Rare Diseases and CDER: Challenges and Opportunities

The Science of Small Clinical Trials

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Learning Objective

To understand how laws and regulations provide opportunities to meet rare disease drug development challenges
Rare diseases are a CDER priority

- Almost 1 in 10 Americans suffer from one of ~ 7000 rare diseases (~ 30 million people)

- Many rare diseases are severe, progressive, and have high mortality

- ~85% are genetic and majority die before their 5th birthday

- Only ~250 diseases have FDA approved therapy
Drug development challenges

• Populations are small, often exceptionally so

• Natural history often incompletely understood

• Robust endpoints, measures, biomarkers lacking

• Large pediatric representation → special trial design and ethical challenges

• Often extraordinary disease burden on patients and families → logistical trial challenges
Meeting these challenges requires destination-focused strategy

“If a man does not know what port he is steering for, no wind is favorable to him.”

Seneca 4BC-65AD
Understand natural history and pathophysiology

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Apply knowledge about mechanism of action/expected effect

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Identify/develop meaningful endpoints

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Robust, efficient, innovative INDs

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Destination: approved drugs
What is Regulatory Science?

…the tools, standards, and approaches to assess safety, efficacy, quality, and performance of FDA-regulated products

www.fda.gov/scienceresearch/specialtopics/regulatoryscience/default.htm
Regulations steer and stabilize

- Maximize the contribution of, and minimize the risk to, patients who volunteer for clinical trials

- Ensure that approved drugs are safe & effective for their intended use
...while providing opportunity to plot a flexible course

Destination ➤ approved drugs for rare diseases
How regulations, legislative acts, and FDA programs help plot that course...
IND Regulations: 21 CFR 312.80

Subpart E

Drugs Intended to Treat Life-Threatening and Severely-Debilitating Illnesses

Establishes procedures to expedite development, evaluation, and marketing...especially where no satisfactory alternative therapy exists
Approval of an Application

While the statutory standards apply to all drugs...the wide range of uses demand flexibility in applying the standards

Thus 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
The Orphan Drug Act 1983

Prompted by patient advocacy, the ODA established policy that federal government would assist in product development for rare disease/condition diagnosis, prevention or treatment.
FDA’s Office of Orphan Products Development

• Designation Program
  • Tax credits up to 50% of qualified clinical trial costs
  • Waiver of user fees
  • 7-years of marketing exclusivity
• Humanitarian Use Device Program
• Orphan Products Grant Program
• Pediatric Device Consortia Grants Program
CDER’s Rare Disease Program

In February 2010, CDER established the Rare Disease Program to facilitate and support the research, development, regulation and approval of drug and biologic products for the treatment of rare disorders

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm221248.htm
CDER’s Rare Diseases Program Mission

• Coordinate development of CDER policy, procedures and training for review and approval of rare disease treatments

• Assist in outside development and maintenance of good science for rare diseases

• Work collaboratively with external and internal rare disease stakeholders to support the development of rare disorder treatments

• Serve as CDER’s focal point to the rare disease drug development community on how best to interact with CDER
The FDA Modernization Act 1997

- *Fast Track Designation* facilitates development and expedited review of drugs that treat serious diseases and fill an unmet medical need.

- *Accelerated approval* based on (1) a surrogate reasonably likely to predict clinical benefit or (2) an effect on a clinical endpoint other than survival or irreversible morbidity.

*Fast Track and Accelerated Approval* are intended to make therapeutically important drugs available at an earlier time; they do not compromise standards for safety and effectiveness of the drugs that become available through these processes.
• PDUFA IV/Food and Drug Administration Amendments Act focused largely on safety

• PDUFA V/FDA Safety and Innovation Act (FDASIA):
  – goal of drug regulation is to ensure a positive balance of benefits and risks
  – risks posed by lack of therapeutic options must be part of the benefit/risk calculation
  – patient centered
    • factor in risk tolerance of patients with unmet medical needs
    • explore endpoints most important to patients
PDUFA V: 1st legislation since ODA to specifically address rare diseases

• Advancing Development of Drugs for Rare Diseases
  – Funding and programmatic direction for CDER’s Rare Disease Program

• Enhancing Regulatory Science & Expediting Drug Development
  – Promoting innovation through enhanced communication
  – Advancing the science of meta-analysis methodologies
  – Advancing use of biomarkers and pharmacogenomics
  – Advancing development of patient reported outcomes and other endpoint assessment tools
  – Advancing development of drugs for rare diseases
Regulatory Science Innovation is Not New at FDA

- U.S. first to approve the vast majority of novel agents between 2001 and 2010; on average, did it most quickly
  *NEJM 366:24 June 2012, Downing et al*

- ~1/3 of new molecular entity approvals are for rare diseases
  *www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm*

- Substantial trial design diversity in applications for rare disease drugs
  *DIA Global Forum 2012;4:24-31, Pariser AR & Bauer LJ*
  ~2/3 of rare disease drug approvals in past 3 years were based on level of evidence other than 2 well-controlled RCT

- Quantum of effectiveness evidence in FDA's approval of orphan drugs: cataloguing FDA's flexibility in regulating therapies for persons with rare disorders
What is innovation if not ‘new’?

John Kao author of *Innovation Nation* defines innovation as…

“…the set of capabilities (individual, company, societal) that allows the continuous realization of a desired future by transforming what is possible into what is valuable for many”
Today’s Learning Objective
To understand how laws and regulations provide opportunities to meet rare disease drug development challenges

transforming what is possible
Learning Objective Challenge Questions

? T/F: Orphan drugs are held to the same statutory standards for effectiveness and safety as other drugs

? T/F: Regulations provide room for flexibility in review of drug treatment applications for rare diseases

? T/F: FDASIA addresses innovation and unmet medical need, but does not include provisions specifically focused on rare disease drug development