Regulatory Agencies and Clinical Trials

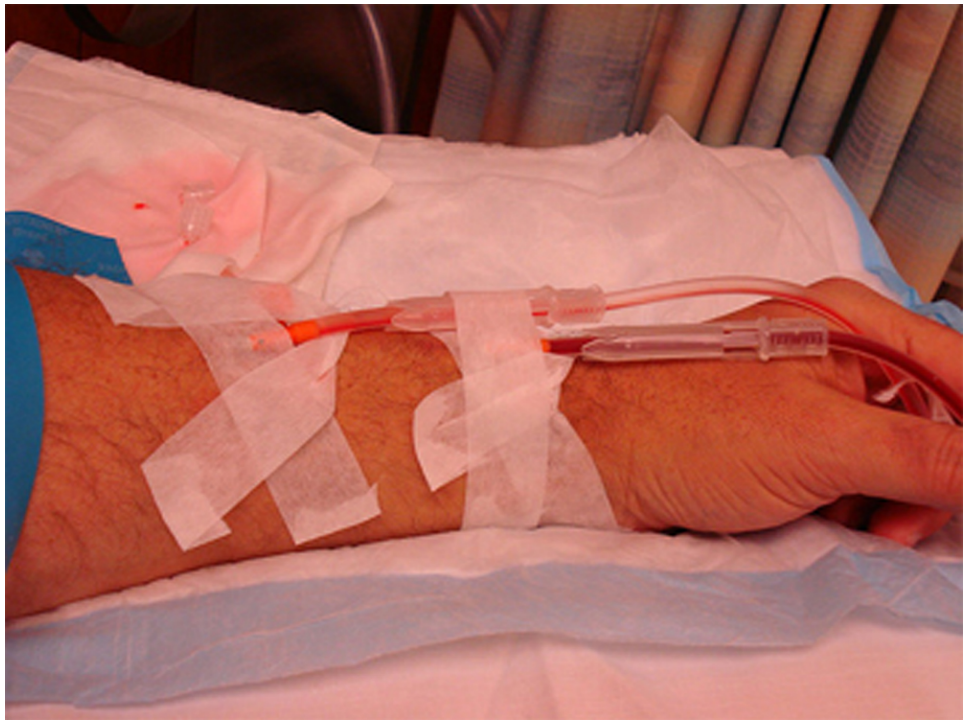


Photo courtesy of canuckshutterer "Bill" (W.J. Gibson) on Flickr.

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

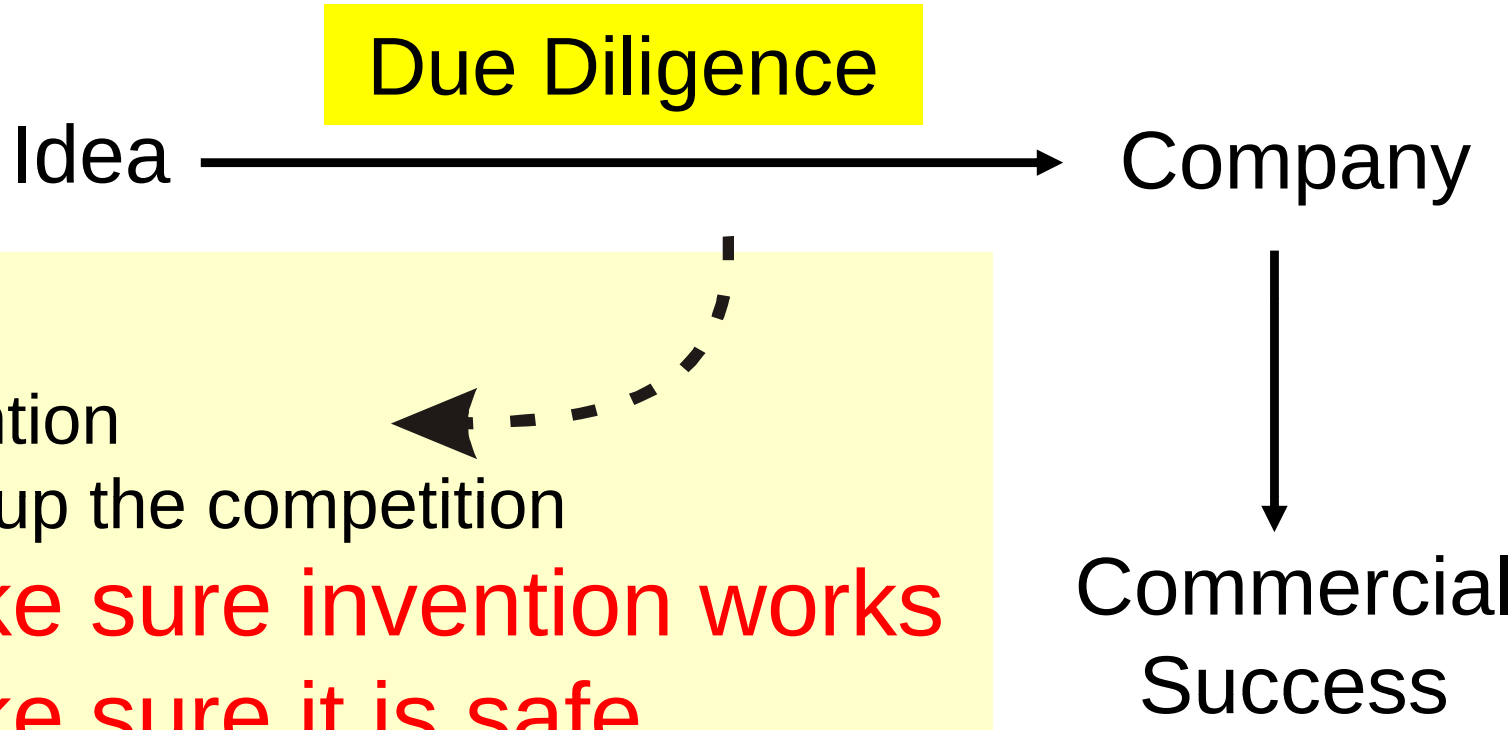
John Essigmann

April 1, 2010

http://online.wsj.com/public/article/SB120354600035281041-pY4IcITvYzE_S9JtWfUReW_3kS4_20080321.html?mod=tff_main_tff_top

http://pubs.acs.org/cen/news/86/i08/8608notw4.html

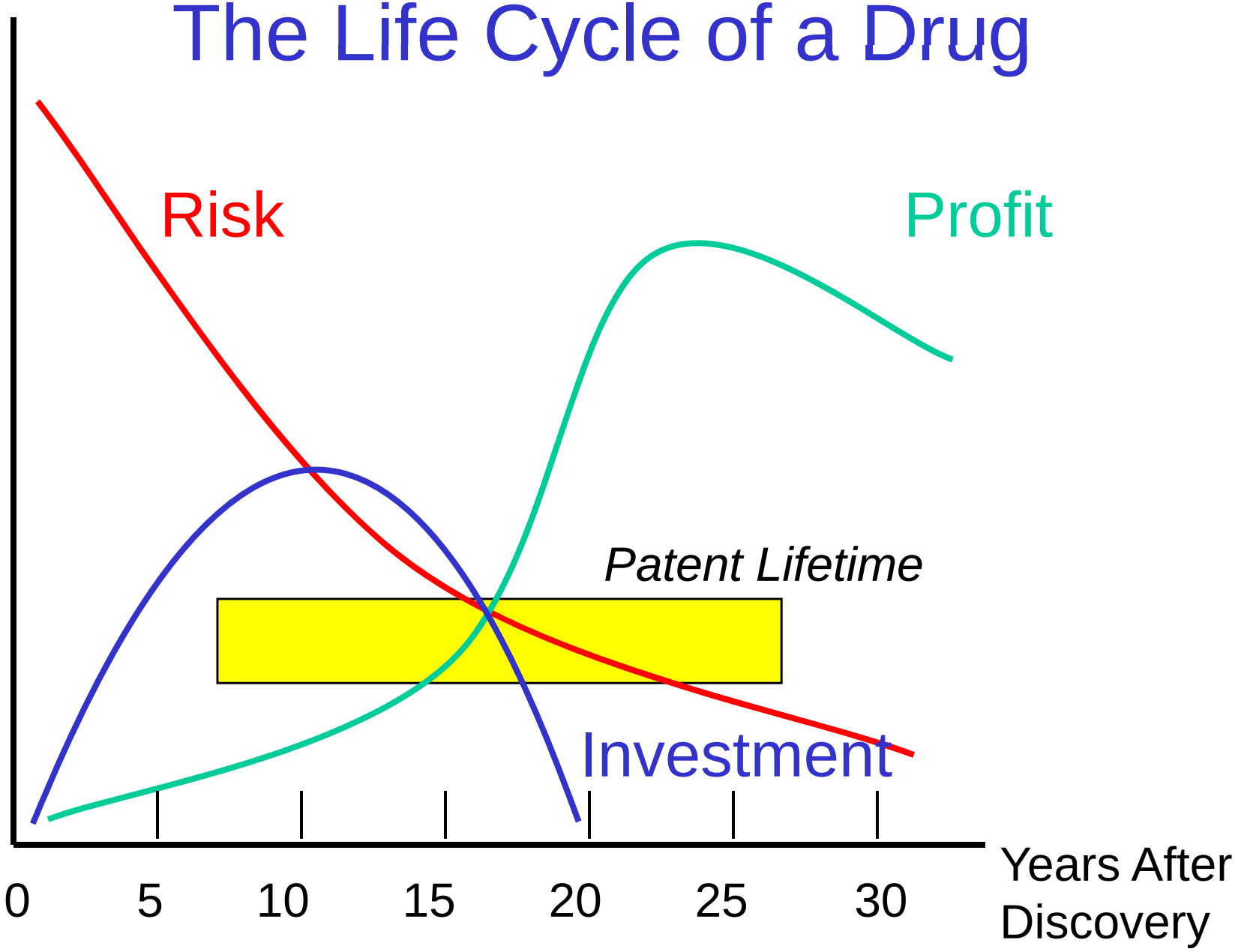
Starting a Company:



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



First of All …

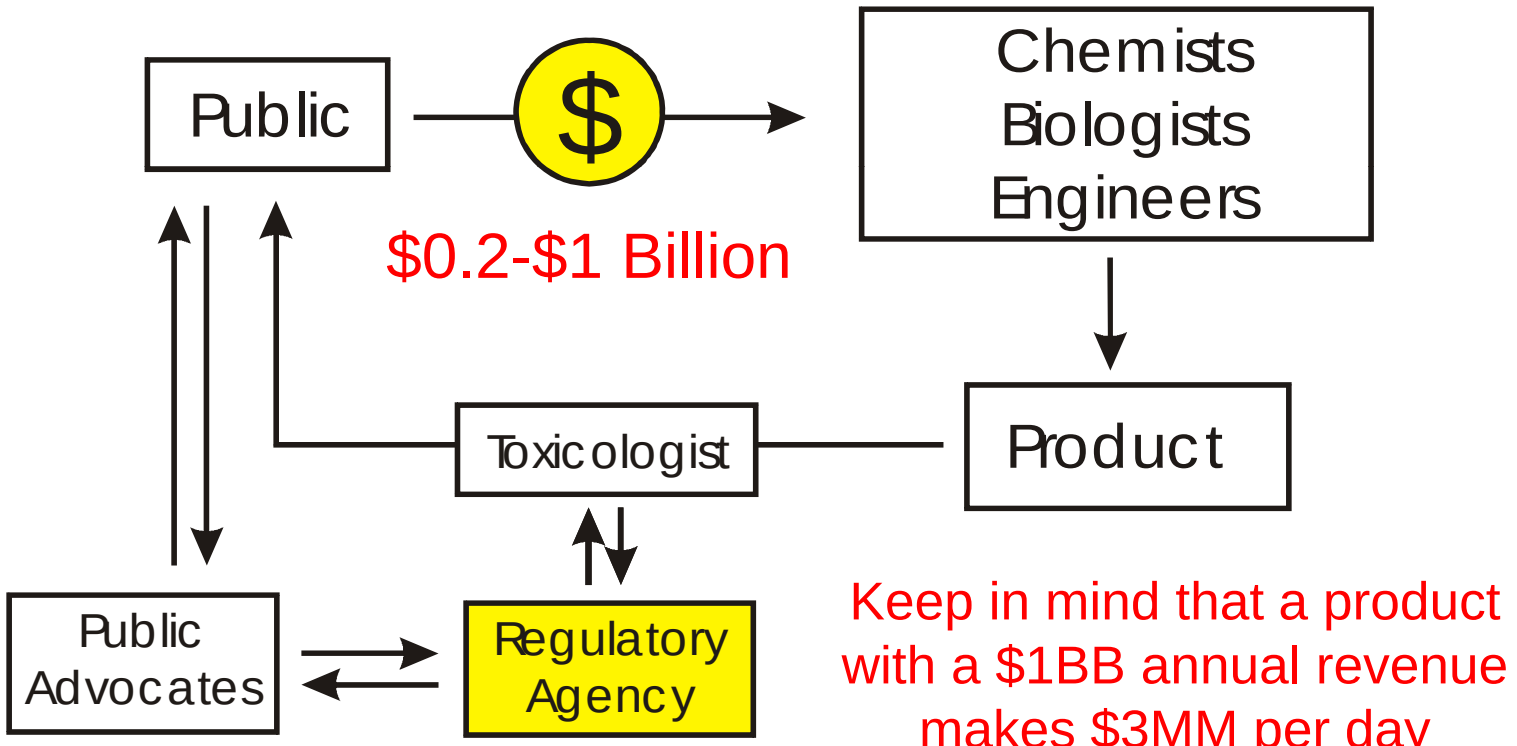
- What annual revenues should you make to be considered a “Commercial Success”?
  - One Million Dollars?
  - One Hundred Million Dollars?
  - One Billion Dollars?
  - One Hundred Billion Dollars?

Today's Blockbuster Drugs

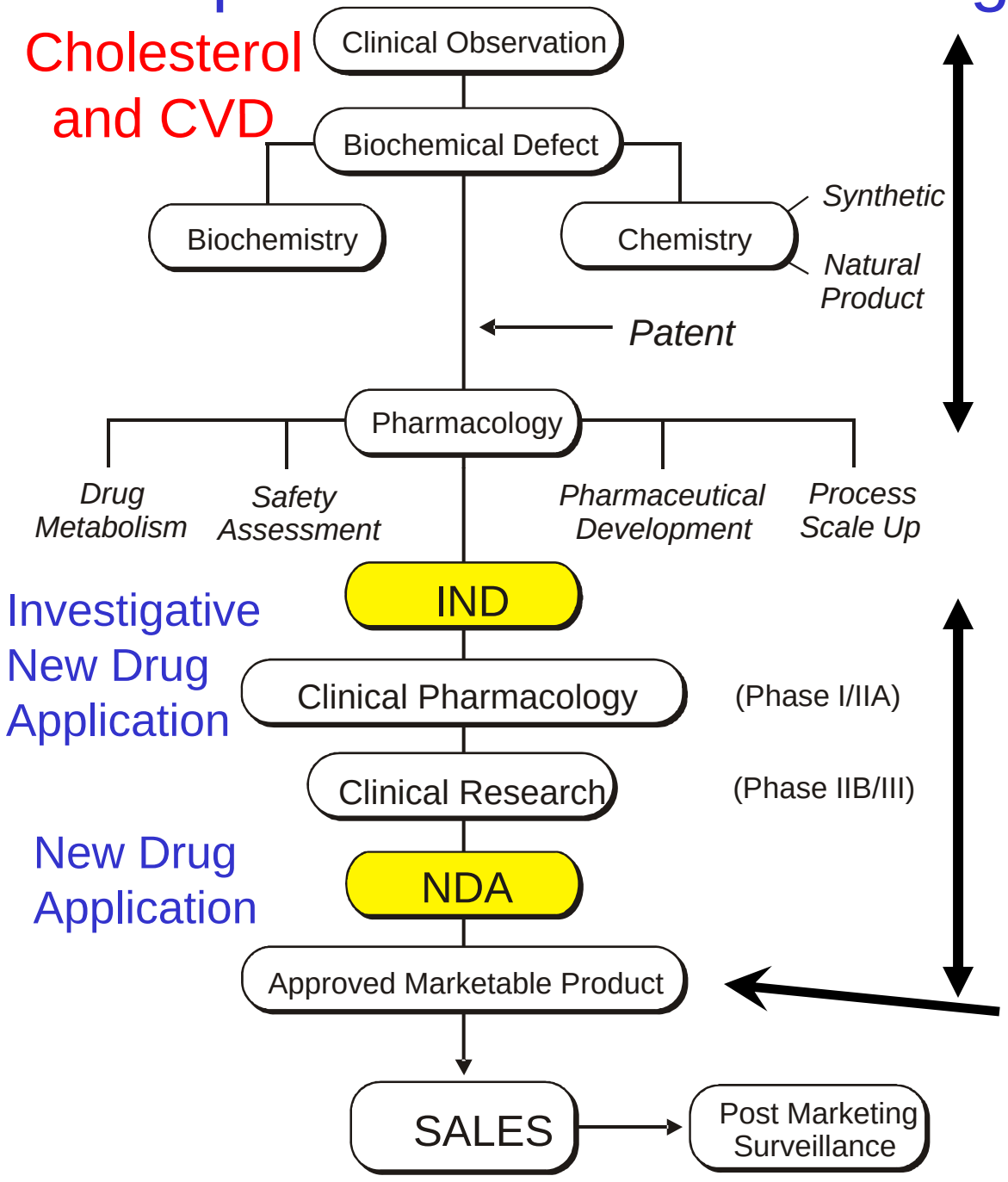
Medication	Trade Name	Company	Sales (billion $), year
atorvastatin	Lipitor	Pfizer	12.9 2006
clopidogrel	Plavix	Bristol-Myers Squibb and Sanofi-Aventis	5.9 2005
enoxaparin	Lovenox/ Clexane	Sanofi-Aventis	3.5 2006
celecoxib	Celebrex	Pfizer	2.3 2007
omeprazole	Losec/ Prilosec	AstraZenica	2.6 2004
esomeprazole	Nexium	AstraZenica	3.3 2003
Fexofenadine	Telfast/ Allegra	Aventis	1.87 2004
quetiapine	Seroquel	AstraZenica	1.5 2003
metoprolol	Lopressor/ Toprol	AstraZenica	1.3 2003
budesonide	Pulmicort/ Rhinocort	AstraZenica	1.3 2003

Pharmaceutical Market Trends, 2006-2010, from Urch Publishing
Blockbuster Drugs 2006: Executive Overview, from Report Buyer

Getting Products to People: Regulatory Agencies are an Important Checkpoint



Sequence of Events in Drug Development



- 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

THE REGULATORY APPROVAL PROCESS

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

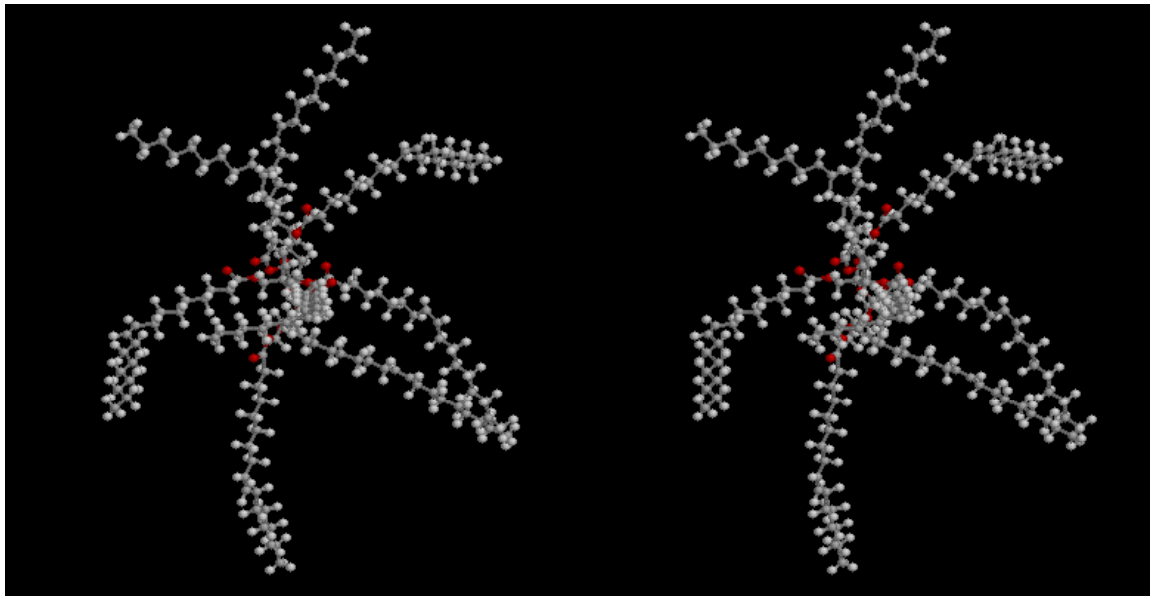
Comprehensive Toxicologic Evaluation (CTE; Literally hundreds of tests)

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

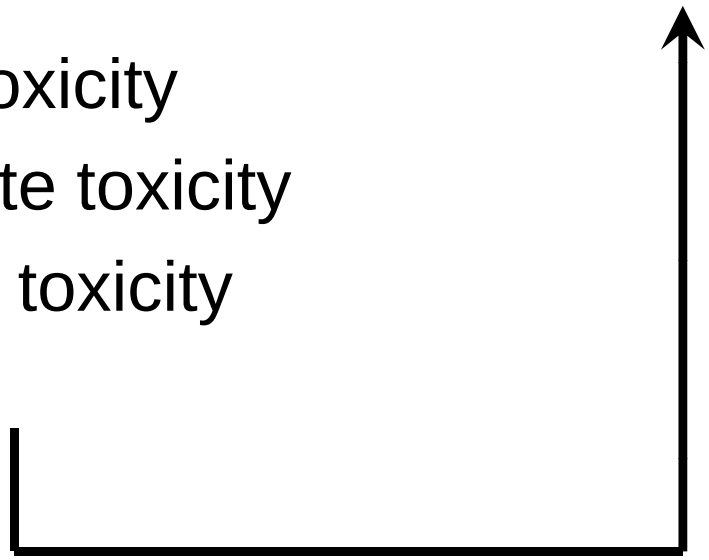
A. Pre-clinical Evaluation (usually animal or single cell studies)

- 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

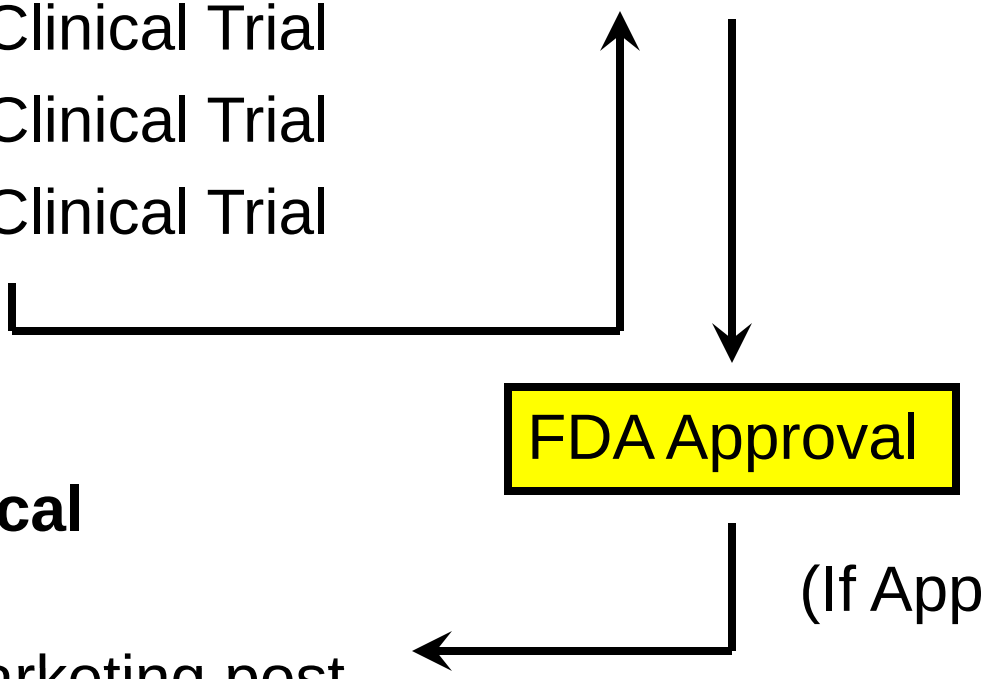
Phase III Clinical Trial

C. Post-Clinical Evaluation

Phase IV: marketing post-market surveillance

Documentation

•**NDA** (New Drug Application)



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

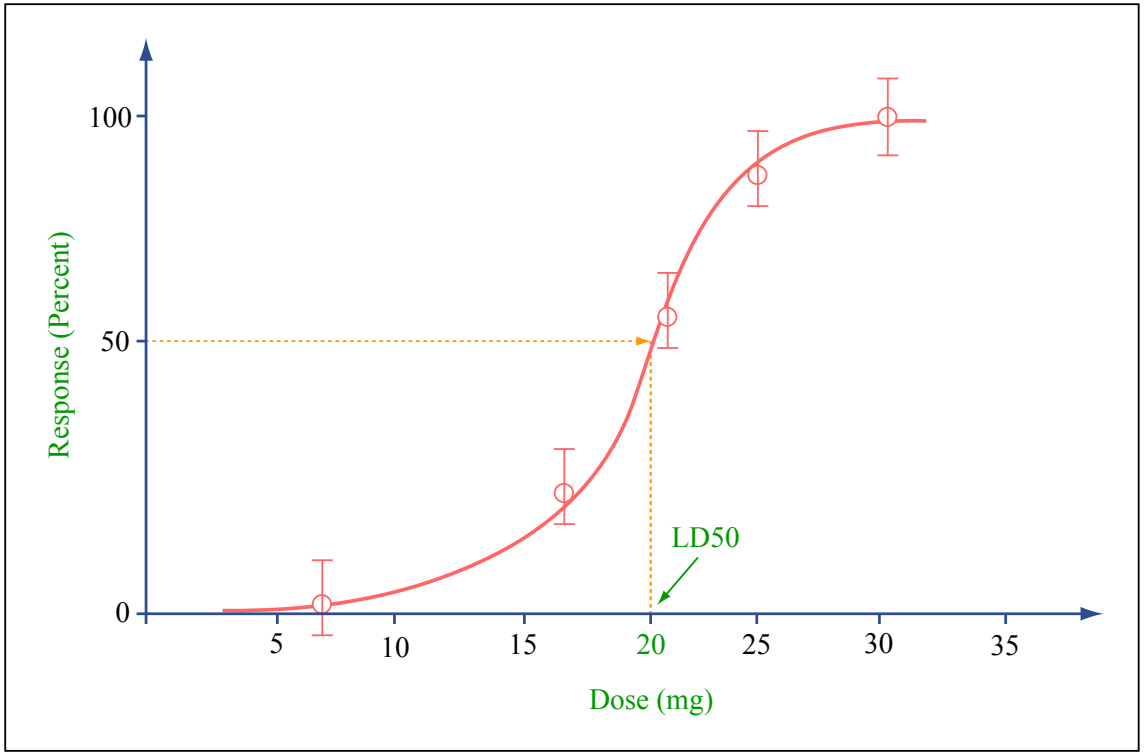


Image by MIT OpenCourseWare.

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 **expen$ive** (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

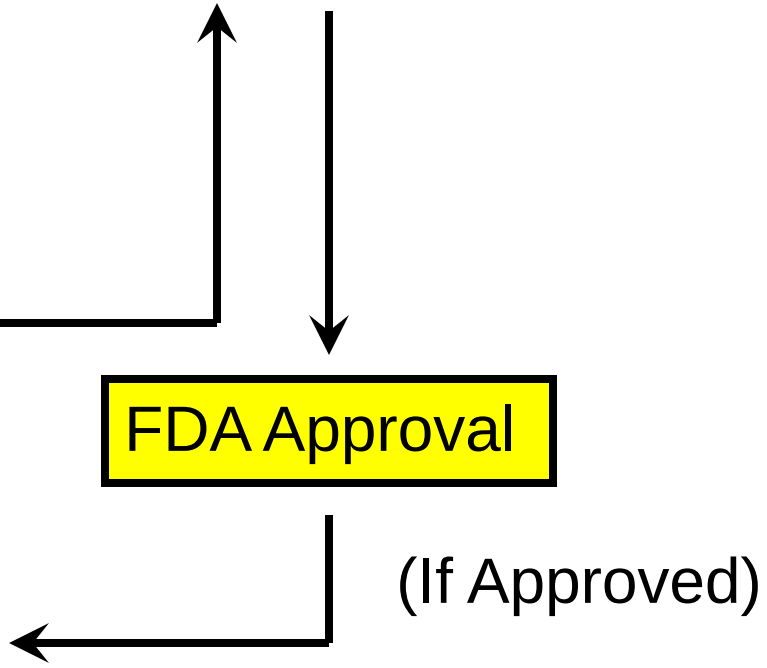
Phase III Clinical Trial

C. Post-Clinical Evaluation

Phase IV: marketing post-market surveillance

Documentation

•**NDA** (New Drug Application)



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.

B. Clinical Phase (Cont.)

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

B. Clinical Phase (Cont.)

3. Phase III: Expanded clinical testing in normal patient population.

- *Number of patients: f(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

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.430

An Example of Phase I, II, III Clinical Trials

A Model Clinical Study

Viagra advertisement removed due to copyright restrictions.

BE Design Case Study, 1999

A Model Clinical Study: **ED**

See SBA here:

http://www.fda.gov/cder/foi/label/2005/020895s021lbl.pdf

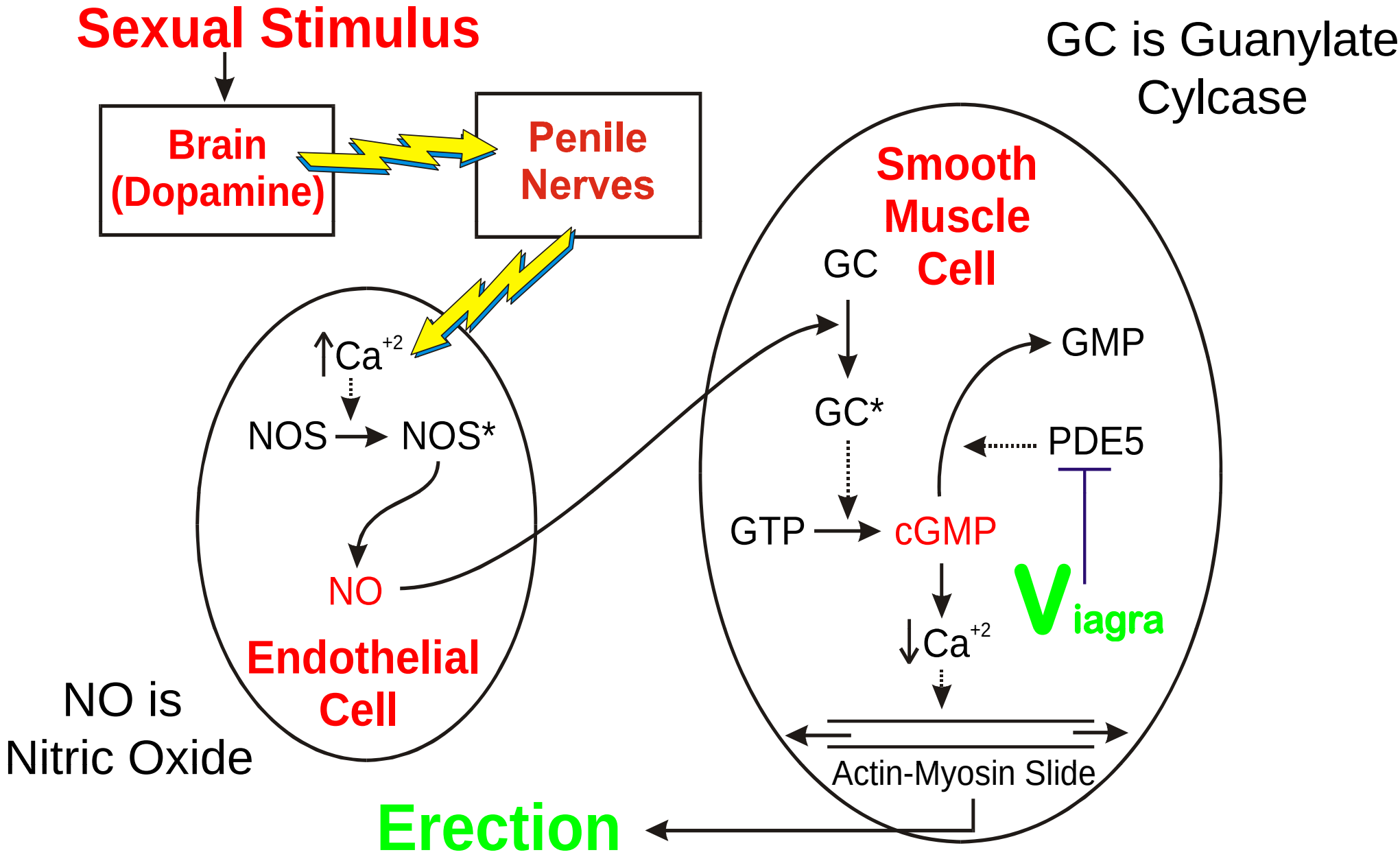
Viagra advertisement removed due to copyright restrictions.

Viagra: Introduced in 1998 to Treat Erectile Disfunction

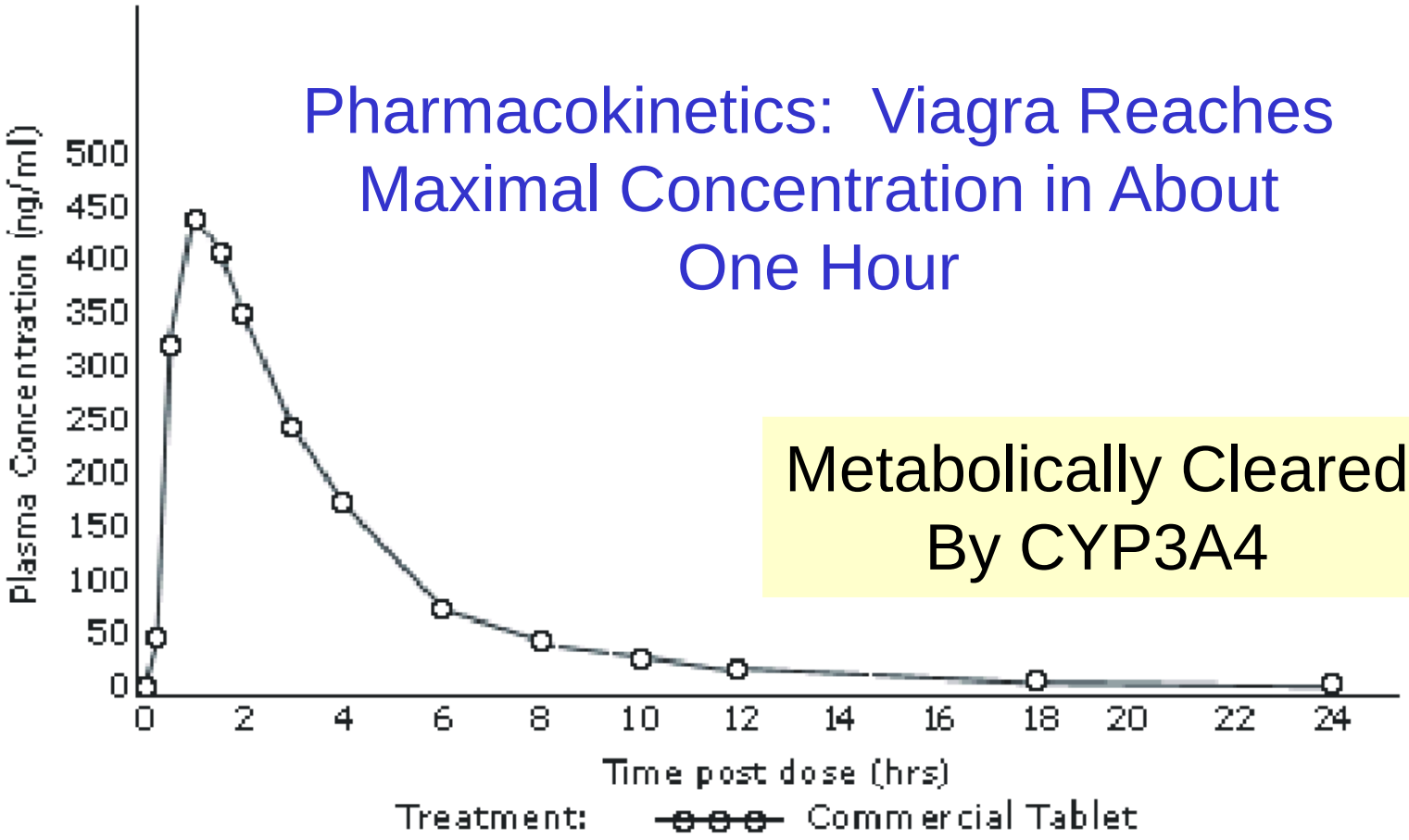
Image of man holding Viagra pills in hand removed due to copyright restrictions.

How was it discovered?

What Causes an Erection?



Phase I



Pharmacokinetics: Viagra Reaches Maximal Concentration in About One Hour

Metabolically Cleared By CYP3A4

Image: U.S. National Library of Medicine, Mean Sildenafil Plasma Concentrations in Healthy Male Volunteers. See drug info for Viagra.

Look at contraindications list on the FDA SBA -- Important

Phase II: Clinical Data That Viagra Works (Finding Clinical Dose)

Dose-Response Relationship

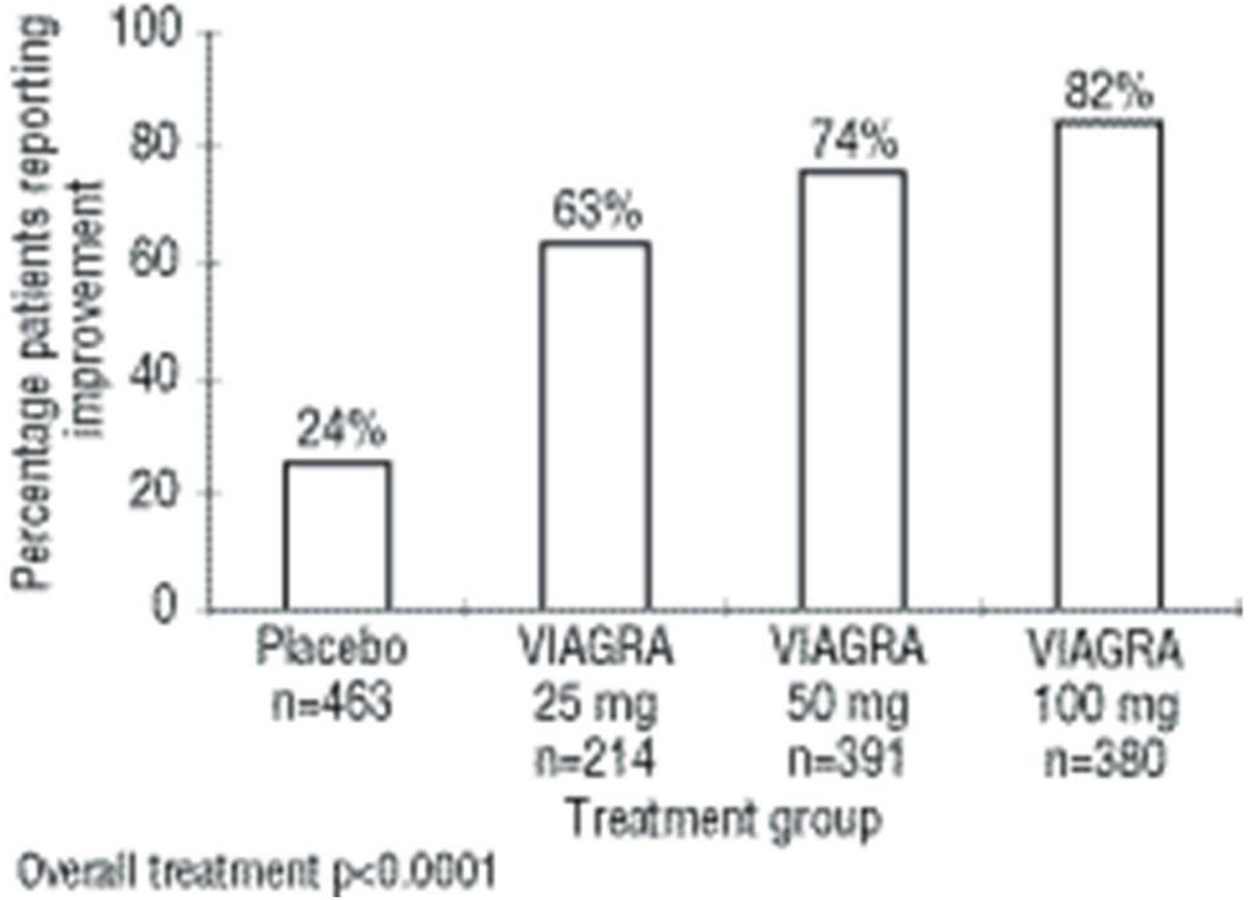
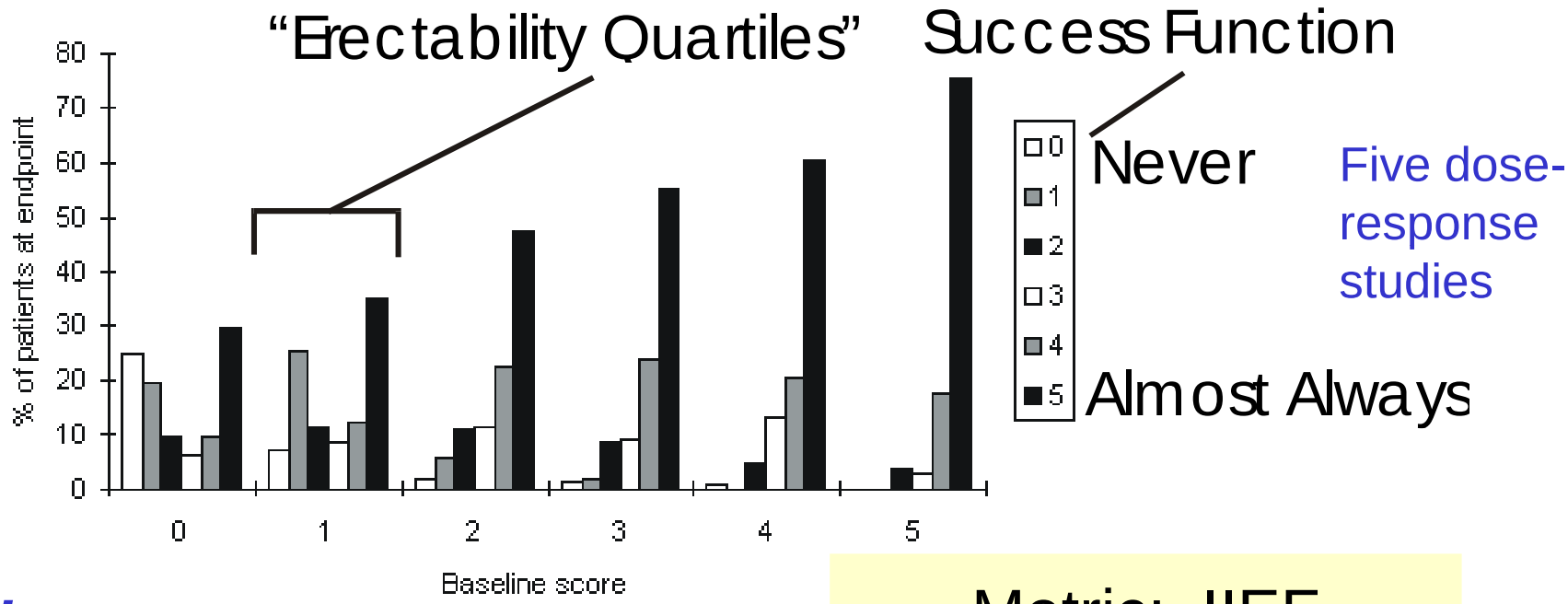


Image: U.S. National Library of Medicine, Mean Sildenafil Plasma Concentrations in Healthy Male Volunteers. See drug info for Viagra.

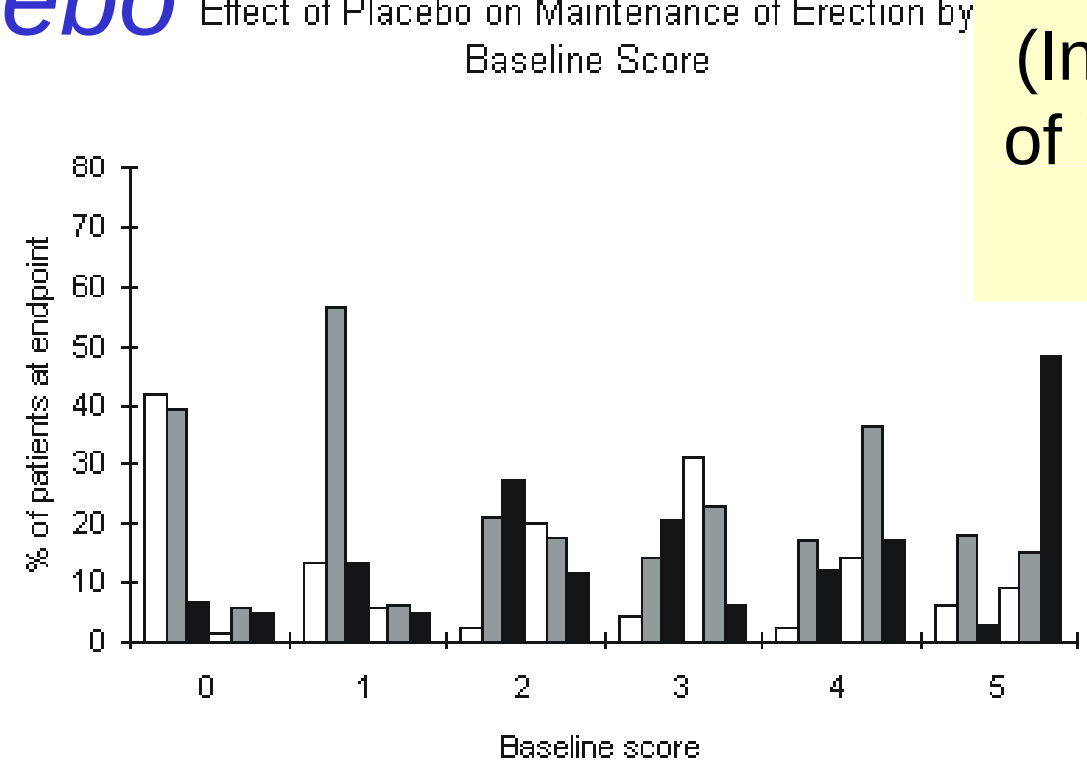
Phase III: Clinical Data on a Large Population

Viagra



Five dose-response studies

Placebo



Metric: IIEF (International Index of Erectile Function)

Image: U.S. National Library of Medicine, Mean Sildenafil Plasma Concentrations in Healthy Male Volunteers. See drug info for Viagra.

http://www.fda.gov/cder/foi/label/1998/viagralabel2.pdf

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

Celebrex

Minoxidil

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.

- 30 Approvals in 1998; 35 in 1999; 65 in 2000; see http://www.centerwatch.com/patient/drugs/drugls02.html and http://www.fda.gov/cder/da/da.htm

- 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)

1964	AZT (zidovidine) developed as potential anticancer agent
Oct., 1984	Pre-clinical trials begin for AIDS
May, 1985	IND submitted
July, 1985	Phase I clinical trial begins
Feb., 1986	Phase II begins
Sept., 1986	Trials terminated early!
Oct., 1986	Treatment IND approved
Dec., 1986	NDA submitted
March, 1987	NDA approved

Most Drugs Take ~10 Years

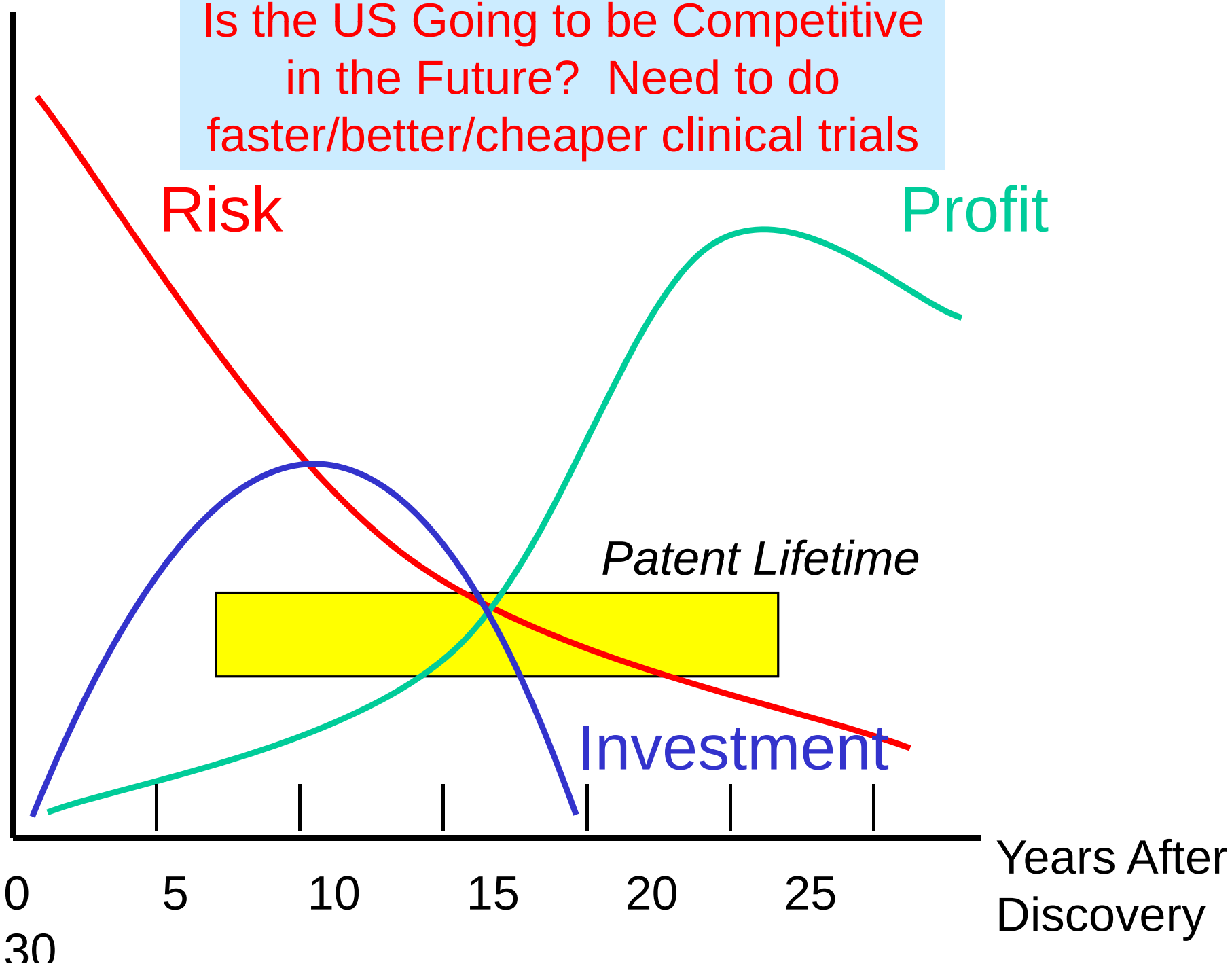
Example: Lovastatin (Cholesterol Lowering Drug)

Late 1978	Lovastatin isolated from *A. terreus*
1979	Pre-clinical trials begin
1980	Drug patented
March, 1984	IND submitted to US FDA
May, 1984	Phase II begins
April, 1985	Phase III trials begin
Nov., 1986	NDA submitted
August, 1987	NDA approved

Lovastatin inhibits HMG-CoA Reductase

The Life Cycle of a Drug

Is the US Going to be Competitive in the Future? Need to do faster/better/cheaper clinical trials



20.380J / 5.22J Biological Engineering Design

Spring 2010