

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

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National Institutes
of Health

Agenda

- Drug development process
 - Basic science
 - Drug discovery
 - Pre-clinical
 - Clinical – Sponsor's role
- FDA's role in drug development

Disclaimer: Drug development refers to both drug and biologic agents

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

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

Essential Roles in U.S. Drug Development

Sponsor (typically a biopharmaceutical company)

- Produces evidence
- Responsible to FDA

Food & Drug Administration (FDA)

- Reviews data
- Grants approval

Sponsors Responsibilities: 4 Broad Areas

- *Preclinical / non-clinical*
- *Manufacturing*
- Clinical
 - Maintain IND
- Post-approval
- May use a CRO
(Contract Research
Organization)



Who is a Sponsor?

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



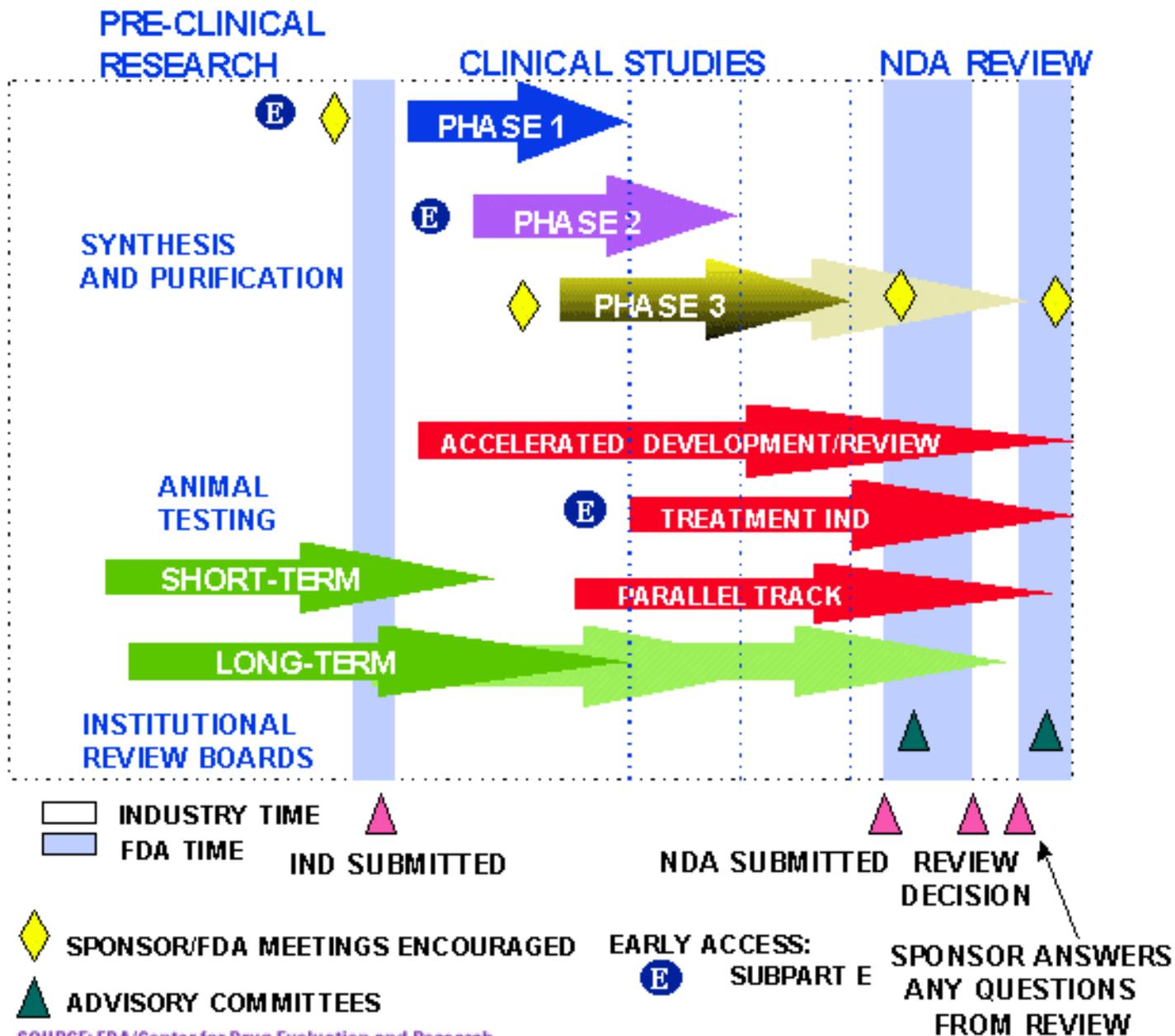
Definition of Sponsor....

- “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

US Drug Development



Drug Development Timeline

	Preclinical testing	Phase I	Phase II	Phase III	FDA	Phase IV
Years	3-6	6-7			0.5-2	Additional Post-marketing testing
Test Population	Laboratory and animal studies	20-80 volunteers (healthy/patient)	100-300 patient volunteers	Thousands of patient volunteers	Review and approval process	
Purpose	Assess safety and biological activity	Determine safety and dosage	Evaluate activity, continued safety	Evaluate effectiveness, continued safety		

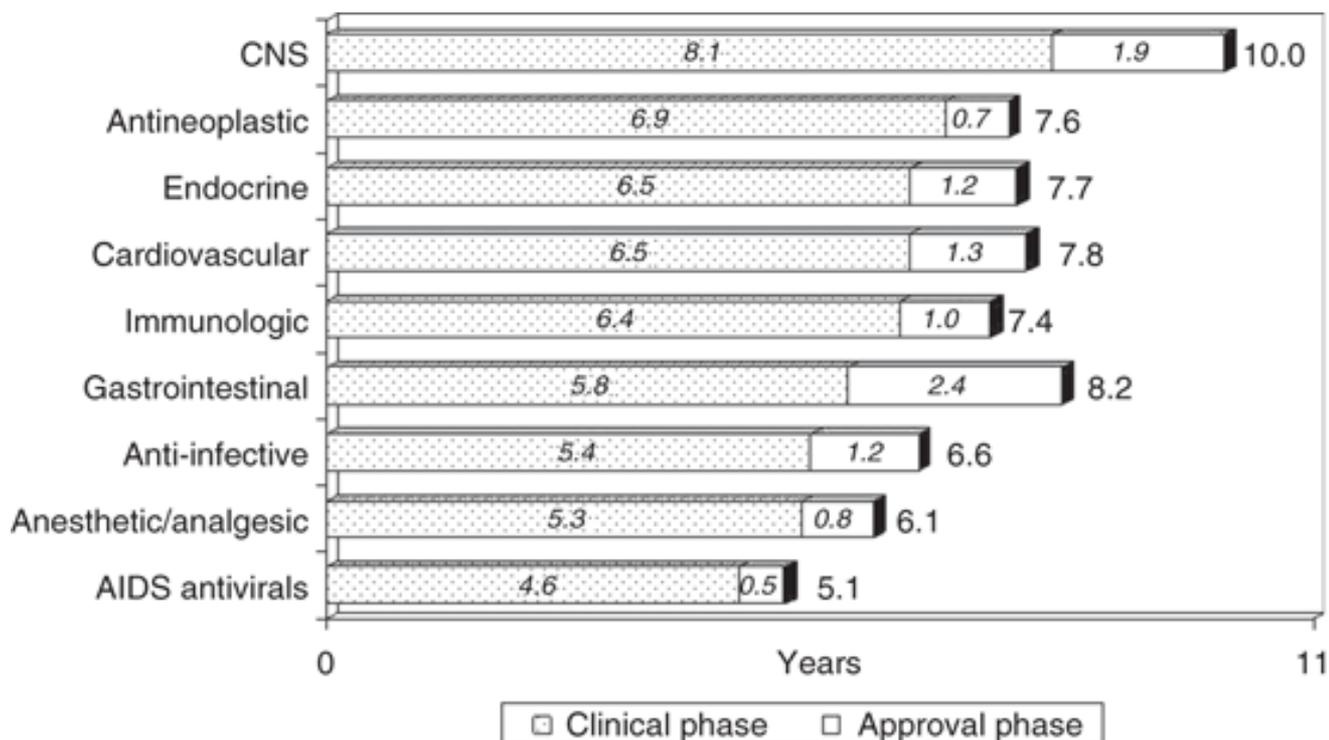
AVERAGE:

Total = 9.5 - 15 years

Clinical Trials to Approval = 6.5 – 9 years

Source: <http://www.phrma.org/innovation/clinical-trials>

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.

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



Drug Discovery

- Find the lead compound
 - A promising molecule that could become a drug by acting on the target to alter a disease
- Sources of Drugs
 - Plant
 - Animal
 - Mineral
 - Microbiology
 - Semi-synthetic/Synthetic
 - Recombinant DNA

Naming of Drugs

- Chemical name
 - Scientific name based on the compound's chemical structure
 - Almost never used to identify the drug in a clinical or marketing situation
- Generic name
 - Granted by the International Union of Pure and Applied Chemistry (IUPAC)
 - Commonly used to identify a drug during its clinical lifetime
 - Appears with the company's trade name on drug labels, advertisements, and other information
- Brand name (Trademark)
 - Created by the company that patents the drug
 - Identifies the drug during the years that the company has exclusive rights to make, sell, and use

Atorvastatin Calcium

- Lipitor
- Stator
- Atoris
- Atorlip
- Lipvas
- Sortis
- Torvast
- Torvacard
- Totalip
- Tulip

Preclinical Testing...

- Lab and animal testing to determine if the drug is safe enough for human testing
 - *In vitro* (“vitro” is “glass” in Latin)
 - Conducted in the lab usually carried out in test tubes and beakers
 - *In vivo* (“vivo” is “life” in Latin)
 - Conducted in living cell cultures and animal models

...Preclinical Testing

- Series of tests to provide an early assessment of the safety of a lead compound
 - Absorption
 - Distribution
 - Metabolism
 - Excretion
 - 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
- Bioequivalence
 - the relationship between two preparations of the same drug in the same dosage form that have a similar bioavailability.
- Ease of use

Drug Development Process



Pre-Clinical

- Basic Science
- Drug Discovery
- Pre-clinical testing



Clinical Trials

- Phase 1
- Phase 2
- Phase 3



U.S. FDA Review

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Investigational New Drug Application (IND)

- Sponsor submits to the FDA
- Descriptive notification of intention to conduct clinical studies with a new drug or biologic drug
- Allows for transportation of product (non-approved drug) across state lines

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 Content and Format...

- Cover Letter
- Cover sheet (FDA Form 1571)
- Statement of Investigator Statement (FDA Form 1572)
- Certificate of Compliance (Form 3674)
- Table of contents
- Introductory statement and general investigational plan

...IND Content and Format

- Chemistry, manufacturing and controls (CMC)*
- Pharmacology and Toxicology*
- Investigator's brochure (IB)
- Clinical Protocols
- Summary of previous human experience with the investigational drug
- Additional information
- [FDA checklist](#)

* *Letter of Authorization for Investigator-Sponsor*

Submission Requirements: Paper

- Jackets (polyethylene or paper)
 - Red: Original
 - Green: Copy
 - Orange: Copy
- Tabs
 - Tab and clearly label each part within a Jacket including sub-section
- Jackets must have an internal hinge
- Hole punches are to be 2 holed on left side consistent with the jacket hinge



FDA Form 1571

page 1

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

Acknowledgment letter

- IND or BB-IND #

Next Page		Export Data		Import Data		Reset Form	
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 PMA 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 312.46)	
1. Name of Sponsor				2. Date of Submission (mm/dd/yyyy)			
3. Sponsor Address				4. Telephone Number (include country code if applicable and area code)			
Address 1 (Street address, P.O. box, company name etc)							
Address 2 (Apartment, suite, unit, building, floor, etc.)							
City				State/Province/Region			
Country				ZIP or Postal Code			
5. Name(s) of Drug (include all available names: Trade, Generic, Chemical, or Code)						6. IND Number (if previously assigned)	
						Continuation Page for #6	
7. (Proposed) Indication for Use						Is this indication for a rare disease (prevalence <200,000 in U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No Does this product have an FDA Orphan Designation for this indication? <input type="checkbox"/> Yes <input type="checkbox"/> No If yes, provide the Orphan Designation number for this indication: <input type="text"/>	
						Continuation Page for #7	
8. Phase(s) of Clinical Investigation to be conducted <input type="checkbox"/> Phase 1 <input type="checkbox"/> Phase 2 <input type="checkbox"/> Phase 3 <input type="checkbox"/> 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 314.400), 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)							
<input type="checkbox"/> Initial Investigational New Drug Application (IND)		<input type="checkbox"/> Response to Clinical Hold		<input type="checkbox"/> Response to FDA Request for Information			
<input type="checkbox"/> Request For Reactivation Or Reinstatement		<input type="checkbox"/> Annual Report		<input type="checkbox"/> General Correspondence			
<input type="checkbox"/> Development Safety Update Report (DSUR)		<input type="checkbox"/> Other (Specify):					
Protocol Amendment(s)		Information Amendment(s)		Request for		IND Safety Report(s)	
<input type="checkbox"/> New Protocol		<input type="checkbox"/> Chemistry/Microbiology		<input type="checkbox"/> Meeting		<input type="checkbox"/> Initial Written Report	
<input type="checkbox"/> Change in Protocol		<input type="checkbox"/> Pharmacology/Toxicology		<input type="checkbox"/> Proprietary Name Review		<input type="checkbox"/> Follow-up to a Written Report	
<input type="checkbox"/> New Investigator		<input type="checkbox"/> Clinical <input type="checkbox"/> Statistics		<input type="checkbox"/> Special Protocol Assessment			
<input type="checkbox"/> PMR/PMC Protocol		<input type="checkbox"/> Clinical Pharmacology		<input type="checkbox"/> Formal Dispute Resolution			
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.)							
<input type="checkbox"/> Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)				<input type="checkbox"/> Individual Patient, Non-Emergency 21 CFR 312.310		<input type="checkbox"/> Intermediate Size Patient Population, 21 CFR 312.315	
<input type="checkbox"/> Charge Request, 21 CFR 312.8				<input type="checkbox"/> Individual Patient, Emergency 21 CFR 312.310(e)		<input type="checkbox"/> Treatment IND or Protocol, 21 CFR 312.320	
For FDA Use Only							
CDER/DCD Receipt Stamp		DDR Receipt Stamp		Division Assignment			
				IND Number Assigned			

FDA Form 1571

page 2

- 30-day review:
 - Medical
 - Chemistry
 - Pharmacology & toxicology
 - Statistical
- FDA will not always contact sponsor if all is OK to proceed, only if a “hold” is needed

Previous Page	Next Page								
<p>13. Contents of Application – This application contains the following items (Select all that apply)</p> <table border="0"> <tr> <td style="vertical-align: top;"> <input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23)(k)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23)(k)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23)(k)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23)(k)(3)) <input type="checkbox"/> 5. Investigator's brochure (21 CFR 312.23)(k)(5)) <input type="checkbox"/> 6. Protocol(s) (21 CFR 312.23)(k)(6)) <table border="0"> <tr> <td><input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23)(k)(6))</td> <td><input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23)(k)(7))</td> </tr> <tr> <td><input type="checkbox"/> b. Investigator data (21 CFR 312.23)(k)(6)(b)) or completed Form(s) FDA 1572</td> <td><input type="checkbox"/> 8. Environmental assessment or claim for exclusion (21 CFR 312.23)(k)(7)(b)(i))</td> </tr> <tr> <td><input type="checkbox"/> c. Facilities data (21 CFR 312.23)(k)(6)(b)(i)) or completed Form(s) FDA 1572</td> <td><input type="checkbox"/> 9. Pharmacology and toxicology data (21 CFR 312.23)(k)(8))</td> </tr> </table> </td> <td style="vertical-align: top;"> <input type="checkbox"/> 4. Institutional Review Board data (21 CFR 312.23)(k)(9)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23)(k)(7)) <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23)(k)(7)(b)(i)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23)(k)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23)(k)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23)(k)(10)) <input type="checkbox"/> 11. Bioclinical User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674) </td> </tr> </table>		<input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23)(k)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23)(k)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23)(k)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23)(k)(3)) <input type="checkbox"/> 5. Investigator's brochure (21 CFR 312.23)(k)(5)) <input type="checkbox"/> 6. Protocol(s) (21 CFR 312.23)(k)(6)) <table border="0"> <tr> <td><input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23)(k)(6))</td> <td><input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23)(k)(7))</td> </tr> <tr> <td><input type="checkbox"/> b. Investigator data (21 CFR 312.23)(k)(6)(b)) or completed Form(s) FDA 1572</td> <td><input type="checkbox"/> 8. Environmental assessment or claim for exclusion (21 CFR 312.23)(k)(7)(b)(i))</td> </tr> <tr> <td><input type="checkbox"/> c. Facilities data (21 CFR 312.23)(k)(6)(b)(i)) or completed Form(s) FDA 1572</td> <td><input type="checkbox"/> 9. Pharmacology and toxicology data (21 CFR 312.23)(k)(8))</td> </tr> </table>	<input type="checkbox"/> a. Study protocol(s) (21 CFR 312.23)(k)(6))	<input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23)(k)(7))	<input type="checkbox"/> b. Investigator data (21 CFR 312.23)(k)(6)(b)) or completed Form(s) FDA 1572	<input type="checkbox"/> 8. Environmental assessment or claim for exclusion (21 CFR 312.23)(k)(7)(b)(i))	<input type="checkbox"/> c. Facilities data (21 CFR 312.23)(k)(6)(b)(i)) or completed Form(s) FDA 1572	<input type="checkbox"/> 9. Pharmacology and toxicology data (21 CFR 312.23)(k)(8))	<input type="checkbox"/> 4. Institutional Review Board data (21 CFR 312.23)(k)(9)(b)) or completed Form(s) FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23)(k)(7)) <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23)(k)(7)(b)(i)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23)(k)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23)(k)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23)(k)(10)) <input type="checkbox"/> 11. Bioclinical User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674)
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<p>14. Is any part of the clinical study to be conducted by a contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, will any sponsor obligations be transferred to the contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> 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 (see continuation page). Continuation Page for #14</p>									
<p>15. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations</p>									
<p>16. Name(s) and Title(s) of the person(s) responsible for review and evaluation of information relevant to the safety of the drug</p>									
<p>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.</p>									
<p>17. Name Of Sponsor or Sponsor's Authorized Representative</p>									
<p>18. Telephone Number (include country code if applicable and area code) 19. Facsimile (FAX) Number (include country code if applicable and area code)</p>									
<p>20. Address</p> <p>Address 1 (Street address, P.O. box, company name, etc.)</p> <p>Address 2 (Apartment, suite, unit, building, floor, etc.)</p> <p>City State/Province/Region</p> <p>Country ZIP or Postal Code</p>									
<p>21. Email Address</p>									
<p>22. Date of Signature (mm/dd/yyyy)</p>									
<p>23. Name of Alternate Contact</p>									
<p>24. Telephone Number of Alternate Contact (include country code if applicable and area code)</p>									
<p>25. Signature Of Sponsor or Sponsor's Authorized Representative Sign</p>									
<p style="text-align: center;">WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).</p>									
<p>The information below applies only to requirements of the Paperwork Reduction Act of 1996.</p> <p>The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:</p> <p style="font-size: small;">*An agency may not conduct or sponsor and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.*</p>									
<p style="text-align: right;">Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer Paperwork Reduction Act (PRA) Staff 1350 Ploard Drive, Room 400 Rockville, MD 20850</p> <p style="text-align: right;">DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF ADDRESS.</p>									
FORM FDA 1571 (10/12)	Page 2 of 2								

IND Status

- Pending
- Active
- Hold
- Partial Hold

Types of IND Amendments

- Protocol Amendments
 - New Protocol, change in protocol, new investigator
- IND Safety Reports
 - Serious and unexpected clinical adverse event or laboratory finding affecting safety
 - Fatal or life threatening within 7 days, 15 days for others
- Annual Reports
 - Must be submitted within 60 days of the anniversary of when IND went into effect
 - See the regulation for content and format
- Information Amendments
 - All other changes

Sponsor's Clinical Responsibilities

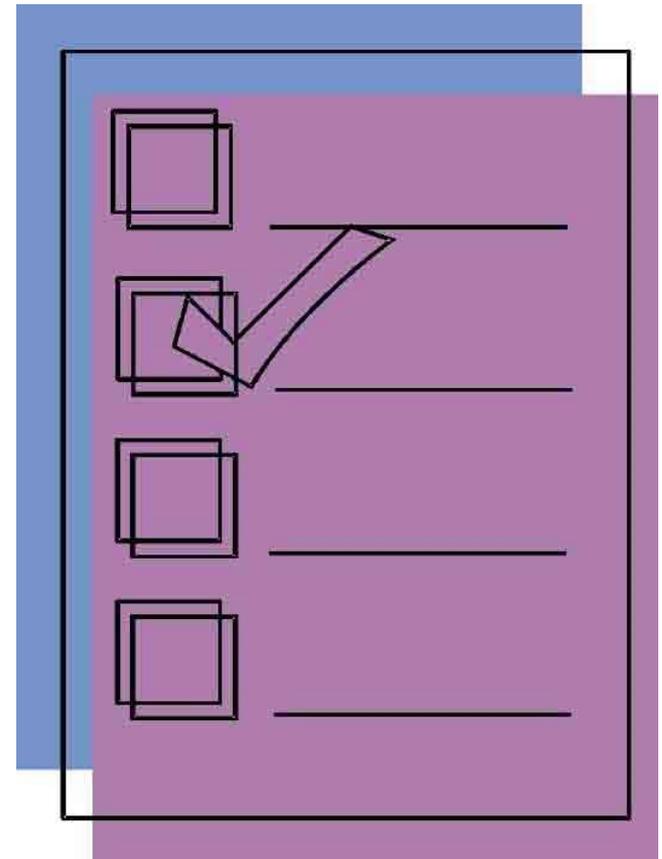
- Select qualified investigators and monitors
- Provide Investigators with needed information
- Ensure study conducted in accordance with Investigational Plan
- Ensure investigation is properly monitored
- Promptly report adverse events and new risks to FDA and all investigators
- Maintain adequate records
- Record keeping and record retention
- Ensuring the return or disposition of unused investigational drug supplies

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).
 - Is there adequate pharmacy space for drug storage?
 - Are there SOPs for freezer alarms?

Financial Disclosure

- Financial interest paid to clinical investigators by the sponsor
- Maintain complete and accurate records concerning all other financial interests of investigators
- FDA Financial Disclosure by investigators – 21 CFR 54
 - [Form 3454](#): certification
 - [Form 3455](#): disclosure



Monitoring of Clinical Trials

- Monitoring is necessary to assure that the:
 - rights and safety of human subjects are protected
 - reported trial data are accurate, complete, and verifiable from source documents
 - conduct of trial is in compliance with protocol, good clinical practice (GCP) and applicable regulatory requirements.
- Sponsor must have written monitoring procedures (SOPs) to assure the quality of the study and ensure that each person involved carries out their duties

Monitor Selection

- Monitor the progress of the investigation
- Monitoring function may be performed by:
 - The sponsor
 - Contract staff
- Select a monitor qualified by training and experience
 - Clinical Research Associate (CRA)

Sponsor Site Visits

- Several types of site visits conducted by the sponsor
 - Pre-study qualification visit
 - Initiation visit
 - Monitoring visit
 - Close-out visit

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

- Regulatory file/binder
- Drug Accountability
- Financial interests
- Records and reports
- Retention 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

FDA Resources

Development & Approval Process (Drugs)

[How Drugs are Developed and Approved](#)

[Types of Applications](#)

[Investigational New Drug \(IND\) Application](#)

[Emergency Investigational New Drug \(EIND\) Applications for Antiviral Products](#)

[IND Forms and Instructions](#)

▶ [Investigator-Initiated Investigational New Drug \(IND\) Applications](#)

[Pre-IND Consultation Program](#)

[Regulatory Information for INDs](#)

Investigator-Initiated Investigational New Drug (IND) Applications

This table provides links to information for investigators about submitting Investigational New Drug (IND) applications to FDA. The resources for application reporting and applications procedures apply to IND applications for both clinical research and clinical treatment.

IND Applications for Clinical Investigations (Product Development)	IND Application Reporting	IND Application Procedures	IND Applications for Clinical Treatment (Expanded Access)
Overview	Overview	Overview	Overview
Contents and Format	Protocol Amendments	Exemptions from IND Requirements	Contents and Format
Regulatory and Administrative Components	Information Amendments	Interactions with FDA	Treatment of a Single Patient in Emergency Setting
Non-clinical Components	Safety Reports	Clinical Hold	Treatment of a Single Patient in Non-emergency Setting
Clinical Components	Annual Reports	Investigator's Responsibilities	Treatment of a Group of Patients

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

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



Application to Market New Drug or Biologic

New Drug Application (NDA)

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

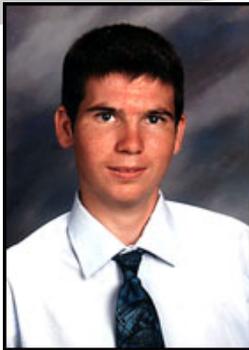
Biologic License Application (BLA)

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

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

<i>Principle</i>	<i>Year</i>	<i>Legislation</i>	<i>Contributing Factor</i>
Labeling of biologics	1902	Biologics Control Act	Tetanus antitoxin
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



Collier's
THE NATIONAL WEEKLY



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



- 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



Thalidomide

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

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

U.S. Review and Approval

Evaluated based on standards of Excellence

GLP

- Good Laboratory Practice

GMP

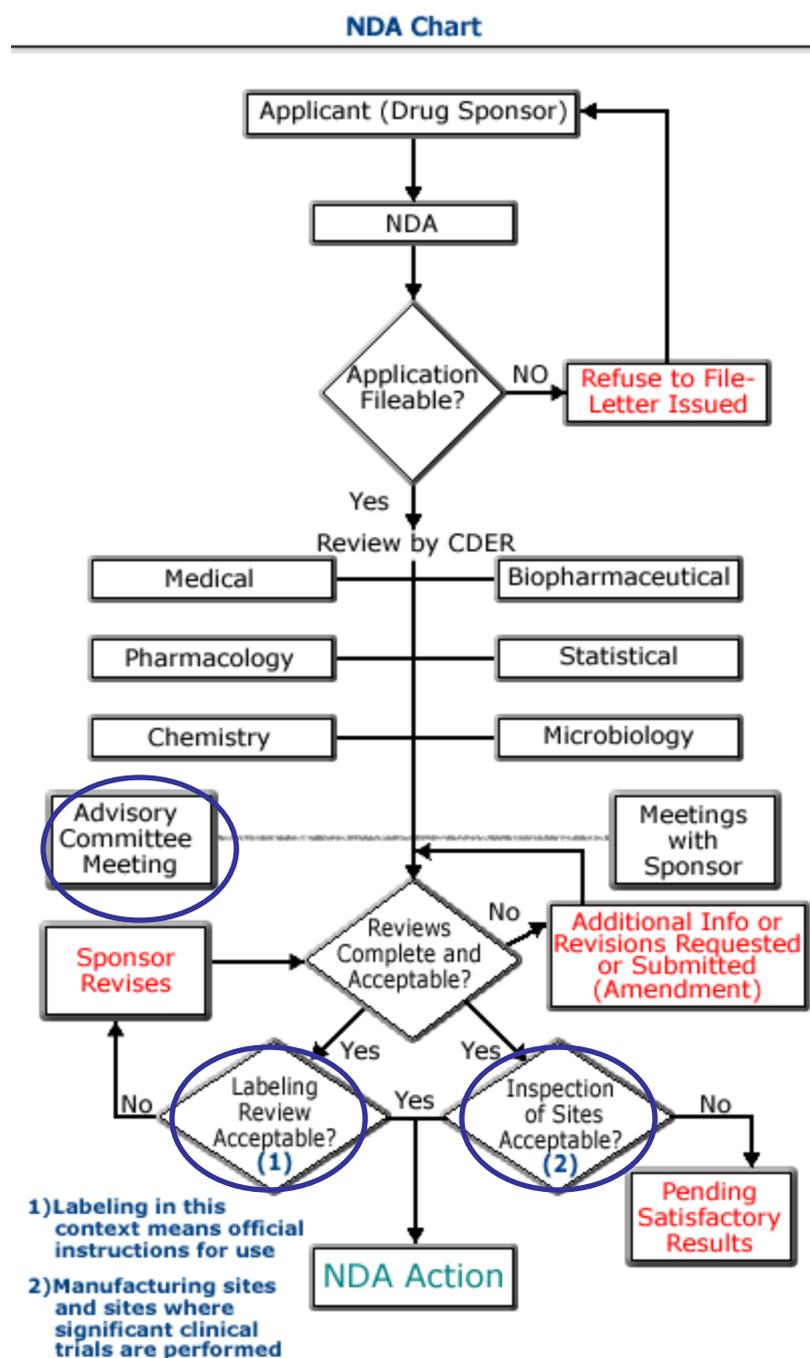
- Good Manufacturing Practice

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)

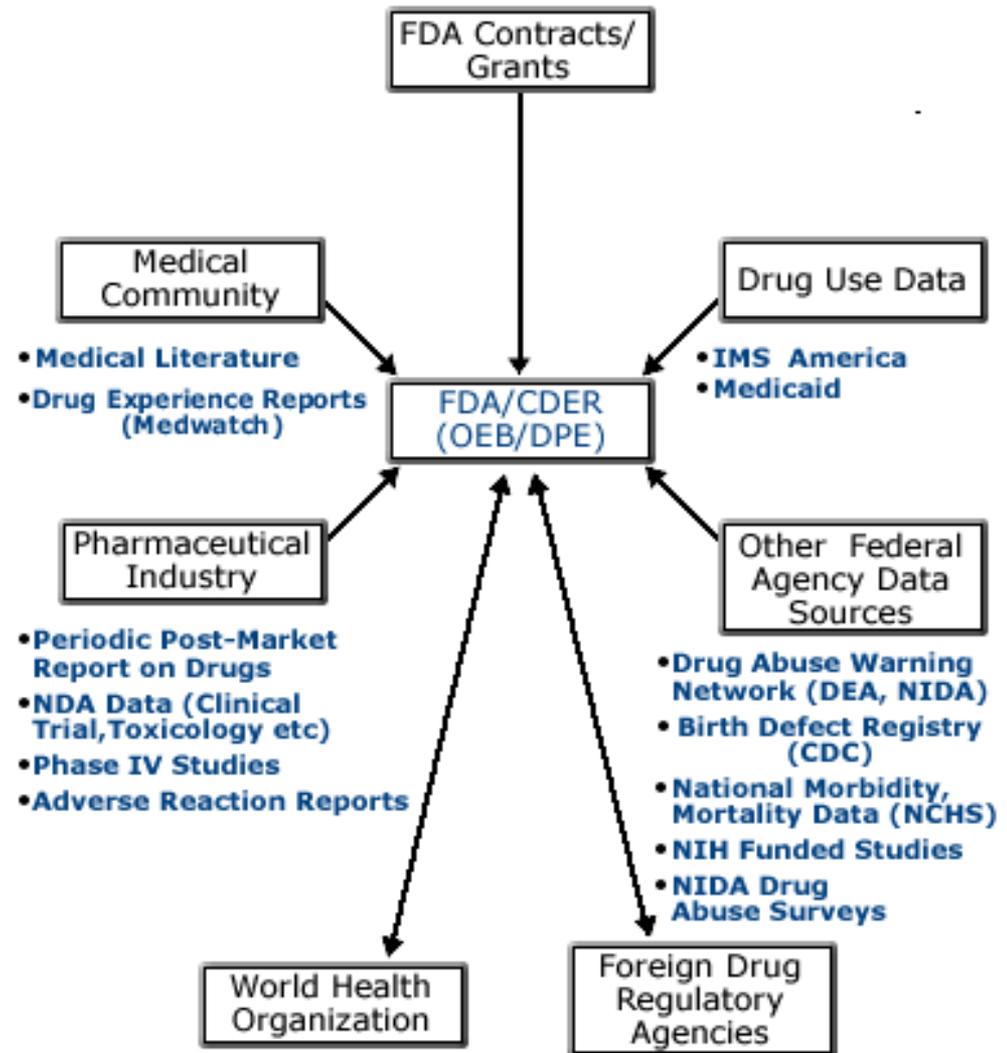
Expediting Review and Approval Processes

- 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*)

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

Let's look at Taxol's Development...

- Derived from the bark of Pacific yew tree
- Used in treatment of breast, lung, and ovarian cancer and Kaposi's sarcoma
- 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
- 1977: NCI confirmed antitumor activity in mouse melanoma model

...Let's look at Taxol's Development...

- 1977: Found mechanism of action
- 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

...Let's look at 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 cancer
- 1994:
 - FDA approved for breast cancer
 - FDA approved semi-synthetic version of Taxol

...Let's look at 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)

Summary



Pre-Clinical

- Basic Science
- Drug Discovery
- Pre-clinical testing



Clinical Trials

- Phase 1
- Phase 2
- Phase 3



U.S. FDA Review

- Safe
- Effective
- Approval

Sponsor

FDA

Questions