Regulatory Agencies and Clinical Trials

How One Puts a New Chemical or Device into the Human Environment

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Starting a Company:

Due Diligence

Idea → Company

**Steps:**
1. Invention
2. Size up the competition
3. Make sure invention works
4. **Make sure it is safe**
5. Patent (secure intellectual property)
6. Figure out best way to make it
7. Figure out how much to make
8. Is it the right thing to do?
The Life Cycle of a Drug

Risk

Profit

Patent Lifetime

Investment

Years After Discovery

0  5  10  15  20  25  30
First of All …

• What annual revenues should you make to be considered a “Commercial Success”?
  • One Million Dollars?
  • One Hundred Million Dollars?
  • One Billion Dollars?
  • One Hundred Billion Dollars?
## Today’s Blockbuster Drugs

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Company</th>
<th>Sales (billion $), year</th>
</tr>
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<tbody>
<tr>
<td>atorvastatin</td>
<td>Lipitor</td>
<td>Pfizer</td>
<td>12.9 2006</td>
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<tr>
<td>clopidogrel</td>
<td>Plavix</td>
<td>Bristol-Myers Squibb and Sanofi-Aventis</td>
<td>5.9 2005</td>
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<tr>
<td>enoxaparin</td>
<td>Lovenox/ Clexane</td>
<td>Sanofi-Aventis</td>
<td>3.5 2006</td>
</tr>
<tr>
<td>celecoxib</td>
<td>Celebrex</td>
<td>Pfizer</td>
<td>2.3 2007</td>
</tr>
<tr>
<td>omeprazole</td>
<td>Losec/ Prilosec</td>
<td>AstraZenica</td>
<td>2.6 2004</td>
</tr>
<tr>
<td>esomeprazole</td>
<td>Nexium</td>
<td>AstraZenica</td>
<td>3.3 2003</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Telfast/ Allegra</td>
<td>Aventis</td>
<td>1.87 2004</td>
</tr>
<tr>
<td>quetiapine</td>
<td>Seroquel</td>
<td>AstraZenica</td>
<td>1.5 2003</td>
</tr>
<tr>
<td>metoprolol</td>
<td>Lopressor/ Toprol</td>
<td>AstraZenica</td>
<td>1.3 2003</td>
</tr>
<tr>
<td>budesonide</td>
<td>Pulmicort/ Rhinocort</td>
<td>AstraZenica</td>
<td>1.3 2003</td>
</tr>
</tbody>
</table>
Getting Products to People: Regulatory Agencies are an Important Checkpoint

Public → $0.2-$1 Billion → Product

Chemists, Biologists, Engineers

Public Advocates ↔ Regulatory Agency

$1BB annual revenue makes $3MM per day
This is the discovery phase of drug development – chemists, biologists, clinicians work in teams to find Developmental Candidates (DCs).

Later, the toxicologist takes over to guide the product through the regulatory (FDA) maze.

Discuss Downsizing at Many Biotechnology Companies.
Regulatory Agencies:  Protect the public by making industry prove that the product you have developed does what it is supposed to do and is safe under conditions of intended use.

Examples (in the USA):  FDA, USDA, NRC, EPA, ... see other handout. There are comparable regulatory agencies in Asia, Europe, ...

Their job:

- Will the product do what you claim?
- Is it not going to cause harm under conditions of use?
- Set tolerances for filth
- Define composition of matter of substances to which public is to be exposed
Comprehensive Toxicologic Evaluation (CTE; Literally hundreds of tests)

Objective: to learn what the toxic effects are (or what we can project them to be) in humans.

A few examples:

- Olestra
- Sugar*

“This Product Contains Olestra. Olestra may cause abdominal cramping and loose stools. Olestra inhibits the absorption of some vitamins and other nutrients. Vitamins A, D, E, and K have been added.” Package Labeling

Public domain image of the olestra molecule, created using the free program RasMol and the olestra.pdb dataset.
Let’s Figure Out How to Put Sugar-Water on The Market – *What questions would the FDA ask?*

* For fun, let’s think of the case one would make to put sugar (sucrose) on the market today. Think of the positive and negative features of sugar and how these features would be responded to by the Food and Drug Administration, which is the relevant regulatory agency.

Photo courtesy of AARON_400D on Flickr.
Comprehensive Toxicology Evaluation -- CTE

Toxicologist brings this list to first meeting with FDA (pre-IND meeting)
Comprehensive Toxicity Evaluation

Scan of a toxicity evaluation form removed due to copyright restrictions.
An Overview of the Phases of Drug Approval

Diagram of phases of drug approval removed due to copyright restrictions.
REGULATORY APPROVAL PROCESS (USA)

Science
A. Pre-clinical Evaluation (usually animal or single cell studies)
   - acute toxicity
   - subacute toxicity
   - chronic toxicity

Documentation
• **IND** (Investigative New Drug Application)

B. Clinical Evaluation
REGULATORY APPROVAL PROCESS (Continued)

Science

B. Clinical Evaluation (humans)
- Phase I: Clinical Trial
- Phase II: Clinical Trial
- Phase III: Clinical Trial

Documentation

- NDA (New Drug Application)

FDA Approval

(If Approved)

C. Post-Clinical Evaluation

Phase IV: marketing post-market surveillance
A. Pre-Clinical Phase

1. Acute toxicity: Effect of a single dose on animals. Duration is 1 - 7 days. Keep the time very short and observe as much as possible.

Key information obtained is the **LD$_{50}$**, or the **median lethal dose**

**Dosing:** i.v., feeding, ... (whatever is logical)

**Choice of species?**

Ramp up dose to cell culture concentration that gave a positive result
A. Pre-Clinical Phase (Cont.)

2. **Subacute toxicity**: Multiple doses over relatively short term. **Duration**: short-term administration over 2 weeks (most common) to 3 months (at 3-4 weeks most neurotoxicity symptoms become evident).

   Helps to **range-find for subsequent chronic study** of drugs that will be given to people over a long period of time.

   **Often used by companies as the basis for selection** of one compound among several candidate drugs.

   **Definitive for one-shot applications** (tPA, THC, EPO, Anticancer Drugs)
A. Pre-Clinical Phase (Cont.)

3. Chronic toxicity: long-term administration. Extraordinarily expensive (about $400K per species) and most controversial from a design point of view.

- **Duration**: Lifetime (2-3 years in rodents)
- Primarily a **cancer test**
- **Two species** (rodent and non-rodent (typically dog or monkey ($$))). [4-Aminobiphenyl and DES as examples]
- **Dosing**: At least three dose levels plus a positive control. *Want the highest dose to be one that shows some toxicity.*
- **Route of administration** -- whatever makes sense, but usually oral
- **Multi-generational tests** [DES and thalidomide as examples] – *DES-grandchildren are now being studied*
Clinical Phase of Testing

IND = Investigative New Drug Application – FDA has 30 days to respond
REGULATORY APPROVAL PROCESS (Continued)

Science

B. Clinical Evaluation (humans)
- Phase I: Clinical Trial
- Phase II: Clinical Trial
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Documentation

- NDA (New Drug Application)

C. Post-Clinical Evaluation
- Phase IV: marketing post-market surveillance

FDA Approval (If Approved)
B. Clinical Phase (You have submitted your IND at this point)

1. Phase I: Normal volunteers. For example, college students (usually males), women of non-childbearing potential (postpartum females, voluntarily sterilized females).  NEED SOME EXTRA MONEY??

Image of a newspaper advertisement removed due to copyright restrictions. The advertisement sought healthy males (ages 18-40) to participate in a study concerning the effects of melatonin on behavior, conducted at the MIT Clinical Research Center.
B. Clinical Phase (You have submitted your IND at this point)

1. **Phase I: Normal volunteers.** For example, college students (usually males), women of non-childbearing potential (postpartum females, voluntarily sterilized females). **NEED SOME EXTRA MONEY??**

   - **Typical studies:** Pharmacokinetics (clearance, metabolism), determination of maximum tolerated dose
   - **Sets range for efficacy trials**
   - **Number of volunteers:** 50-100
   - **Duration:** about one week (watch patients carefully for first three or four hours). Could be longer than one week.
2. Phase II: Patients for the disease your drug treats. 

**Efficacy trials** -- i.e., these data show you whether the drug actually works in people.

- **Typical studies:** Usually severely ill people or those with the most pronounced symptoms. Must include a control (placebo). In the case of a disease such as **cancer or AIDS**, the control is usually a patient group treated by the conventional protocol.
- **Goal:** to set the pharmacological dose
- **Number of patients:** 100 or so
- **Duration:** about one month

- Number of patients: \( f(\text{efficacy parameter}) \)

- How do you feel today?

- Rare but fatal disease – 80-100 patients total

- More common case (analgesic, oral contraceptive) – about 25 patients per dose; many dose levels; thousands of patients total

- Duration – Months to years
Final Points on Clinical Trials

- Sometimes it is hard to find enough patients for a (statistically) good clinical trial
  - **Novelos** – Lung Cancer – There are lots of drugs already under evaluation at lots of different clinics – It took years to accrue patients

- When your NDA is approved the FDA will publish a **Summary Basis of Approval** (SBA), which is available through the Freedom of Information Act

An Example of Phase I, II, III Clinical Trials
A Model Clinical Study

BE Design Case Study, 1999

Viagra advertisement removed due to copyright restrictions.
A Model
Clinical Study: ED

See SBA here:


Viagra advertisement removed due to copyright restrictions.
Viagra: Introduced in 1998 to Treat Erectile Dysfunction

How was it discovered?
What Causes an Erection?

Sexual Stimulus

Brain (Dopamine) → Penile Nerves →

Endothelial Cell

NOS → NOS* → NO →

Smooth Muscle Cell

GC → GMP

GTP → cGMP →

Viagra

Actin-Myosin Slide

Erection

NO is Nitric Oxide

Nitric Oxide

GC is Guanylate Cyclase
Pharmacokinetics: Viagra Reaches Maximal Concentration in About One Hour

Metabolically Cleared By CYP3A4

Look at contraindications list on the FDA SBA -- Important
Phase II: Clinical Data That Viagra Works (Finding Clinical Dose)

Dose-Response Relationship

Phase III: Clinical Data on a Large Population

Viagra

“Erectability Quartiles”

Success Function

Never

Five dose-response studies

Almost Always

Metric: IIEF (International Index of Erectile Function)

Placebo

Effect of Placebo on Maintenance of Erection by Baseline Score


Phase IV Clinical Evaluation

4. **Phase IV (post-NDA) approval:** FDA often asks for *post-marketing surveillance* to address unanswered but minor questions from phase III

- Color vision issues with Viagra, “heart attacks with Vioxx,” etc.
- Unexpected drug-drug interactions may be detected in this period
  - P. Hartman
  - Ketoconazole and Seldane (replaced by Allegra)

- Question: If a drug is approved for X, can you use it for Y, and Z?
  - Breast Implants
  - Taxol
  - Minoxidil
  - Celebrex
How Many New Drugs Are Approved Per Year?

• VERY FEW! In the USA there were 23 new molecular entities approved in 1990; 7 of these were 1A, i.e., they showed significant therapeutic gains over existing therapies. There were a total of 229 approvals, but this includes the generics.


• Average time for average drug development plus approval is now 9.9 years (for the 23 above). The approval process alone (i.e., the decision-making process on the part of the FDA) is averaging a little more than 2 years.

• Epoetin alpha (Amgen), which helps the AZT-caused anemia in AIDS patients, was approved by the FDA in 3.5 months. This is an example of "fast-tracking."
Early On, Most AIDS Drugs Were Fast-Tracked

Example: AZT (A little more than 2 years)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>AZT (zidovudine) developed as potential anticancer agent</td>
</tr>
<tr>
<td>Oct., 1984</td>
<td>Pre-clinical trials begin for AIDS</td>
</tr>
<tr>
<td>May, 1985</td>
<td>IND submitted</td>
</tr>
<tr>
<td>July, 1985</td>
<td>Phase I clinical trial begins</td>
</tr>
<tr>
<td>Feb., 1986</td>
<td>Phase II begins</td>
</tr>
<tr>
<td>Sept., 1986</td>
<td>Trials terminated early!</td>
</tr>
<tr>
<td>Oct., 1986</td>
<td>Treatment IND approved</td>
</tr>
<tr>
<td>Dec., 1986</td>
<td>NDA submitted</td>
</tr>
<tr>
<td>March, 1987</td>
<td>NDA approved</td>
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</table>
Most Drugs Take ~10 Years
Example: Lovastatin (Cholesterol Lowering Drug)

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late 1978</td>
<td>Lovastatin isolated from <em>A. terreus</em></td>
</tr>
<tr>
<td>1979</td>
<td>Pre-clinical trials begin</td>
</tr>
<tr>
<td>1980</td>
<td>Drug patented</td>
</tr>
<tr>
<td>March, 1984</td>
<td>IND submitted to US FDA</td>
</tr>
<tr>
<td>May, 1984</td>
<td>Phase II begins</td>
</tr>
<tr>
<td>April, 1985</td>
<td>Phase III trials begin</td>
</tr>
<tr>
<td>Nov., 1986</td>
<td>NDA submitted</td>
</tr>
<tr>
<td>August, 1987</td>
<td>NDA approved</td>
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</tbody>
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Lovastatin inhibits HMG-CoA Reductase
Is the US Going to be Competitive in the Future? Need to do faster/better/cheaper clinical trials.

The Life Cycle of a Drug

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Profit

Patent Lifetime

Investment

Years After Discovery

0          5         10        15        20        25        30