Last week

1

Science, Economy and Law

- Rapid increase in **understanding** of the molecular mechanisms of life since the mid-twentieth century (Science)
- This understanding has created the **biotechnology industry** (Economy)
- These industrial developments could not exist, however, without supporting **legal structures** (Law)

2

Model for drug development

- **Basic science** is largely funded by governments or charitable foundations
- **Application of that science** takes place at research-intensive private firms.

3

Patent law

- Patent **monopolies**
- As developments in the science of biology have progressed, the objects of these patents have changed: from small, biologically active molecular compounds to complex proteins and molecules of DNA, including entire **genes**.
- This shift has led to unprecedented **controversies** over intellectual property in biology and, in particular, over patenting genes.

4

5

OUTLINE

- What is a drug? (Science)
- Regulatory framework (Law)
- The challenge of drug development (Economy)

6

1. What is a Drug ?

7

What is a drug?

- Drugs are **substances** that affect the functions of living things and are administered to treat, prevent, or cure unwanted diseases and symptoms.
- The United States Food and Drug Administration (FDA) **regulates** drug marketing, requiring manufacturers to prove their products to be safe, effective, and appropriately labeled.
- Scientists start with simple, defined, model systems that enable them to identify potential drugs. These potential drugs are then tested in increasingly complex and real-world situations to prove their efficacy.

8

- **Enzymes** /ˈɛnzaɪmz/ are proteins that act as biological catalysts (biocatalysts). Catalysts accelerate chemical reactions.
- https://www.youtube.com/watch?v=yk14dOOvwMk
- https://www.youtube.com/watch?v=PhfhMBO-w9Q

9

PHARMACEUTICAL VS. BIOTECHNOLOGY DRUG

- Traditional pharmaceutical drugs differ from biotechnology-derived drugs in the methods by which they are **discovered and manufactured**.
- Example therapeutic **insulin**: pharmaceutical companies extracted insulin from the pancreas of pigs while Genentech produced recombinant human insulin by synthesizing it in bacteria.

10

PHARMACEUTICAL VS. BIOTECHNOLOGY DRUG

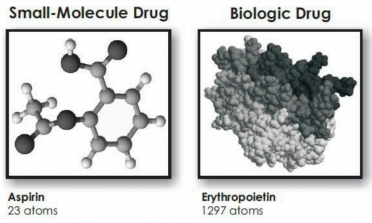
- **Traditional pharmaceutical drug** discovery was based on
  - **trial-and-error** screening of synthetic compounds
  - directed **selection of biological extracts** that can affect model systems.
  - the emphasis of research was to understand **biological systems** in order to find potential drug targets.
- **Molecular biology techniques** used by biotechnology firms
  - **directed design of biological compounds** as drug candidates.

Traditional pharmaceutical development was limited to chemical synthesis and biological extracts

11

PHARMACEUTICAL VS. BIOTECHNOLOGY DRUG

- traditional pharmaceutical drugs tend to be **small molecules** that are orally doseable as tablets, capsules, or liquids.
- biotechnology drugs are **proteins**, such as growth factors, monoclonal antibodies, hormones, and cytokines. Other categories include nucleic acids and vaccines.
- Biotechnology drugs are **larger and more complex** than traditional pharmaceutical drugs.
- Drug **delivery** is an issue for biotechnology-derived drugs



12

PHARMACEUTICAL VS. BIOTECHNOLOGY DRUG

- Biosimilars vs. generic drugs
- https://www.statnews.com/2019/02/05/biosimilars-biologics-explainer-video/

13

Breakthroughs In Biomedicine

- 2001: Gleevec, first of a new class of drugs based on molecular biology (tyrosine kinase inhibitor), $C_{29}H_{31}N_7O$
- 2004: Avastin, angiogenesis inhibitor (VEGF), $C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$
- 2006: Sutent, approved for RCC and GIST simultaneously, $C_{22}H_{27}FN_4O_2$
- 2008: First cancer genome (leukemia) sequenced by Wash U. Genome Institute, Nature 456 (2008):66-72.
- 2012: Dr. Lukas Wartman, Wash U. "cured" of acute lymphoblastic leukemia via RNA analysis and Sutent
- 2012: David Aponte "cured" of same type of leukemia using immunotherapy (T-cells targeting CD19)
- 2017: Luxturna gene therapy approved for treating Leber's congenital amaurosis

15

Biomedicine Is At An Inflection Point

"I went outside when it was snowing, and I was like, 'Oh! I can see the snowflakes!'…It was really cool to actually see something that I've never seen in my life before."

18

2. The regulatory framework

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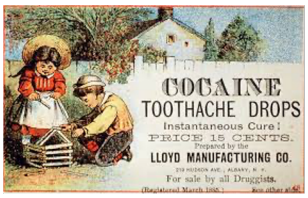

An advertisement from 1885 endorsing cocaine drops to alleviate toothaches for children.

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It was an extremely popular dental nostrum, was intended to quiet a child during the teething process. However, it contained generous levels of alcohol and morphine sulfate which could cause coma, addiction or death in an infant.

21

Where all began…

FDA

has grown from a single chemist in the US Department of Agriculture in 1862 to a staff of 9,100 employees in 2001….

18,062 employees in 2020

30

With a budget of $5,000, Wiley organized in 1902 a volunteer group of healthy young men, called the Poison Squad, who tested the effects of chemicals and adulterated foods on themselves.

32

The Poison Squad

In 1902 Volunteers "poison squad" of young men: their meals came from a government-run kitchen, where they ingested common—and previously untested—food preservatives.

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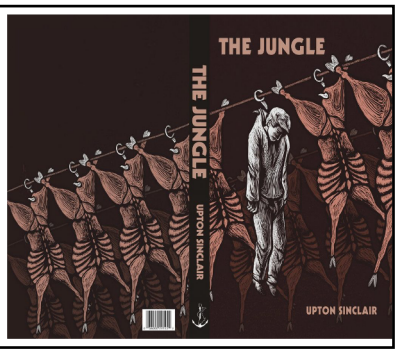
- 1906 novel portraying the harsh conditions of immigrants workers in the Food industry

- the public was horrified by the food processing



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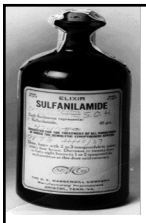

However…

Continuing problems with dangerous drugs that fell outside the parameters of law

Elixir Sulfanilamide (antibiotic drug) disaster in 1937.

Because it contained diethylene glycol as a vehicle, a chemical analogue of *antifreeze*, over 100 people died, many of whom were children.

37

Provisions lacking in the 1906 law were corrected in 1938 when President Franklin D. Roosevelt signed the Federal Food, Drug, and Cosmetic Act.

All new drugs be proved safe before marketing

Therapeutic devices and cosmetics become subject to regulation

Standards of identity and quality be instituted for foods

38

THE THALIDOMIDE TRAGEDY

A Pharmaceutical company applied to FDA for permission to market a drug [very popular sleeping pill in Europe] in the US

Application was assigned to "new" staff member Frances O. Kelsey.

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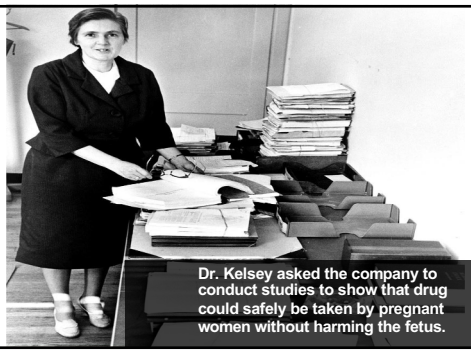

Dr. Kelsey asked the company to conduct studies to show that drug could safely be taken by pregnant women without harming the fetus.

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Frances Kelsy received the Distinguished Federal Civilian Service Award from President John F. Kennedy August 1962.

17 American babies were born with the deformity because [at the time] the company was permitted to provide free samples to physicians as soon as the company applied for FDA licensing permission.

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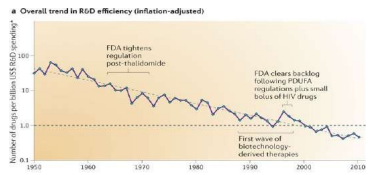

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The Drug Development Process

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3 stages

Producing and selling drugs consists of three basic stages:
- Discovery
- Development
- Commercialization.

Less than **1 percent** of early candidate compounds make it through the drug development process.

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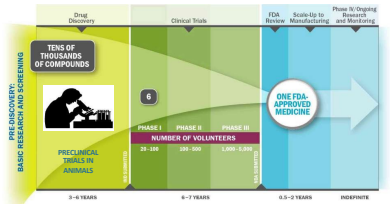
The Challenge of Drug Development

15.480



46

So the question is, why?

STEP 1: IDENTIFY A USEFUL DISEASE TARGET

- Scientists start with an understanding of the molecular processes affecting conditions they wish to treat
- Test hypotheses about which drugs are likely to be effective for a condition.
- Early-stage model systems may be as simple as a set of molecules in a test tube (subject to knowledge of disease processes) and later-stage model systems may be live animals with diseases similar to human conditions (subject to availability of relevant animal disease models).

47

STEP 2: FIND AND REFINE A LEAD COMPOUND

- Potential lead compounds typically originate from one of two sources: purified naturally occurring compounds, or de novo design and synthesis of new compounds.
- Traditional pharmaceutical method for drug discovery involves screening libraries of natural or synthetic compounds to find those that achieve the desired effect.
- Molecular biology techniques used in biotechnology drug development permit the design of novel biological compounds.

48

STEP 3: TEST LEAD IN PRE-CLINICAL DEVELOPMENT

- In pre-clinical development, lead compounds that emerge from the lead optimization process are subjected to a range of standardized animal, cellular, and biochemical tests
- Many products that work well in laboratory tests fail in clinical settings for unforeseen reasons (ex. drugs may not be taken up properly by cells; they may be metabolized into inactive or toxic forms by the liver; they may interact with other parts of the body to produce undesired effects; or they may simply not be sufficiently active)

49

STEP 4: CLINICAL TRIALS IN HUMANS

- Clinical trial data is submitted to the FDA as part of a New Drug Application (NDA) or Biologics License Application (BLA).
  - Phase 1
  - Phase 2
  - Phase 3

50

STEP 5: OBTAIN APPROVAL; MARKET AND SELL DRUG

- The FDA requires that drugs be approved prior to marketing. While **safety** is the primary concern, a drug with detrimental side effects may be acceptable if there are no better treatments and the severity of the disease warrants it.
- Development time for small-molecule drugs is **10-15 years** with an estimated average cost of **$802 million** per approved drug (one-third of the expenditures are attributed to pre-clinical activities and the remaining two-thirds to clinical activities).
- Five in **five thousand** small-molecule compounds that enter pre-clinical testing make it to human testing. Of these five, only **one** is approved.

51

The Challenge of Drug Development

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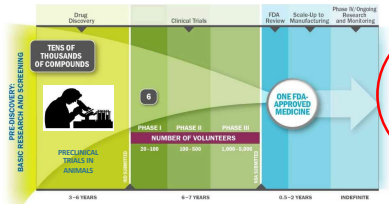


3 Features:

1. Costly
2. Low PoS
3. Long duration

= decreasing productivity of RD

52

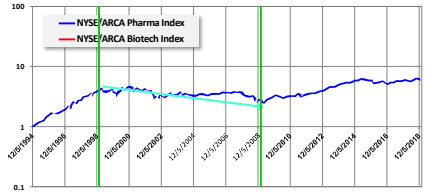
3. The challenge of drug development

53

Biotech breakthrough on the Stock Market

Pharma vs. Biotech

December 5, 1994 to February 1, 2019



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Pharma industry

- The pharma industry is composed of **publicly traded companies and** shared value went down during the decade between the late 1990s and early 2000s.
- **Wall Street told the pharma industry you should get out of the research business and focus instead on the M&A business:** acquire companies or deals, do joint ventures, licensing deals, and bring it in-house as opposed to trying to do it yourself.

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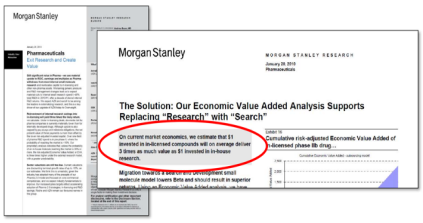

Morgan Stanley

Morgan Stanley

MORGAN STANLEY RESEARCH

The Solution: Our Economic Value Added Analysis Supports Replacing "Research" with "Search"

On current market economics, we estimate that $1 invested in in-licensed compounds will on average deliver 3 times as much value as $1 invested in in-house research.

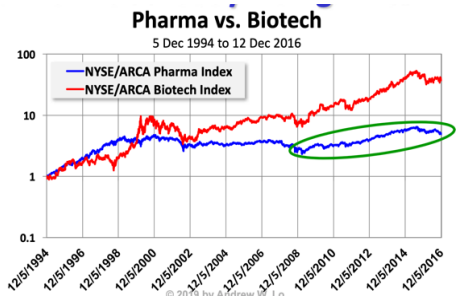
$1 invested in in-license compounds-- licensed from other companies in to your company-- will, on average, deliver three times as much value as $1 invested in in-house research.

57

Pharma industry listened to Wall Street

- From 2008 to 2013 the pharma industry **fired about 150,000 people, most of whom were in R&D.**
- Cutting costs, reducing risk, increasing their Sharpe ratio is working.
- **Share value went up during the last decade but this has also created the valley of death** because we now have less money in the early stages of R&D.

58



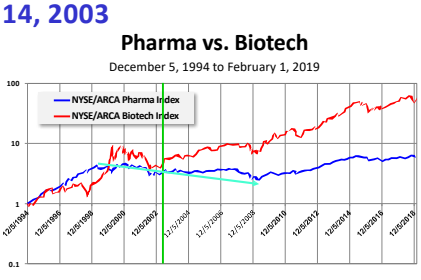
59

Amgen

- *Ex. pharma company, Amgen in 2016 third quarter had about $38 billion of cash sitting on its balance sheets.*
- *Amgen financed the vast majority of that by issuing bonds. So $30 billion of that $38 billion of cash is long-term debt.*
- *Amgen is not investing it in early stage projects but keeps cash on hand to go shopping for other companies. They are looking for is high Sharpe ratio investments, meaning good return, low risk.*
- *If you look at Amgen's growth over time, you can see all of the different acquisitions that they've made.*

60

April 14, 2003



61

Combination Therapies

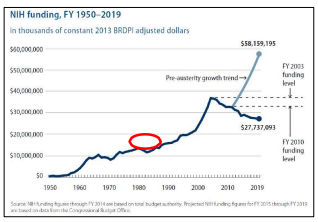
- 2,800 approved drugs
- 3,918,500 pairs
- 3,654,747,600 triplets
- 1,429,081,599,400,560 quintuplets
- Other parameters:
  - Dosage regimens
  - Biomarkers
  - Resistance
  - Side-effects, litigation
  - Pricing, FDA, etc.

62

Is private sector investing in biotechnology?

63

Funding Declining



64

Funding Declining

Table 2 Number of active VC firms

Region	2008	2009	2010	2011	2012	2013	2014
Canada	10	6	10	16	9	7	5
China	2	4	5	4	3	4	11
Europe	105	106	111	74	76	76	81
India	1	3	1	5	8	5	
Israel	12	6	5	5	7	3	5
United States	201	163	143	128	141	147	138
Global total[a]	309	256	252	204	202	211	208

[a]The global total is not a sum of all regions, as an investor that invested in many regions counts only once in the global total. Source: Dow Jones VentureSource

Source: Huggett, NBT May 2015

65

So Why Is Funding Declining?

67

So the question is, why?

- At the very early stages of drug discovery-- funding for preclinical phase 1 or phase 2, has been going down.
- It's gotten so bad that people now call this the **"valley of death" because it's very hard to raise money from that preclinical period**

68

Increasing risk and uncertainty

69

What Do Investors Want?

High Returns and Low Risk → High Sharpe

Example: which would you prefer as an investor?

- "me-too" oncology drug in Phase 3
- Gene therapy to **cure** Alzhaimer's

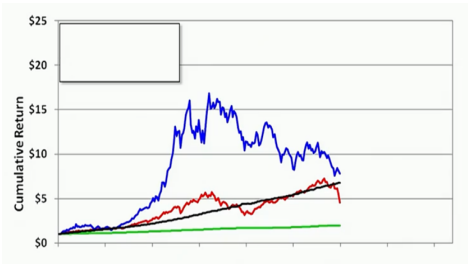
71

Pop Quiz

72

How you want to invest your own money?

73



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Let me tell you what you picked

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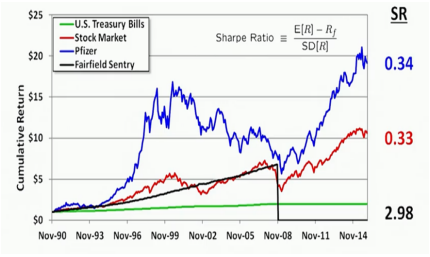

76

Hollywood film industry

77

Five big movie studios

- There are still today five big movie studios as they were 30 years ago. But the five big movie studios have a very **different business model** today than 30 years ago.
- The movie industry is about **two different kinds of businesses**:
- one business is making movies and making movies is really hard. Nobody knows how to predict a winner or loser.
- the second business is in licensing and distributing films. That is a great business, high margin, high return, low volatility business. (example, striking a deal between Sony Pictures and Netflix in order to make a few movies and then have Netflix distribute them).

78

Distribution business

- distribution business is a very **profitable** business
- The probability of a blockbuster movie in Hollywood is about 5%...bout the probability of producing a cancer drug.

79

DreamWorks SKG

- *DreamWorks SKG started up in 1994 by three film veterans, Steven Spielberg, Jeff Katzenberg, and David Geffen. And they decided to partner together with Paul Allen, one of the co-founders of Microsoft, to create a new film studio, and they produced lots of movies from 1994 on.*
- *In 2002, they raised $1 and 1/2 billion of money, and they raised it not in the form of equity, but in the form of debt (bonds) and pledged as collateral a slate of movies, the next, say 25 movies. They borrowed money from investors to make those films….*
- *What happens if they do not pay back?*

80

They borrowed money from investors to make those films with the obligation that if they don't pay back the promised interest, investors get to take the pot.

This is called slate financing

81

Gun Hill Road

- *In 2005, Gun Hill Road, a company that was formed as a joint venture between Sony and Universal, they raised $600 million for a slate of 17 pictures from hedge funds. Hedge funds invested in that.*

82

Slate financing is growing

- Billion dollar transactions happen routinely in financing Hollywood movies…despite the fact that nobody knows anything, despite the fact that it's a **5% probability of success**.
- The point is that if you have the right portfolio, you can finance it.

83

Can we do the same for biotech?

84