FDA from a Former FDAer: “Secrets and insights” into regulatory review and drug development

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Other Working Title: Advancing Precision Medicine: Taking advantage of new regulatory opportunities and new legislation

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I have the following financial relationships to disclose:
1. Employee of Amicus Therapeutics, Inc.
2. Stockholder in Amicus Therapeutics, Inc.
Developing new precision medicines for lysosomal diseases holds great promise and a number of challenges

- What are the existing tools and what new tools are needed to design and develop therapies based on unique genetic characteristics in LSDs?
- What will be the role of biomarkers and Patient reported outcomes (PROs) in precision medicine drug development?
- What are the current gaps?
The WORLD of Precision Medicine

http://www.theworldin.com/article/12775/medicine-gets-personal
Substantial Evidence of Effectiveness

• Adequate and well-controlled study:
  – Study has been designed well enough so as to be able “to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation” (§314.126)
  – Clinical benefit:
    • The impact of treatment on how patient feels, functions or survives
Adequate and Well-Controlled Study

• Must incorporate generally accepted scientific principles for clinical trials
  – Major elements of the study design:
    • Clear statement of purpose
    • Permits a valid comparison with a control
      – Concurrent: placebo, no-treatment, active, dose-comparison
      – Historical
    • Method of selection of subjects
    • Method of assigning patients to treatment/control groups
    • Adequate measures to minimize bias
    • Methods of assessment of response are well-defined and reliable
    • Analysis of the results is adequate to assess the effects of the drugs
“Flexibility”

• Regulations provide room for flexibility in reviewing treatments for rare diseases
  – There are “many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards”
  – “...FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.”
(§314.105)
The Critical Path for Medical Product Development

Best access to safe and effective treatment is having an approved product on the market.
Clinical Development Challenges for Rare Diseases

– Rare = few patients available for study
  • Makes “getting development right” critical from the start
– Chronic, progressive, serious, life-limiting and life-threatening with unmet medical need
– Many different clinical presentations
– Natural history often not well understood
– Well defined endpoints, outcome measures/tools/instruments, biomarkers can be lacking
Pathway to An Approved Product

– How do we get there?
– What are the obstacles?
– How can a partnership among stakeholders facilitate achievement of this shared goal?
  • Assist in identification of clinically meaningful, measurable and interpretable endpoints
  • Assist in identifying acceptable designs for trials that can enroll AND answer key questions
  • Share a commitment to completion of a successful drug development program
Drug Development Challenges

• Before initiating pivotal clinical efficacy trials, it is critical to:
  – Map out the clinical development program
  – Conduct a natural history study early in development
  – Design efficient early phase trials to inform the design of pivotal efficacy trial(s)

• Assess safety and tolerability throughout the entire drug development process
Evidentiary Standard for Approval

Regulatory Challenge:

– Orphan drugs held to same evidentiary standard:
  
  – Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50) and **Adequate and well-controlled clinical studies** (§314.126)

  – Direct evidence of treatment benefit is derived from studies with endpoints that measure survival, or how patients feel and function in daily life
Advances in Precision Medicine

• 2012: FDA published a draft guidance: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, to address approaches on selecting a study population in clinical trials for new drugs and biologics
• US Congress overwhelmingly passed the 21st Century Cures Act which was signed into law on December 13, 2016.
An innovation game-changer, a once-in-a-generation, transformational opportunity to change the way we treat disease.

The House Energy and Commerce Committee and the Senate HELP Committee have engaged in a public, nonpartisan conversation with patients, researchers, innovators, and health care providers about what steps can be taken to expedite the discovery, development, and delivery of new treatments and cures and maintain America’s global status as the leader in biomedical innovation.

The 21st Century Cures Act ("Cures") is the product of that conversation.
Decreasing Heterogeneity – Practical Enrichment
To increase ability to demonstrate a treatment effect, FDA suggests certain strategies to decrease heterogeneity, or the variability of effects not related to the drug:

1) Define entry criteria carefully and exclude patients unlikely to tolerate the study drug

2) Find likely compliers prospectively before randomization and encourage patient compliance

3) Eliminate placebo responders in a lead-in period.
   – Treat patients with a placebo prior to randomizing them, in order to eliminate patients from the trial who improve spontaneously or have large placebo responses.

4) Eliminate people taking drugs that could interact with or drugs that have the same effect as the study drug.

5) Exclude those who might drop out for non-medical reasons.
Prognostic Enrichment -- Identifying High-Risk Patients

• Through prognostic enrichment strategies, sponsors choose patients more likely to have the medical condition under study (study endpoint) or have a large change in the endpoint being measured during the study.

• Strategies for cardiovascular disease or cancer trials aim to reduce the rate of death or serious events, as well as trials intending to delay progression of diseases such as Alzheimer’s or Parkinson’s.

• These strategies may allow for a trial to have a smaller sample size, because they increase the trial’s “absolute effect size.”
Predictive Enrichment -- Choosing Patients More Likely to Respond to Treatment

In order to increase a trial’s absolute and relative effect size, select patients with a greater likelihood of responding to the study drug which provides “proof of concept” (feasibility of conducting a study) and facilitate selection of appropriate doses for subsequent studies.

- Predictive enrichment strategy is appropriate to show effectiveness when the number of patients responding to the drug is a “small fraction of all patients, say 20%,” and even facilitates “development and approval” for significantly toxic drugs, because it avoids toxicity exposure in patients not benefiting from treatment.

- Selecting patient characteristics (e.g., pathophysiology, genomic) or empiric factors (e.g., patient history of response to similar drugs, past response to the test drug in a randomized withdrawal study).
Role of biomarkers and PROs in precision medicine drug development

Steps to Selecting Appropriate Efficacy Endpoints and Clinical Outcome Assessment

1. Define disease population
2. Define context of use
3. Select concept(s) of measurement that will define treatment benefit
4. Select or develop well-defined and reliable outcome assessments to measure each concept for the proposed context of use

Observable
- No Clinical Judgment
  - Self-report?
    - NO → ObsRO
    - YES → PRO
  - Clinical Judgment
    - ClinRO
Non-Observable
- PRO
Physiologic or lab findings that can be measured without human assessment
- Biomarker

Understanding the Disease or Condition 1

A. Natural history of the disease or condition
   • Onset/Duration/Resolution
   • Diagnosis
   • Pathophysiology
   • Range of manifestations

B. Patient subpopulations
   • By severity
   • By onset
   • By comorbidities
   • By phenotype

C. Health care environment
   • Treatment alternatives
   • Clinical care standards
   • Health care system perspective

D. Patient/caregiver perspectives
   • Definition of treatment benefit
   • Benefit-risk tradeoffs
   • Impact of disease

Conceptualizing Treatment Benefit 2

A. Identify concept(s) of interest for meaningful treatment benefit, i.e., How a patient:
   • Survives
   • Feels (e.g., symptoms)
   • Functions

B. Define context of use for clinical trial:
   • Disease/Condition entry criteria
   • Clinical trial design
   • Endpoint positioning

Selecting/Developing the Outcome Measure 3

A. Search for existing COA measuring concept of interest in the context of use:
   • Measure exists
   • Measure exists but needs to be modified
   • No measure exists
   • Measure under development

B. Begin COA development
   • Document content validity (qualitative or mixed methods research)
   • Evaluate cross-sectional measurement properties (reliability and construct validity)
   • Create user manual
   • Consider submitting to FDA for COA qualification for use in exploratory studies

C. Select clinical outcome assessment (COA) type:
   • Patient-Reported Outcome (PRO)
   • Observer-Reported Outcome (ObsRO)
   • Clinician-Reported Outcome (ClinRO)
   • Performance Outcome (motor, sensory, cognition)

   C. Complete COA development:
      • Document longitudinal measurement properties (construct validity, ability to detect change)
      • Document guidelines for interpretation of treatment benefit and relationship to claim
      • Update user manual
      • Submit to FDA for COA qualification as effectiveness endpoint to support claims

Types of Outcome Assessments

• Survival
• Clinical outcome assessments (COAs)
  – Patient-reported outcomes (PROs)
  – Clinician-reported outcomes (ClinROs)
  – Observer-reported outcomes (ObsROs)
  – Performance outcomes (PerfOs)
• Surrogates
  – Often a biomarker* that is intended as a substitute for how a patient feels, functions, or survives
  – Two types for use in clinical trials to support product approval:
    • Established Surrogates (for regular approval)
    • Reasonably likely to predict clinical benefit (for accelerated approval; require post-marketing studies to confirm clinical benefit)
When is a Clinical Outcome Assessment Adequate for use?

- Regulatory standard: measures are *well-defined and reliable*
  - Empiric evidence demonstrates that the score quantifies the concept of interest in the targeted context of use
- What does this mean?
  - This means measuring the right thing (concept of interest), in the right way in a defined population (targeted context of use), and the score that quantifies that ‘thing’ does so accurately and reliably, so that the effects seen in the outcome assessment can be interpreted as a clear treatment benefit.
Clinical Outcome Assessments including PRO Instruments

- Appropriate for the target population
- Appropriate for the target indication
- Adequate measurement properties
  - E.g., content validity: PRO development relies on patient input to support content validity

Does the instrument measure the outcome of interest?
Well-defined and Reliable

- Regulatory standard: measures are *well-defined and reliable supported by evidence* that score quantifies the concept of interest in the targeted context of use
- What does this mean?
  - Measuring the concept of interest in a defined population (targeted context of use), and the score that quantifies that ‘thing’ does so accurately and reliably, so that the effects in COA reflect a clear treatment benefit.
- Tool adequately measures the concept of interest in context of interest
- To assess this, we review the tool’s measurement properties:
  - Content validity, Construct validity, Reliability
  - Ability to detect change
  - Information to support interpretation of change
Defining Context of Use

Each of the following variables can impact the adequacy of a COA to support a claim:

• **Disease definition including, if appropriate**
  – Disease subtype
  – Disease severity
  – History of previous treatment

• **Patient subpopulations**
  – Patient demographics
  – Reporting ability
  – Culture and language
What Is Content Validity?

- Content validity is the extent to which the content of an instrument represents important aspects of a given concept for an intended use and for a defined target population
  - Appropriate
  - Comprehensive
  - Interpretable
- Establishing content for a new instrument may involve both qualitative and quantitative research methods
- Quantitative data can contribute to content validity evidence, but are not sufficient alone:
  - Qualitative Concept Elicitation Interviews
  - Cognitive Debriefings
Clinical Outcome Assessment Considerations

• Not all patient reported, clinical-reported, observer-reported, or performance outcome assessments are appropriate Clinical Outcome Assessments (COAs) for use in clinical trials to support approval and labeling

  – May be useful for other purposes:
    • Diagnostic
    • Prognostic
    • Trial eligibility and trial enrichment
    • Epidemiologic or population studies
    • Clinical practice decision-making

  – Measures used successfully for these other purposes will not necessarily be appropriate COA since they may not be able to detect treatment benefit reliably in clinical trials or support labeling claims
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<th>EoE</th>
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Fiorentino, Pariser, Liu and Mulberg, J Allergy Clin Immunol 2012
Key Points for Rare Diseases

- Clinical development program must be based on a solid scientific foundation
  - MOA and pathophysiology well-understood, patient population
  - Disease natural history needs to be defined
- Study design considerations based on population under study, drug/product and disease characteristics, etc.
- Personalized approaches
  - relapsing remitting vs. chronic progressive
  - Potentially curative vs. ameliorating an aspect of disease
- The program must demonstrate substantial evidence of effectiveness
  - Flexibility in how that is achieved
  - Multiple pathways defined in existing guidance, e.g. single study with:
    - Pharmacologic/pathophysiologic endpoints
    - Multiple endpoints, different events (measures)
    - Statistically persuasive findings
Regulation and Investigation: The FDA's Role In Advancing Innovation

• Outline
  – Congressional Mandate: FDASIA
  – Breakthrough Designation
  – Accelerated Pathway to Drug Development in Rare Diseases
Background

• Longstanding FDA goal to facilitate and expedite development and review of new drugs to address unmet medical need for serious conditions

• Existing Programs
  – Subpart E regulations (1988) - speeding the availability of new therapies for serious conditions with unmet medical need, while maintaining safety and efficacy standards
  – Accelerated Approval Regulations (1992)
  – Fast Track (1997)
  – Priority Review (1992)
Concepts: Serious Condition

• Associated with morbidity that has substantial impact on day-to-day functioning, and
• Drug should be intended to have an effect on a serious aspect of a condition
• No significant changes from existing fast track guidance
• Qualifying criteria for each expedited program
Concepts: Unmet Medical Need

- A medical need not addressed adequately by available therapy
- Will consider a range of potential advantages
  - Ability to address an emerging or anticipated public health need (e.g., drug shortage or antibacterial resistance)
  - Does not need to show direct efficacy or safety advantage, could provide sufficient public health benefit for expedited programs
- Exists if the only available therapy was approved under accelerated approval based on a surrogate or intermediate clinical endpoint and the clinical benefit has not been verified
The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, expands the FDA’s authorities and strengthens the agency's ability to safeguard and advance public health by:

- **Promoting innovation** to speed patient access to safe and effective products;
- **Increasing stakeholder involvement** in FDA processes; and
- **Enhancing the safety of the drug supply chain**
- **Giving the authority to collect user fees** from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products;
FDASIA gave FDA a new and powerful expedited drug development tool, known as the "breakthrough therapy" designation.

This new designation helps FDA assist drug developers to expedite the development and review of new drugs with preliminary clinical evidence that indicates the drug may offer a substantial improvement over available therapies for patients with serious or life-threatening diseases.

Regulation and Investigation: The FDA's Role In Advancing Innovation

• FDASIA also sought to further medical device innovation. The FDA has released a draft guidance on the process for approving applications for clinical investigations of medical devices, and is also using its authority under FDASIA to review "direct" de novo device submissions.
Breakthrough Designation
1. Breakthrough Designation

• A breakthrough therapy is a drug:
• intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and
• preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.
Breakthrough Designation

- If a drug is designated as breakthrough therapy, FDA will expedite the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt, and FDA will either grant or deny the request.
Substantial Improvement on Clinically Significant Endpoints

Preliminary evidence of substantial improvement

- Greater response rate (on its own or added to available therapy)
- Treats the underlying disease or reverses disease progression, in contrast to available therapy that treats only symptoms

Important safety advantage

Clinically significant endpoint - measures an effect on irreversible morbidity or mortality (IMM) or on symptoms that represent serious consequences of the disease

- An effect on a surrogate or clinical endpoint that could be used for AA
- An effect on a pharmacodynamic biomarker that suggests the potential for a clinically meaningful effect on the disease

Improved safety profile with evidence of similar efficacy
Accelerated Pathway to Drug Development in Rare Diseases
Accelerated Approval- Background

- Existing regulations- 21 CFR part 314, subpart H, and part 601, subpart E
- No existing guidance
- FDASIA provides additional flexibility and clarity to the accelerated approval pathway
  - Flexibility: Approval takes into account the availability or lack of alternative treatments
  - Clarity: Approval can be based on a clinical endpoint (intermediate clinical endpoint) that can be measured earlier than irreversible morbidity or mortality (IMM) that is reasonably likely to predict an effect on IMM or other clinical benefit.
Accelerated Approval- Definitions

- Surrogate endpoint- marker (i.e., laboratory measurement, radiographic image, physical sign) or other measure thought to predict clinical benefit
- Clinical endpoint- characteristic or variable that directly measures a clinical effect of a drug—an effect on how a patient feels, functions, or survives
- Clinical benefit- clinical effect that is clinically meaningful in the context of a given disease
- Intermediate clinical endpoint- endpoint that measures a clinical effect that is considered reasonably likely to predict the ultimate clinical benefit of a drug, such as an effect on IMM.
General Considerations for Expedited Development

- Communication with FDA
- Manufacturing considerations
- Nonclinical considerations
- Clinical considerations
Take Home Messages

• FDA and stakeholders including industry and academia can work together to achieve innovation and an appropriate balance between:
  — Providing access to promising drugs/biologics for patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy
  — Protecting patient safety