The challenges of biomarker development in a changing development landscape

CPATH Biomarker Workshop September 2019

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Overview

• A changing landscape for drug development and regulation
• Fitting biomarkers into the regulatory framework
• A (brief) overview of biomarkers
• The challenges of biomarker development
The drug development – and drug regulatory landscape: change is the only constant

**Changing science**
- Increasing genomic/genetic characterization of diseases – providing new targets
- Increase molecular subtyping of diseases - targeting disease or subtype specific targets
- Recognition of molecular drivers in cancer
- New platforms for “undruggable” targets: e.g., ASOs, siRNA, dual targeted Mabs, cellular and gene-based therapies

**Changing development and regulatory context**
(PDUFA VI, Cures, SUPPORT)
- Increasing role of patients and caregivers: patient-focused drug development
- Focus on biomarkers/COAs: BQP, standardizing approach to surrogate endpoints for AA
- New approval pathways (e.g., LPAD) and rising requests for breakthrough, fast track designations, use of AA
- Changing nosology: tissue agnostic drug approvals
- Master protocols / platform trials / basket trials
- Rising efforts on decentralized trials, use of mobile technologies for trial endpoints and monitoring
- Efforts to integrate clinical research into practice (EHR to eCRF) to support pragmatic trials and RWE generation and focus on use of RWE in a wider range of regulatory decisions
- Adaptive trial designs and of other novel trial designs: Bayesian approaches, model-informed drug development
- Development of a common protocol template

**Changing the types & targets of drugs**
- Fewer drugs targeting common diseases with more drugs targeting rare diseases
- Focus on disease subtypes: late stage disease or phenotypic or genetic subgroups; small population development
- Dramatic increase in targeted cancer drugs
- Rise in biosimilar and complex generics
- Focus on drug cost: FDA role - Drug Competition Action Plan, Biosimilar Action Plan
### The evolution of drug targets over 10 years

<table>
<thead>
<tr>
<th>Category</th>
<th>2007-2008</th>
<th>2018</th>
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</thead>
<tbody>
<tr>
<td>Rare Disease</td>
<td>16%</td>
<td>32%</td>
</tr>
<tr>
<td>Uncommon Cancer &amp; Targeted Therapy</td>
<td>2%</td>
<td>17%</td>
</tr>
<tr>
<td>Targeted Therapy</td>
<td>18%</td>
<td>49%</td>
</tr>
<tr>
<td>Non-rare Cancer</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-rare, Chronic Disease</td>
<td>60%</td>
<td>30%</td>
</tr>
<tr>
<td>Common Infectious Disease</td>
<td>11%</td>
<td>15%</td>
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</tbody>
</table>

**Graph notes:**
- Preliminary, not validated

- **Increased proportion of targeted therapies**
- **Increased proportion are drugs for rare diseases**
- **Among drugs for common, chronic diseases – most targeting late stage / failing other therapies, subgroups or subtypes of disease**
Approving a new drug: a “two step” process

• “Step 1”: demonstrated **effectiveness**: substantial evidence
  = the effectiveness standard

• “Step 2”: an appropriate *benefit / risk balance* – how FDA interprets “**safe for use...**”

Effectiveness = the drug provides patients with a clinically meaningful benefit
– how a patient **feels, functions, or survives**
Substantial evidence - a statutory standard for approval

• As defined in Section 505(d), substantial evidence is:
  o “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

• FDAMA (1997) added flexibility: one A&WC trial and confirmatory evidence, if considered appropriate

• The FDA standard requirement for two A&WC studies

• Replication as scientific standard approach: reduces risk of false positive findings, bias or confounding in a single trial
What is an “adequate and well-controlled study”?

**Selected Key Characteristics**

- There is a **clear statement of objectives** of the investigation and **methods of analysis**
- The study uses a **design** that permits a **valid comparison** with a **control** to provide a **quantitative assessment of drug effect**: placebo-control, dose-comparison control, no treatment control, active-treatment control, historical control.
- Adequate measures are taken to **minimize bias** on the part of the subjects, observers, and analysts of the data.
- The **methods of assessment** of subjects’ response are **well defined and reliable**.
- The **method of selection** of subjects provides adequate assurance that they have the disease/condition being studied.
- The **method of assigning patients** to treatment and control groups **minimizes bias** and is intended to assure comparability of the groups with respect to pertinent variables. Ordinarily....assignment is by randomization...
- There is an **analysis of the results of the study adequate to assess the effects of the drug**

*From 21 CFR 314.126*
“Flexibility” – established in regulation

- **Subpart E- Drugs Intended to Treat Life-Threatening and Severely-debilitating Illness** 21 CFR 312.80 (+ 21 CFR314.105(c)):
  - “...while the **statutory standards of safety and effectiveness apply to all drugs**, the many kind of drugs that are subject to them, and the wide range of uses.....**demand flexibility**.... FDA has determined that it is appropriate to exercise the broadest flexibility in applying the statutory standard, while preserving appropriate guarantees for safety and effectiveness.”
  - “These procedures reflect the recognition that **physicians and patients are generally willing to accept greater risks** or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses.”

For drugs for life-threatening or severely-debilitating illnesses:

- The statutory standard is not altered, **but**
- FDA can determine what evidence is needed to meet the standards
Use of one trial plus confirmatory evidence

• Added by FDAMA in 1997
  – “If [FDA] determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence.” (bold, italics added)

• Decision to accept one trial + confirmatory evidence includes a number of factors
  – Persuasiveness of the single trial
  – Robustness of the confirmatory evidence
  – Seriousness of the disease and unmet need
  – Size of the patient population
  – Feasibility and ethics of conducting more than one A&WC trial
Single trial plus confirmatory evidence: types of evidence

Single A&WC clinical trial supported by:

- **Results from trials in a related indication**
  - Two or more completed A&WC trials demonstrating efficacy in an indication – FDA may accept one trial in a related indication (i.e., similar drug MOA in producing clinical benefit)

- **Compelling mechanistic information from earlier clinical or non-clinical studies**
  - Reliance on pharmacodynamic endpoint with well-established relationship to clinical endpoint
  - Reliance on well-established, translatable animal model

- **Well described natural history of disease**
  - Evidence clearly describing natural history of disease: may be natural history study, registry, compelling case series

- **Adequate and well controlled trials from other members of same drug class**
  - Same pharmacological target
Biomarkers, Surrogates, and COAs: definitions

• A **clinical outcome** describes or reflects how a patient feels, functions or survives, or are events that impact how a patient feels, functions, or survives or are events that directly impact how a patient feels, functions or survives

• A **Clinical Outcome Assessment**: assesses (describes, measures, reflects) a clinical outcome through report by a clinician (ClinRO), or a patient (PRO), or a trained observer measuring performance (PerfO) (+ mobile-health technology-based endpoints)

• **Biomarker** is a “defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. *Molecular, histologic, radiographic, or physiologic characteristics* are types of biomarkers.”
  
  — A biomarker is not an assessment of how a patient feels or functions

• A **Surrogate** is a biomarker that predicts (but does not directly measure) clinical outcomes
  
  — So a surrogate would predict the risk of hypoglycemia or bacterial pneumonia or MI, while a **COA or clinical outcome endpoint** would measure, identify, or reflect such events
BEST Resource: Biomarkers, EndpointS, and other Tools

• 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 harmonizes terms and definitions and addresses nuances of usage and interpretation among various stakeholders, including:
  • Biomedical scientists
  • Translational and clinical researchers
  • Medical product developers
  • Patient/disease advocacy groups
  • Government officials
  • Clinicians
BEST (Biomarkers, EndpointS, and other Tools) Classification: range of biomarker types

- Susceptibility / risk biomarker
- Diagnostic biomarker
- Prognostic biomarker
- Monitoring biomarker
- Predictive biomarker
- Pharmacodynamic/Response biomarker – including surrogate endpoints
- Safety biomarker

Measures of disease presence and status

Measure aspects of response to treatment
Disease-Focused Biomarkers

Non-disease population

Susceptibility or risk predictor biomarkers

Individuals at high risk of disease or pre-clinical disease population

Diagnostic biomarker

Diagnostic biomarker

Patients with disease

Diagnostic biomarker

Diagnostic biomarker

Disease Subtype 1

Disease Subtype 2
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Prognostic biomarker

Patients with disease at higher risk of disease-related outcome(s)

Prognostic biomarker

Diagnostic biomarker

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Disease-Focused Biomarkers

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Diagnostic biomarker

诊断生物标志物

非疾病人群

诊断生物标志物

患者具有疾病

诊断生物标志物

Disease Subtype 1

诊断生物标志物

Disease Subtype 2

诊断生物标志物

患者具有疾病，更有可能发生疾病相关结果

诊断生物标志物

疾病相关结果
Disease-Focused Biomarkers

- Susceptibility or risk predictor biomarkers
  - Individuals at high risk of disease or pre-clinical disease population

**Non-disease population**

**Diagnostic biomarker**

**Monitoring biomarker:** assess disease status

**Patients with disease**

- Disease Subtype 1
- Disease Subtype 2

- Prognostic biomarker

**Patients with disease at higher risk of disease-related outcome(s)**

**Disease-related outcome(s)**

**Diagnostic biomarker**
Treatment-Related Biomarkers

Patients with disease

Predictive biomarker

Responder or higher responder population

Lower or non-responder population
Patients with disease

Predictive biomarker

Responder or higher responder population

Lower or non-responder population

Phase 1, 2a (early stage biomarkers)

Target engagement biomarker

Drug is hitting target

Pharmacodynamic biomarker

Relevant pathway is modulated

Drug Treatment

Pharmacodynamic/Response Biomarkers

Proof of Pharmacology

Proof of Concept
Patients with disease

Predictive biomarker

Responder or higher responder population

Lower or non-responder population

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Target engagement biomarker
Drug is hitting target

Pharmacodynamic biomarker
Relevant pathway is modulated

Phase 1, 2a (early stage biomarkers)

Phase 2b, 3 (later stage biomarkers)

Reasonably likely surrogate endpoint
Endpoint likely to predict outcome or clinical benefit (AA)

Validated surrogate endpoint
Endpoint predicting outcome or clinical benefit (Full Approval)

Intermediate clinical endpoint
Earlier change in definitive endpoint (accelerated approval)

Pharmacodynamic/Response Biomarkers

Proof of Pharmacology
Proof of Concept

Surrogate Endpoints

Disease morbidity / mortality (“survives”)
Clinical benefit (“feels or functions”)

Validated surrogate endpoint
Endpoint predicting outcome or clinical benefit (Full Approval)

Intermediate clinical endpoint
Earlier change in definitive endpoint (accelerated approval)

Reasonably likely surrogate endpoint
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Phase 2b, 3 (later stage biomarkers)

Phase 1, 2a (early stage biomarkers)

Drug is hitting target
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Phase 2b, 3 (later stage biomarkers)

Reasonably likely surrogate endpoint

Validated surrogate endpoint

Intermediate clinical endpoint

Earlier change in definitive endpoint (accelerated approval)

Disease morbidity / mortality ("survives")

Clinical benefit ("feels or functions")

Safety biomarkers: assess treatment-related toxicity

Drug Treatment

Pharmacodynamic/Response Biomarkers

Proof of Pharmacology

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Surrogate Endpoints

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Clinical Outcomes

Clinical Outcomes

Drug Treatment
The limitations of surrogate endpoints

- Not a direct measure of how a patient **feels, functions or survives** (difference between a biomarker and a COA or outcome event)
- Intended to reflect and predict clinical benefit not measure the outcome
- In using a surrogate endpoint, the benefit to risk balance is based on assumptions regarding clinical benefit
  - Challenges of translating from **indirect measure** to **direct measure clinical benefit**
    - Surrogate may accurately reflect one key process modified by drug – clinical endpoint (especially a composite) may integrate multiple pathways towards benefit(s) – and safety as well
    - Often more limited trial safety exposure with surrogate endpoint (shorter, smaller program) – so less precision on “risk”
    - **However**, can still can estimate “**quantum**” of **benefit vs harm**, **even if more challenging**
- And biomarkers may **fail** to predict clinical benefit – residual risk that strength (or presence) of relationship to clinical endpoint is not valid
  - Many examples of “sure thing” biomarkers that failed – e.g., NSVT and death
Types of pharmacodynamic biomarkers or surrogates

**Causal Biomarker**
- Reflecting causal factor
  - Genetic or genetic-related defective function (e.g., gene variant, decreased enzyme level or function)
  - Environmental exposure (e.g., blood lead level, etc.)
  - Microbiologic (e.g., HIV, HCV, bacterial culture, AFB smear)
  - Tumor mass (e.g., endpoints such as CR/PR or ORR, PFS)

**Pathway or mediator biomarker**
- In pathway of disease: reflecting mediator of damage
  - LDL-C
  - Blood pressure
  - A1C
  - TG (pancreatitis)
  - Uric acid (gout)

**Organ injury biomarker**
- Reflecting organ injury
  - Organ 1
    - Sites of Injury
    - Organ 1 Injury BM
  - Organ 2
    - Organ 2 Injury BM
  - Organ 3
    - Organ 3 Injury BM
  - Sites of Injury
    - Organ 1 Injury BM
    - Organ 2 Injury BM
    - Organ 3 Injury BM

**Clinical function**
- Functional measures
  - 6 minute walk
  - FEV1
  - ETT
  - Cognitive function (e.g., UPSA)
  - Future: mobile technology enabled: ambulation, GPS, vital signs, oximetry, other sensors

**Clinical Outcomes**
- eGFR
- Bilirubin, PT
- Cardiac ECHO
- Dynamometry (muscle strength)
- Neurocognitive function tests (e.g., DSST)
Types of pharmacodynamic biomarkers or surrogates: Limitations of each “type”

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**Pathway or mediator biomarker**

In pathway of disease: reflecting mediator of damage

- For atypical mycobacteria – commensural vs infection? Do we understand what “clearance” with treatment means?
- Will ORR translate clinical benefit such as survival, improved function, improved quality of life

**Organ injury biomarker**

Sites of Injury

- Organ 1: Tissue injury BM
- Organ 2: Tissue injury BM
- Organ 3: Tissue injury BM

Reflecting organ injury

- Organ Function BM
  - ALT/alk phos
  - CPK/troponin
  - Urinary kidney injury BMs
  - Urinary microalbumin
  - CSF analytes
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**Pathway or mediator biomarker**

- In pathway of disease: reflecting mediator of damage
  - Is the biomarker on a major pathway leading to organ damage?

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**Pathway or mediator biomarker**

- In pathway of disease: reflecting mediator of damage
  - Even if levels of correlate with outcome, how drug-induced changes also predict the outcome? Does the mechanism of increase matter?
  - Sites of Injury
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How specific are these markers? How much increase and for how long predicts organ damage and functional losses?
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How much change predicts a meaningful clinical outcome? What is the minimally clinically meaningful change?
The limitations of surrogate endpoints: complex relationships between disease – biomarker – and clinical outcome

- Surrogate on causal pathway modulated by drug
- Biomarkers may reflect changes induced by outcome of disease

- Surrogate not on pathway of drug MOA (so BM may only indirectly correlate with outcome)

- Multiple disease MOAs may lead to clinical outcome – and drug may impact only one

- Drug may induce adverse effects on desired clinical outcome through a pathway not reflected by BM
- May lead to other toxicities = BM does not adequately predict benefit / risk balance

After Fleming Statistics in Medicine 2012
The changing landscape: implications for biomarker development

- **Increasing capabilities for mobile, digital technologies**
  - Marked rise in sources of information (active or passive) on daily patient status and functioning

- **Increased efforts to enable decentralized trials**
  - Enabled by rise in use and capabilities of mobile technologies

- **Increasing focus on “Real World Evidence” (21st Century Cures)**
  - Data collected from health care interactions, and other patient derived data including use of mobile technologies

- **Challenge of converting wide array of mobile-technology data into meaningful, interpretable endpoints**
  - Validation of a wide range of data sources will be required

- **Decentralized trials will require robust endpoints acquired in the “real world” environment**
  - Use of photographic, video, “skype”-based assessments

- **RWD reliability and quality issues**
  - Less or no standardization of assays, tests, measurement
  - Limited access to patient-level data
Mobile devices: enhancing trial conduct and data collection

Wide range of possible uses, such as

- Tracking adherence
- Collecting patient reports: diaries, ePROS
- *Novel* trial endpoints: passively (e.g., ambulation, vital signs) *or* actively assessed (e.g., timed tasks)
- Safety monitoring
- Recruitment and retention – connecting and engaging patients

Wide range of sources

- ePROs for patient information entry
- Smart phones: for videos, photographs of lesions, behaviors, other findings
- Wide range of mobile technologies: pedometers, accelerometers, ECGs, temp sensors, EEGs, movement sensors, GPS, glucometers, spirometers, pulse ox

Interpretation and regulatory implications: *from data to endpoints*

- Reliability of measurements: accuracy, reproducibility, data source
- Challenges of interpretation – creating meaningful endpoints: how patients *feel and function*
  - Relating passive mobile data (e.g., ambulation, vital signs, sleep patterns) to meaningful clinical outcomes
  - Relating digital data to patient reported data
The challenges of biomarker development

• Disease characteristics that challenge biomarker development:
  – Slowly progressive disorder impeding biomarker validation: long course to outcomes
  – Uncommon or rare diseases
  – Diseases that are genetically and phenotypically heterogeneous, especially with differences in pathogenetic mechanisms: multiple subtypes
  – Lack of widely accepted “gold standard” for diagnosis – creating “noise” for qualification of biomarker
  – “Remote” organ involvement – limiting disease tissue access for biomarker validation

• Limited understanding of disease pathogenesis
  – Many changes in proteomic, lipidomic, gene expression profile, changes in imaging etc – but limitations in separating pathogenic vs epiphenomenon (“downstream” of disease, or unrelated)

• Development program-related
  – Lack of clarity on biomarker purpose – biomarker development program aimed too broadly, seeking to validate multiple COUs – lack of focus
  – Lack of adequate analytic validation efforts early – unreliable assays undermining observations
  – Lack of cohesive planning – focused purpose, focused program
NME approvals in CDER: proportion of rare NMEs of total NMEs

<table>
<thead>
<tr>
<th>Year</th>
<th>Total NME</th>
<th>Rare NME</th>
<th>Rare NME %</th>
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<tbody>
<tr>
<td>2015</td>
<td>46%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>45%</td>
<td></td>
<td></td>
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<tr>
<td>2017</td>
<td>39%</td>
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<td></td>
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<tr>
<td>2018</td>
<td>58%</td>
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Biomarker development – in rare diseases

• Usual approach requires extensive biomarker “validation”
  – Analytic validation
  – Clinical validation

• Challenges in rare diseases
  – Small populations limits breadth of biomarker and endpoint development opportunities
  – Limited natural history may limit understanding of outcomes of importance, rates of changes, heterogeneity of the disease
  – Lack of “gold standard” endpoint

• Opportunities
  – Standardized instruments for manifestations that are common across disorders
  – Adapting biomarkers used in related diseases (e.g., storage disorders)
  – Detailed mechanistic understanding may support relevance of proposed biomarker
  – Early launch of natural history studies – with collection of biological specimens to support biomarker development
  – Registries with collection of standardized samples and related clinical / demographic information
  – Networks and collaboration among stakeholders – essential not to “divide” wealth of information
Effect of ivacaftor on lung function in patients with cystic fibrosis in a responsive mutation

From S Rowe et al NEJM 2005

Mutations causing decrease in CFTR transporter function

Mutations causing absence of CFTR transporter protein

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

From Ivacaftor prescribing information
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**

**Mutations showing response** – increase in chloride transport

**Specific mutations added to labeled indication**

**No response**

**Not indicated**

- Drug approval based upon RCT (in G551D genotype)
- Expanded labeling (adding genotypes) based up *in vitro* assay testing drug-genotype response
- Supporting information on response from registry
The challenges of biomarker development (cont.)

• Many disease areas with unmet needs have insufficient drug development tools

• Biomarker development is a long and resource-intensive process
  – Biomarker discovery: biased or unbiased screening in animal, clinical, epidemiological datasets
  – Early animal translational models
  – Clinical or epidemiology observational studies
  – Analytic validation efforts: assure accuracy / reproducibility of measure
  – Interventional studies with “gold standard” endpoints compared to candidate – with multiple different treatments (different MOAs) to show that BM works across drug classes

• Many stakeholders in the mix – with potential for competing interests
  – Academic investigators at multiple institutions, US and ex-US
  – Often several academic societies in disease area with different viewpoints and membership
  – Different companies – both drug and device-focused may be working in the area
  – May be different patient stakeholder organizations

• Lack of infrastructure to align varying interests into cohesive development program

• The challenge: how to prioritize biomarker needs, focus resources, and integrate efforts across stakeholders
The challenges of biomarker development (cont.)

- Many disease areas with **unmet needs** have insufficient drug development tools
- Biomarker development *is a long and resource-intensive process*
  - Biomarker *discovery*: biased or unbiased screening in animal, clinical, epidemiological datasets
  - Early animal *translational* models
  - Clinical or epidemiology observational studies
  - *Analytic validation* efforts: assure accuracy / reproducibility of measure
  - Interventional studies with “gold standard” endpoints compared to candidate – with multiple different treatments (different MOAs) to show that BM works across drug classes

- **Many stakeholders** in the mix – with potential for **competing interests**
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- **Lack of infrastructure** to align varying interests into cohesive development program
- **The challenge**: how to **prioritize** biomarker needs, **focus** resources, and **integrate** efforts across stakeholders
Thanks for your attention....