cancer
  - Hepatocellular cancer 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

- Microsatellite instability/mismatch repair deficiency lead to increased neoantigen burden in tumors
- May augment immune-targeting by T cells
- Wide range of tumor types with these defects
- Increases susceptibility to immune modulatory drug

- Bonneville et al., JCO Precision Oncology, 2017
Changing definition of disease: tissue agnostic approval

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• Bonneville et al., JCO Precision Oncology, 2017
Data supporting pembrolizumab MSI-H, dMMR approval – agnostic of cancer type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N</th>
<th>ORR N (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>90</td>
<td>32 (36%)</td>
<td>(26, 46)</td>
</tr>
<tr>
<td>Non-CRC</td>
<td>59</td>
<td>27 (46%)</td>
<td>(33, 59)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>14</td>
<td>5 (36%)</td>
<td>(13, 65)</td>
</tr>
<tr>
<td>Biliary</td>
<td>11</td>
<td>3 (27%)</td>
<td>(6, 61)</td>
</tr>
<tr>
<td>Gastric/GEJ</td>
<td>9</td>
<td>5 (56%)</td>
<td>(21, 86)</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>6</td>
<td>5 (83%)</td>
<td>(36, 100)</td>
</tr>
<tr>
<td>Small Int.</td>
<td>8</td>
<td>3 (38%)</td>
<td>(9, 76)</td>
</tr>
<tr>
<td>Breast</td>
<td>2</td>
<td>PR, PR</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
<td>PR, SD</td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>1</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Esophageal</td>
<td>1</td>
<td>PR</td>
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</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>PD</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal</td>
<td>1</td>
<td>PR</td>
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<tr>
<td>SCLC</td>
<td>1</td>
<td>CR</td>
<td></td>
</tr>
<tr>
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<td>1</td>
<td>PD</td>
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</tbody>
</table>

KM-DOR in 59 responding patients

At time of approval, responses observed in at least 14 MSI-H/dMMR tumor types; many ongoing

Implication: indication related to common defects across cancer types (MSI-H, dMMR), not specific cancer type = tissue agnostic indication

Source: Keytruda labeling, BLA submission, FDA review documents
CDER number of breakthrough-designated development programs continues to grow

* Data as of 10/1/17. Figures includes total # of granted breakthrough designations for drug/indications under active IND development but have not yet received marketing approval or rescission decision.
Multiple applications pertaining to a single new molecular/biologic entity are only counted once. Original BLAs that do not contain a new active ingredient are excluded.

* This information is accurate as of December 31st, 2017. In rare instances, it may be necessary for FDA to change a drug’s new molecular entity (NME) designation or the status of its application as a new biologics license application (BLA). This note applies to all references to NME/Original BLAs in this presentation.

Since applications are received and filed throughout a calendar year, the filed applications in a given calendar year do not necessarily correspond to an approval in the same calendar year. Certain applications are within their 60-day filing review period and may not be filed upon completion of the review.
Development phase work continued to grow in 2017

Data are from the PDUFA Workload Adjuster and represent a 12 month period of July 1st - June 30th
BEST: Biomarkers, Endpoints, and other Tools resource

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
“BEST” biomarker classes

• Susceptibility/Risk:
• Diagnostic
• Monitoring
• Prognostic/Predictive
• Pharmacodynamic/Response
• Safety
**Disease-Related Biomarkers**

- **Non-disease population**
  - Susceptibility or risk predictor biomarkers
  - High risk of disease or pre-clinical disease population
  - Diagnostic biomarker

- **Patients with disease**
  - Disease Subtype 1
  - Disease Subtype 2
  - Prognostic biomarker
  - Patients at higher risk of disease-related outcome(s)
  - Monitoring biomarker
  - Disease-related outcome

**Treatment-Related Biomarkers**

- **Patients with disease**
  - Lower or non-responder population
  - Responder or higher responder population

- **Phase 1, 2a (early stage biomarkers)**
  - Target engagement biomarker
  - Pharmaco-dynamic biomarker
  - Drug is hitting target
  - Relevant pathway is modulated

- **Phase 2b, 3 (later stage biomarkers)**
  - Intermediate clinical endpoint
  - Reasonably likely surrogate endpoint
  - Validated surrogate endpoint
  - Earlier change in definitive endpoint
  - Endpoint likely to predict outcome or clinical benefit
  - Endpoint predicting outcome or clinical benefit

**Clinical Outcomes**

- Disease morbidity / mortality
- Clinical benefit ("feels or functions")

**Safety biomarkers:** assess Rx-related injury

- Phase 1, 2a (early stage biomarkers)
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**Surrogate endpoints or efficacy-response BM**

**Proof of concept biomarkers**

**Proof of pharmacology**
**Broad Range of Biomarker Needs in NASH**

- **Non-disease population**
  - Susceptibility or risk predictor biomarkers
  - High risk of disease or pre-clinical disease population
  - Diagnostic biomarker
  - Patients with disease
    - Diagnostic biomarker
    - Disease Subtype 1
    - Disease Subtype 2
    - Prognostic biomarker
    - Patients at higher risk of disease-related outcome(s)
    - Monitoring biomarker
    - Disease-related outcome

- **Patients with disease**
  - Responder or higher responder population
  - Predictive biomarker
  - Lower or non-responder population
  - Phase 1, 2a (early stage biomarkers)
    - Target engagement biomarker
    - Drug is hitting target
    - Pharmaco-dynamic biomarker
    - Relevant pathway is modulated
  - Phase 2b, 3 (later stage biomarkers)
    - Intermediate clinical endpoint
    - Earlier change in definitive endpoint
    - Reasonably likely surrogate endpoint
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- **Safety biomarkers:** assess Rx-related injury
  - Proof of pharmacology
  - Proof of concept biomarkers
  - Surrogate endpoints or efficacy-response BM
  - Phase 1, 2a (early stage biomarkers)
  - Phase 2b, 3 (later stage biomarkers)
  - Disease morbidity / mortality
  - Clinical benefit (“feels or functions”)
Drug development tool qualification at CDER

- Drug development tools (DDTs) are methods, materials, or measures that aid drug development
- *Qualification* is a conclusion that within the stated *context of use*, the DDT *can be relied* upon to have a specific interpretation and application in drug development and *regulatory review*
- *Types of Tools:*

  - **Clinical Outcome Assessments**
  - **Biomarkers**
  - **Animal Models** *(Animal Rule)*

- Potential for wide applicability to support drug development programs:
- Usually in narrow context of use *(biological, radiological threats)*
Pathways to biomarker acceptance for regulatory decisions

- Not mutually exclusive – one pathway may follow another (e.g., IND to BQP)
- Common concepts regarding biomarker validation
- Data driven acceptance
The Specific Context of Use for a Biomarker Drives the Extent of Evidence Needed for Qualification

**Analytical Validation**
- Establish performance and acceptance characteristics of the biomarker assay
  - Reference Ranges/Decision Points
  - Pre-Analytical and Assay Performance Characteristics
  - Analytical Rigor/Reproducibility
  - Sample Handling/Stability

**Clinical Validation**
- Establish that the biomarker acceptably identifies, measures, or predicts the concept of interest
  - Study Design Acceptability
  - Clinical Meaningfulness/Decision Points
  - Benefit/Risk Assessment
21st Century Cures legislation: Section 507 Qualification of Drug Development Tools

• 21st Century Cures and PDUFA VI identifies supporting development of new drug development tools as a key FDA role

• Formalizes a three-step submission process
  – Letter of Intent
  – Qualification Plan
  – Full Qualification Package

• A transparent process – so all stakeholders are aware of tools in development, stage, and FDA determinations/recommendations

• Requires setting and implementing “reasonable timeframes” for submission review/decision
Three-tiered internal review

• DDT program assessment and recommendations
  – Work with requestor to clarify tool, COU, and project proposal
  – Provide tool-specific recommendations based on past and ongoing projects

• Discipline-specific SME assessment and recommendations
  – Includes OND division management participation
  – Evaluate based on regulatory precedent, current disease-specific challenges, and level of impact on drug development program

• CDER DDT committee assessment, recommendations, and decision
  – Opportunity for broad senior CDER input early and throughout in the process
  – Work towards greater consistency across therapeutic areas and divisions
Critical path innovation meetings (CPIM)

• A forum for an interactive discussion between FDA and outside organizations (including industry, academic or patient organizations) on specific drug development topics

• Discussion of the science, medicine, and regulatory aspects of innovation in drug development

• Intent is an forum for scientific communication – not to obtain regulatory advice (“non-binding” input)

• Not a meeting about a specific approval pathway

• Wide scope: biomarkers, COAs, natural history studies, technologies (not manufacturing), and clinical trial designs and methods

• [Link to the FDA document](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417627.pdf)
CPIM Topics

- Clinical Trial Endpoints
  - Biomarker Development
  - Drug Development Tools
    - Innovative Trial Designs
  - Clinical Trial Networks

- Natural History Studies
  - COA Development
  - Rare Diseases
    - Databases
    - Registries

*Development and Adoption of Biomarkers for Molecularly Targeted Cancer Therapies: Workshop Summary*
Thank You