20.109 Module 2
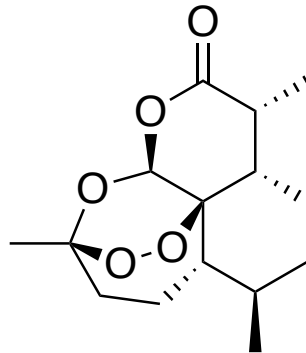
Lecture #1: **Introduction to Drug Discovery**

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What is a drug?

- A substance recognized by an official pharmacopoeia or formulary.

- A substance intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease.

- A substance (other than food) intended to affect the structure or any function of the body.

- A substance intended for use as a component of a medicine but not a device or a component, part or accessory of a device.

- Biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)

How were drugs previously discovered?

• Extracts from natural products (usually plants)

Poppy
ca. 1500 BC
"pain relief; sedation"

Opiates

Willow tree extract
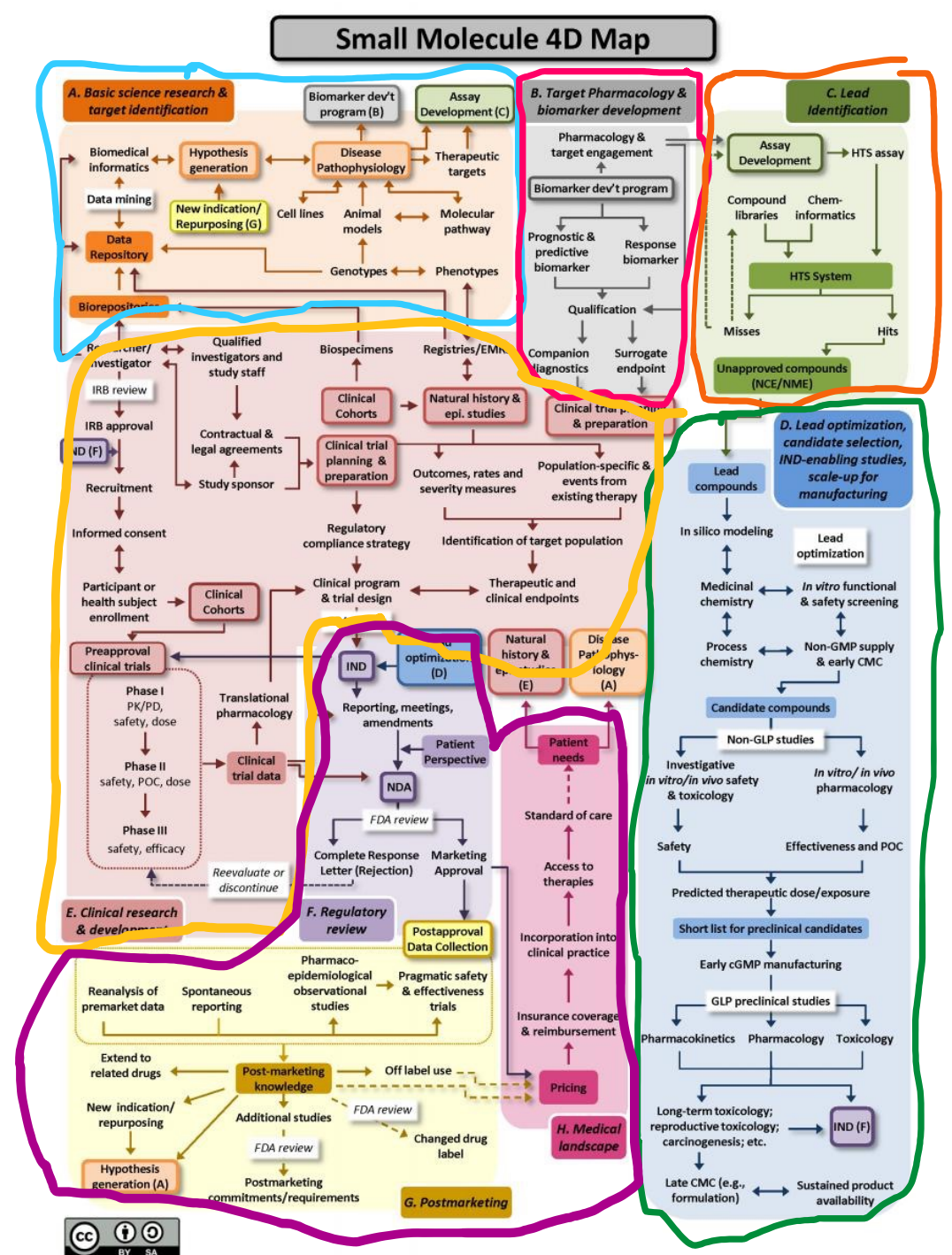ca. 3000-1500 BC
"pain reliever"

Aspirin

Artemisia annua L.
ca. 168 BC
"fever"

Artemisinin

How are drugs discovered now?

A. Basic science research and target identification

B. Target pharmacology and biomarker development

C. Lead identification

D. Lead optimization and candidate selection
   - Improving pharmacologic, metabolic, safety profiles of lead toward use in humans

E. Clinical research & development
   - Clinical trials to establish efficacy and safety

F. Regulatory review (FDA approval)

G. Post-marketing
   - Surveillance (adverse effects)
   - Repurposing
   - Off-label use

H. Medical landscape

References:
1) Wagner et al; Nature Reviews Drug Discovery; 2018;
2) https://ncats.nih.gov/translation/maps
3) 4D Map (interactive): https://4dmap.ncats.nih.gov/#/

Small Molecule 4D Map
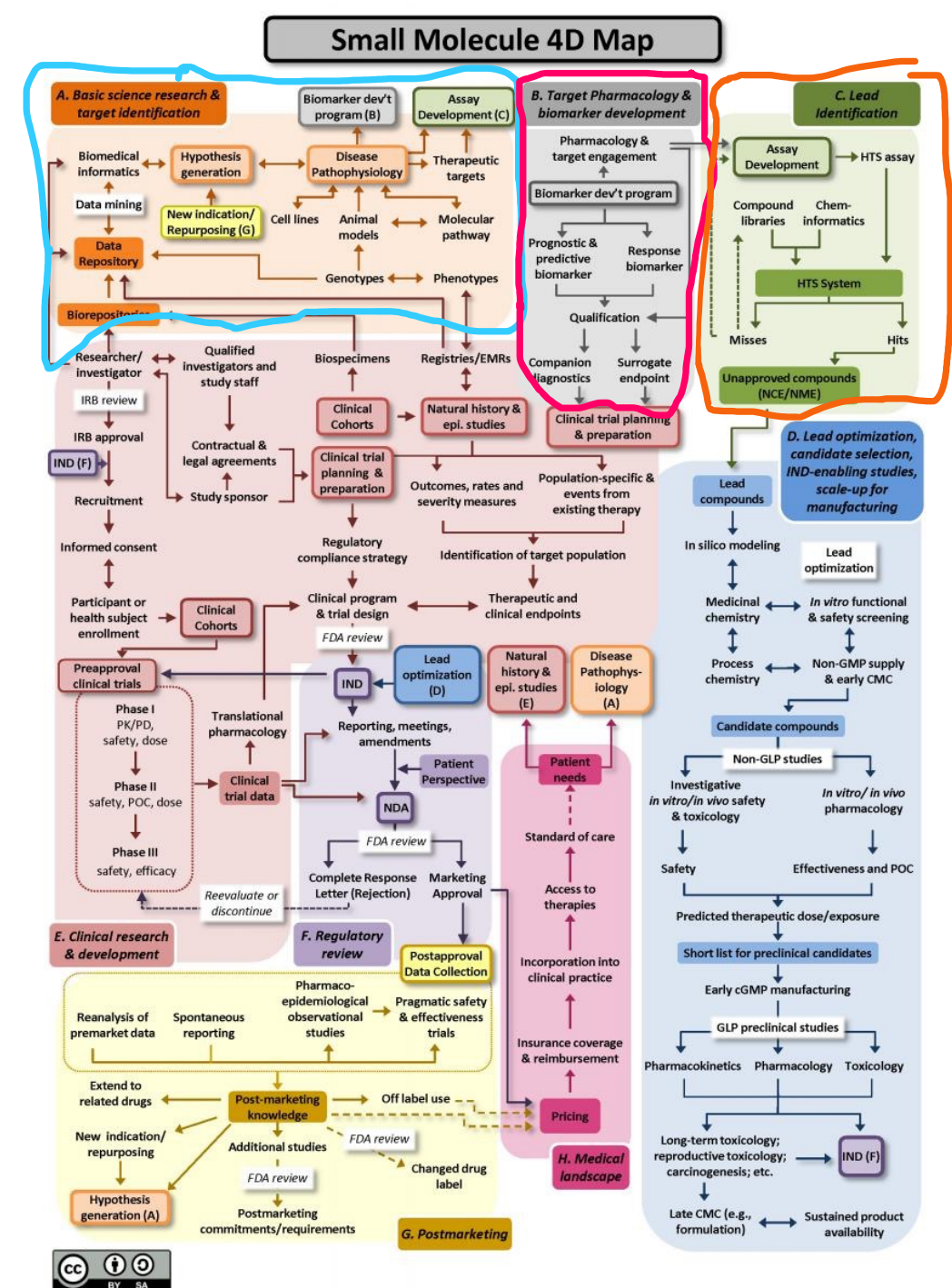
Modern framework for drug discovery and development

A. **Basic science research and target identification**

B. **Target pharmacology and biomarker development**

C. **Lead identification**

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Small Molecule 4D Map

Contrasting old with modern framework for drug discovery and development

- Intentional and broad search for therapeutic agents
- Engages fundamental understanding of disease biology and mechanism
- Highly multidisciplinary
  - biologists, chemists, engineers, bioinformatics, clinicians, business, legal, …
- High burden-of-proof to establish safety and efficacy

- Business model:
  - Incentivized process (profits) for innovating therapeutic solutions to diverse diseases impacting health
  - Potential skewing of disease areas preferentially prioritized for investment in drug discovery activities

Progression in the overall process of drug discovery and development
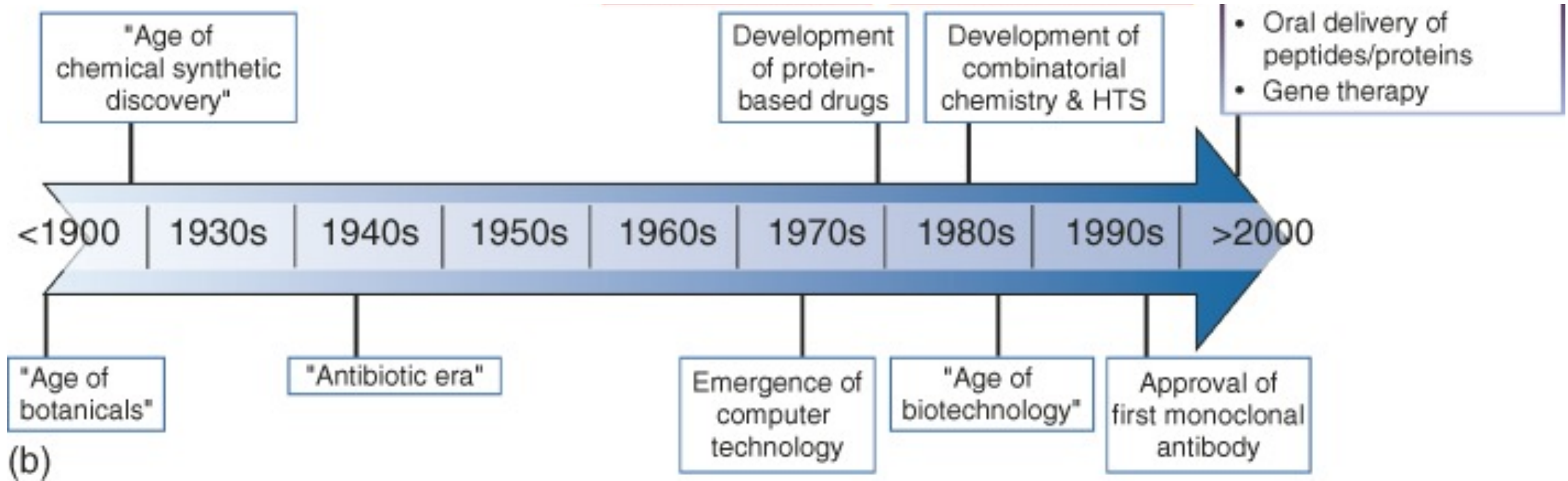
Adapted from: Rebecca Bader & David Putnam; Engineering Polymer Systems for Improved Drug Delivery; 2014

Timeline for new drug discovery process

De novo drug discovery and development
- ? **year process**

Target discovery	Discovery & screening	Lead optimization	ADMET	Development	Registration
• Expression analysis • *In vitro* function • *In vivo* validation; for example, knockouts • Bioinformatics	Discovery • Traditional • Combinatorial chemistry • Structure-based drug design Screening • *In vitro* • *Ex vivo* and *in vivo* • High throughput	• Traditional medicinal chemistry • Rational drug design	• Bioavailability and systemic exposure (absorption, clearance and distribution)	• Must start clinical testing at Phase I (Phase I/II for cancer)	• United States (FDA) • Europe (EMEA or country-by-country) • Japan (MHLW) • Rest of world

Market

A	B	C	D	E	F	G
? years	? years	? years	? years	? years	? years	?

Preclinical phase **Clinical phase**

Ashburn, T.T. & Thor, K.B. (2004). Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. *Nature Reviews Drug Discovery.* **3,** 673-683.

Timeline for new drug discovery process

De novo drug discovery and development
- ***10-17 year process!***

A 2-3 years	**B** 0.5-1 years	**C** 1-3 years	**D** 1-2 years	**E** 5-6 years	**F** 1-2 years	**G** Lifetime

Preclinical phase   **Clinical phase**

Ashburn, T.T. & Thor, K.B. (2004). Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. *Nature Reviews Drug Discovery.* **3,** 673-683.

Probability of successfully developing a new drug that comes to market

De novo drug discovery and development
- ***10-17 year process!***

A	B	C	D	E	F	G
2-3 years	0.5-1 years	1-3 years	1-2 years	5-6 years	1-2 years	Lifetime

Preclinical phase attrition   *Clinical phase attrition*

Ashburn, T.T. & Thor, K.B. (2004). Drug Repositioning: Identifying and Developing New Uses for Existing Drugs. *Nature Reviews Drug Discovery.* **3,** 673-683.

Preclinical phase attrition/ streamlining

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Small Molecule 4D Map

Clinical phase:
Brief overview of clinical research and development

| PRE-CLINICAL | CLINICAL TRIALS | REVIEW/APPROVAL PROCESS |

PRE-CLINICAL

Testing on animals for toxicity.

INVESTIGATIONAL NEW DRUG APPLICATION

Describes the manufacturer's plans for testing the drug in clinical trials.

If approved by FDA, the manufacturer becomes the sponsor of an "existing IND."

CLINICAL TRIALS

Phase I

Clinical trials test for safety and dosing ranges.
No. of patients: 20 to 80
Approximately 63.2% moved to phase II

Phase II

Clinical trials test for efficacy in the patients that the drug is intended to treat.
No. of patients: a few dozen to hundreds
Approximately 30.7% moved to phase III

Phase III

Clinical trials test for efficacy in the patients that the drug is intended to treat.
No. of patients: hundreds to thousands
Approximately 58.1% moved to the new drug application process

REVIEW/APPROVAL PROCESS

New drug application review

Once the drug has successfully completed the phase III trials, the manufacturer generally submits a new drug application to FDA.
Approximately 85.3% are approved

FDA approval results

FDA either approves or denies approval for the drug or biologic for marketing and sales in the U.S.

Attrition along the drug discovery pipeline

| Therapeutic group	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
	Total paths	$POS_{1,2}$, % (SE, %)	Total paths	$POS_{2,3}$, % (SE, %)	$POS_{2,APP}$, % (SE, %)	Total paths	$POS_{3,APP}$, % (SE, %)	POS, % (SE, %)
Oncology	17 368	57.6 (0.4)	6533	32.7 (0.6)	6.7 (0.3)	1236	35.5 (1.4)	3.4 (0.2)
Metabolic/ Endocrinology	3589	76.2 (0.7)	2357	59.7 (1.0)	24.1 (0.9)	1101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2810	73.3 (0.8)	1858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4924	73.2 (0.6)	3037	51.9 (0.9)	19.5 (0.7)	1156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ Inflammation	5086	69.8 (0.6)	2910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3963	70.1 (0.7)	2314	58.3 (1.0)	35.1 (1.0)	1078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (Infectious Disease)	1869	76.8 (1.0)	1235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41 040	66.4 (0.2)	21 180	48.6 (0.3)	21.0 (0.3)	7532	59.0 (0.6)	13.8 (0.2)
All without oncology	23 672	73.0 (0.3)	14 647	55.7 (0.4)	27.3 (0.4)	6296	63.6 (0.6)	20.9 (0.3)

- 185,994 unique trials of over 21,143 compounds from Jan 2000 through Oct 2015
  - 13.8% of drug programs make it from Phase I to approval
    - 20.9% if cancer excluded
  - (Higher than the often-touted estimates of 5% or 10%)

- Probability of success varies by disease area
  - **Why might this be**?

Reference Wong et al; Biostatistics, Volume 20, Issue 2, April 2019, 273–286
https://academic.oup.com/biostatistics/article/20/2/273/48175243

Attrition along the drug discovery pipeline

a Success rates by phase
Percentage likelihood of moving to next phase, 3-year rolling average*

Phase III
Phase I
Phase II
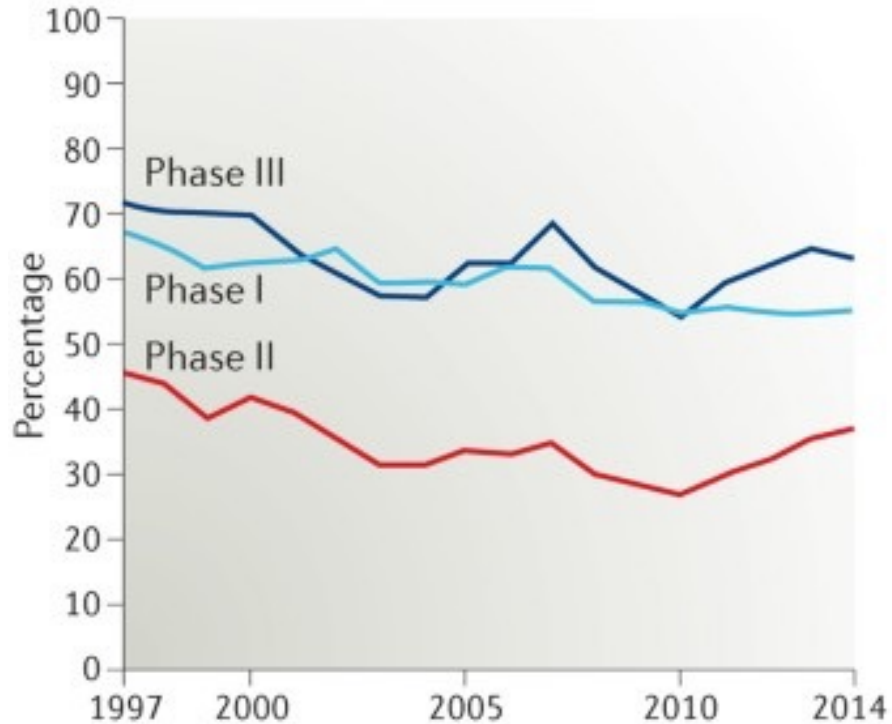
b Cumulative success rate Phase I to launch
Percentage likelihood of moving from Phase I to launch

16.4
10.8
10.0
7.5
11.6

1996–1999
2000–2003
2004–2007
2008–2011
2012–2014

Nature Reviews | Drug Discovery
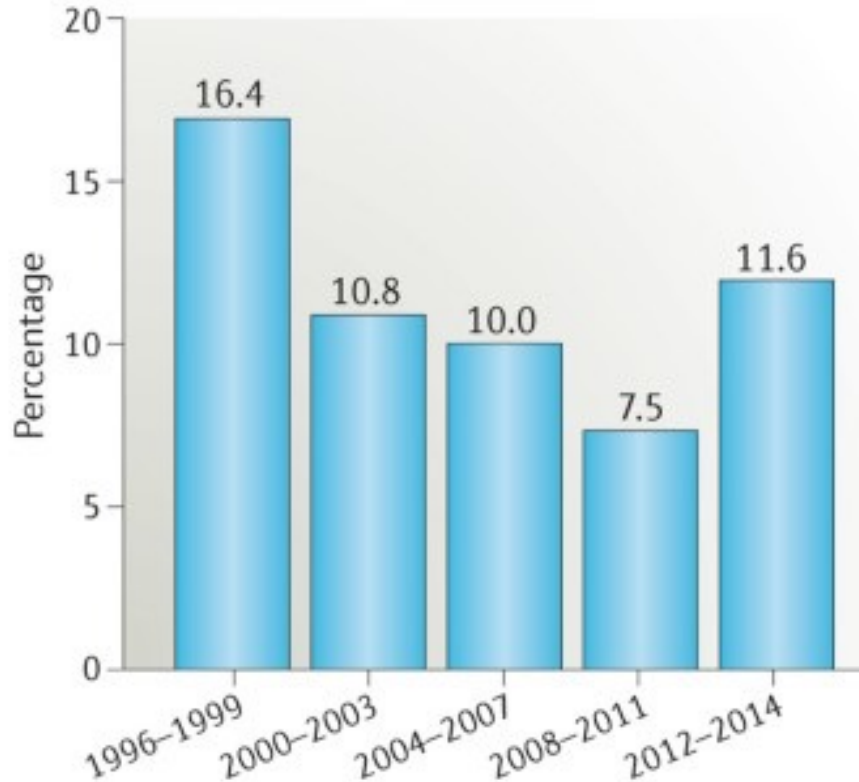
- Phase II success rates lowest
  - Why might this be so?

- Overall success rates steadily declining 1996-2011, but improved since 2012

Regulation of drug approval in the U.S.

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Small Molecule 4D Map
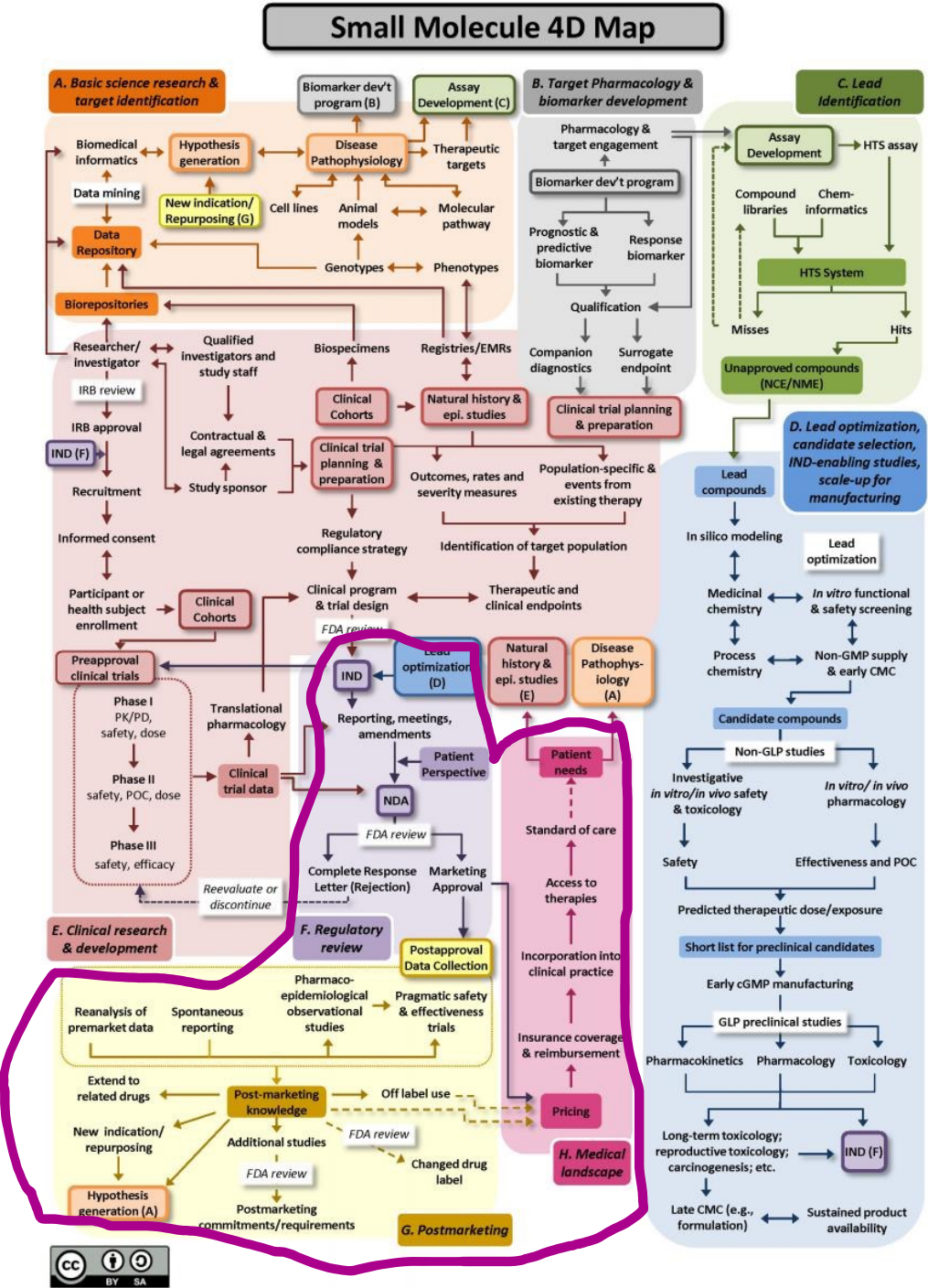
Regulation of drug approval in the U.S.

- What needs to be regulated?

- How is this regulation achieved?
  - FDA
  - United States Pharmacopeia-National Formulary (USP-NF)

- What are some implications of this regulation for the drug discovery and marketing process?
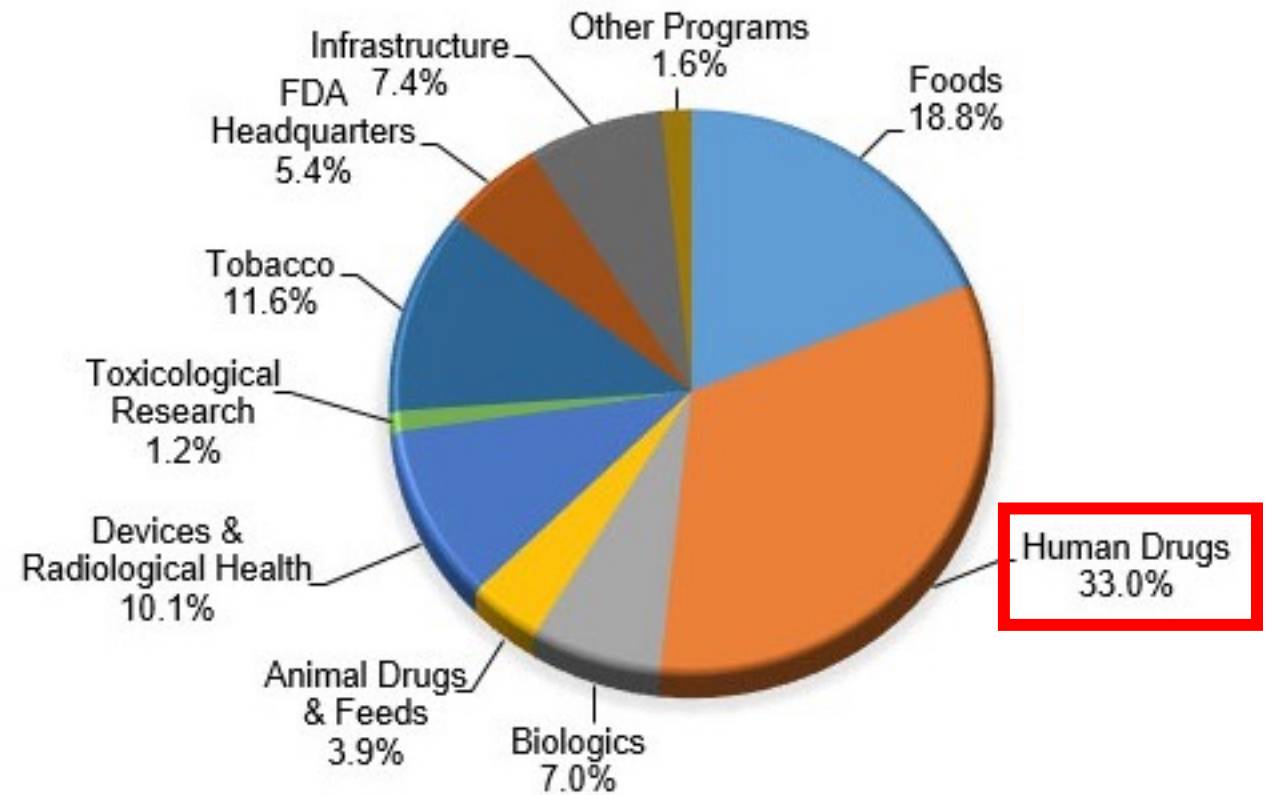

Small Molecule 4D Map
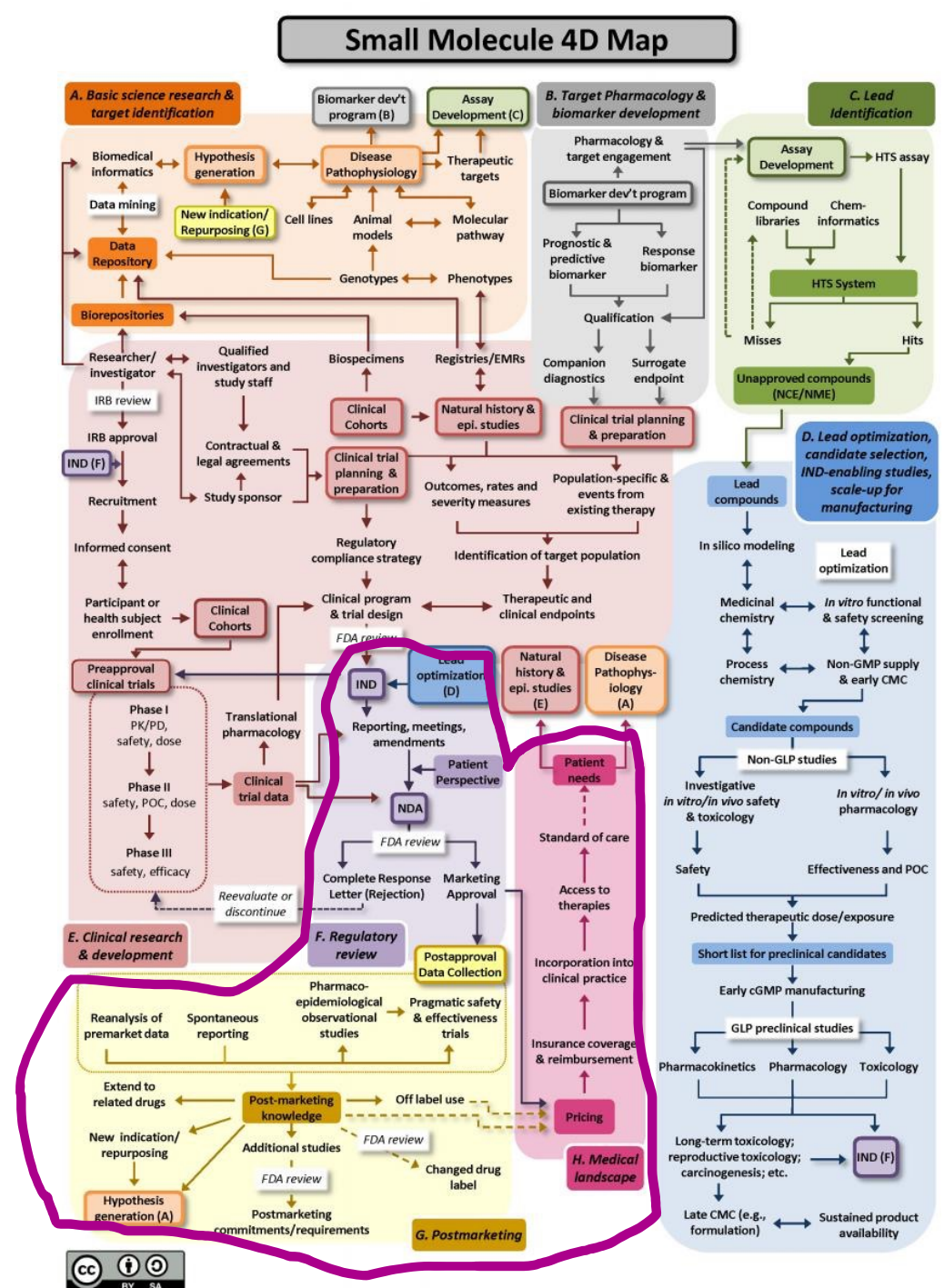
Food and Drug Association (FDA)

- FDA is an agency within the U.S. Department of Health and Human Services

- Protects public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices.

- Over **20,000 FDA-regulated** prescription drug products approved for marketing
  - 1,600 FDA-approved animal drug products
  - 400 FDA-licensed biologics products

- FDA budget sources
  - ~ 55 percent ($3.1 billion) from federal government
  - ~45 percent ($2.6 billion) from industry fees.

FY 2019 FDA Budget by Program (Total = $5.7 billion)

Infrastructure 7.4%
Other Programs 1.6%
FDA Headquarters 5.4%
Foods 18.8%
Tobacco 11.6%
Toxicological Research 1.2%
Devices & Radiological Health 10.1%
Animal Drugs & Feeds 3.9%
Biologics 7.0%
Human Drugs 33.0%

Notes: Infrastructure includes rent, rent related activities, FDA buildings and facilities, and White Oak consolidation. Other programs includes Export Certification and Color Certification Fund.
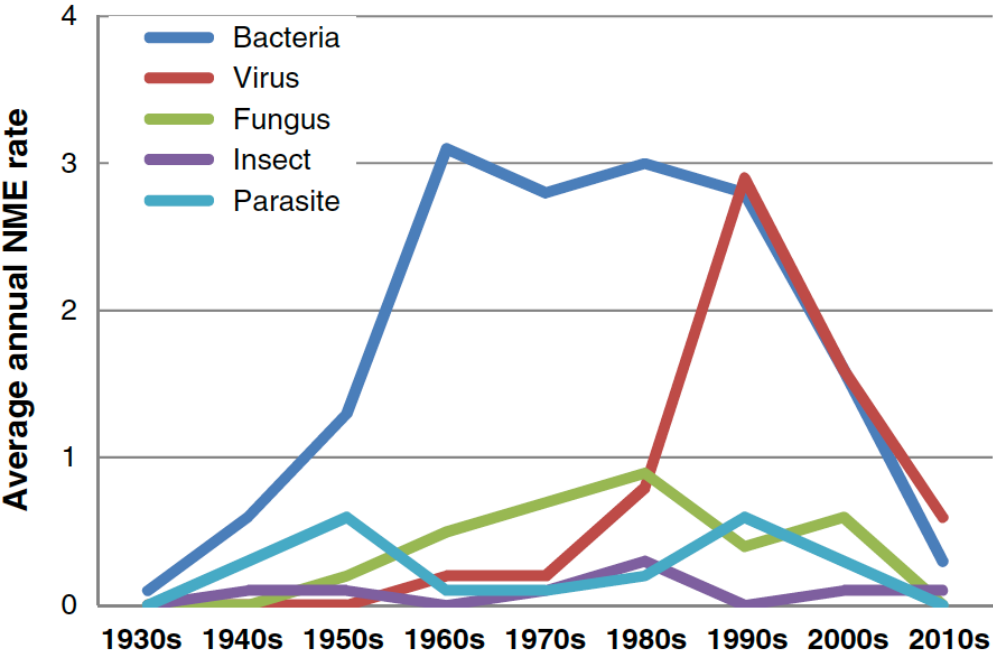
Reference:
1) FDA at a Glancet: https://www.fda.gov/media/131874/download

FDA approved drugs and distribution across disease indication areas
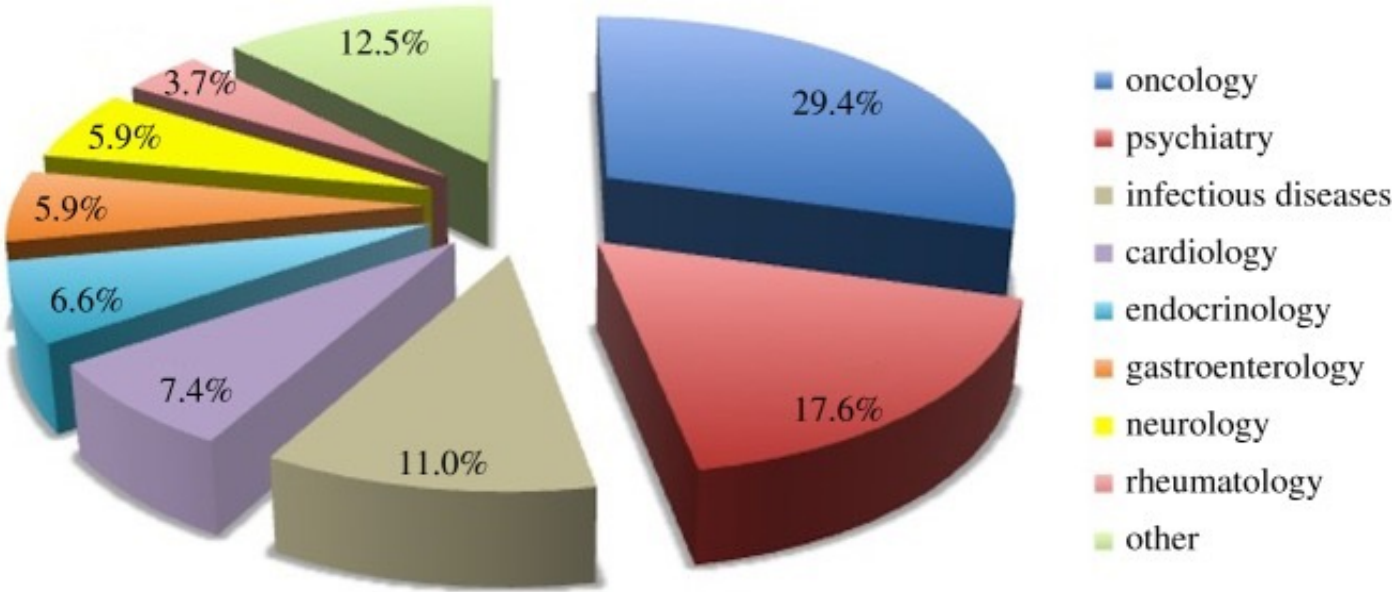
Breakdown of new infectious disease drugs
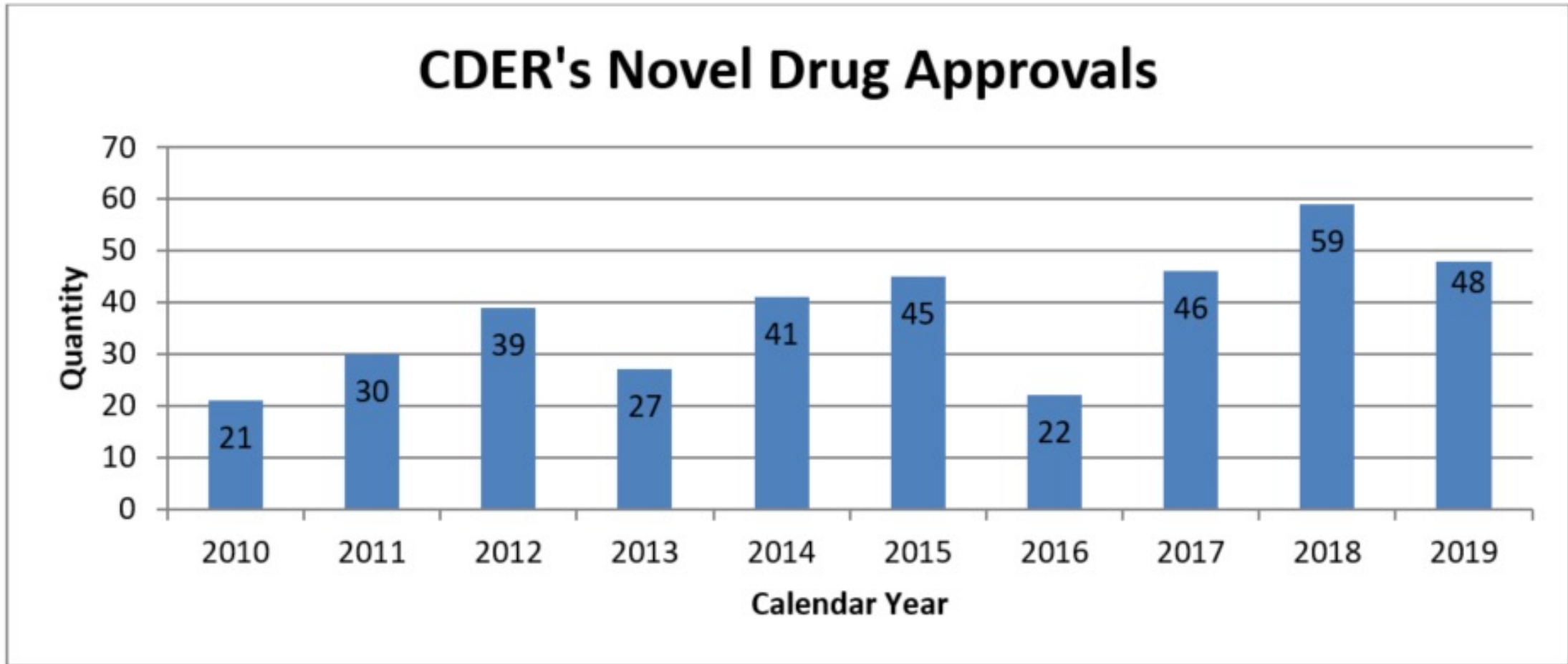

Antibacterial: 55%

Antiviral: 22%

Antifungal: 12%

Antiparasitic: 8%

Insecticidal: 3%

References:
1) FDA at a Glancet: https://www.fda.gov/media/131874/download
2) Kinch et al; Drug Discovery Today; 2012

Annual new FDA drug approvals

CDER's Novel Drug Approvals

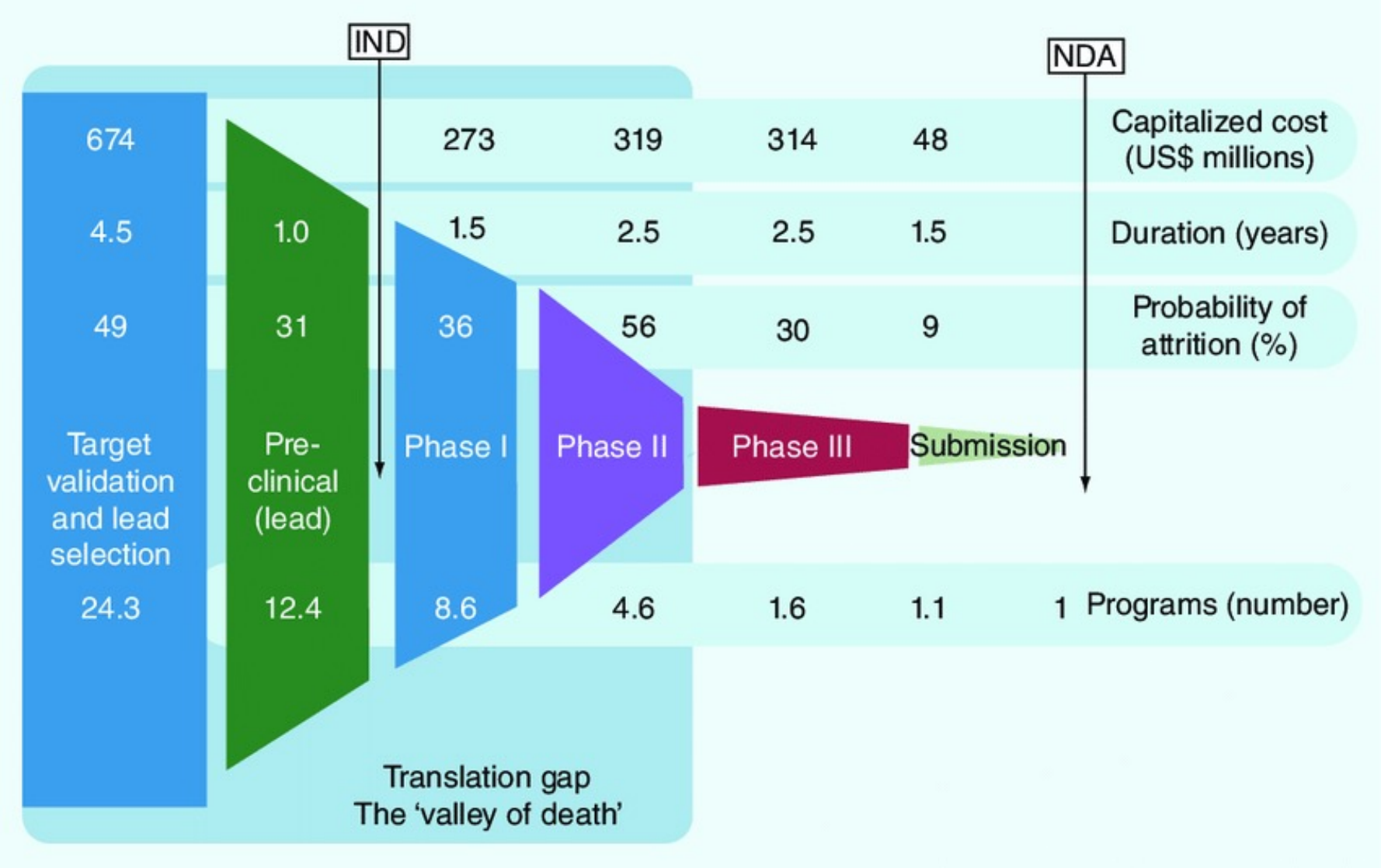| Year	Quantity
2010	21
2011	30
2012	39
2013	27
2014	41
2015	45
2016	22
2017	46
2018	59
2019	48

- In 2019, 20/48 FDA approved drugs were "first in class"
  - Possess distinct mechanisms of actions from previously approved drugs

United States Pharmacopeia – National Formulary (USP-NF)

References:
https://qualitymatters.usp.org/pharma-co-what

New drug discovery is expensive … with no guarantee of success!

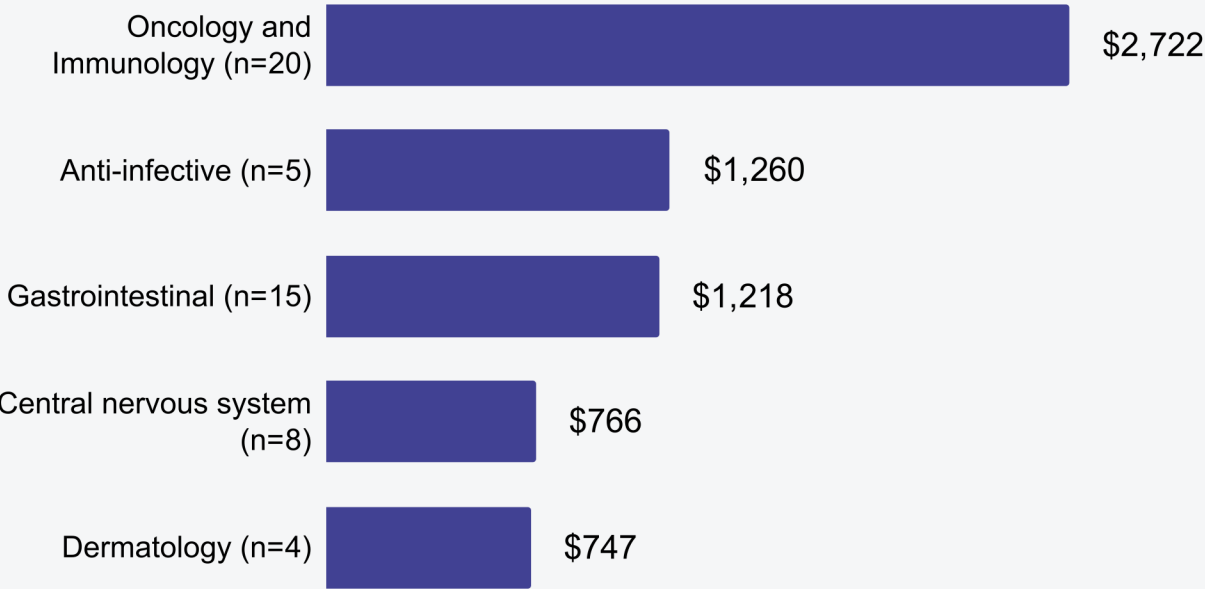|						
674	273	319	314	48		Capitalized cost (US$ millions)
4.5	1.0	1.5	2.5	2.5	1.5	Duration (years)
49	31	36	56	30	9	Probability of attrition (%)
Target validation and lead selection	Pre-clinical (lead)	Phase I	Phase II	Phase III	Submission	
24.3	12.4	8.6	4.6	1.6	1.1	1 Programs (number)

IND

NDA

Translation gap
The 'valley of death'

Between 2009 –2018, the median cost of developing a new drug was $985 million, while the average total was $1.3 billion!

New drug discovery is expensive ... with no guarantee of success!

R&D costs highest for cancer, immunology medicines

Estimated median expense on new drugs approved by U.S. FDA between 2009-2018, in millions of dollars

Oncology and Immunology (n=20): $2,722
Anti-infective (n=5): $1,260
Gastrointestinal (n=15): $1,218
Central nervous system (n=8): $766
Dermatology (n=4): $747

Cost of developing a new drug (2009 –2018 data):

Median: $985 million
Average: $1.3 billion

Reference:
Wouters et al; JAMA. 2020;323(9):844-853. doi:10.1001/jama.2020.1166

Summary

- Drug discovery and development is a highly complex, multidisciplinary process

- The goal is to develop safe and effective medicines across a broad portfolio of health needs

- Stringent regulation and monitoring during and after new drug approval by federal and independent organizations are vital to ensuring safety, product authenticity and efficacy

- Both the preclinical and clinical phases of drug development are very costly AND success is not guaranteed (failure is the norm?)!

Small Molecule 4D Map