U. S. Drug Development and Regulatory Oversight of IND Clinical Trials

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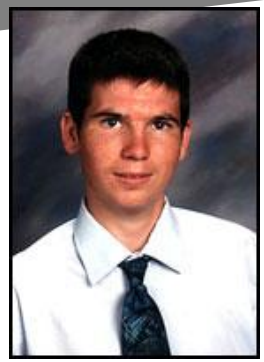
Agenda

- Regulatory history
- Drug development process
- FDA’s role in drug development

Why Do We Need Regulation & Oversight?

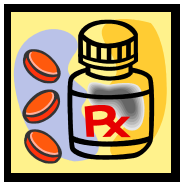
- To minimize risk and determine benefit
- To review the evidence
- To set standards of excellence

FDA Seeks to Penalize Gene Scientist
(Post, Dec. 12, 2000)

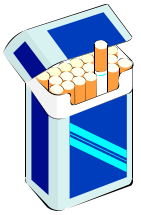


7 Die in Tylenol Scare, 1982

The FDA is the main consumer watchdog for numerous products in U.S



- Drugs and biologics (rx and OTC)
- Food
- Medical devices
- Animal drugs and feed
- Cosmetics
- Radiation-emitting products
- Tobacco



Structure of the U.S. FDA

- Office of the Commissioner
  - Office of Foods
    - Center for Food Safety and Applied Nutrition (CFSAP)
    - Center for Veterinary Medicine (CVM)
  - Center for Drug Evaluation and Research (CDER)
  - Center for Biologics Evaluation and Research (CBER)
  - Center for Devices and Radiological Health (CDRH)
  - Center for Tobacco Products (CTP)

Regulations & Guidelines for Drug Development

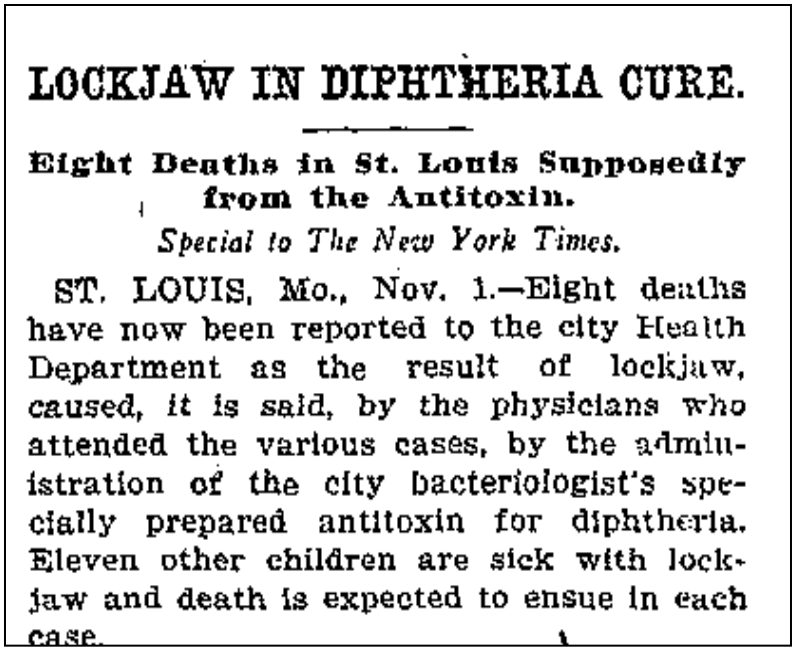
- FDA (Title 21):
  - Informed consent
  - Institutional Review Boards
  - Financial disclosure by clinical investigators
  - Electronic Records; Electronic Signatures
  - Application to begin clinical trials
  - Application to market new drug
- International Conference on Harmonization (ICH) Guidelines

Major Regulatory Principles

Principle	*Year*	*Legislation*	*Contributing Factor*
Labeling of biologics	1902	Biologics Control Act	Tetanus antitioxin
Labeling of drugs	1906	Pure Food and Drug Act	opium
Safety	1938	Food, Drug and Cosmetic Act	sulfanilamide
Efficacy	1962	Amendment to FD&C Act	thalidomide
Incentives	1983	Orphan Drug Act	Tourette's syndrome

Diphtheria/Tetanus: Tragedy of 1901

- 1880-1900s animal anti-sera therapy developed
- Diphtheria antitoxin made from horse serum
- “Jim "Horse was sick with tetanus
- People inadvertently infected by tetanus



LOCKJAW IN DIPHTHERIA CURE.

Eight Deaths in St. Louis Supposedly from the Antitoxin.

Special to The New York Times.

ST. LOUIS, Mo., Nov. 1.—Eight deaths have now been reported to the city Health Department as the result of lockjaw, caused, it is said, by the physicians who attended the various cases, by the administration of the city bacteriologist's specially prepared antitoxin for diphtheria. Eleven other children are sick with lockjaw and death is expected to ensue in each case.

New York Times 11/2/1901

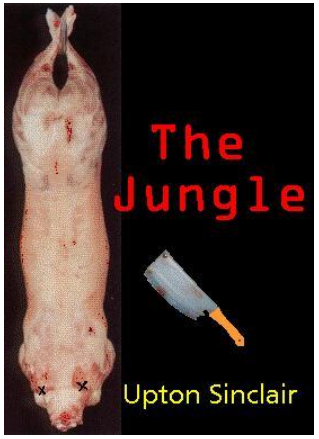
Biologics Control Act of 1902

- Annual licensing of establishments to manufacture & sell biologics
- Labeling required with name & license of manufacturer
- Production supervised by qualified scientist
- Inspections were authorized

Misbranding & Adulteration

- Misbranding
  - Misrepresent the contents of a product
  - Omission of pertinent information
  - Usually in writing and with regards to labeling

- Adulteration
  - Change actual substance without authorization
  - Tampering with the product



The Pure Food and Drug Act of 1906

- Prohibited the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors
- Law required only that drugs meet standards of strength and purity
  - Official standards for drugs
    - *US Pharmacopoeia (1820)*
    - *National Formulary*
- Required product labeling to include 11 dangerous ingredients
  - label warnings on habit-forming drugs

1937 Elixir of Sulfanilamide

- 353 patients received during a 4 week period
- 107 deaths
  - 34 kids
  - 71 adults
- 30% fatality rate

Elixir of Sulfanilamide

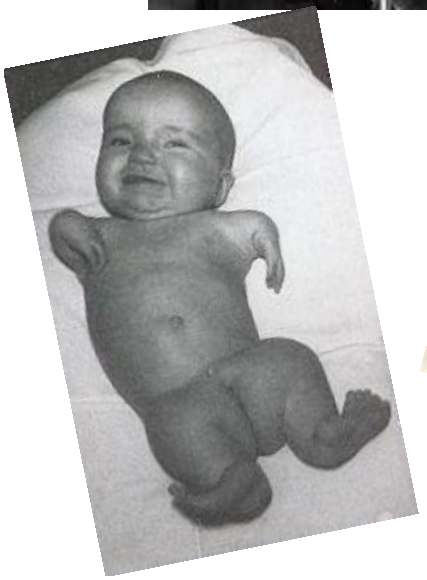
The Food Drug and Cosmetic Act of 1938

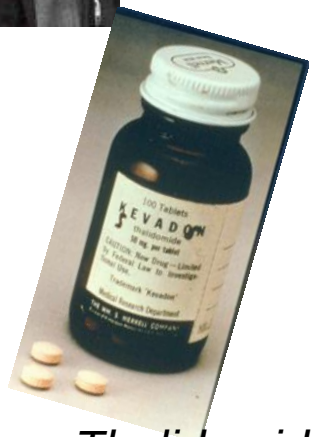
- Prove new products were safe *before marketing*
- Introduced the New Drug Application (NDA)
- Authorized factory inspections
- Outlawed bogus therapeutic claims
- Required directions/warnings on labels
- Launched the requirement for non-narcotic prescription only drugs

Limitations of FDC Act

- Proof of efficacy was not required
- Animal testing was not standardized
- Human trials were poorly executed
- FDA did not review a New Drug Application until manufacturer completed testing
- Drugs tested in premarketing trials were exempt from review
- If the FDA failed to consider a NDA within 60 days the drug was automatically approved
- A single FDA reviewer could approve a NDA

Thalidomide 1961





Thalidomide

- Commercially available in Europe as a sedative and anti-emetic for pregnancy
- Merrell Pharmaceutical Co in US distributed for investigation use:
  - 2,500,000 tablets
  - 1,270 physicians
  - 20,000 patients
  - 624 pregnant women
  - 10 cases of thalidomide embryopathy

Kefauver-Harris Amendments of 1962

- FDA: monitor *all stages* of new drug development
  - Comprehensive animal testing *before* human testing
  - Proof of safety and efficacy mandated
  - Retroactive for products approved <1962
  - Time constraints for review removed
  - Consent required
  - Reporting of Adverse Events
- Good Manufacturing Practice

Fundamental transformation of the FDA

Drug Development Process

Pre-Clinical

- Basic Science
- Drug Discovery
- Pre-clinical testing

Clinical Trials

- Phase 1
- Phase 2
- Phase 3

U.S. FDA Review

- Safe
- Effective
- Approval

What is a Drug?

- Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease
- Articles (other than food) intended to affect the structure or any function of the body of man or other animals
- Articles recognized in the official U.S. Pharmacopeia, National Formulary, Homœopathic Pharmacopœia of the U.S. or any supplement to any of them

Food Drug and Cosmetic Act, sec. 201(g)(1)

What is a Biological Product?

- "…virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, … applicable to the prevention, treatment, or cure of a disease or condition of human beings."

Section 351 of the Public Health Service (PHS) Act

Disclaimer: Drug development refers to both drug and biologic agents

Essential Roles in U.S. Drug Development

Sponsor (typically a biopharmaceutical company)

- Entire development
  - Pre-Clinical
  - Clinical
  - Manufacturing
  - Post-approval
- Produces evidence
- Responsible to FDA

Food & Drug Administration (FDA)

- Reviews data
  - Safety
  - Efficacy
- Grants approval
- Inspections

Who is a Sponsor?

- The sponsor can be:
  - Individual
  - Pharmaceutical company
  - Government agency
  - Academic institution
  - Private organization
  - Other organization

Definition of Sponsor….

- “A person who takes responsibility for and initiates a clinical investigation. … The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.” (CFR)
- “An individual, company, institution or organization which takes responsibility for the initiation, management, and / or financing of a clinical trial.” (ICH)

….Definition of Sponsor

- In general, sponsor is commercial manufacturer that has developed a product in which it holds the principal financial interest
- Hold an IND (Investigational New Drug) or IDE (Investigational Device Exemption)
- File for approval after clinical trials conducted

Public and Private Collaborations

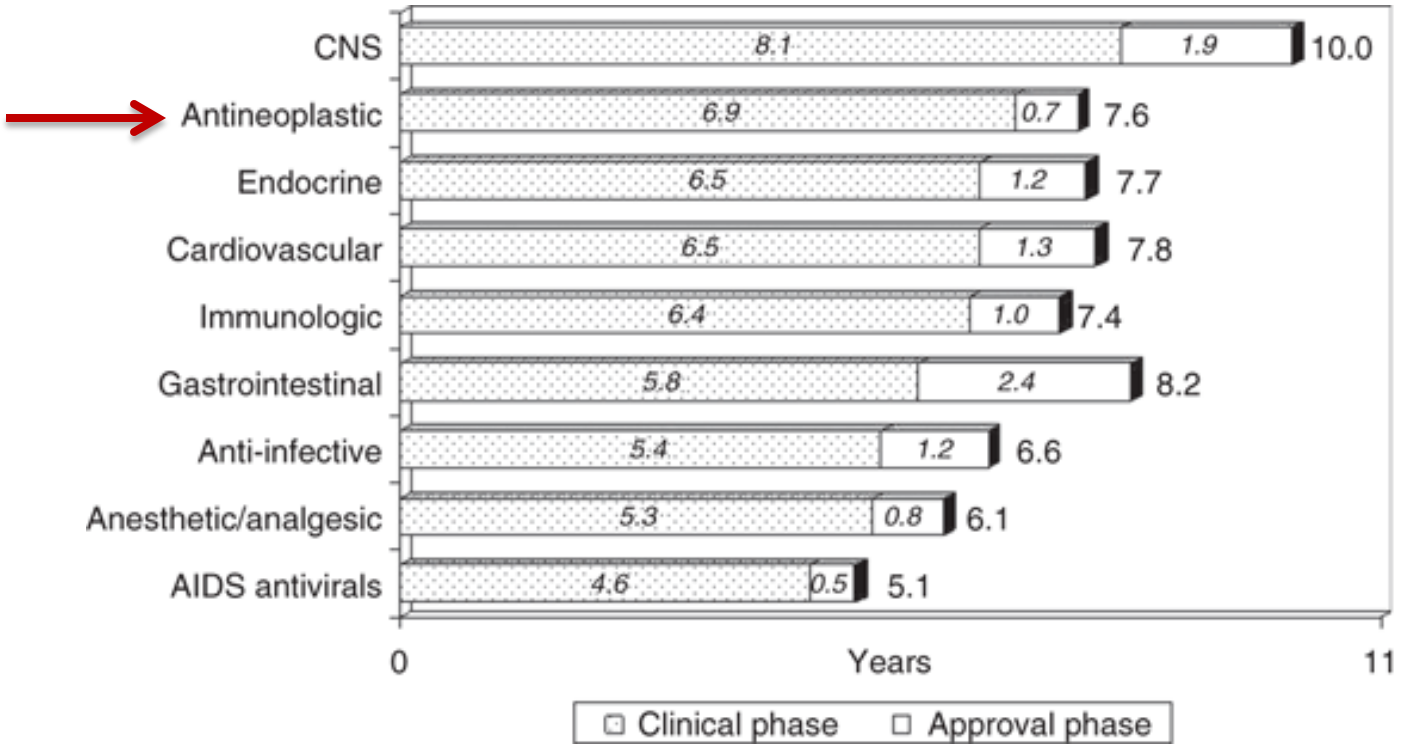
- Roles are interdependent to translate basic research into interventions
- Biopharmaceutical companies are primary source of R&D
- NIH:
  - Provides leadership and funding support to universities, medical schools, research centers and other non-profit institutions
  - Stimulates basic research and early stage development

Drug Development Timeline

	Preclinical testing	Phase I	Phase II	Phase III	FDA	Phase IV
Test Population	Laboratory and animal studies	20-80 volunteers (healthy/ patient)	100-300 patient volunteers	Thousands of patient volunteers	Review and approval process	Additional Post-marketing testing
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate activity, continued safety	Evaluate effectives, continued safety		

AVERAGE:
Total =11.5 - 19+ years
Clinical Trials to Approval = 7.5 – 12 years

Timeline for NME & Biologics in Common Diseases:2005-2009



Kaitin, K.L. & DiMasi, J.A. (2011). Pharmaceutical Innovation in the 21st Century: New drug Approvals in the First Decade, 2000-2009. Clinical *Pharmacology & Therapeutics*, *89(2)*:183-188.

Preclinical Testing

- Lab and animal testing to determine if the drug is safe enough for human testing
- Series of tests to provide an early assessment of the safety of a lead compound
  - ADME
  - Toxicological
    - Acute toxicity profile
    - Chronic toxicity profile

Features of a Successful Drug

- Absorbed into the bloodstream
- Distributed to the proper site of action in the body
- Metabolized efficiently and effectively
- Successfully excreted from the body AND
- Demonstrated to be not toxic

Drug Formulation

- Dosage form: capsule, tablet, injection, elixir, other
- Additive: filler, lubricant, coating, stabilizer, color, binder, disintegrator
- Bioavailability
  - Subcategory of absorption
  - Describes the fraction of an administered dose reaches systemic circulation
- Ease of use

Application to Begin Clinical Trials

- Investigational New Drug (IND) Application
- Documentation that allows investigational clinical testing of a new drug
- Must be filed with FDA before drug administered to humans
- Provide mechanism so FDA can allow interstate shipment of drug not yet approved for marketing

IND Sections

- FDA Form 1571
- Table of contents
- Intro statement
- General investigative plan
- Investigator's Brochure (IB)
- Clinical protocols
- CMC (chemistry manufacturing and control) data
- Pharmacology & toxicity data
- Previous human experience
- Additional information

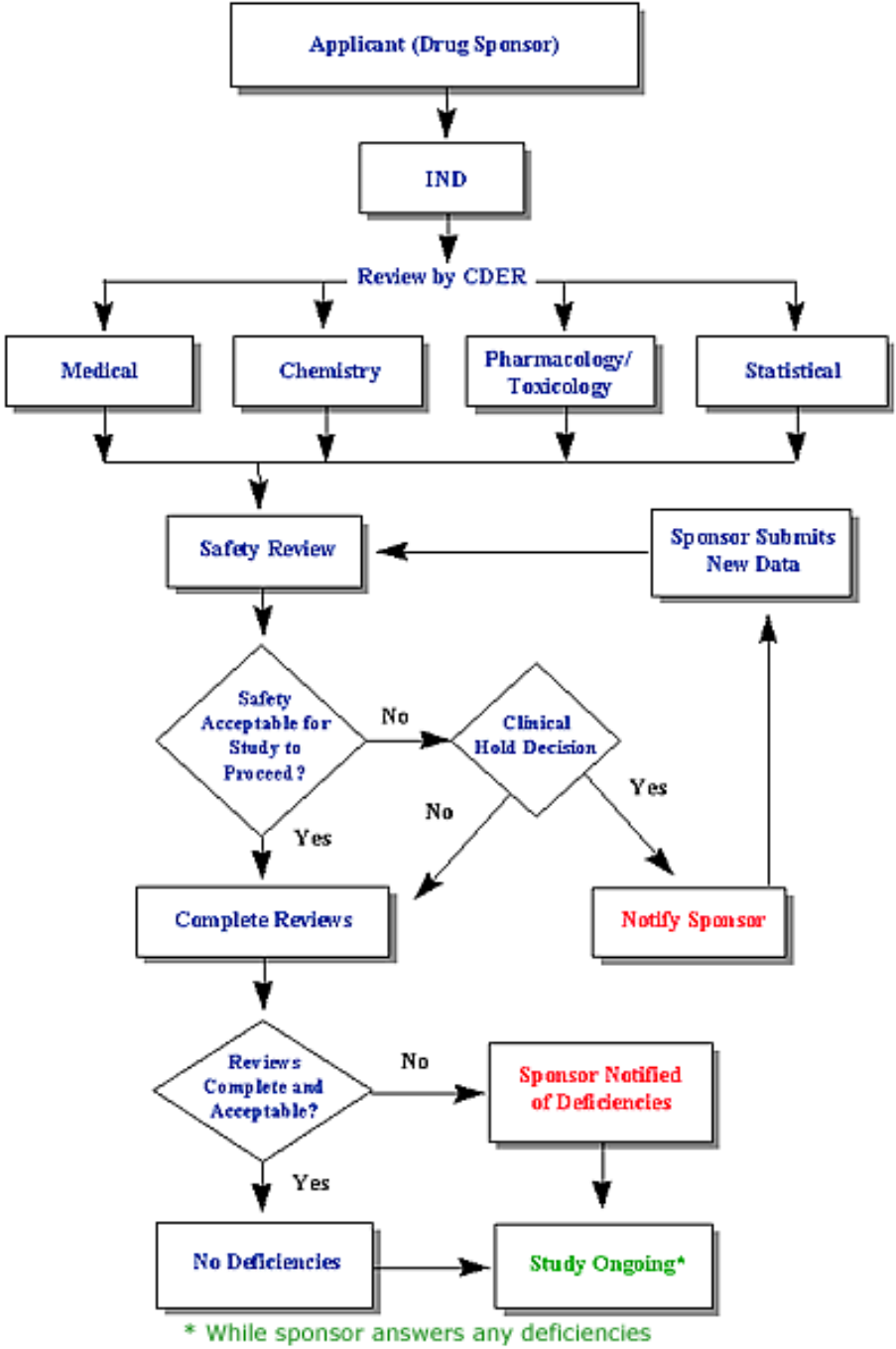
Types of INDs

- Commercial
  - Goal is to obtain FDA-approval to market
- Non-commercial
  - Investigator-held IND (Research IND)
  - Emergency Use IND
  - Treatment IND
  - Exploratory IND (Screening or Micro-dose)

IND Review

30-day review

- Medical
- Chemistry
- Pharmacology & toxicology
- Statistical



Source: FDA

Application to Market New Drug or Biologic

New Drug Application (NDA)

Demonstration of efficacy with acceptable safety in adequate and well-controlled studies

Biologic License Application (BLA)

- Products meets standard designed to insure continued safety, purity, and potency of the product
  - "Potency" interpreted as "efficacy"

U.S. Review and Approval

Evaluated based on standards of Excellence

GLP

- Good Laboratory Practice

GMP

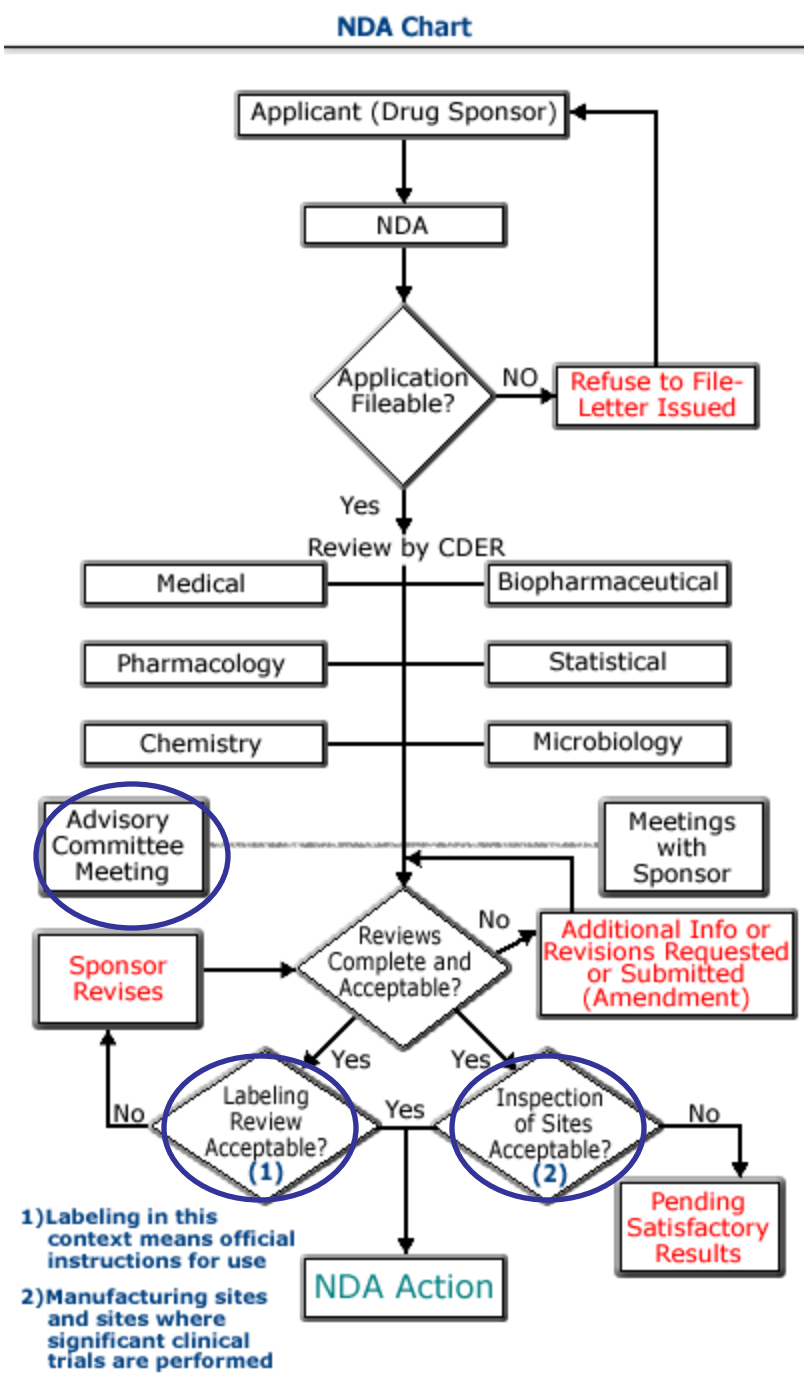
- Good Manufacturing Practice

GCP

- Good Clinical Practice

Review Process

- Medical
- Pharmacology
- Chemistry
- Biopharmaceutical
- Statistical
- Microbiology



Source: FDA

Product Label

- Federal government licenses for interstate commerce a ***claim about the use of a product*** that is determined to be safe and effective
- A product is not licensed without a use
- Each specific use is termed an Indication
- A product may have more than one Indication
- The license and description of the safe and effective use of the product is in the approved package insert (product label)

Expediting Review and Approval Processes

- Goal: Make therapeutically important drugs available at an earlier time without compromise to safety and effectiveness
- Approaches:
  - Fast Track
  - Priority Review
  - Accelerated Approval
  - Breakthrough Therapy *(new program)*

Orphan Diseases & Drugs

- Disease prevalence <200,000 in U.S.
- 7, 000 diseases classified as rare/orphan
- Limited $ incentive to develop drugs
- Orphan Drug Act of 1983
  - Exclusivity (2 extra years)
  - Additional incentives

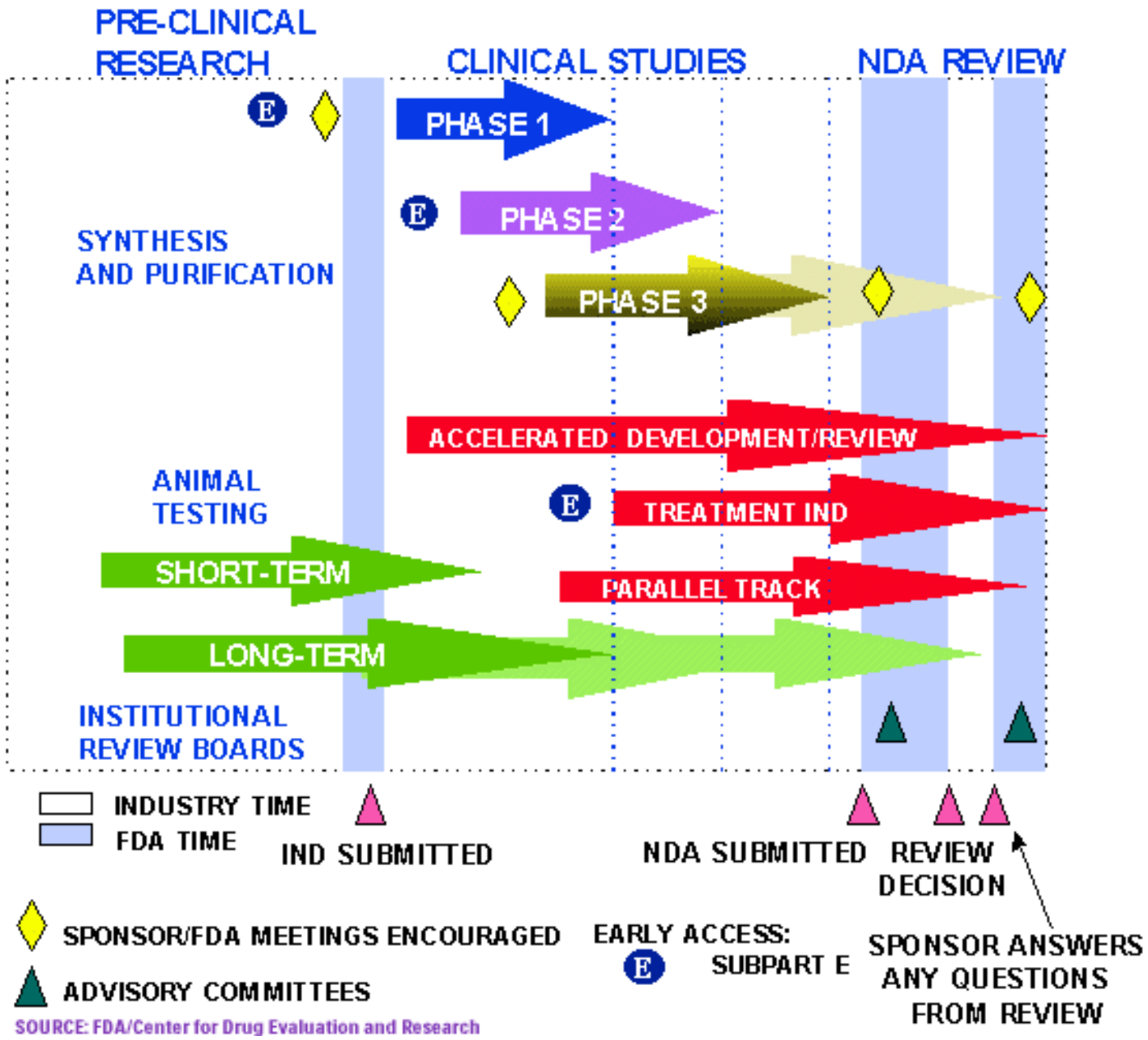
Quincy, M.E.

Marketing Exclusivity

- New Chemical Entity — 5 years
- "Other" Exclusivity — 3 years
  - supplemental use of an already approved product
- Pediatric Exclusivity — 6 mo added on
- Orphan Drug — 7 years

Patent: 20 years from date of filing

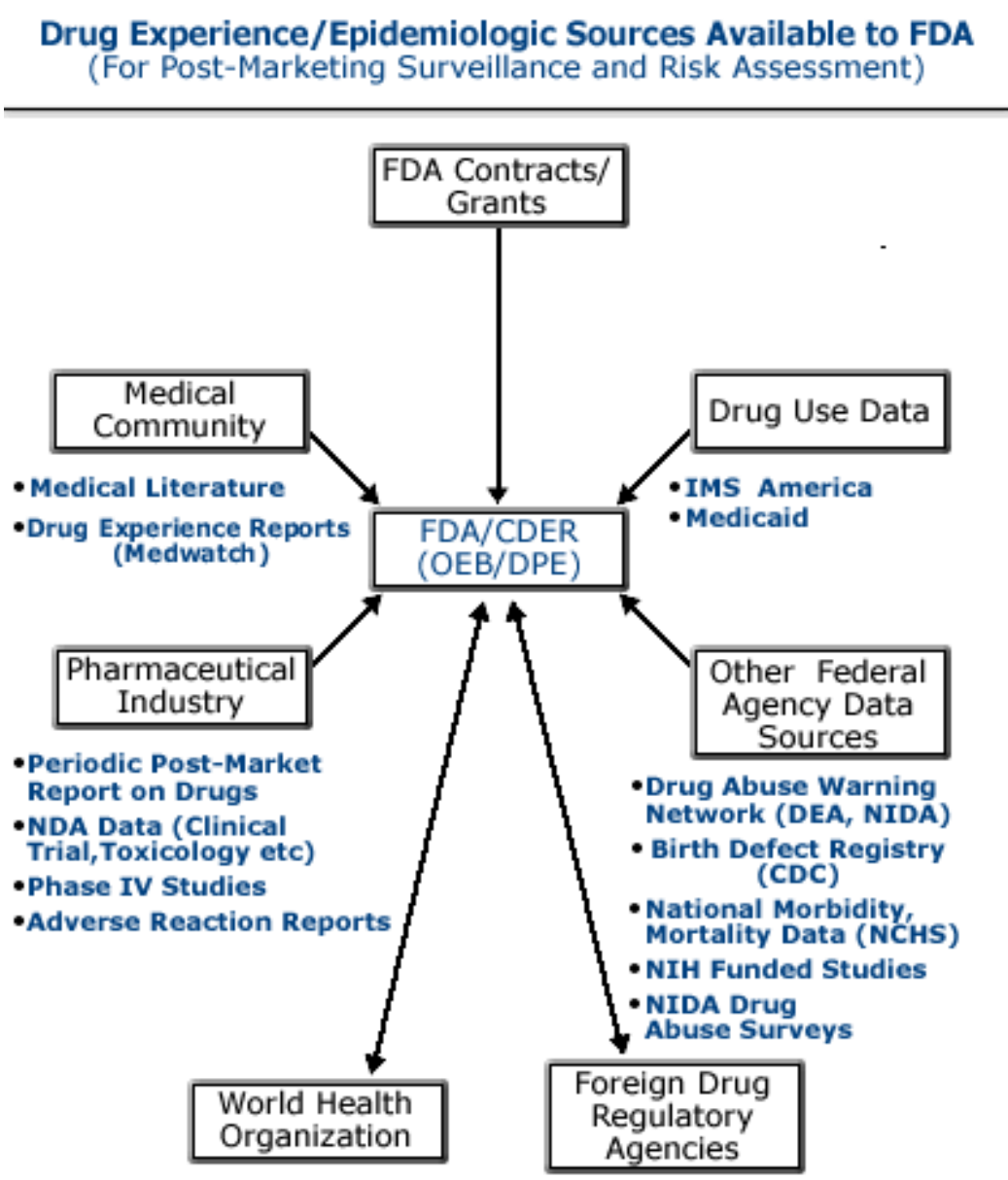
US Drug Development



Post Approval

- Phase 4 Studies
- Supplemental NDA
  - Manufacturing and control methods
  - Dosage form or route of administration
  - Indication
  - Ingredients or strength
  - Dosage schedule
  - Labeling
  - Container and closure system
- Periodic and annual reports to FDA
- Post marketing surveillance for safety

Post-Marketing Surveillance



Potential Regulatory Action for Post-marketing Safety Issues

- Labeling Change
- Scientific publication
- "Dear Doctor" letter (for specific warnings)
- Restricted use
- Restricted distribution
- Patient Medication guide
- Product withdrawal

Taxol's Development…

- 1962: samples collected by researchers from USDA under contract with NCI
- 1964: extracts from bark contained cytotoxic activity
- 1965: began identification and purification of the extract's most active component – paclitaxel
  - NCI assigned the compound an NSC number
- 1977:
  - NCI confirmed antitumor activity in mouse melanoma model
  - Dr. Susan Horwitz from Albert Einstein College of Medicine of Yeshiva University found mechanism of action

…Taxol's Development…

- Acquisition and formulation issues:
  - Difficulties harvesting Taxol and complexities involved in synthesizing the compound
    - Method was derived to extract a precursor of Taxol from the common yew
  - Difficult to formulate into a delivery system acceptable for human use
    - Formulated in an ethanol, cremophor, and saline solution

…Taxol's Development…

- 1984: NCI began phase I clinical trials in CC
- 1991: NCI signs a cooperative agreement with BMS to commercialize
  - No patent filed
  - BMS received 5 years marketing exclusivity
- 1992: FDA approved for ovarian cancer1994
  - FDA approved for breast cancer
  - FDA approved semi-synthetic version of Taxol

…Taxol's Development

- 1997: FDA approved for AIDS-related Kaposi Sarcoma
- 1998: FDA approved in combination with cisplatin for NSCLC
- 1999: FDA approved in combination for adjuvant breast cancer
- 2000: FDA approved generic version (Onxol)

IND not required for marketed products

- Generally not required when **all** criteria met:
  - No intent to support new use or labeling change
  - No intent to support change in advertising
  - No factor such as route of administration, dosage, or study population significantly increases risk
  - Compliance with FDA informed consent and IRB review requirements
  - No promotion or representation of product as safe or effective treatment for condition under study


Enforcement
INVESTIGATOR
FOOD AND DRUG ADMINISTRATION
PUBLIC HEALTH SERVICE
FDA
1
Correcting Problems
FDA

FDA Enforcement Powers

- Administrative
  - Inspections
  - Form FDA 483
  - Warning Letters
  - Delay, suspension or withdrawal of product approval
- Judicial Action by the US Dept. of Justice

  (serves as trial counsel to the FDA)
  - Injunctions
  - Civil seizures
  - Criminal actions

FDA Audits & Inspections

- Manufacturing: GMP
- Laboratory (animal): GLP
- Clinical Sites: GCP
  - Study Oriented Inspections
    - Data verification
    - Pivotal study
  - Investigator-Oriented Inspections
    - Extensive investigation
    - Multiple studies

FDA Inspections

- FDA will often assess the validity of data and safety and protection of human subjects through on site inspections of clinical investigators, sponsors and IRBs
- Bioresearch Monitoring (BIMO) Program

Types of Inspections

- For-Cause Inspections (Complaints)
  - Based on complaints from any source
  - Allegations that raise concerns regarding data integrity or the rights, welfare, and safety of study subjects have been compromised
- PDUFA-Related Inspections (NDA)
  - Done in support of marketing applications
  - Pivotal studies
    - Foreign inspections when study not conducted under IND or data in support of application is only from foreign sites
  - Also may be referred to as “Routine” Inspections

What FDA Inspects

The FDA Inspection compares

➔Source Document Medical Record Data

vs

➔Case Report Forms

vs

➔Data Listing Submitted to NDA

FDA Inspection

Verify:

- Source of subjects; Did subjects exist?
- Did they meet inclusion/exclusion criteria?
- IRB Review Obtained? Consent obtained?
- Adherence to protocol?
- Verify primary efficacy measurements
- Adverse events?
- Safety data: Labs, EKG etc.
- Drug Accountability? Blinding of data?

Roles & Responsibilities of the IND Sponsor

Role of the Sponsor

- Maintain effective IND with respect to the investigations
- Select qualified investigators
- Provide investigators with information needed to conduct study properly
- Ensure:
  - Study is conducted in accordance with the general investigational plan and protocols contained in the IND
  - FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug
  - Proper monitoring of the investigation
  - Adequate recordkeeping and record retention

IND Amendments

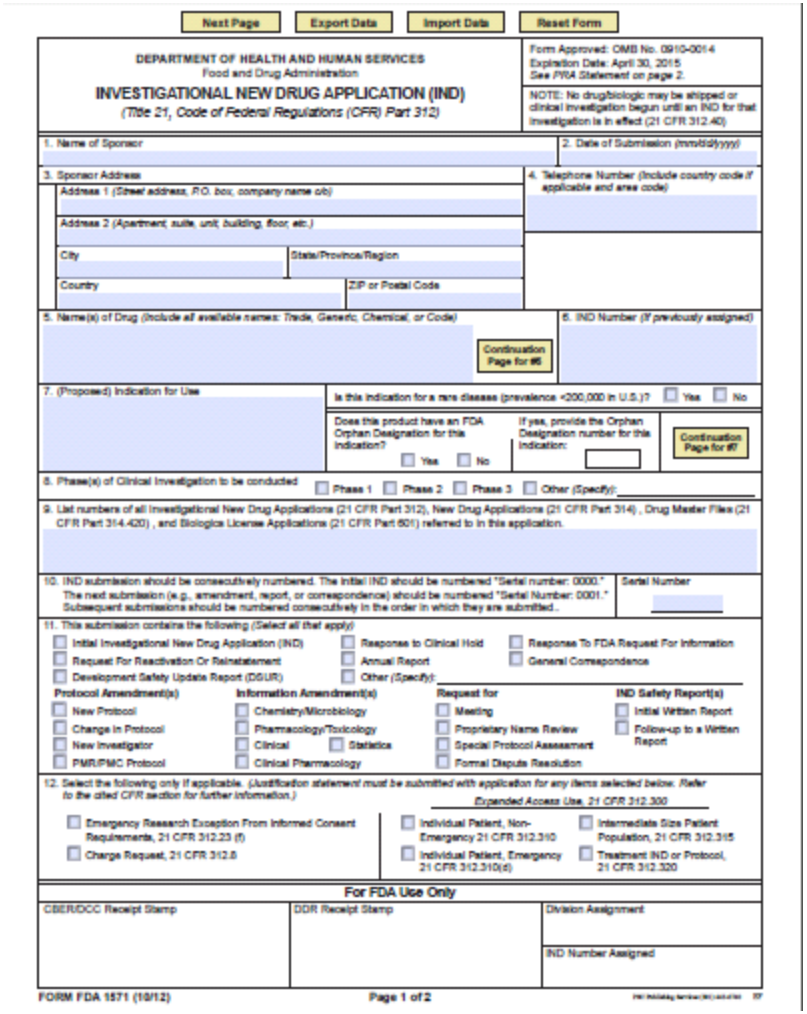
- Any document from the sponsor in support of their IND
- Made at any time during the life of the IND
- Types of amendments
  - Protocol Amendments
  - Safety reports
  - Annual reports
  - Information Amendments

FDA From 1571 page 1

Submitted with the initial IND submission and each subsequent submission to the IND

Acknowledgment letter

- IND or BB-IND #



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
See PRA Statement on page 2.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

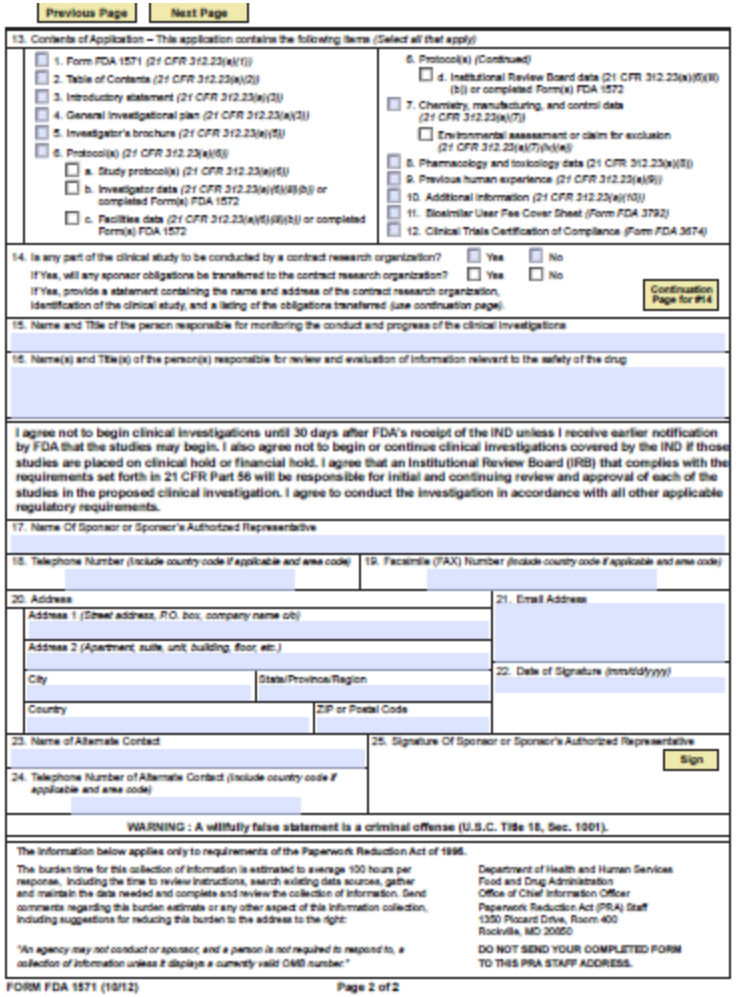
1. Name of Sponsor
2. Date of Submission (mm/dd/yyyy)
3. Sponsor Address
Address 1 (Street address, P.O. box, company name c/o)
Address 2 (Apartment, suite, unit, building, floor, etc.)
City
State/Province/Region
Country
ZIP or Postal Code
4. Telephone Number (Include country code if applicable and area code)
5. Name(s) of Drug (Include all available names: Trade, Generic, Chemical, or Code)
Continuation Page for #5
6. IND Number (If previously assigned)
7. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? Yes No
Does this product have an FDA Orphan Designation for this indication? Yes No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
8. Phase(s) of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify):
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..
Serial Number
11. This submission contains the following (Select all that apply)
Initial Investigational New Drug Application (IND)
Request For Reactivation Or Reinstatement
Development Safety Update Report (DSUR)
Response to Clinical Hold
Annual Report
Other (Specify):
Response To FDA Request For Information
General Correspondence
Protocol Amendment(s): New Protocol; Change in Protocol; New Investigator; PMR/PMC Protocol
Information Amendment(s): Chemistry/Microbiology; Pharmacology/Toxicology; Clinical; Statistics; Clinical Pharmacology
Request for: Meeting; Proprietary Name Review; Special Protocol Assessment; Formal Dispute Resolution
IND Safety Report(s): Initial Written Report; Follow-up to a Written Report
12. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)
Expanded Access Use, 21 CFR 312.300
Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)
Charge Request, 21 CFR 312.8
Individual Patient, Non-Emergency 21 CFR 312.310
Individual Patient, Emergency 21 CFR 312.310(d)
Intermediate Size Patient Population, 21 CFR 312.315
Treatment IND or Protocol, 21 CFR 312.320

For FDA Use Only
CBER/DCC Receipt Stamp
DDR Receipt Stamp
Division Assignment
IND Number Assigned

FORM FDA 1571 (10/12) Page 1 of 2

FDA From 1571 page 2

The FDA has 30-days to review the protocol. FDA will not contact sponsor if all is OK to proceed, only if a “hold” is needed.



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13. Contents of Application – This application contains the following items (*Select all that apply*)

1. Form FDA 1571 (*21 CFR 312.23(a)(1)*)
2. Table of Contents (*21 CFR 312.23(a)(2)*)
3. Introductory statement (*21 CFR 312.23(a)(3)*)
4. General investigational plan (*21 CFR 312.23(a)(3)*)
5. Investigator's brochure (*21 CFR 312.23(a)(5)*)
6. Protocol(s) (*21 CFR 312.23(a)(6)*)
   - a. Study protocol(s) (*21 CFR 312.23(a)(6)*)
   - b. Investigator data (*21 CFR 312.23(a)(6)(iii)(b)*) or completed Form(s) FDA 1572
   - c. Facilities data (*21 CFR 312.23(a)(6)(iii)(b)*) or completed Form(s) FDA 1572
6. Protocol(s) (Continued)
   - d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form(s) FDA 1572
7. Chemistry, manufacturing, and control data (*21 CFR 312.23(a)(7)*)
   - Environmental assessment or claim for exclusion (*21 CFR 312.23(a)(7)(iv)(e)*)
8. Pharmacology and toxicology data (21 CFR 312.23(a)(8))
9. Previous human experience (*21 CFR 312.23(a)(9)*)
10. Additional information (*21 CFR 312.23(a)(10)*)
11. Biosimilar User Fee Cover Sheet (*Form FDA 3792*)
12. Clinical Trials Certification of Compliance (*Form FDA 3674*)

14. Is any part of the clinical study to be conducted by a contract research organization? Yes No
If Yes, will any sponsor obligations be transferred to the contract research organization? Yes No
If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred (*use continuation page*). Continuation Page for #14

15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations

16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

17. Name Of Sponsor or Sponsor's Authorized Representative

18. Telephone Number (*Include country code if applicable and area code*)

19. Facsimile (FAX) Number (*Include country code if applicable and area code*)

20. Address

Address 1 (*Street address, P.O. box, company name c/o*)

Address 2 (*Apartment, suite, unit, building, floor, etc.*)

City

State/Province/Region

Country

ZIP or Postal Code

21. Email Address

22. Date of Signature (mm/dd/yyyy)

23. Name of Alternate Contact

24. Telephone Number of Alternate Contact (*Include country code if applicable and area code*)

25. Signature Of Sponsor or Sponsor's Authorized Representative

Sign

WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

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Food and Drug Administration
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DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF ADDRESS.

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Investigator Selection

- Assess qualification of PI and Sub-investigators
  - Qualified by training & experience
  - Ability to supervise administration of product
  - Investigational Product shipped to them
- Assess site (physical plant capabilities). Examples:
  - Is there adequate pharmacy space for drug storage?
  - Are there SOPs for freezer alarms?

Informing Investigators

- All investigators must be fully informed of investigational product research findings
  - Investigator Brochure
  - Reprints / published articles
  - Reports / letters to investigators
  - IND Safety Reports

Monitoring of Clinical Trials…

- Medical Monitor
  - Individual responsible for the development and oversight of all clinical trials in a portfolio of study agents
- Monitor clinical trial conduct
- Review and evaluate
  - Safety and effectiveness data
  - Investigator compliance with:
    - Protocol
    - CFR
    - GCP

…Monitoring of Clinical Trials

- Sponsor must have written monitoring procedures (SOPs) to assure the quality of the study and ensure that each person involved carries out their duties
- SOPs should include:
  - How often will visits occur
  - Who will attend
  - What will be reviewed
  - How will problems be resolved
  - Communication flow

Potential Actions for Non-compliance

- Secure compliance OR stop product shipments to the investigator
- Terminate the investigator's participation in the study
- Secure return or disposal of investigational product

Recordkeeping and Record Retention

- Drug Accountability
- Financial interests
- Records and reports
- Test article

Drug Accountability

- Records showing:
  - Receipt
  - Shipment
  - Other disposition of the investigational drug
- Include, as appropriate:
    - Name of investigator who was shipped the drug
    - Date
    - Quantity
    - Batch or code mark of each such shipment

Financial Interests

- Financial interest paid to clinical investigators by the sponsor
- Maintain complete and accurate records concerning all other financial interests of investigators

Records and Reports

- Applies to investigational drug records, investigator financial interest records, and patient case histories (medical record and case report forms)
- Timeframe
  - 2 years after a marketing application is approved
  - If application not approved, 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified

Test Article

- Reserve samples of any test article and reference standard identified in, and used in any of the bioequivalence or bioavailability studies described
- Release the samples to FDA upon request

Withdrawal of IND

- Can do so at any time prejudice
- FDA shall be so notified
- All clinical investigations conducted under the IND shall be ended
- All current investigators notified
- All stocks of the drug returned to the sponsor or otherwise disposed of
- If withdrawn for safety, sponsor shall promptly inform FDA, all participating investigators, and all reviewing IRBs with reason

Questions

Thank you to Maureen Edgerly for many of the FDA history slides.