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## **ACS WEBINARS**

***From a Beaker to a Bottle: Overview of the Drug  
Discovery and Development Process for  
Small Molecule Therapeutics***



Speaker: Ann Newman  
Seventh Street Development Group



Moderator: Karen Rossi  
Bristol-Myers Squibb

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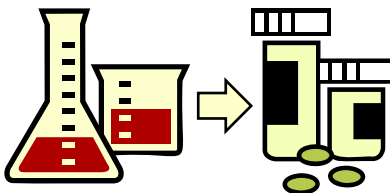
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## ***From a Beaker to a Bottle: Overview of the Drug Discovery and Development Process for Small Molecule Therapeutics***



Ann Newman  
Seventh Street Development Group  
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May 6, 2010 ACS Webinars

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# Introduction

There are three requirements for approval of a new drug:

1. the drug is safe
2. it is effective in treating the disease
3. it can be manufactured correctly and reproducibly each time

So how does a new drug go from a beaker to a bottle on the shelf?



Tablets



Suspensions/solutions



Capsules



Soft gel capsules



Syringes



Transdermal



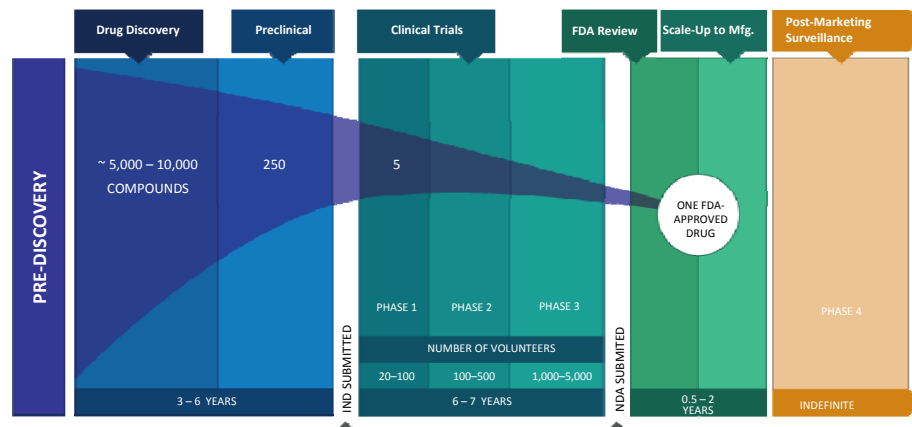
Inhaler



Pens



# Innovator Product Development Cycle

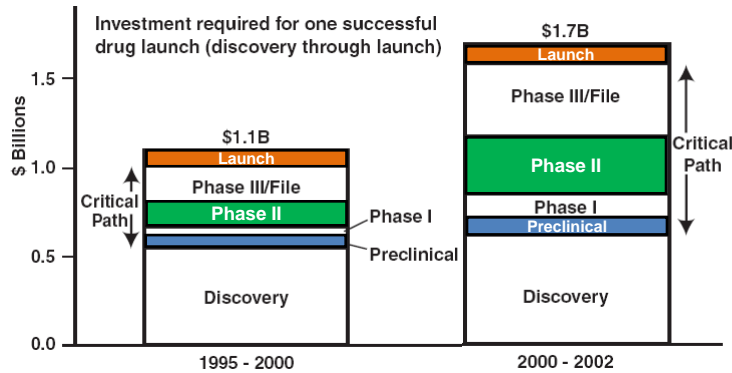


- It takes **10-15** years on average to get a new drug on the market
- Drugs launched in 2010 were starting discovery in **1995**



# Cost

How much does it cost to get one drug on the market?



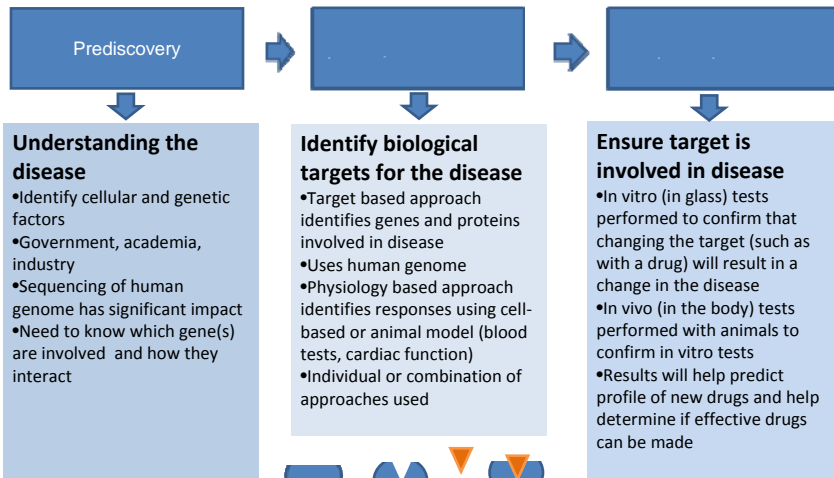
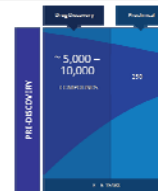
SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

Innovation or Stagnation? Challenge and opportunity on the critical path to new medical products, FDA Report, March 2004.



# Prediscovery

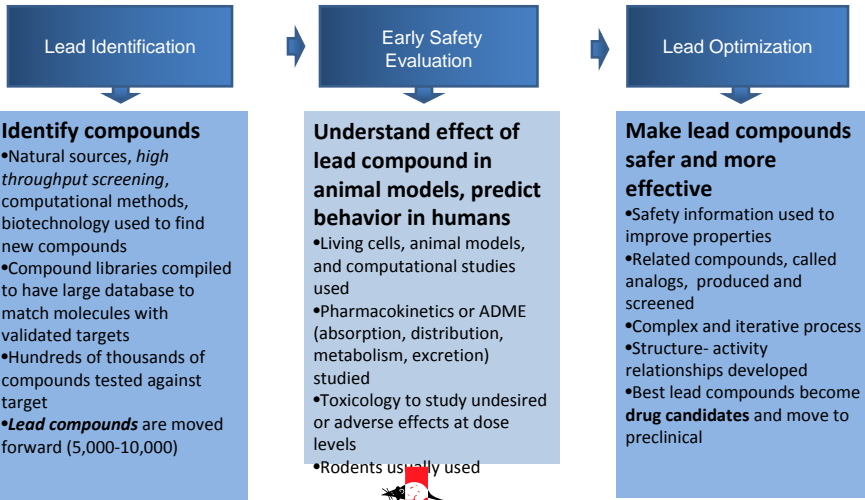
Understanding the disease





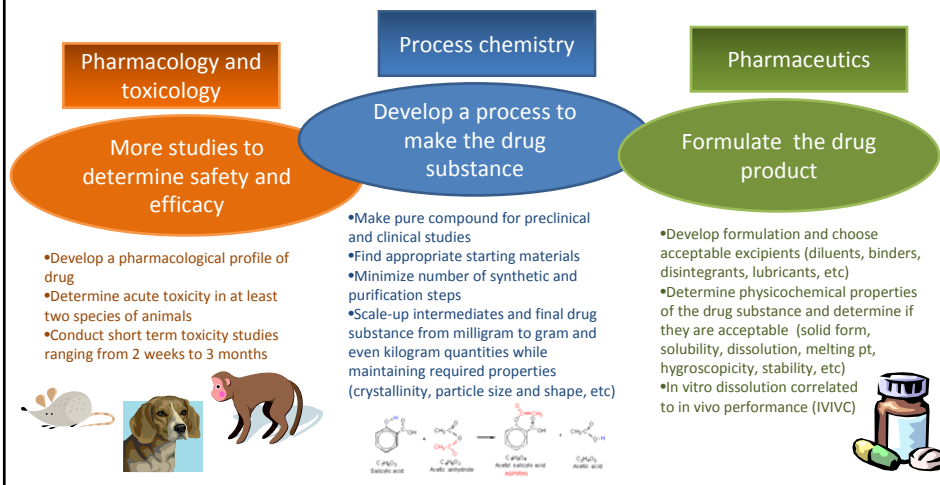
# Drug Discovery

Identify compounds that can treat the disease



# Preclinical

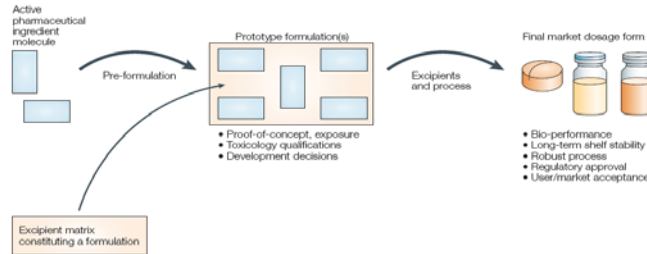
Making the drug candidate a drug product (capsules, solutions, tablets) for human clinical trials





# Preclinical

- Formulations need to be developed to deliver drug to animals, humans
- Additional ingredients called excipients added to help properties (flow, dissolution, etc)
- Early formulations are somewhat simple and new formulations will be developed for later phase clinical trials and marketed products



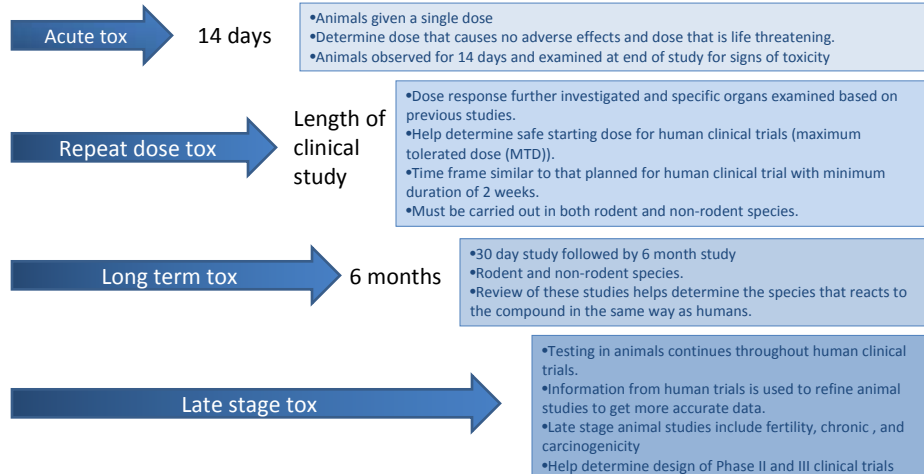
**Process formulation.** Schematic representation of the process of formulating an active compound through proof-of-concept studies (including toxicology evaluation) and to the marketed formulation. An active compound is almost always delivered in a formulation that must meet certain minimum criteria. The ability to co-optimize — or at the very least, consider together all criteria for developability — at an early stage helps to avoid downstream problems such as inadequate stability, low solubility or slow dissolution rate resulting in poor absorption.

Gardner et al. *Nature Rev Drug Discov.* 2004, 11, 926-934



# Preclinical

## Toxicology studies

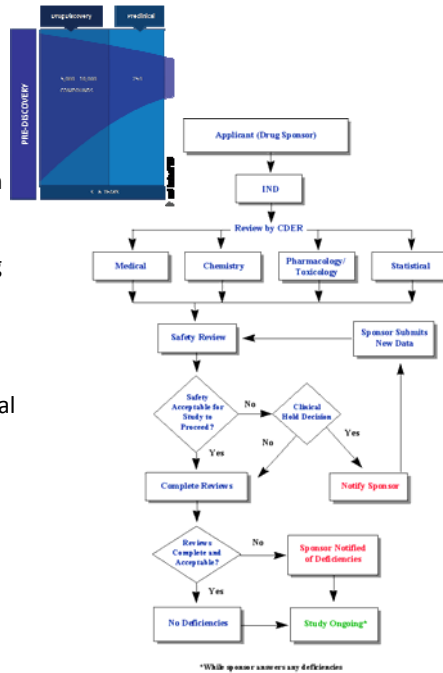




# IND

## Investigational New Drug (IND) Application

- Submitted to Food and Drug Administration (FDA)
- Summary of all work done to date
- Needs to be filed and approved before drug can be used in human clinical trials
- Include information on
  - Animal pharmacology and toxicology studies
    - Is product reasonably safe for initial testing in humans
  - Manufacturing information
    - Drug substance and drug product
  - Clinical protocols and investigator information
    - Detailed protocols for proposed human trials
- Sponsor must wait 30 calendar days before initiating studies while FDA reviews IND



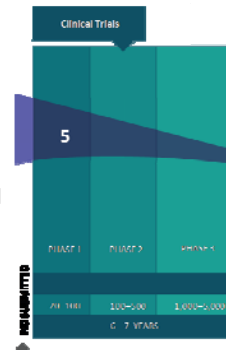
FDA Center for Drug Evaluation and Research. "Drug applications review flow chart" <http://www.fda.gov/cder/handbook/ind.htm>



# Clinical Trials

## Only 5 drug candidates make it to Phase I clinical trials

- First time new drugs are dosed to humans
- The cost of clinical trials accounts for 50-70% of the drug discovery and development price tag
- Clinical trials are carried out by physicians in hospitals, offices, and clinics globally in close coordination with the sponsor company
- FDA can impose a clinical hold at any time during a clinical trial for safety reasons or if risks were not adequately provided by sponsors
- US trials can be found on the web at <http://clinicaltrials.gov>
- Various clinical trial designs are used



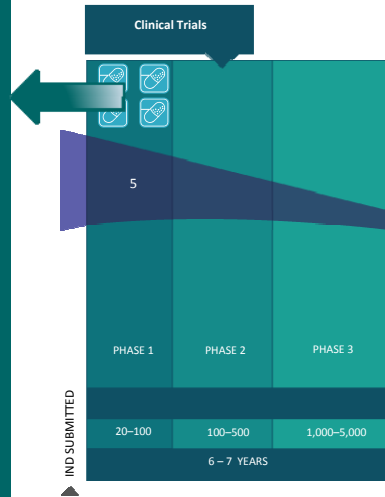
Type of Study	Description
Placebo controlled	Some subjects receive the new drug and some receive a placebo. In some cases, a new drug will be tested against a marketed drug rather than a placebo.
Randomized	Each subject is assigned randomly to one of the treatments.
Double blinded	The researchers and subjects do not know which treatment is delivered until the end of the study.



# Clinical Trials

## Phase 1: Healthy volunteers

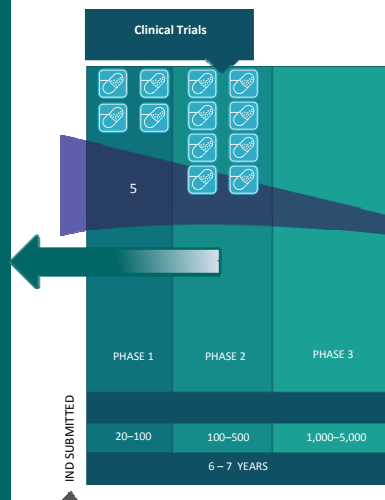
- Obtain information on safety and dose
- 20-100 patients in trial
- 6-18 months
- Patients receive single dose of drug based on maximum tolerated dose (MTD) obtained in animal toxicological studies
- Side effects with increasing dose are determined
- Data are used to design additional multidose studies as well as the Phase 2 studies
- **40% of new drugs will fail in Phase I studies**



# Clinical Trials

## Phase 2: Patients with the disease

- Obtain information on efficacy, side effects and possible risks
- 100-500 patients in trial
- 6 months to 2-3 years
- Usually randomized and double blind trials
- Can compare new drug with placebo and current standard treatment
- Data are used to design Phase 3 studies
- **62% of Phase 1 drugs will fail in Phase 2 studies**

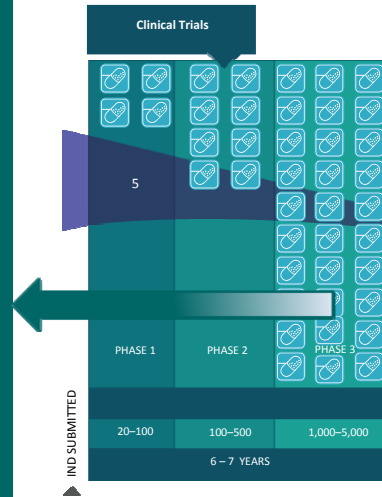




# Clinical Trials

## Phase 3: Patients with the disease

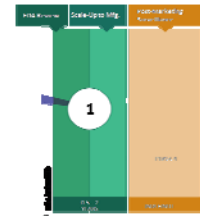
- Obtain statistically significant data on efficacy, side effects, risks, and benefits
- 1000-5000 patients in trial
- 2-4 years or longer
- Usually randomized and double blind trials
- Compare new drug with placebo and possibly current standard treatment
- Information for label and possible drug interactions
- **40% of Phase 2 drugs will fail in Phase 3 studies**



# NDA

## New Drug Application (NDA)

- Submitted to Food and Drug Administration (FDA)
- Summary of all work done to date including
  - Data from IND
  - Additional data on preclinical, drug substance and product manufacturing, and animal studies
  - Clinical trial results
- NDAs can contain up to 15 different sections
- One NDA can be 100,000 pages



### NDA Sections

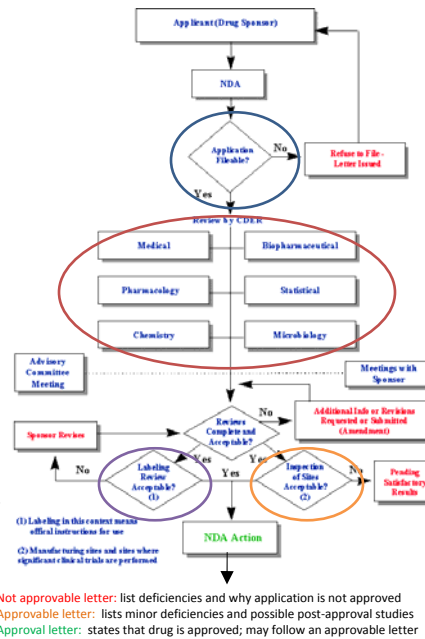
- Index
- Summary
- Chemistry, Manufacturing and Control (CMC)
- Samples, Methods Validation Package, and Labeling
- Nonclinical Pharmacology and Toxicology
- Human Pharmacokinetics and Bioavailability
- Microbiology (for anti-microbial drugs only)
- Clinical Data
- Safety Update Report (typically submitted 120 days after NDA submission)
- Statistical
- Case Report Tabulations
- Case Report Forms
- Patent Information
- Patent Certification
- Other information



# NDA

## New Drug Application (NDA)

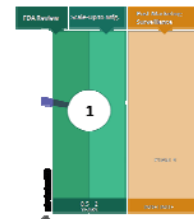
- Review begins once NDA is submitted
  - Completeness review**
    - If incomplete, sponsor receives a "refuse-to-file" letter within 60 days
  - Reviewer teams evaluate sections**
  - Preapproval on-site inspections** of manufacturing plants (drug substance and product) and clinical trial sites performed
  - Package insert** (drug product labeling) with instructions for use is also part of the approval process
- Review process can take up to 18 months**
- Once NDA is approved, drug can be marketed immediately



# Post-Marketing

## Phase 4 Clinical Trials

- Some approved drugs may need additional studies after it is on the market as part of the NDA approval
- Several hundred to several thousand patients can be enrolled
- Reasons include:
  - Determine long-term risks/benefits
  - Determine if drug is effective against other diseases
  - Test different drug products (tablets, syrups, etc)



## Post-Marketing Surveillance

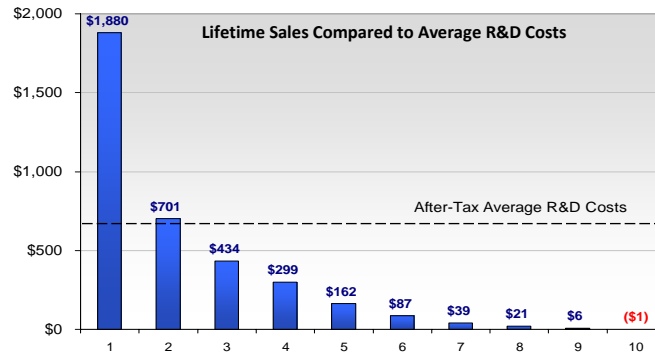
- Companies continue to monitor the drug and submit reports to FDA
- Include cases of adverse effects
- Data analyzed to determine any major problems which could change use or labeling
- In some cases drugs are taken off the market
- FDA is working on ways to access and monitor drugs more effectively and find problems sooner (such as the Sentinel initiative to put together a national network of existing electronic data systems - such as electronic health records and medical claims databases)

Drug (Indication)	Approved	Withdrawn	Years Delay	Reason Drug was Pulled
Vioxx (pain)	1999	2004	5	Heart attack, stroke
Baycol (anticholesterol)	1997	2001	4	Muscle deterioration
Raplan (airway muscle relaxant)	1999	2001	2	Bronchospasm
Lotronox (IBD)	2000	2000	9 mos	Ischemic colitis, constipation
Propulsid (nocturnal heartbeat)	1993	2000	7	Cardiac arrhythmia
Razar (antibiotic)	1997	1999	2	Severe cardiovascular problems
Hismanal (allergies)	1988	1999	11	Heart arrhythmia



# Marketed Products

Only TWO out of ten approved drugs recoup the cost of development



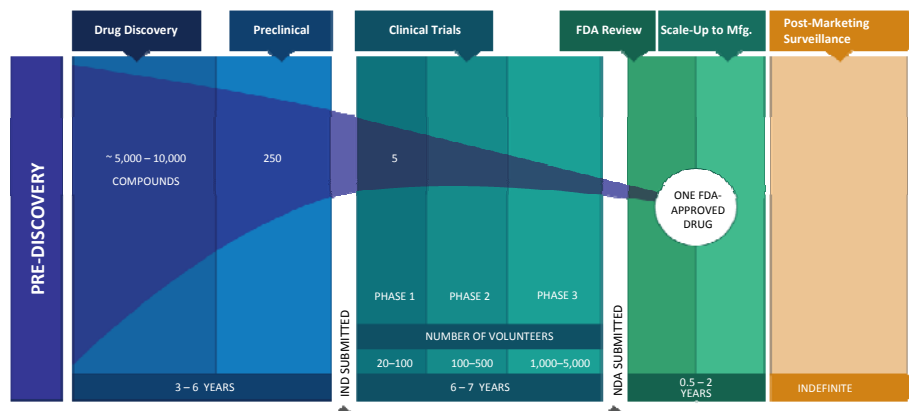
Note: Drug development costs represent after-tax out-of-pocket costs in 2000 dollars for drugs introduced from 1990-94. The same analysis found that the total cost of developing a new drug was \$1.3 billion in 2006. Average R&D Costs include the cost of the approved medicines as well as those that fail to reach approval.

Sources: J. A. Vernon, J. H. Golec, and J.A. DiMasi, "Drug development costs when financial risk is measured using the Fama-French three-factor model." Health Economics, (2009). ; J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?," Managerial and Decision Economics, 2007.

graphic from innovation.org



# Drug Development



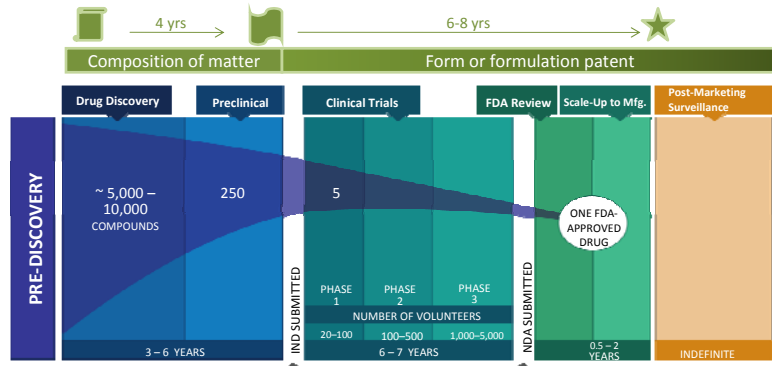
10-15 years \$1.2 - 17 billion per drug	R&D Spending in 2008: • \$65.2B* • 17.4% of total sales	ONLY 2 of 10 marketed drugs return revenues that match or exceed R&D costs
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\*2006 data from PhRMA 2009 Profile



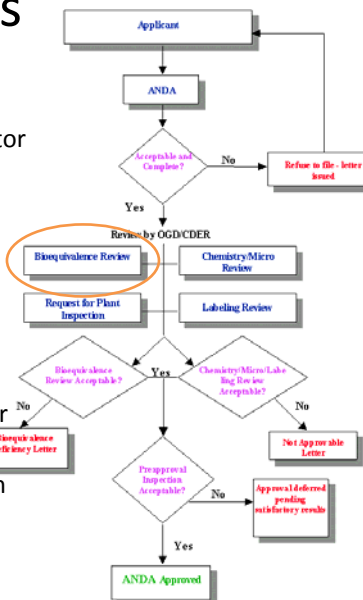
# Patents

- A number of pharmaceutical patents can be filed including
  - composition of matter (compound, forms, formulations)
  - methods of use
  - manufacturing processes (synthetic route)
- A pharmaceutical patent has an average life of 11.5 years instead of 20 years



# Generic Drugs

- Generic drugs come on the market after the patents have expired for the branded or innovator drug
- Generic company must file an Abbreviated New Drug Application (ANDA) to the FDA.
- Generic companies are not required to include preclinical (animal) or clinical (human) data to establish safety and effectiveness
  - Must demonstrate that their product is **bioequivalent** (performs in the same manner as the innovator drug)
    - Dissolution testing or in-vivo comparison to marketed product





# Generic Drugs and Patents



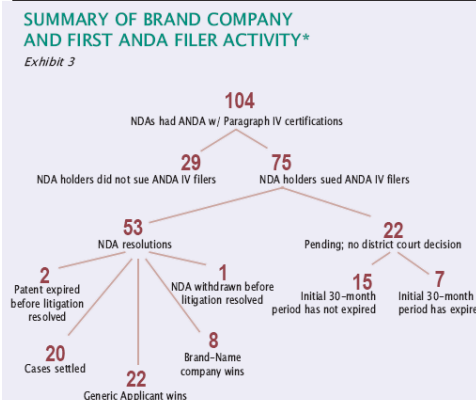
- FDA maintains a public and detailed list of drugs and drug products in US
  - Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book, <http://www.fda.gov/cder/ob/>)
  - Patents are included in the NDA file and are listed in the Orange Book
- Hatch-Waxman Act (The Drug Price Competition and Patent Term Restoration Act of 9184)
  - Allow generics to get on market more quickly once patents have expired
  - Generics build off safety and efficacy of innovator (ANDA)
  - Innovators receive patent term extensions and market exclusivities
  - Generic companies can begin development while patent is still in place
  - Generic drugs cannot be approved if the patent has not expired
- Generic company must make a certification that addresses patents in the Orange Book



# Generic Drugs and Patents

- Paragraph I.
  - No patents listed in Orange Book
  - ANDA can be approved immediately
- Paragraph II.
  - Patent listed in Orange Book has expired
  - ANDA can be approved immediately
- Paragraph III.
  - Patent is listed in Orange Book and generic will not be marketed until patent is expired
  - ANDA cannot be approved until patent expiration date.
- Paragraph IV.
  - Patent is listed in Orange Book and generic company plans to market drug before patent expiration date; claims patent is invalid, unenforceable, or product will not infringe
  - Innovator has 45 days to start litigation
  - ANDA cannot be approved for 30 months

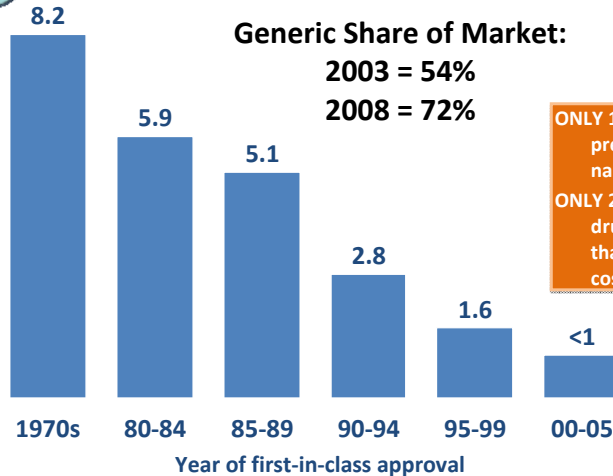
## Summary of ANDA filings up to 2002



\*As of June 1, 2002  
 SOURCE: July 2002 FTC Study: *Generic Drug Entry Prior to Patent Expiration*  
[http://www.ropesgray.com/files/Publication/59926b69-21c3-4b89-85d8-f372f73fba8c/Presentation/PublicationAttachment/31bfd42-c51a-457f-a852-509128658d5c/Article\\_June%202003\\_The%20Battle%20for%20IP.pdf](http://www.ropesgray.com/files/Publication/59926b69-21c3-4b89-85d8-f372f73fba8c/Presentation/PublicationAttachment/31bfd42-c51a-457f-a852-509128658d5c/Article_June%202003_The%20Battle%20for%20IP.pdf)



## Innovators Have Less Time to Recoup Their R&D Costs



ONLY 11 of the top 50 most prescribed drugs are brand name products.  
ONLY 2 out of 10 marketed drugs ever return revenues that match or exceed R&D costs.

Source: FDA; The Pink Street; Morgan Stanley; DiMasi; Paquette; Pharmacoconomics 2004, 22 (Suppl 2): 1-14; IMS; team analysis  
IMS Health, National Sales Perspectives, National Prescription Audit, March 2009  
AARP, The 50 Most Prescribed Drugs, October 2009.



## What's Next

- It is recognized by both the pharmaceutical industry and the FDA that improvements are needed
- Scientific advances will help get better drugs on the market faster
- It is important to get into clinical trials faster to determine if a drug is a viable candidate for development
- Pharmaceutical companies need to innovate and make processes more efficient while the FDA has to help with regulatory relief during development without compromising safety
- Lifecycle management will be an area of growth with many large selling drug patents expiring before 2012



## What Have We Learned

- It takes 10-15 years to develop a new medicine
- \$1,300,000,000 to \$1,700,000,000 is the average cost to develop one medicine
- 1 new medicine will result from every 5,000-10,000 compounds screened
- New medicines initially need to get through drug discovery, preclinical and IND stages
- After the IND, three phases of clinical trials are needed before an NDA can be filed
- Once an NDA is approved, the drug can be sold
- 2 out of 10 new medicines will produce revenues that match or exceed average research and development costs
- Generic drugs do not need preclinical data or extensive clinical trials
- Generic drugs are not approved until innovator patent has expired
- 11-12 = Years of effective patent life for medicines - about 6-7 years shorter than other products



## Resources

- Food and Drug Administration (FDA): [www.fda.gov](http://www.fda.gov)
- Pharmaceutical Research and Manufacturers of America, "Drug discovery and development" <http://www.innovation.org/insideRandD>
- A. Newman, "From Beaker to Bottle" ebook, [www.seventhstreetdev.com/downloads](http://www.seventhstreetdev.com/downloads)
- J. Eckstein, "ISOA/ARF Drug Development Tutorial" <http://www.alzforum.org/drg/tut/tutorial.asp>. (February 2005).
- A. E. Guttmacher, F. S. Collins. "Realizing the Promise of Genomics in Biomedical Research" **JAMA**, 2005, 294(11), 1399-1402.
- N. Variankaval et al. "From Form to Function: Crystallization of Active Pharmaceutical Ingredients" **AICHe Journal** 2008, 54, 1682-1688.
- D. Lowe. "Aspirin: Not Approvable. Why many familiar medicines might flunk FDA approval today" **Medical Progress Today**. November 17, 2005. [http://www.medicalprogresstoday.com/spotlight/spotlight\\_indarchive.php?id=1039](http://www.medicalprogresstoday.com/spotlight/spotlight_indarchive.php?id=1039)
- R. Butler. "Patent Life-cycle" **Chemistry and Industry**, April 19, 2004. [http://findarticles.com/p/articles/mi\\_hb5255/is\\_8/ai\\_n29087810/pg\\_2?tag=artBody:col1](http://findarticles.com/p/articles/mi_hb5255/is_8/ai_n29087810/pg_2?tag=artBody:col1)
- J.A. DiMasi. "Risks in new drug development: Approval success rates for investigational drugs" **Clin Pharmacol Ther**, 2001, May, 297-307.
- "Innovation or Stagnation. Challenge and Opportunity on the Critical Path to New Medical Products" 2004. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>
- "Optimizing Drug Development Strategies" **Contract Pharma**. March, 2007. <http://www.contractpharma.com/articles/2007/03/optimizing-drug-development-strategies>
- S. M. Paul and et al. "How to Improve R&D Productivity: the Pharmaceutical Industry's Grand Challenge" **Nature Reviews Drug Discovery**, 2010, published online Feb 19, 2010; doi: 10.1038/nrd3078.

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## Q&A SESSION

### *From a Beaker to a Bottle: Overview of the Drug Discovery and Development Process for Small Molecule Therapeutics*



Speaker: Ann Newman  
Seventh Street Development Group



Moderator: Karen Rossi  
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