Legal and Regulatory Framework For Clinical Investigations and Approval/Licensure of Drugs and Biological Products

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Agenda

- Legal/Regulatory Landscape for Initiation and Oversight of Clinical Studies
  - Investigational New Drug Applications
    - Why, What, How
    - Clinical Holds
- Legal Landscape for Marketing Submissions and Approval
  - New Drug Applications; Biologics License Application
  - Standards for Approval of Drug and Biological Product Applications

Why Legal Standards are Important

- Common goal across rare disease ecosystem – find drugs that are effective and where benefits outweigh the risks
- Without legal standards for what is safe and effective, we would have no benchmarks for determining benefit and therefore whether the benefits outweigh the risks
- There would also be no way to ensure that the product you are taking is the product it claims to be
- Ultimately, impedes our goal of finding treatments and cures for patients who need them
- Legal standards also help facilitate consistent treatment of applications across review divisions

Legal Landscape: Statute

- Statutes
  - Passed by U.S. Congress; signed into law by the President
  - Where FDA derives legal authority to regulate medical products and clinical studies for investigational products
  - Federal Food, Drug, and Cosmetic Act
  - Public Health Service Act (biological products)
  - Codified in the United States Code

Legal Landscape: Regulations

- Regulations
  - Published by FDA to implement the relevant statutes
  - Subject to notice and comment by interested parties (including you!)
  - Force and effect of law and establishes requirements
  - Codified in the Code of Federal Regulations
    - Title 21 – Food and Drugs

Guidance Documents

- Represent FDA's current thinking on a topic
- Describe FDA's interpretation of our policy on a regulatory issue
- Generally non-binding – can use another approach to satisfy legal requirements
- Examples:
  - Disease-specific guidance (Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment)
  - Design guidance (Considerations for Rare Disease Drug Development)

Disclosure Laws

- Why doesn't FDA reveal information about pending development programs?
- Federal laws protect certain confidential commercial information and trade secrets from disclosure
- More information available once a product is approved
- Sponsor can share information before approval if they choose, but not typically done

INVESTIGATIONAL NEW DRUG APPLICATIONS (INDS)

Investigational New Drug Application (IND)

- Under Section 505 of the FDCA, can't put an unapproved new drug into interstate commerce
  - An IND allows manufacturers to ship investigational drugs in interstate commerce for the purposes of clinical trials of the drug
  - Most clinical trials (aka clinical investigation) of drugs in the U.S. require an IND (commercial or not)
    - Limited exemptions for studies of approved drugs that meet certain criteria

Role of the IND

- Provides critical data for FDA to ensure the safety and rights of individuals who will participate in the clinical studies
- Help ensure the scientific quality and adequacy of clinical studies intended to evaluate a drug's safety and effectiveness

Content of an IND

- **Animal pharmacology and toxicology studies** – generally lets us know whether it's safe to test in humans
- **Manufacturing Information** – lets us know whether drug and be produced and supplied consistently
- **Clinical protocols and investigator information** – let's us know what the study is, whether the persons conducting it are qualified, and plans for ensuring informed consent and ethical oversight.

When Is an IND "In Effect"?

- A clinical investigation must not begin until it is subject to an IND that is "in effect"
- IND goes into effect **30 days** after FDA receives the IND, unless:
  - FDA provides earlier notification; or
  - FDA issues a clinical hold (partial, full)

Regulatory Flexibility

- IND regulations have entire section devoted to regulatory flexibility for drugs intended to treat life-threatening and severely-debilitating illnesses
- FDA works closely with sponsors to apply this flexibility while generating robust data and information that ensures appropriate safeguards for safety and that required evidence for effectiveness is met
- We work closely with rare disease sponsors to provide early feedback on development programs and trial design so that a future application can be in the best shape for review
  - Our regulations provide for early consultation with FDA-reviewing officials to reach agreement on the design of preclinical and clinical trials

EXPEDITED PROGRAMS: SPEEDING THE AVAILABILITY OF DRUGS

Expedited Programs: Fast Track

- A drug that is intended to treat a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need
- FDA takes actions to expedite development and review
- Eligible for “rolling review” – required parts of a marketing application come in at different times

Expedited Programs: Breakthrough Therapy Designation

- Drug that treats a serious condition and preliminary clinical evidence shows drug may demonstrate substantial improvement over available therapy
- All Fast Track designation features
- FDA provides extensive advice on efficient drug development
- Organizational commitment involving senior managers

Expedited Programs: Priority Review

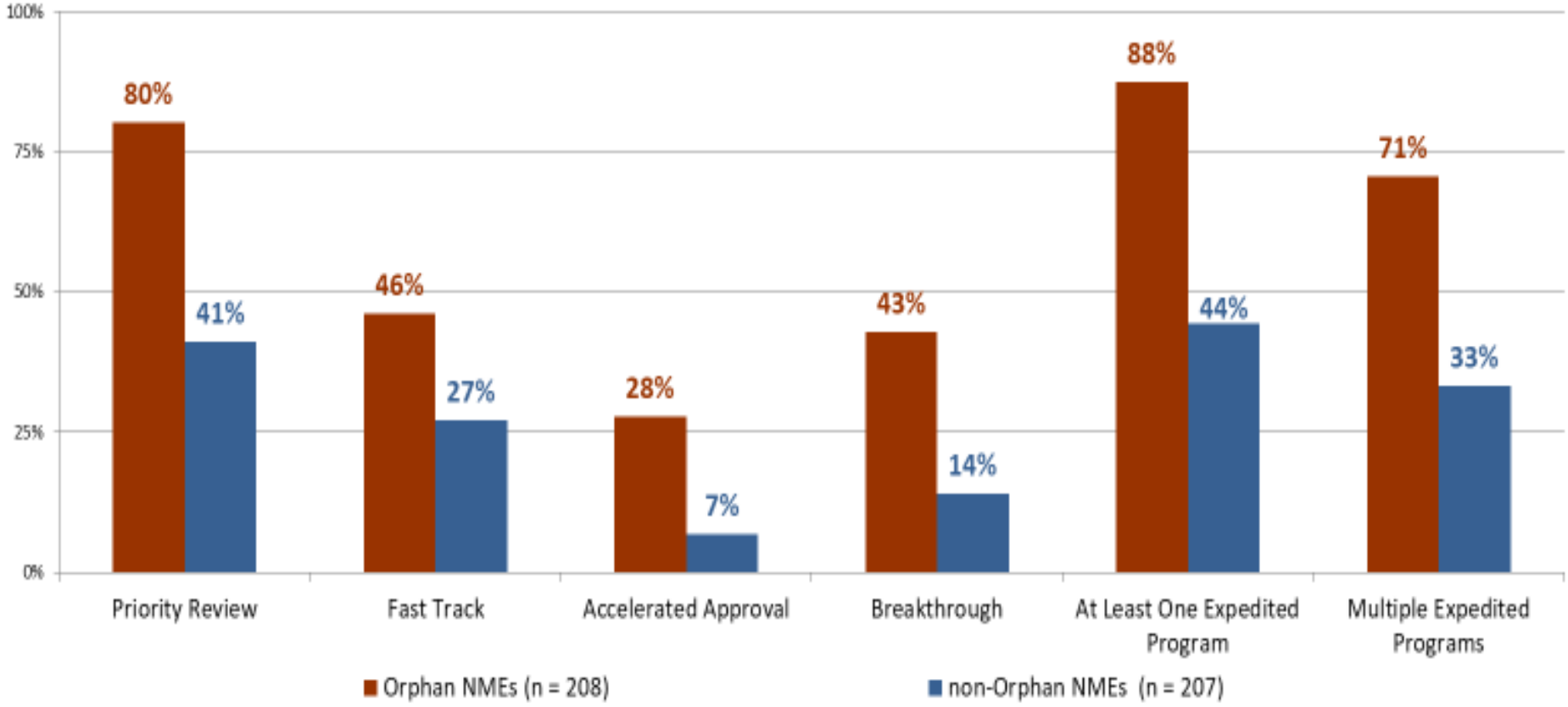
- A drug may receive a priority review designation and qualify for priority review if the drug treats a serious condition and, if approved, would provide significant improvement in safety or effectiveness
- An application may also qualify for priority review by redeeming a priority review voucher
- Shorter review clock compared to standard review (6 months vs. 10 months)

Expedited Programs: Accelerated Approval

- A drug that treats a serious condition and provides meaningful advantage over available therapies and demonstrates effect on a surrogate endpoint reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality
- Allows earlier approval before full clinical benefit demonstrated; must verify and confirm clinical benefit in a post-approval clinical study
- Example of surrogate endpoint is increase in hemoglobin for reduced cerebral blood flow velocity and stroke risk

CDER Use of Expedited Programs

NME and New Biologic Approvals CY 2015 - 2023



NEW DRUG APPLICATIONS (NDA) AND BIOLOGICS LICENSE APPLICATIONS (BLA)

What is a Drug

Drug is defined in § 201(g) of the FD&C Act as:

(A) articles recognized in the official United States Pharmacopeia, official Homeopathic Pharmacopeia of the United States, or official National Formulary; and

(B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and

(C) articles (other than food) intended to affect the structure or any function of the body of man or other animals

(D) articles intended for use as a component of any article specified in (A), (B), or (C).

What is a Biological Product

Biological product is defined in § 262 of the Public Health Service Act as:

"…a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."

Drugs vs. Biological Products

- All biological products meet the definition of a drug under the FDCA. Biological products are a subset of drugs
- Generally, biological products are large, complex products derived from living material; drugs generally are small molecules that are chemically made
- NDAs and BLAs have similar requirements for demonstrating the safety and effectiveness of drugs and biological products

NDA vs. BLA

- New Drug Application (NDA)
  - Required for an applicant who wants FDA to approve a new pharmaceutical for sale and marketing in the U.S.
  - NDA is considered an “approval”
- Biologics Licensing Application (BLA)
  - Required for applicant who wants to sell or market a biological product
  - BLA is considered a “Licensure” (no practical difference from approval)
- **FDA does not approve or license products without a marketing application**

Substantial Evidence: Adequate and Well-Controlled Study

- Legal standard: substantial evidence of effectiveness
- FDA regulations list the characteristics of an AWC study
- These are generally agreed on principles for good study designs and analysis plans that provide the foundation for **being able to determine whether there is an effect of the drug**
- Principles include appropriate comparator, proper design and analysis plan, appropriate participant population, measures to minimize bias, etc.

How Many AWC Studies?

- Generally, two or more
  - Possible that one very persuasive trial with features that are the legal and scientific equivalent to two trials could meet this standard
- Where FDA determines it is appropriate, and often seen in the rare disease setting, one AWC clinical study plus "confirmatory evidence"

DECISIONS ON MARKETING APPLICATIONS

When Legal Standards Met

- Approve/License
  - Traditional
  - Accelerated (must confirm clinical benefit)
- Approve/License with restriction to assure safe use (REMS)
  - E.g., requirement to use contraception
  - E.g., use restricted to certain environments

When Standards Not Met: Complete Response Letter

- Complete Response Letter – indicates review is over and identified problems that prevent approval, e.g.:
  - Lack of substantial evidence of effectiveness
  - Safety concerns
  - Labeling is false or misleading
  - Manufacturing facility concerns

CR Response Options

- Applicant can meet with FDA in an “End of Review Conference” to talk about needs to be done to move forward
- Within 1 year:
  - Address all deficiencies identified in the letter
  - Withdraw application
  - Request an opportunity for a hearing
- Can also follow Formal Dispute Resolution process to seek a different decision

Acknowledgements

- FDA Staff who contributed to this presentation:
  - David Faranda
  - Heather Dorsey
  - David Markert
  - Kristiana Brugger
  - Alaina Kupperman