FDA and Rare Diseases

Anne Pariser, M.D.
Office of New Drugs
Center for Drug Evaluation and Research
FDA
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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

Bench ← → Bedside

Basic Science → Translational → Clinical → Postmarket

FDA

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

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<th>Program</th>
<th>Qualifying Criteria: Serious condition and…</th>
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| **Breakthrough Therapy** | - 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
#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
#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