20.109 Module 2

Lecture #1: **Introduction to Drug Discovery**

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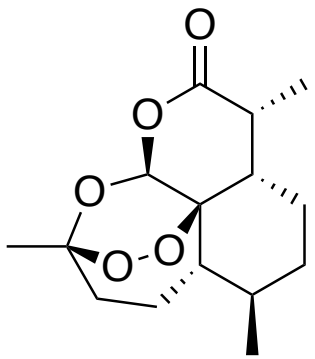
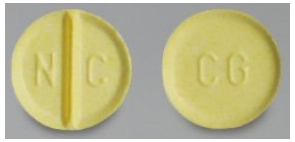
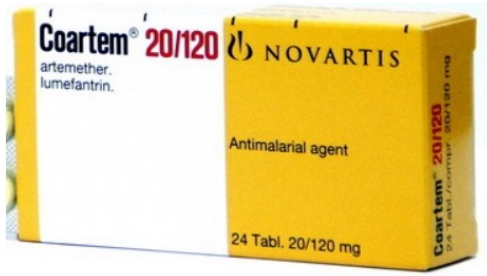






Introduction to Module 2/ Learning Objectives/ Organization

- Why include a module on drug discovery in 20.109?
  - *Well-aligned with the BE philosophy of knowledge to translational impact*
- Emphasize gaining *conceptual* familiarity with the drug discovery process
- Learn valuable and transferrable *biological reasoning* and *laboratory/ analytical* skills
  - *When do you know enough to translate knowledge into impact?*
  - *Small molecule drugs/ biologics/ gene delivery/ cellular therapies*
  - *Ensuring efficacy without sacrificing safety*
- Lectures will emphasize high-level concepts of the drug discovery process
- In-lab instruction will build your technical and analytical competencies involved in implementation

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 *versus* biological).

FDA Website:
https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#:~:text=or%20an%20injectable.-,Drug,any%20function%20of%20the%20body.

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”

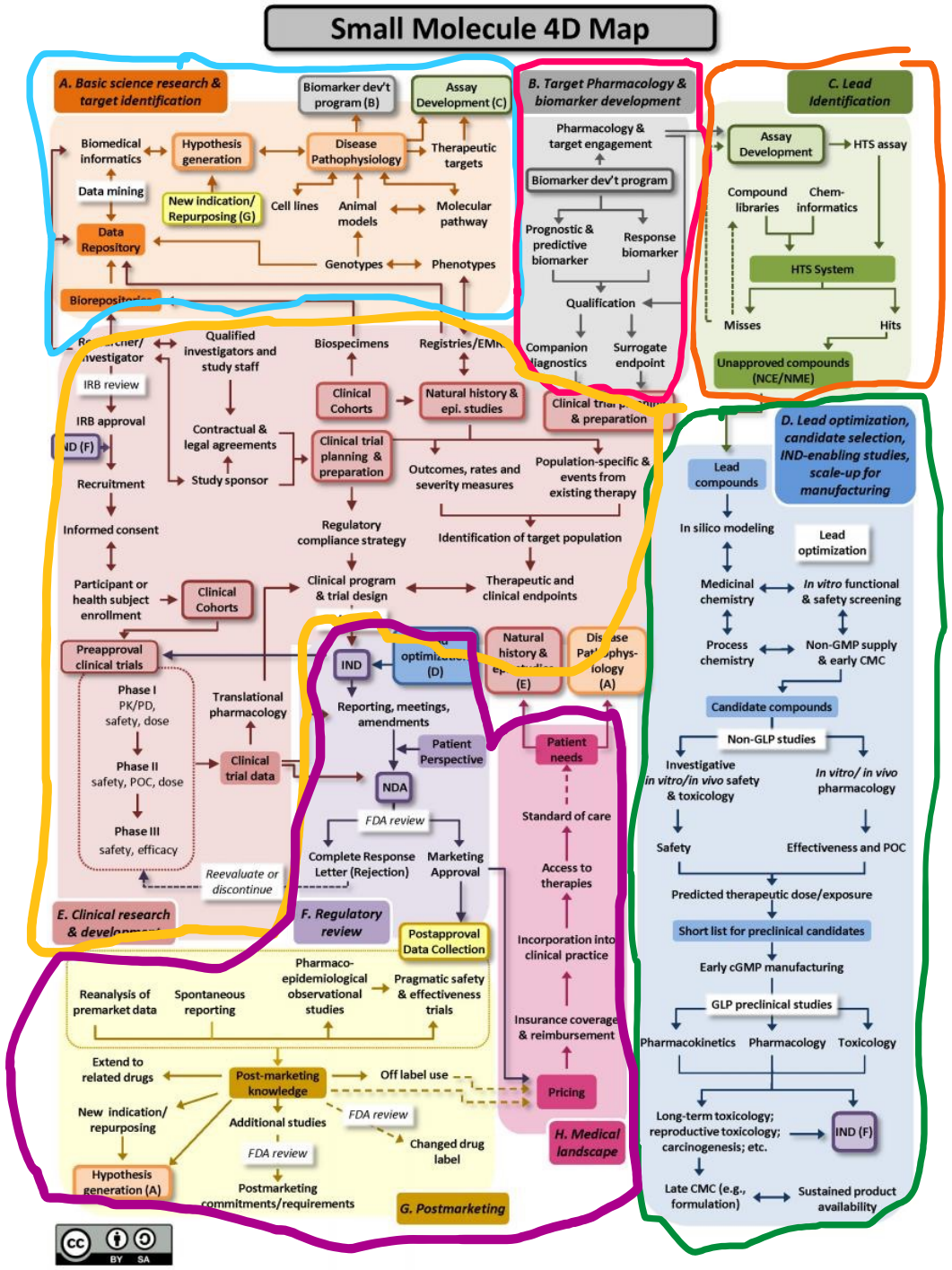
Aspirin

Artemisia annua L.
ca. 168 BC
“fever”

Artemisinin

How are drugs discovered today?

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/#/

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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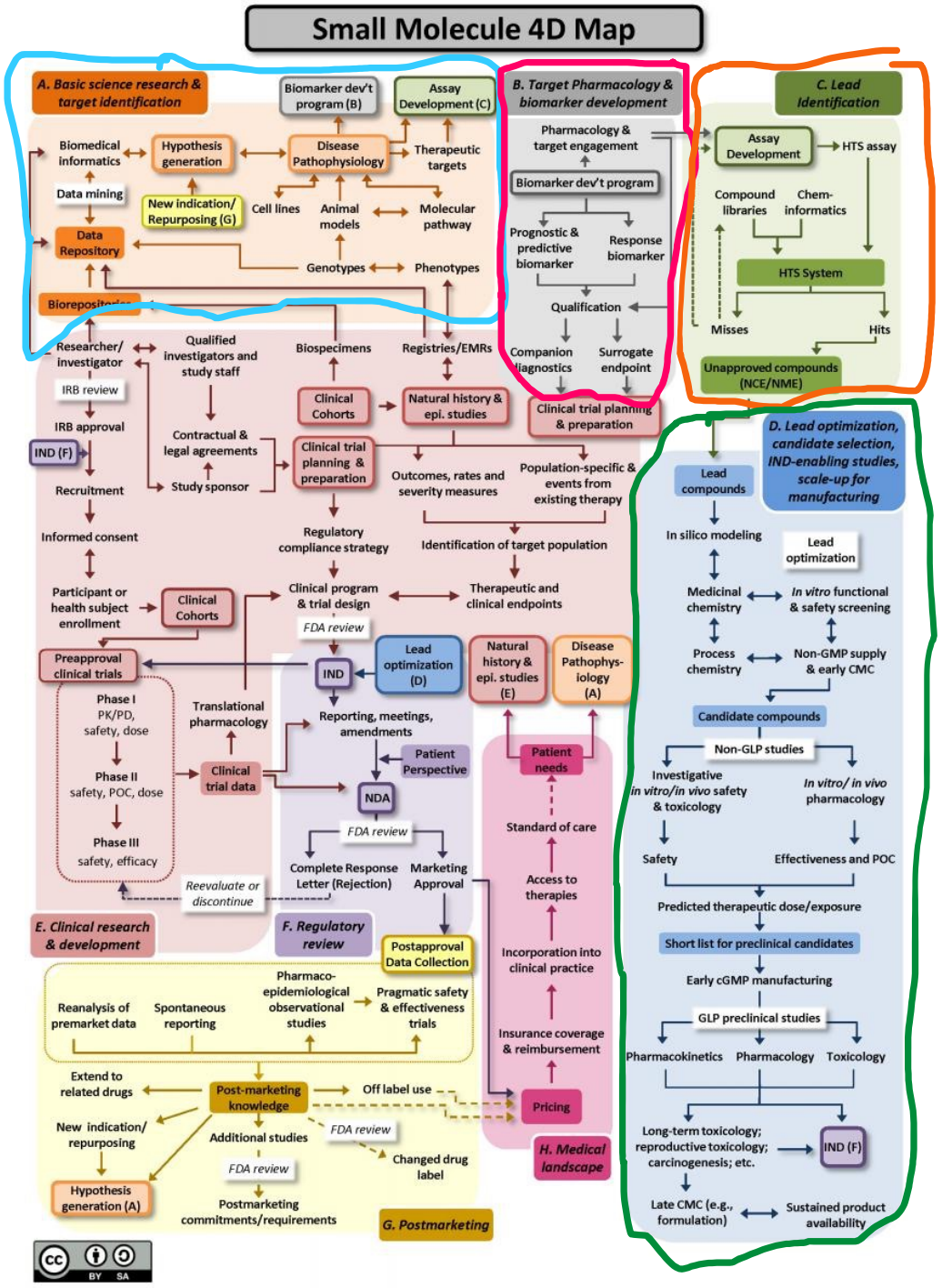

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Contrasting old with modern framework for drug discovery and development

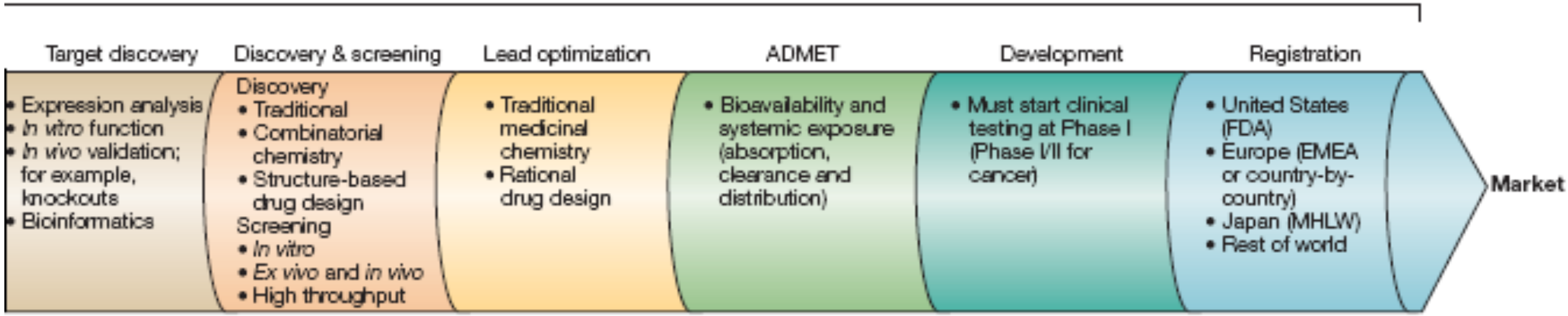
- Intentional and broad search for therapeutic agents
- Engages fundamental understanding of disease biology and mechanism
- Highly multidisciplinary
  - biologists, chemists, engineers, bioinformatics, clinicians, business, legal, …
- High burden-of-proof to establish safety and efficacy

- 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

Timeline for new drug discovery process

Question:
What's the average duration of the various drug discovery phases?

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



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

Preclinical phase ("discovery")

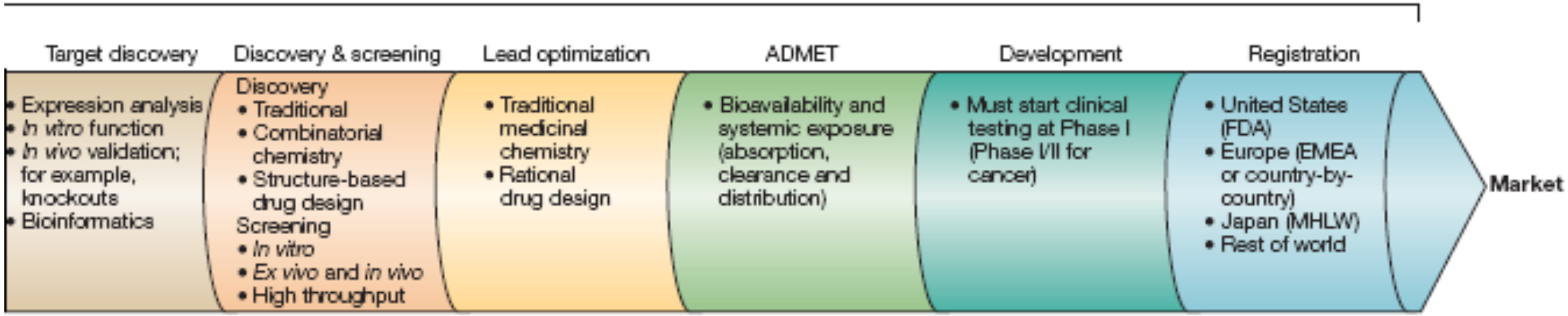
Clinical phase ("testing")

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	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 ("discovery")

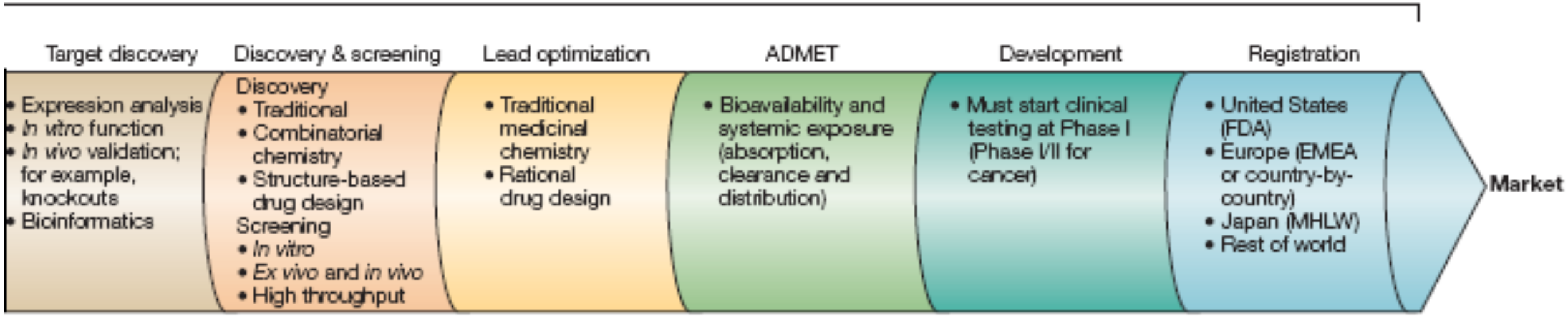
Clinical phase ("testing")

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!***



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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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B. Target pharmacology and biomarker development
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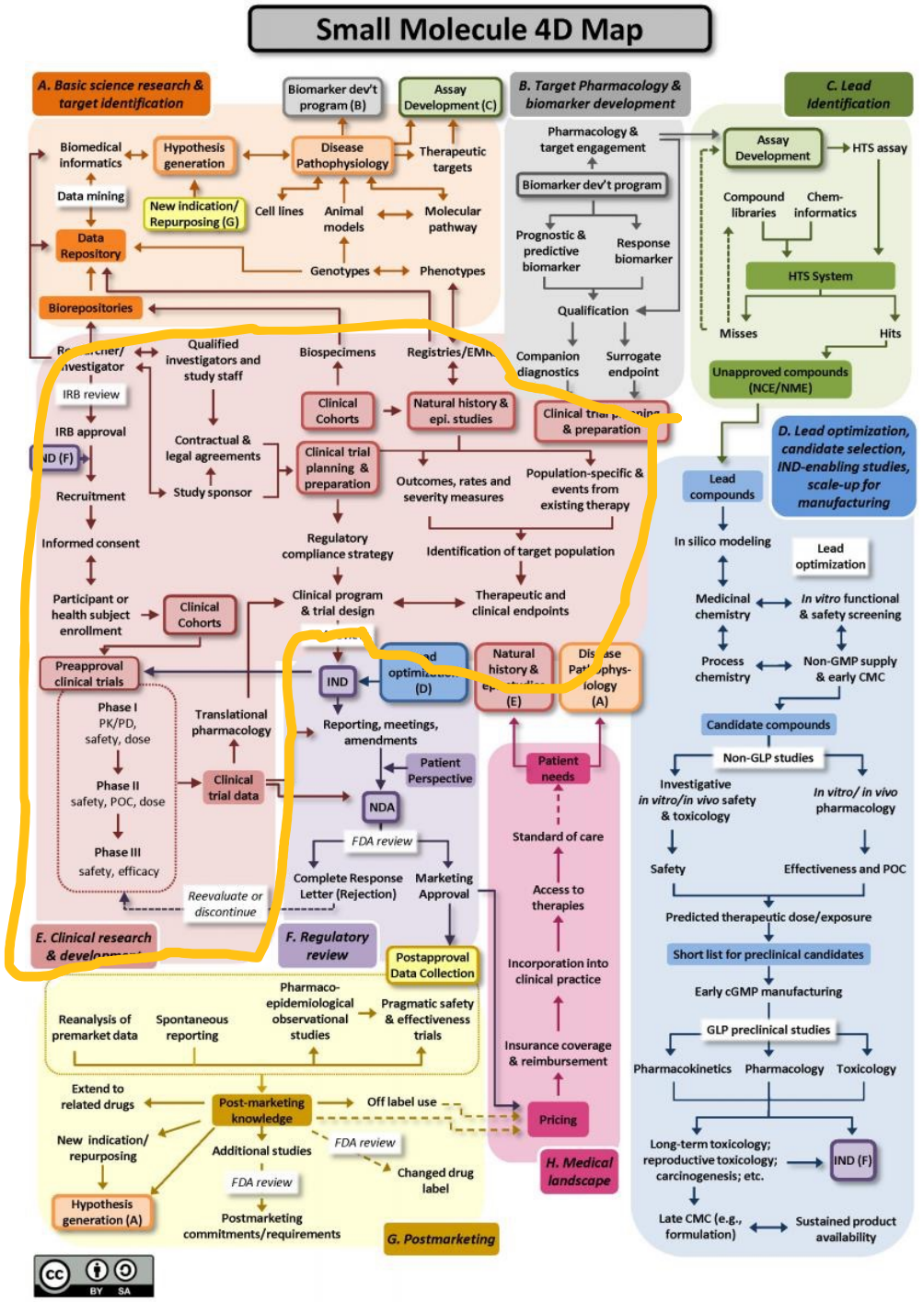
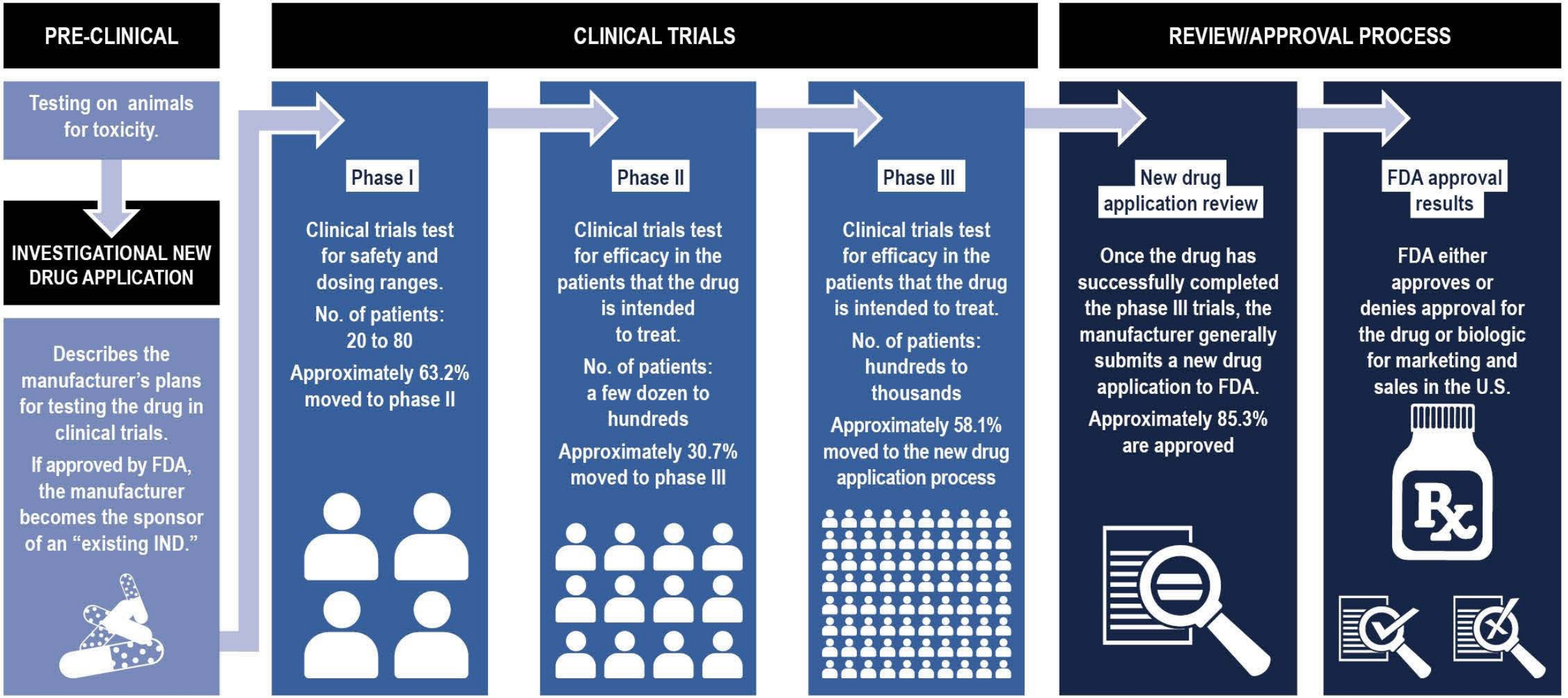


Clinical phase:
Brief overview of clinical research and development



Source: GAO analysis of FDA data and a 2016 collaborative study by Biotechnology Innovation Organization, Biomedtracker, and Amplion.[a] | GAO-17-564

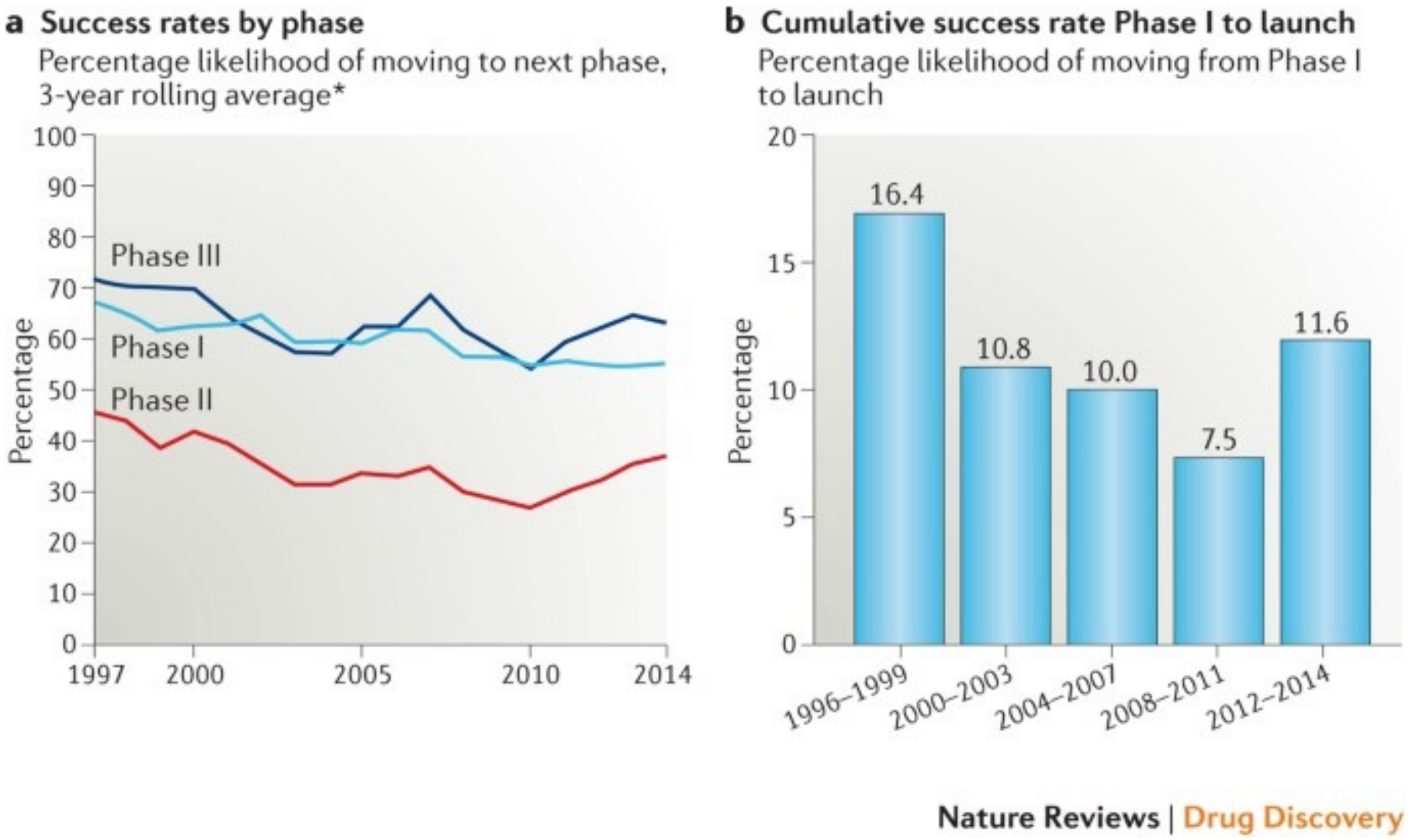
Attrition along the drug discovery pipeline

	Phase 1 to Phase 2		Phase 2 to Phase 3			Phase 3 to Approval		Overall
Therapeutic group	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



- Phase II success rates lowest
  - Why might this be so?
- Overall success rates steadily declining 1996-2011, but improved since 2012

Reference Katarzyna Smietana et al; Nature Reviews Drug Discovery volume 15, pages379–380(2016)

Regulation of drug approval in the U.S.

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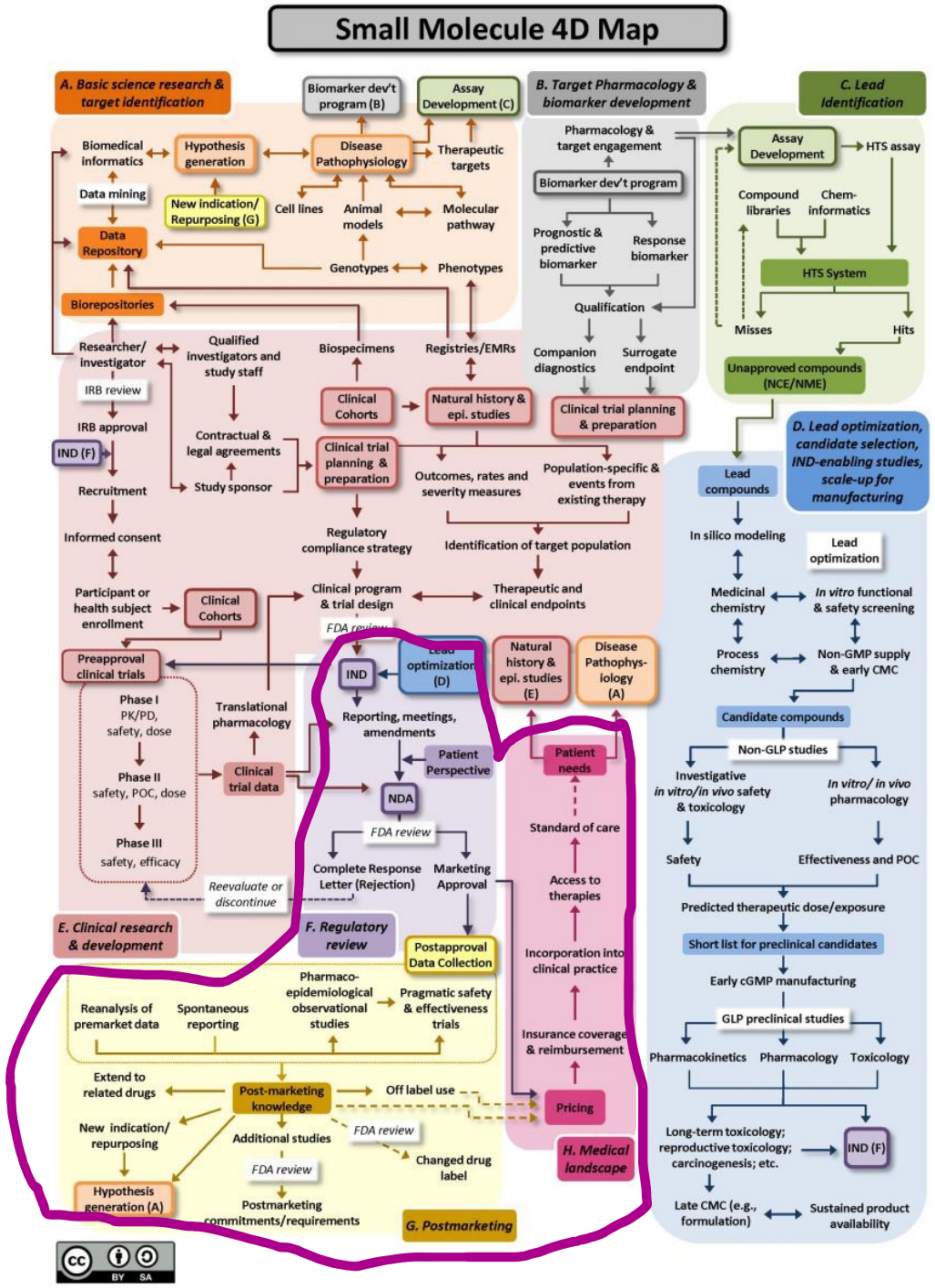
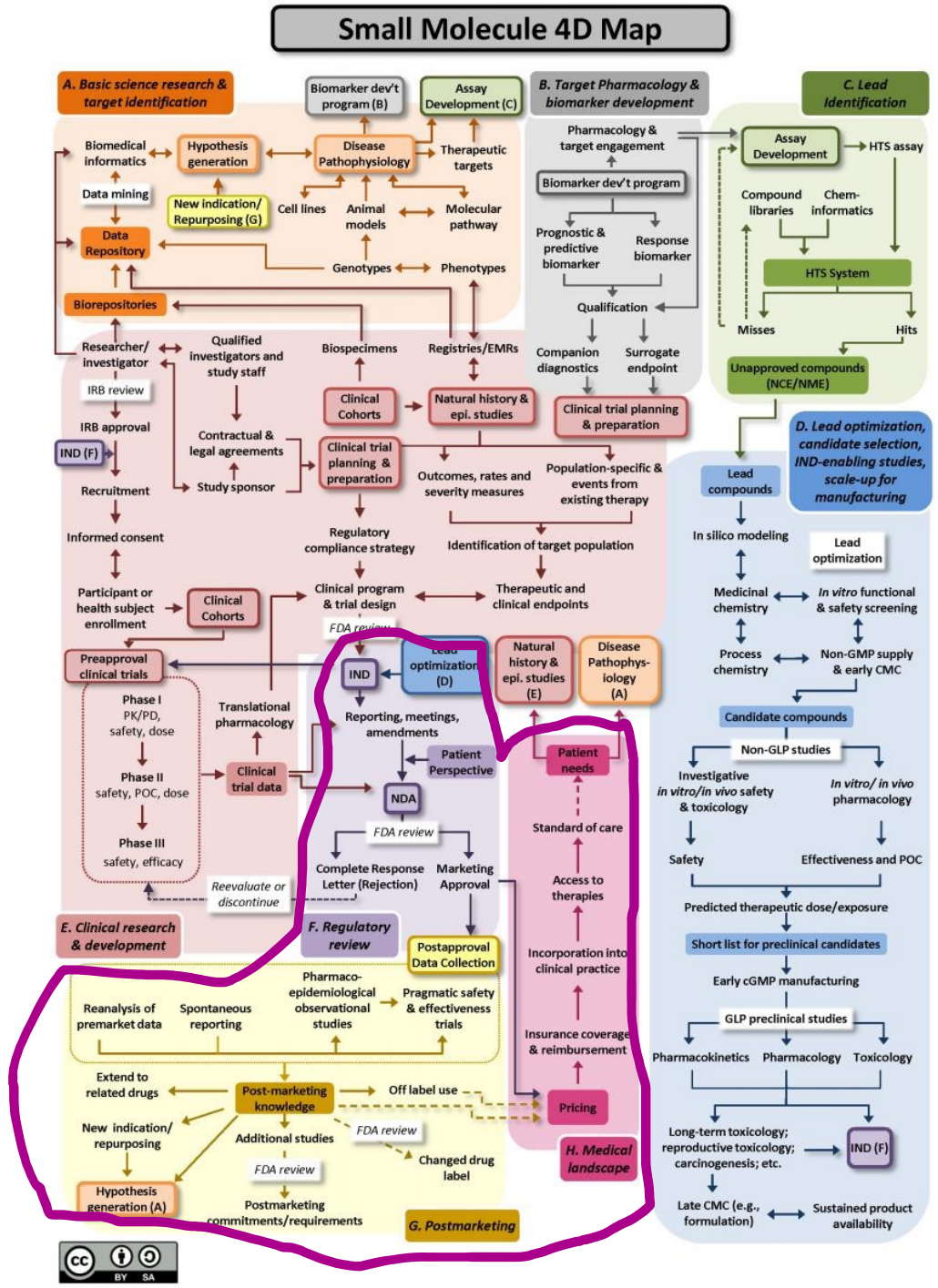


Regulation of drug approval in the U.S.

- 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?



[FDA Website]

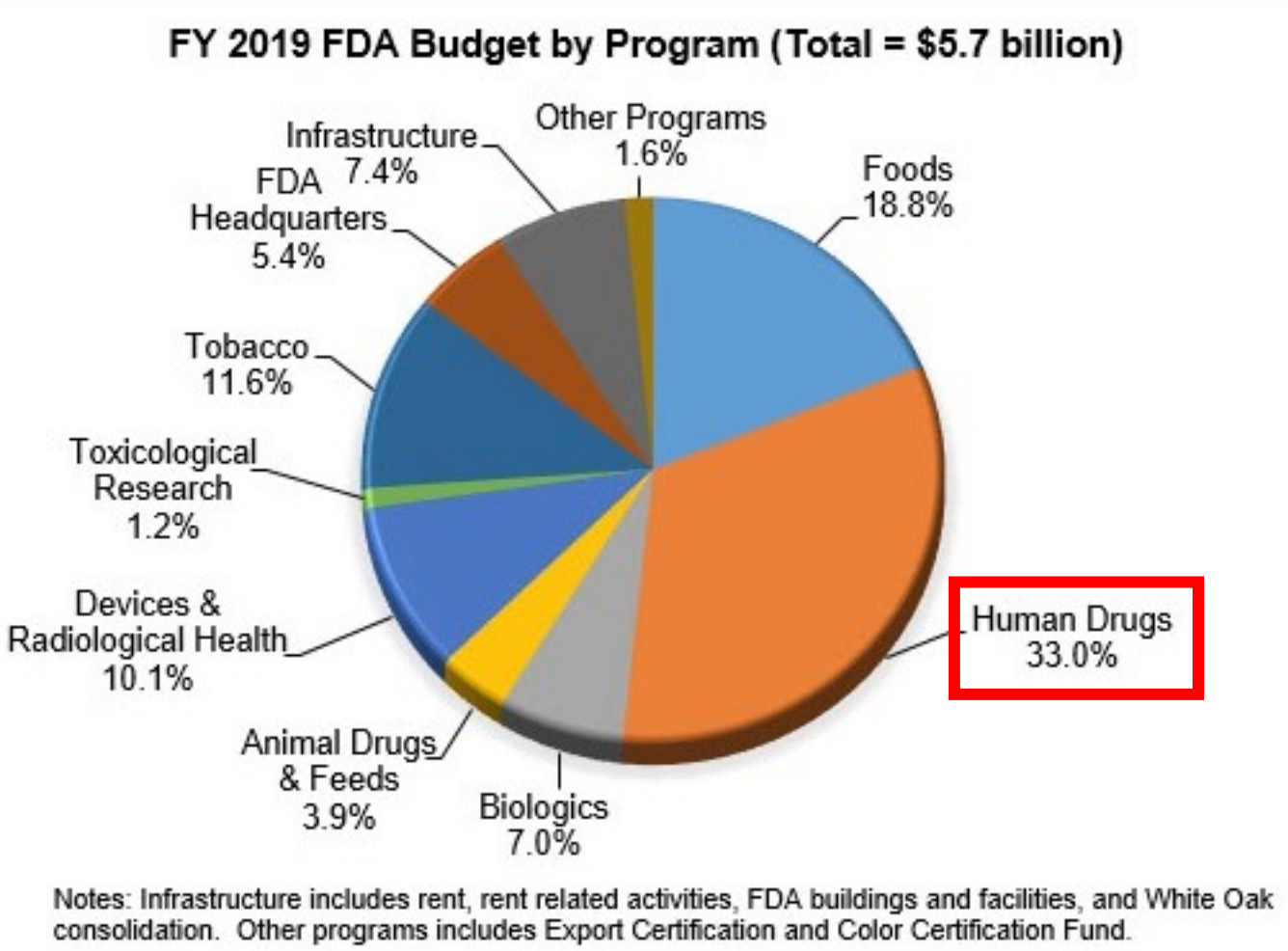
Food and Drug Association (FDA)

- 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

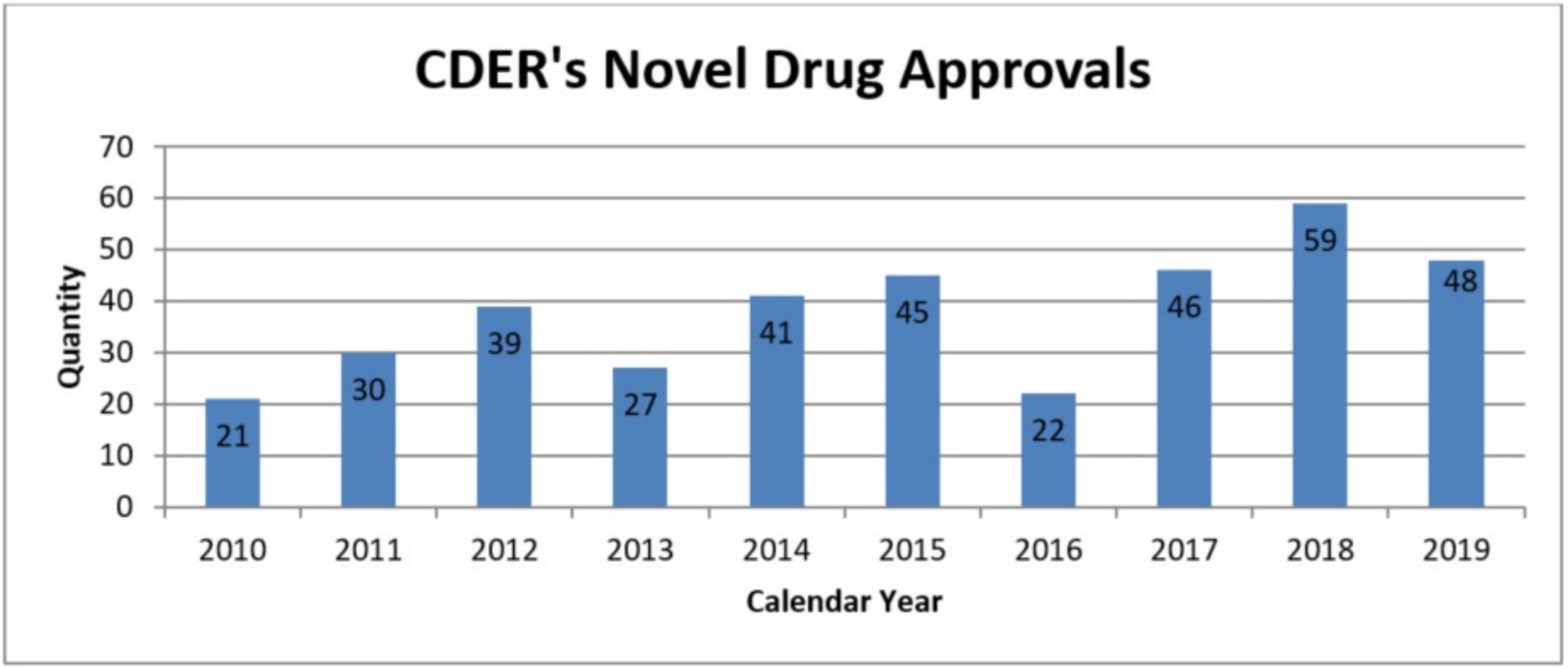
- FDA budget sources
  - ~ 55 percent ($3.1 billion) from federal government
  - ~45 percent ($2.6 billion) from industry fees.



Reference:

1) FDA at a Glancet: https://www.fda.gov/media/131874/download

Annual new FDA drug approvals



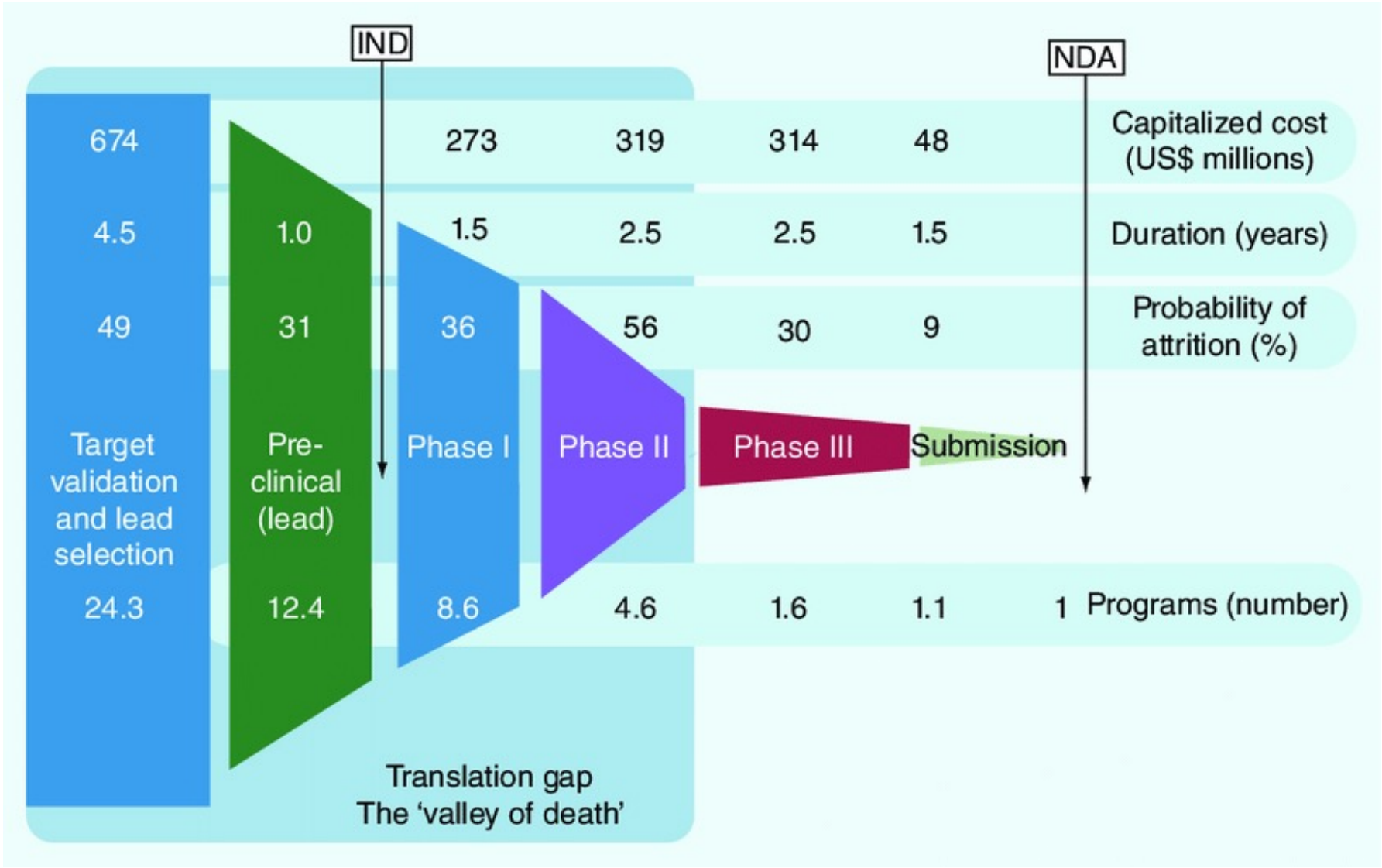
- In 2019, 20/48 FDA approved drugs were “first in class”
  - Possess distinct mechanisms of actions from previously approved drugs

FDA Website:
https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/new-drug-therapy-approvals-2019

United States Pharmacopeia – National Formulary (USP-NF)

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

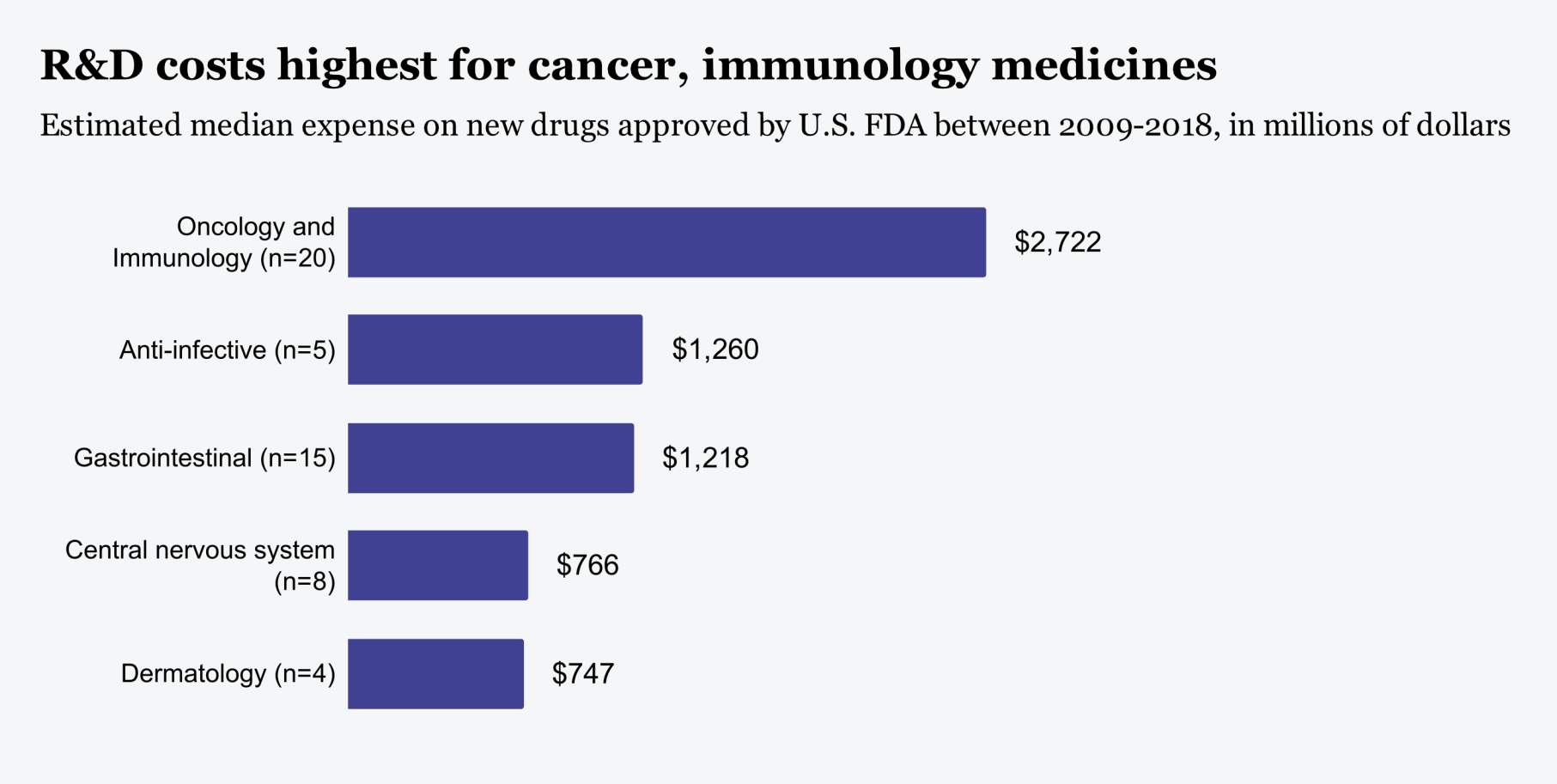
New drug discovery is expensive … with no guarantee of success!



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

Reference: Jesus Zurdo; Pharm. Bioprocess. (2013) 1(1)
DOI: 10.4155/PBP.13.3

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



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?)!