FDA and Rare Diseases

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Common Ground

Effective, safe, quality treatments for patients with rare diseases

FDA Center for Drug Evaluation and Research (CDER)'s mission:

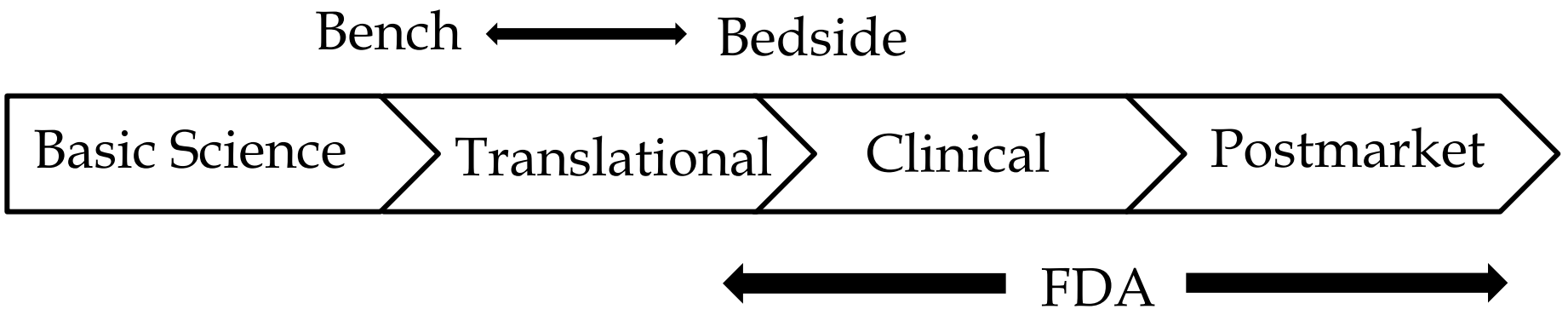
"To promote and protect the public health by ensuring that safe and effective drugs are available to Americans"

FDA CDER: What we do

- CDER regulates:
  - Drugs (Rx and OTC), and therapeutic biological products
  - Other Centers and Products
    - Blood products, products derived from human or animal tissue, stem cell and genetic therapies, vaccine (CBER)
    - Nutritional supplements, medical foods (CFSAN)
    - Devices, diagnostic tests (CDRH, CBER)
- CDER Office of New Drugs (OND) responsibilities:
  - Provide regulatory oversight for investigational (IND) studies during drug development
  - Make decisions regarding marketing approval for new drugs
  - Provide guidance to regulated industry on a wide variety of clinical, scientific and regulatory matters

CDER's Role

Drug development overview



E.g.,
Drug discovery/MOA
Animal models
Endpoint development
Natural history

FDA's oversight begins when testing investigational new drug in human subjects

Rare Diseases and Orphan Drugs

- Fastest growing area of clinical research and drug development
- ~450 orphan drugs approved (9/8/13)
  - ~1/2 novel products, ~1/2 are repurposed drugs
  - Increases by ~20-25 orphan products/year
- Large public health considerations
  - Collectively, ~25 million Americans with rare diseases
  - ~7,000 different diseases
  - Most are serious and have unmet medical needs
  - Many affect vulnerable populations (e.g., children)

Rare Diseases (2)

- Considerations for Clinical Development
  - Small numbers of patients with the individual disorders
    - Limited opportunity for study and replication of results
    - Drug approval requires "substantial evidence" of effectiveness, safety and product quality, usually from at least 1 adequate and well-controlled trial
  - Hard to diagnosis, long delays in diagnosis
    - Few healthcare professionals familiar w/individual disorders
    - Centers of Excellence few, often sparsely dispersed
  - Highly diverse collection of disorders
    - Substantial heterogeneity between and within the rare diseases
    - Diseases incompletely understood
  - Most rare diseases do not have approved treatments
    - Lack regulatory precedent
    - Often lack accepted endpoints, outcome assessments, instruments and tools

FDA and Rare Diseases

- Many offices, programs and initiatives
- A few:
  - Office of Orphan Products Development
  - Office of Special Health Issues
  - CDER Rare Diseases Program
  - Small Business Assistance
  - Critical Path
  - Expedited development pathways
  - New legislation - FDASIA

FDASIA/PDUFA V

- FDASIA = Food and Drug Administration Safety and Innovation Act
- Signed into law July 9, 2012
  - PDUFA = Prescription Drug User Fee Act
  - PDUFA V agreement provides FDA with additional funding for new activities during FY 2013-2017
- Major goals
  - Bring to market critical new medicines for patients
  - Maintain FDA's high standards for safety, efficacy and quality
  - Build on success of 20-year history of PDUFA
  - Focus on regulatory science, benefit/risk framework, and patient-focused drug development

Expedited Programs for Serious Conditions – Drugs and Biologics

Program	Qualifying Criteria: Serious condition and…	Features
Breakthrough Therapy New	-Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinical significant endpoint over available therapies	-All Fast Track features -Intensive guidance on efficient drug development -Organizational commitment
Accelerated Approval	-Provides meaningful advantage over available therapies -demonstrates effect on surrogate or clinical endpoint that can be measured earlier than IMM	-Approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit
Priority Review	-Would provide a significant improvement in safety or effectiveness -Or, other qualifying programs	-Shorter review clock goal for marketing applications (6 mo vs 10 mo)
Fast Track	-Nonclinical or clinical data demonstrate potential to meet an unmet medical need -Or, QIDP	-Actions to expedite development and review --E.g., meetings -Rolling review

QIDP = qualifying infectious disease pathogen; IMM = irreversible morbidity or mortality

Expedited Programs (2)

- Philosophy first codified into regulations in the 1980s
  - 21 CFR 312.80 Subpart E: Drugs Intended to Treat Serious and Severely-debilitating Illnesses
    - exercise "broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness"
    - "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"
    - Evaluate drug in light of the severity of the disease being treated
  - General Procedures, include (but not limited to):
    - Early consultation (§312.82)
    - Treatment protocols (Expanded Access after Phase 2) (§312.83)
    - Risk-benefit analysis (§312.84)
    - Phase 4 studies (§312.85)
    - Safeguards for patient safety (§312.88)

Other Programs

- Incentives, e.g.
  - Orphan Drug Act
  - Pediatric Rare Disease Priority Review Voucher (PRV) (new)
  - Neglected Tropical Disease PRV
  - GAIN
- Advice/interactions
  - E.g., CDER OND Rare Diseases Program. Goals:
    - Coordinate the development of RD policy, procedures and training
    - Assist in development of good science as the basis for treatments for RD
    - Work collaboratively with external and internal RD stakeholders
    - Maintain collaborative relationships with CDER's review divisions to promote consistency and innovation for RD

FDA & PCORI

- #1 Patient identification and diagnosis
  - Gaps, e.g.,
    - Diagnostic testing, assays, biomarkers
    - Disease etiology and pathophysiology
      - E.g., genetic basis lying disorder
    - Symptom complex, targeted testing
- #2 Patient-focused drug development
  - I.e., what disease manifestations are important to patients?
  - Gaps, e.g.,
    - Patient Reported Outcomes (PROs)
    - Clinical Outcome Assessment (COA) tools and other measurement science

FDA & PCORI (2)

- #3 Patient involvement in translational science
  - Gaps, e.g.,
    - Prospective and comprehensive assessment of disease descriptions
    - Prevalence/incidence estimates
    - Use of EMR?
    - Standard terminology, dictionaries
    - Build upon existing community efforts
- #4 Best practices, Centers of Excellence
  - Gaps, e.g.,
    - Lacking for most diseases
    - Build upon existing practice
    - Disease awareness, training and education of healthcare community

FDA & PCORI (3)

- #5 Enhanced communication and collaboration across agencies and groups
  - Basic and translational science are the foundation of all clinical development programs
  - Rare diseases, in general, are poorly understood
  - Important and essential role for translational science in rare disease drug development to facilitate efficient clinical development programs