Introduction to FDA Drug and Biologic Review Process

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Outline

• Regulatory background
  – US Laws and FDA Regulations
  – History of Regulation

• Review and Approval process

• Clinical Trial Review Process
Basis for Regulation

• **Statutes**: THE LAW (Act) --- passed by Congress and signed by the President
  – USC (United States Code)

• **Regulations**: Detail interpretation of the law - -- written by the Agency and approved by the Executive Branch
  – CFR (Code of Federal Regulations)

• **Guidance**: Issued by individual agencies to reflect current thinking, not binding.
Legal Requirement for Approval

- **Accurate and adequate label**
  - Food and Drug Act (1906)
- **Safety**
  - Food, Drug and Cosmetic Act (FDC Act) (1938)
- **Effectiveness**
  - FDC Act amended 1968
History of US Drug and Biologic Regulations
1901 13 children in St. Louis died of tetanus after receiving diphtheria antitoxin from a horse named Jim.

9 children die of tetanus from contaminated smallpox vaccine

1902 Biologics Control Act authorizes Hygienic Laboratory to issue regulations to ensure purity and safety of serums, vaccines, and similar products

1944 PHS Act incorporates provisions for biologics regulation. Outlines licensing requirements that are independent from pre-marketing requirements for drugs.

1973 Blood, blood products, and allergenics included in the PHS Act
Food and Drug Act

1905  Samuel Hopkins Adams published “The Great American Fraud,” a commentary on the patent medicine industry exposing cure-all claims for worthless and dangerous patent medicines.

Upton Sinclair publishes “The Jungle” with shocking disclosures of insanitary conditions in meat-packing plants.

1906  Food and Drug Act prohibits interstate commerce in misbranded and adulterated foods, drinks, and drugs.
Food, Drug, and Cosmetic Act

1937 Sulfanilamide elixir containing diethylene glycol killed 107 people

1938 Food, Drug, and Cosmetic Act required new drugs to be shown safe before marketing — starting a new system of drug regulation. It also authorized factory inspections and other provisions.
Kefauver-Harris Amendments

1962 Thalidomide, a new sleeping pill, was found to have caused birth defects in thousands of babies born in western Europe. Over two million pills distributed in the United States for investigational studies.

1962 Kefauver-Harris Drug Amendments passed to ensure drug efficacy and greater drug safety. It required drug manufacturers to prove the effectiveness of their products before marketing them, gave FDA control over drug advertising, and allowed FDA to regulate investigational studies.
A new biologic, drug, or device may not be entered into interstate commerce unless:

– **It is approved by the FDA as safe and effective**
  (biological license application [BLA], new drug application [NDA], pre-market approval [PMA], or other marketing approval)

OR …

– **An IND (Investigational New Drug Application) is in effect**
  (exempting the study from the premarketing approval requirements that are otherwise applicable)
Laws affecting FDA

• More than 20 Statutes affecting FDA
• Two main Laws concerning human drugs and biologicals
  – Public Health Service Act (enacted in 1944), United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories
Food, Drug, and Cosmetic Act (FD&C Act)

• Enacted in 1938 and amended in 1968
  – foods are pure and wholesome, safe to eat, and produced under sanitary conditions
  – drugs and medical devices are safe and effective for their intended uses. This includes drugs used in medicated feeds for animals.
  – cosmetics are safe and properly labeled.
  – packaging and labeling of these products is truthful and informative.
• Amended 20 times (latest: August, 2004)
Major amendments for FD&C Act

• Orphan Drug Act (Jan. 4, 1983)
• Prescription Drug User Fee Act (PDUFA) of 1992
• Safe Medical Devices Act of 1990
• Food and Drug Administration Modernization Act (FDAMA) of 1997
• Medical Device User Fee and Modernization Act
Public Health Service Act

• United States Code (U.S.C.) Title 42, Chapter 6A Part F - Licensing of Biological Products and Clinical Laboratories

• The Secretary shall approve a biologics license application on the basis of a demonstration that the **biological product** that is the subject of the application is safe, pure, and potent
• "Biological product" defined in this section, the term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, 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.
Regulations on Drug Approval

• 21 CFR 314.126
  – Determination of **substantial evidence** to support the claims of **effectiveness** for new drugs.
  – Primary basis: **Adequate and well-controlled investigations**

• 21 CFR 314.126
  – Acceptable safety

• 21 CFR 201
  – Product label
    • Defines an appropriate patient population
    • Provides adequate information to enable safe and effective use
Two Types of Approvals

- Regular (Full) Approval or
- Accelerated Approval
Regular (full) Approval

• **Direct clinical benefits**
  – Prolongation of overall survival (live longer)
  – Improvement of symptoms (live better)
  – Favorable effect on established surrogate
  – Composite endpoints
Accelerated Approval

- 21 CFR 314.510 for drugs (subpart H)
- 21 CFR 691.41 for biologics (subpart E)
- The product
  - Treats serious or life-threatening illnesses
  - Provides meaningful therapeutic benefit to patients over existing treatments
  - Is tested in adequate and well-controlled clinical trials
  - Has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Fulfils post-marketing commitment to verify and describe its clinical benefit
Drug/Biological Development

- An orderly process starting from scientific discovery
- Multiple components involving critical decision making
- Time and cost
Traditional Paradigm for Drug Development

Discovery (2–10 Years)

Preclinical Testing
Laboratory and animal testing

Phase I
20–80 healthy volunteers used to determine safety and dosage

Phase II
100–300 patient volunteers used to look for efficacy and side effects

Phase III
1,000–5,000 patient volunteers used to monitor adverse reactions to long-term use

FDA Review/Approval

Additional Post-marketing Testing

Compound Success Rates by Stage

5,000–10,000 screened

250 enter preclinical testing

5 enter clinical testing

approved by the FDA
10-Year Trends in Major Drug and Biological Product Submissions to FDA

- Total NMEs Rec'd by FDA
- Original BLAs

Submissions to FDA

Year:
- 1993
- 1994
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
Review Process

• Starts with the sponsor’s application

• NDA: New Drug Application
  – Mainly in the Center for Drugs

• BLA: Biological Licensure Application
  – Mainly in the Center for Biologics and some in Center for Drugs
Review Process

• Team approach
  – Clinical reviewer in collaboration with biostatistician: clinical data to determine the efficacy and safety
  – Other disciplines reviewers:
    • Clinical pharmacologist
    • Toxicologist
    • Chemistry, Manufacturing and Control (CMC) reviewer (chemist or biologist)
Application status

- Regular: 10 month
- Priority: 6 month
- Mid-cycle Review Team Meeting
FDA Advisory Committee Meeting (1)

- Advisors
  - Special Government Employees (SGEs)
  - Pre-screened for Conflict of Interests (COI)
- Meeting agenda and dates announced in advance in Federal Register
- Briefing Package
  - From Sponsor
  - From FDA
  - Made public prior to the meeting
FDA Advisory Committee Meeting (2)

• Presentations
  – Sponsor
  – FDA
  – Public (need to pre-register)

• Committee discussion of questions posed by FDA

• Committee Votes if there are voting questions
FDA Advisory Committee Meeting (3)

- FDA makes its own decision whether to approve a product or not after AC meeting
Public Information after Approval

- For approved drugs and biologics, information (letters, labeling, reviews) is accessible
  - [http://www.fda.gov/cber/products.htm](http://www.fda.gov/cber/products.htm)

- Food and Drug Administration Amendments Act of 2007 (FDAAA) requires internet web posting after approval
  - Immediate publication of summary review, no later than 48 hours
  - Action Package no later than 30 days
    - Review memos
    - Action letters
The IND Process

• Preclinical testing/investigation
  – *In vitro* tests/animal testing
    • “reasonably safe” determination *(21 C.F.R. § 312.23)*
  – Pharmacological data
  – Toxicity testing

• “Good Laboratory Practice” (GLP) *(21 C.F.R. Part 58)*
  – Governs preclinical testing conduct
    • Organization, personnel, facilities, study conduct, and records retention
• Clinical testing/investigation and “Good Clinical Practice” (GCP)
  – Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects.
• Details GCP principles
Regulatory Considerations in reviewing 1st in-human use of investigational agents (phase I)

- The product manufacturing and characterization?
- The level of safety assurance needed for beginning clinical trials
- Clinical study design
Review Process for Phase 1 Trials

1. Pre-IND meetings with the sponsor (although not a requirement)
2. IND submission
3. Non-Clinical Review
4. Clinical Review
5. CMC
6. Pharm/Tox
Decision (within 30 days) for IND to proceed

**CMC**
- Product manufacturing, characterization and testing
- Pre-clinical studies
  - Dosing, toxicity, biodistribution, proof of concept, safety monitoring

**Pharm/Tox**

**Clinical Review**
- Patient population
- dose, schedule and administration
- dose escalation
- DLT definition and Optimal Maximum Dose determination
- Stopping rules
- Safety monitoring and evaluation
- Informed consent

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Review process for phase I trials --- continued
Proposed clinical trials may proceed

Review process for phase II, III trials

CMC
Pharm/Tox

- Product manufacturing, characterization and testing and Potency
- Pre-clinical studies

Clinical Review

Proposed clinical trials may proceed
Phase 2 studies

- Begin if Phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on
  - whether the drug has effect in a defined patient population
  - the relationship between dose and effectiveness.
- Continue to evaluate safety and short-term side effects.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment -- usually a placebo or a different drug.
Phase 3 studies

• Begin if preliminary evidence of effectiveness is shown during phase 2.

• Gather more information about safety and effectiveness in a defined population.

• May form the primary basis of an efficacy claim
Some considerations of phase II and phase III studies

- **Protocol design**
  - Patient population
  - Choice of endpoints
  - Choice of control (placebo vs. active control)
  - Evaluation

- **Study conduct and execution**
  - Study sites
  - Investigator’s brochure
  - DSMB
  - CRF

- **Protocol design**
  - Data collection and Evaluation
  - Statistical analytic plan
  - Assumption of effect size, power and sample size

- **Implications for labeling.**
  - Currently available therapies for the indication sought
  - possibility of the study to generate data to support the claim
Special protocol assessment

[Section 505(b)(4)(c) of the FDA Modernization Act].

- Agreement between the sponsor and FDA documented in writing
  - Protocol design
  - Primary efficacy endpoints
  - Study conduct
  - Data analyses
  - Clearly described labeling statements one could expect if the data are supportive and the product is approved
  - whether the design and planned analysis of a study adequately address objectives in support of a regulatory submission.

- The sponsor submits protocols with specific questions
  - Animal carcinogenicity protocols,
  - Final product stability protocols or
  - clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim

- FDA documents in writing within 45 days any agreement or disagreement to the sponsor
Interactions with FDA

- Early interactions with FDA are critical
- Know your guidance documents
- Consider early in translational research the questions that will be asked at the clinical trial phase
- Phone, face to face; formal or informal: dialogue is encouraged
Interactions with FDA

- Scientific meetings, conferences, workshops
- Pre-Pre-IND
- Pre-IND meetings
- End of Phase 1 meeting
- End of Phase 2 meeting
- Special Protocol Assessment review
- Fast Track program application
- New protocol submission under existing IND
Conclusion

• Drug and biologic development is an orderly process involving multiple components
• Academia, industry and regulatory bodies are integral parts of this process
• Many challenges exist for product characterization as well as testing the safety and effectiveness in humans throughout the life cycle of the product development
• FDA critical path and other initiatives aim to help the development of drugs and biologics
• Frequent and early engagement with FDA are strongly encouraged
Contact Information

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