JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

Drug Development and Approval Process, Part 1

Hemalkumar B. Mehta, PhD, MS
Johns Hopkins University

Motivation to Understand the Drug Approval Process

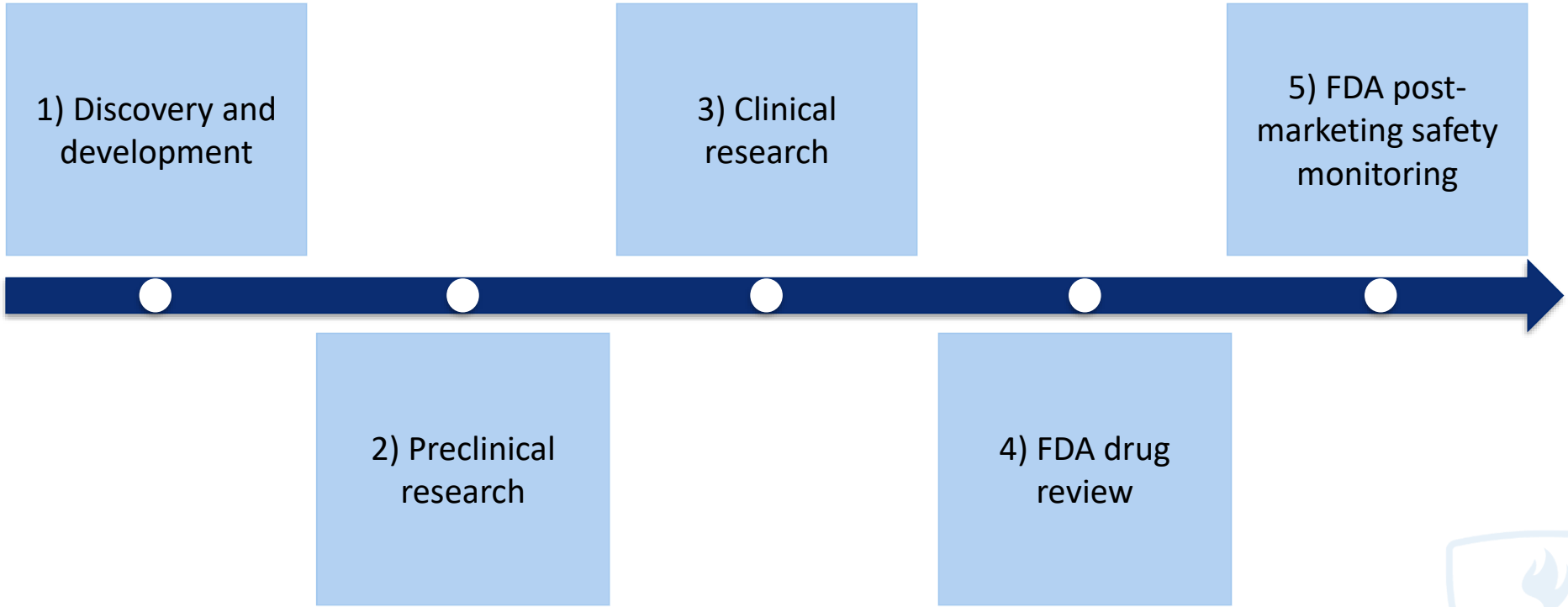
- Have you ever taken Tylenol (acetaminophen)?
- Did you wonder who approved it for use?
- What was the approval process?

Image source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/about-fda/fda-history-exhibits/drug-therapeutics-regulation-us

Contents

Overview of the Drug Development and Approval Process

Drug Development Process: From Lab to Patients



Step 1: Discovery and Development

- Goal is to discover a molecule that may have a therapeutic effect
  - Identify biological targets: protein, receptor, enzyme
  - Identify molecules that interact with biological target
- Thousands of molecules are discovered and screened at this stage (~10,000)
  - A small number of them move to the next step (10 to 20)
- Experiments are conducted to study …
  - Absorption, distribution, metabolism, excretion
  - Benefits and mechanism of action
  - Best dose and route of administration
  - Effectiveness and toxicity profile of molecule

Image source: Microsoft stock image.

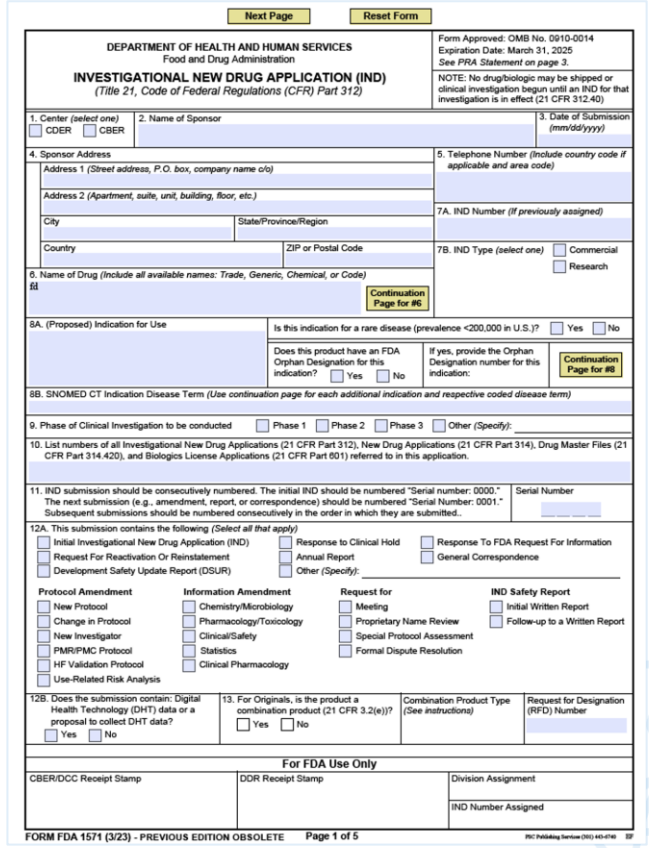
Step 2: Preclinical Research—1

- Two types of preclinical research
  - In vitro: Latin for “in glass”
  - In vivo: Latin for “within the living”
- Test compounds for toxicity in animals
  - Use multiple species to collect information on the safety and efficacy of compounds
  - All preclinical studies should be conducted using good laboratory practices (GLP) regulations
- Review findings to decide the potential to test in humans
  - Submit an Investigational New Drug application (IND) to the FDA

Image source: Microsoft stock image.

Step 2: Preclinical Research—2

- The company submits an IND
  - Animal pharmacology and toxicological studies
  - Manufacturing information
  - Clinical protocols and investigator information
- Detailed information on IND forms and procedures is on the FDA website
- FDA reviews IND within 30 calendar days



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2025
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Center *(select one)* ☐ CDER ☐ CBER
2. Name of Sponsor
3. Date of Submission *(mm/dd/yyyy)*
4. Sponsor Address
   Address 1 *(Street address, P.O. box, company name c/o)*
   Address 2 *(Apartment, suite, unit, building, floor, etc.)*
   City | State/Province/Region
   Country | ZIP or Postal Code
5. Telephone Number *(Include country code if applicable and area code)*
7A. IND Number *(If previously assigned)*
7B. IND Type *(select one)* ☐ Commercial ☐ Research
6. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
   fd
   Continuation Page for #6
8A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No
Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #8
8B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*
9. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other *(Specify)*:
10. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.
11. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.. Serial Number
12A. This submission contains the following *(Select all that apply)*
☐ Initial Investigational New Drug Application (IND)
☐ Request For Reactivation Or Reinstatement
☐ Development Safety Update Report (DSUR)
☐ Response to Clinical Hold
☐ Annual Report
☐ Other *(Specify)*:
☐ Response To FDA Request For Information
☐ General Correspondence

Protocol Amendment	Information Amendment	Request for	IND Safety Report
☐ New Protocol	☐ Chemistry/Microbiology	☐ Meeting	☐ Initial Written Report
☐ Change in Protocol	☐ Pharmacology/Toxicology	☐ Proprietary Name Review	☐ Follow-up to a Written Report
☐ New Investigator	☐ Clinical/Safety	☐ Special Protocol Assessment	
☐ PMR/PMC Protocol	☐ Statistics	☐ Formal Dispute Resolution	
☐ HF Validation Protocol	☐ Clinical Pharmacology		
☐ Use-Related Risk Analysis			

12B. Does the submission contain: Digital Health Technology (DHT) data or a proposal to collect DHT data? ☐ Yes ☐ No
13. For Originals, is the product a combination product (21 CFR 3.2(e))? ☐ Yes ☐ No
Combination Product Type *(See instructions)*
Request for Designation (RFD) Number

For FDA Use Only

CBER/DCC Receipt Stamp | DDR Receipt Stamp | Division Assignment | IND Number Assigned

FORM FDA 1571 (3/23) - PREVIOUS EDITION OBSOLETE Page 1 of 5

Image source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-forms-and-instructions

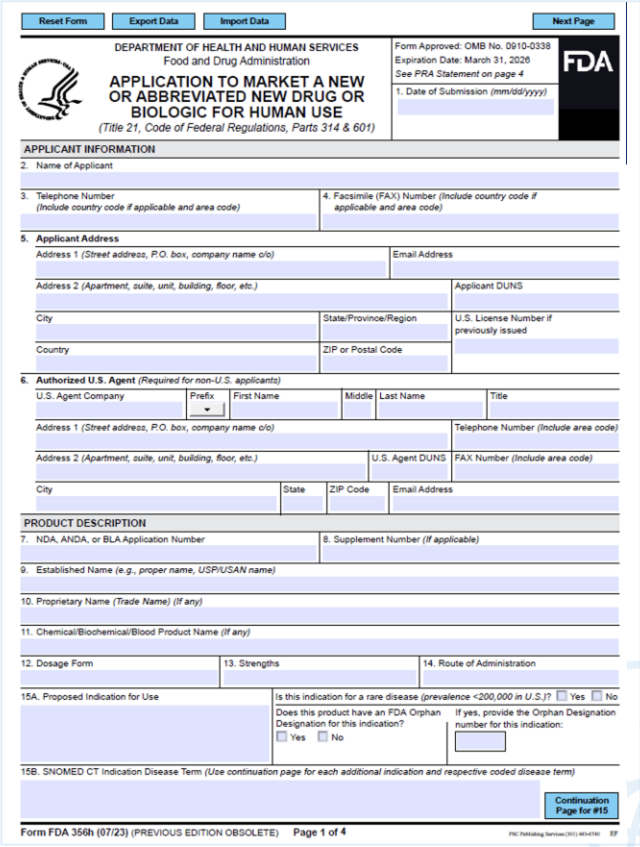
Step 3: Clinical Research

- FDA reviews the IND to ensure that human subjects are not at unreasonable risk of harms
- Once FDA approves the IND, clinical research can begin

Clinical trial	Main purpose	Number of participants
Phase 1	Safety and dosage	20 to 100
Phase 2	Efficacy and side effects	Several hundred
Phase 3	Efficacy and adverse reactions	300 to 3,000

Step 4: FDA Drug Review—1

- If a company feels that a drug works, i.e., it is safe and effective for its intended use, the company files a New Drug Application (NDA)
- FDA has 60 days to ensure the application is complete or not
- If it is complete, FDA takes 6 to 10 months to review it and make a decision
  - Advisory committees to get independent, expert advice
- Drug labeling and facility inspection



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

APPLICATION TO MARKET A NEW OR ABBREVIATED NEW DRUG OR BIOLOGIC FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2026
See PRA Statement on page 4

FDA

1. Date of Submission *(mm/dd/yyyy)*

APPLICANT INFORMATION

2. Name of Applicant

3. Telephone Number *(Include country code if applicable and area code)*

4. Facsimile (FAX) Number *(Include country code if applicable and area code)*

5. **Applicant Address**

Address 1 *(Street address, P.O. box, company name c/o)*

Email Address

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

Applicant DUNS

City

State/Province/Region

U.S. License Number if previously issued

Country

ZIP or Postal Code

6. **Authorized U.S. Agent** *(Required for non-U.S. applicants)*

U.S. Agent Company | Prefix | First Name | Middle | Last Name | Title

Address 1 *(Street address, P.O. box, company name c/o)*

Telephone Number *(Include area code)*

Address 2 *(Apartment, suite, unit, building, floor, etc.)*

U.S. Agent DUNS

FAX Number *(Include area code)*

City | State | ZIP Code | Email Address

PRODUCT DESCRIPTION

7. NDA, ANDA, or BLA Application Number

8. Supplement Number *(If applicable)*

9. Established Name *(e.g., proper name, USP/USAN name)*

10. Proprietary Name *(Trade Name) (If any)*

11. Chemical/Biochemical/Blood Product Name *(If any)*

12. Dosage Form | 13. Strengths | 14. Route of Administration

15A. Proposed Indication for Use

Is this indication for a rare disease *(prevalence <200,000 in U.S.)*? ☐ Yes ☐ No

Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No

If yes, provide the Orphan Designation number for this indication:

15B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*

Continuation Page for #15

Form FDA 356h (07/23) (PREVIOUS EDITION OBSOLETE) Page 1 of 4

Image source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/drugs/types-applications/new-drug-application-nda

Step 4: FDA Drug Review—2

- Drug approval process can take a long time (10 to 15 years)
- How can FDA accelerate the process so that patients can access it quickly?
- FDA developed four programs to accelerate drug approval

Program	Description
Fast track	Expedites the review of drugs to treat serious conditions and fill unmet medical needs
Breakthrough therapy	Expedites the development and review of drugs which may demonstrate substantial improvement over available therapy
Accelerated approval	Allows drugs for serious conditions that fill unmet medical needs to be approved based on surrogate endpoints
Priority review	FDA will take action on an application within six months

Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review

Step 5: FDA Post-Marketing Drug Safety Monitoring

- Although Phase 1 to Phase 3 clinical trials provide data on safety and efficacy, it is difficult to know all the safety issues of a drug
  - It can take months or years to know the long-term safety of drugs
  - It may not be possible to learn rare adverse events of drugs

- Phase 4: post-marketing drug safety monitoring
  - MedWatch Adverse Event Reporting Program
  - Sentinel initiative for active surveillance of drugs for possible safety signals

Role of Regulatory Agencies Around the World for Drug Approval

Regulatory Agencies

Country	Regulatory agency	Acronym
US	**Food and Drug Administration**	**FDA**
Australia	Therapeutic Goods Administration	TGA
Canada	Health Canada	HC
China	National Medical Products Administration	NMPA
Europe	European Medicines Agency	EMA
India	Central Drug Standard Control Organization	CDSCO
Nigeria	National Agency for Food And Drug Administration and Control	NAFDAC
UK	Medicines and Healthcare Products Regulatory Agency	MHRA

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

- Aims to achieve greater harmonization worldwide for the development and approval of safe, effective, and high-quality medicines in the most resource-efficient manner
  - Develop guidelines through consensus
  - Regulators implement final guidelines

- Launched in 1990
  - Twenty-three members
    - US, Europe, and Japan
  - Two standing observers
    - World Health Organization, International Federation of Pharmaceutical Manufacturers & Associations

Image source: ICH. Retrieved December 3, 2024, from https://www.ich.org/

Similarities in the Drug Approval Process in the US and Europe

Purpose and mission	Regulatory authority	Guidelines and standards	Post-market surveillance
▶ Both FDA and EMA* aim to protect public health by ensuring the safety, efficacy, and quality of medicines and medical devices	▶ Both FDA and EMA are involved in approving or rejecting new drugs and medical devices, requiring pharmaceutical companies to provide extensive data to support applications	▶ Both FDA and EMA develop regulatory guidelines and standards for drug development, manufacturing, and marketing	▶ Both FDA and EMA conduct post-market surveillance, monitor for adverse drug reactions, conduct inspections, and require risk management plans

*European Medicines Agency

Source: Van Norman G. A. (2016). Drugs and devices: Comparison of European and U.S. approval processes. *JACC. Basic to Translational Science, 1*(5), 399–412. https://doi.org/10.1016/j.jacbts.2016.06.003

Differences in the Drug Approval Process in the US and Europe

Food and Drug Administration	European Medicines Agency
▶ Geographic jurisdiction: US	▶ Geographic jurisdiction: EU
▶ Centralized federal agency under the US Department of Health and Human Services	▶ Decentralized agency working with regulatory authorities in each member state
▶ Directly authorizes or approves products	▶ Offers suggestion to European Commission about approval
▶ Nonpublished trial data is publicly available	▶ Nonpublished trial data is not publicly available

Source: Van Norman G. A. (2016). Drugs and devices: Comparison of European and U.S. approval processes. *JACC. Basic to Translational Science, 1*(5), 399–412. https://doi.org/10.1016/j.jacbts.2016.06.003

Comparison of EMA and FDA for New Drugs: 2014–2016

- There was high concordance (98%) in the EMA and FDA final approval decisions
- The FDA and EMA also raised very similar concerns when viewing the same application
- Differences in conclusions about efficacy data were the most common reason for disagreement between the FDA and EMA
- Results suggest overall consistency in regulatory science between the FDA and EMA

		Final EMA outcome, N=107		
		Approved (100)	Not approved (1)	Withdrawn (6)
Final FDA outcome, N = 107	Approved (98)	98	0	0
	Not approved (6)	2	1	3
	Withdrawn (3)	0	0	3

**Green shaded cells indicate concordant results

Data source for figure: Kashoki, M., et al. (2020). A comparison of EMA and FDA decisions for new drug marketing applications 2014–2016: Concordance, discordance, and why. *Clinical Pharmacology and Therapeutics, 107*(1), 195–202. https://doi.org/10.1002/cpt.1565. Creative Commons BY-ND-NC.

Example of Differences in Approval Decisions

Drug	Indication	FDA Decision	EMA Decision
Abaloparatide	Osteoporosis	Approved in 2017	• Refused in 2019 due to insufficient evidence about efficacy and concerns about cardiac safety • Later authorized in 2022
Ataluren	Duchenne's muscular dystrophy	Not approved	• Authorized in 2014

Sources: Pham, C., Le, K., Draves, M., & Seoane-Vazquez, E. (2023). Assessment of FDA-approved drugs not recommended for use or reimbursement in other countries, 2017–2020. *JAMA Internal Medicine, 183*(4), 290–297. https://doi.org/10.1001/jamainternmed.2022.6787; Kashoki, M., et al. (2020). A Comparison of EMA and FDA decisions for new drug marketing applications 2014–2016: Concordance, discordance, and why. *Clinical Pharmacology and Therapeutics, 107*(1), 195–202. https://doi.org/10.1002/cpt.1565

The US Food and Drug Administration (FDA)

The FDA Mission

"The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of **human and veterinary drugs, biological products, and medical devices** [emphasis added]; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation."

Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/about-fda/what-we-do

FDA at a Glance

- FDA oversees the safety of more than **$2.9 trillion** worth of food, tobacco, medical products
- Regulating 21 cents of every dollar spent by consumers

- Over **20,000** prescription drugs approved for marketing
- **6,500** medical device products
- **671** biological products

- Budget **$6.3 billion**
  - 54% through federal budget authorization
  - 46% industry fees

Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/media/176816/download

FDA Regulates Many Products Through Different Centers

Drugs	Biologics, vaccines	Medical devices	Other products
▶ Center for Drug Evaluation and Research (CDER)	▶ Center for Biologics Evaluation and Research (CBER)	▶ Center for Devices and Radiological Health (CDRH)	▶ Cosmetics, tobacco products, veterinary products, radiation-emitting product

Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/about-fda/fda-organization

FDA's Regulations for Drugs and Biologics

Drugs	Biologics
▶ Drugs are small molecules and simple chemical compounds ▶ Prescription drugs ▶ Over-the-counter drugs ▶ Aspirin ▶ Center for Drug Evaluation and Research (CDER)	▶ Biologics are large molecules made from living cells ▶ Vaccines for humans ▶ Cellular and gene therapy products ▶ Insulin ▶ Center for Biologics Evaluation and Research (CBER)

What the FDA Does Not Do

- Does not regulate the practice of medicine
- Does not regulate price or availability of drugs
- Does not assess cost versus benefit for a drug or device
- Does not determine whether one drug is better than another
- Does not approve every use to which a product may be used
- Does not require large trials that will identify all potentially rare complications

Key Food and Drug Administration (FDA) Drug Regulations

Need for Federal Regulations for Drugs

- Early 1900s
  - No federal regulations to protect public from dangerous drugs

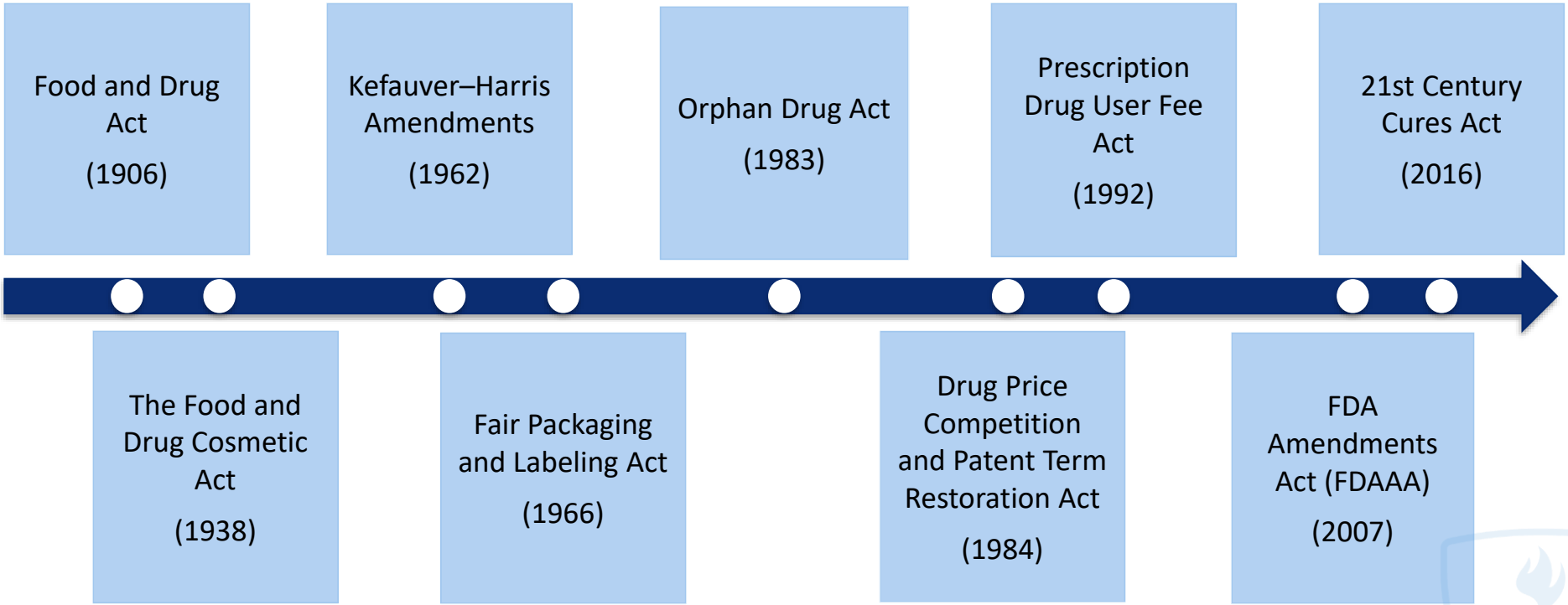
"It was a menacing marketplace filled with products such as William Radam's Microbe Killer and Benjamin Bye's Soothing Balmy Oils to cure cancer"

"Products like these were, at minimum, useless remedies that picked the pocket of the user, but they could also be downright harmful"

— John Swann, PhD, Historian at FDA

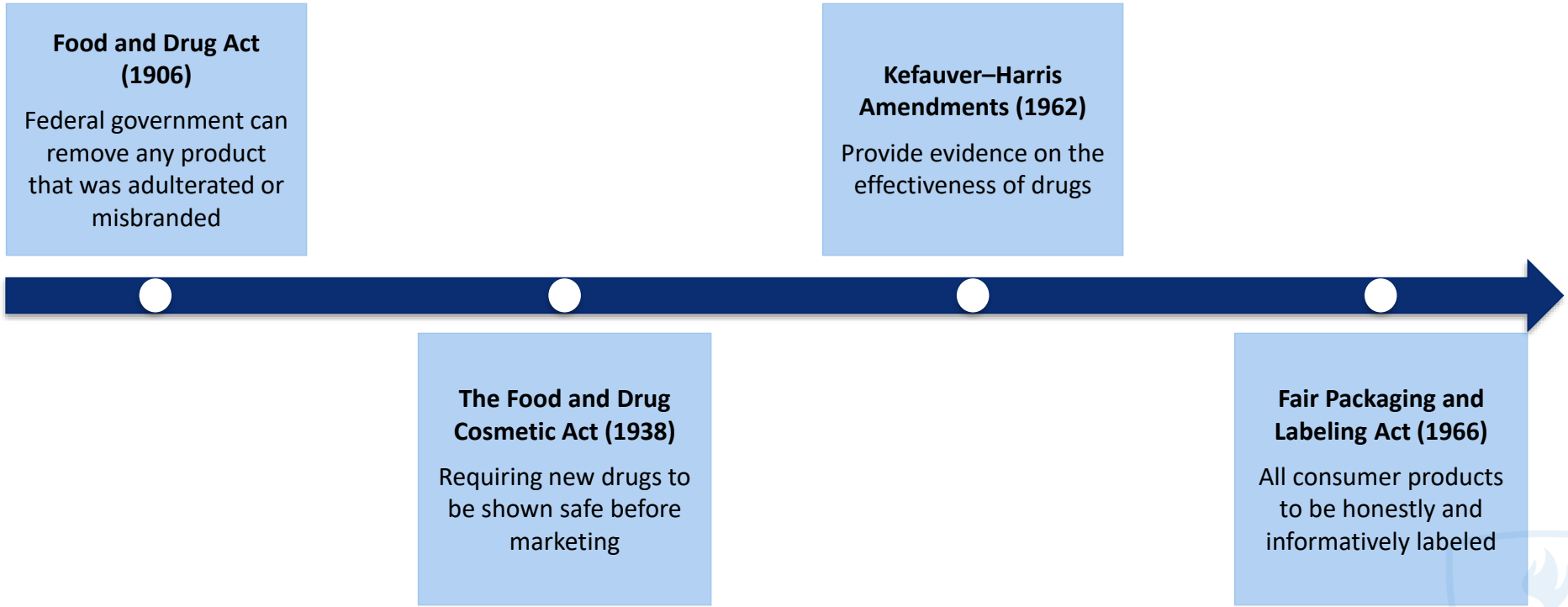
Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/about-fda/histories-product-regulation/promoting-safe-effective-drugs-100-years

History of Drug Regulation in the US—1



Source: FDA. Retrieved December 3, 2024, from https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law and https://www.fda.gov/files/Promoting-Safe-and-Effective-Drugs-for-100-Years-%28download%29.pdf

History of Drug Regulation in the US—2



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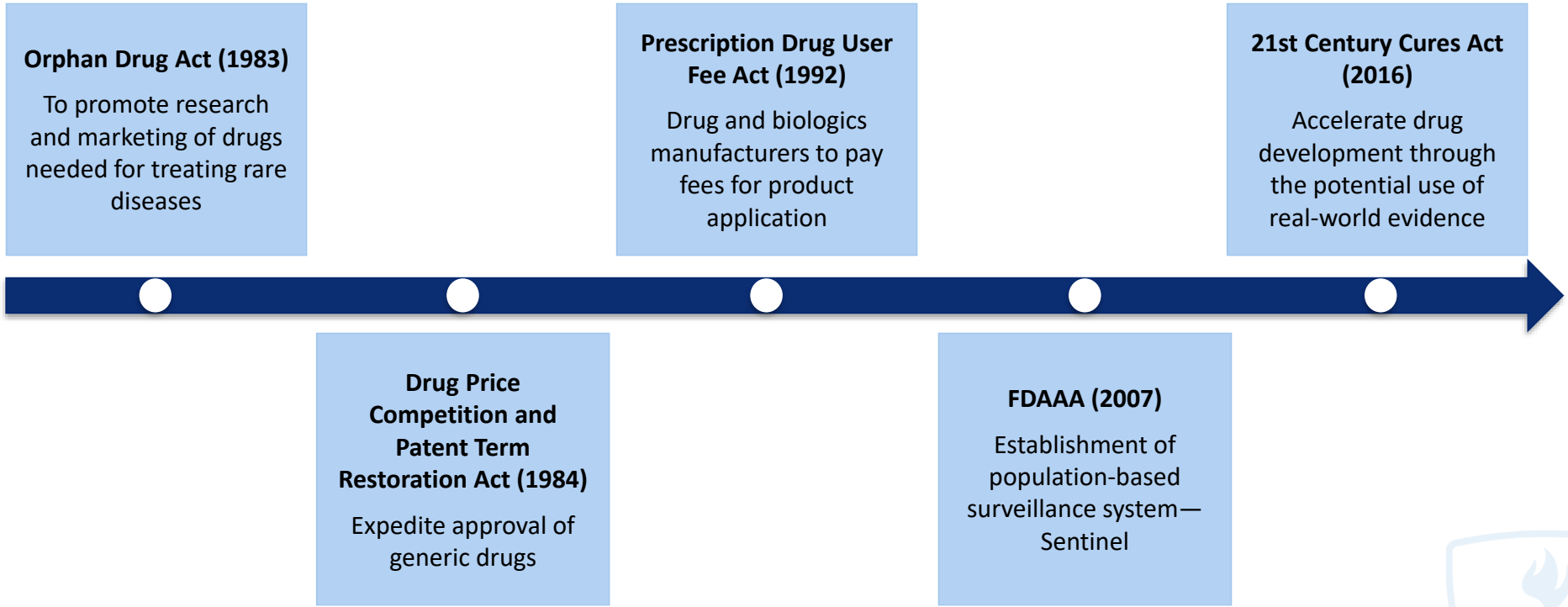
History of Drug Regulation in the US—3



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Prescription Drug Advertising and Promotions

Ask your doctor if …

Talk to your doctor …

FDA's Role in Prescription Drug Advertising and Promotions

- FDA oversees prescription drug advertisements
- Federal Trade Commission (FTC) oversees non-prescription drugs

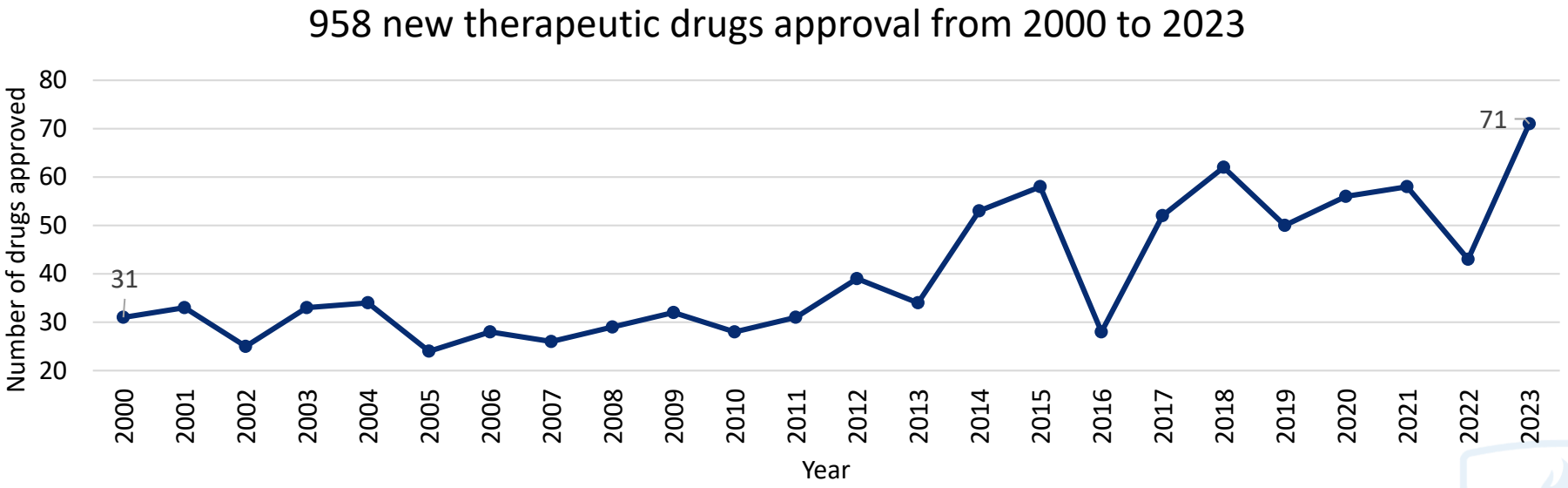
Type of advertisement	Description
Product claim	• Must include name of drug, at least one FDA approved use, and most significant risks
Reminder	• Includes name of drug, but not drug uses • Not required to include risk information, but may not suggest anything about benefits
Help-seeking	• Describes disease or condition, but does not recommend specific treatments • May include drug company's name and phone number • Not considered a drug ad and is not regulated by FDA

Source: FDA. Retrieved December 4, 2024, from https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads

Drug Approval in Numbers

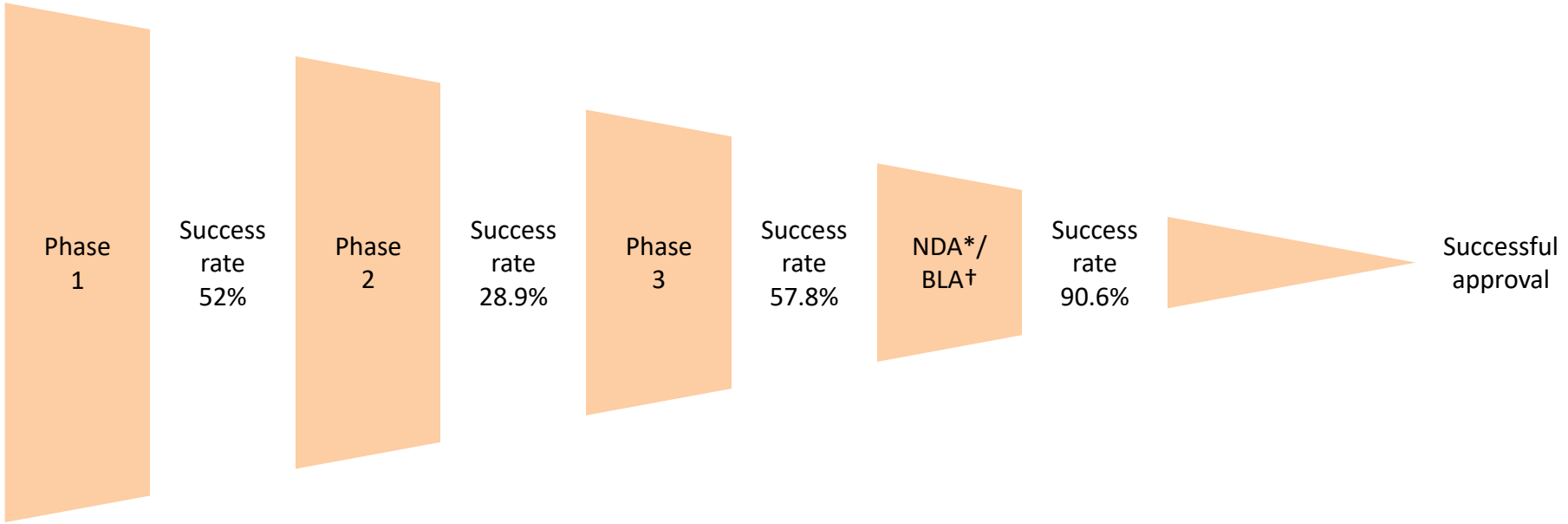
The Number of Drug Approvals

- There are over 20,000 prescription drug products approved for marketing by the US FDA



Data source: Baedeker, M., Ringel, M. S., & Möller, C. C. (2024). 2023 FDA approvals: Unprecedented volume at moderate value. *Nature Reviews. Drug Discovery, 23*(2), 98. https://doi.org/10.1038/d41573-024-00011-9

Success Rate for Drug Approval

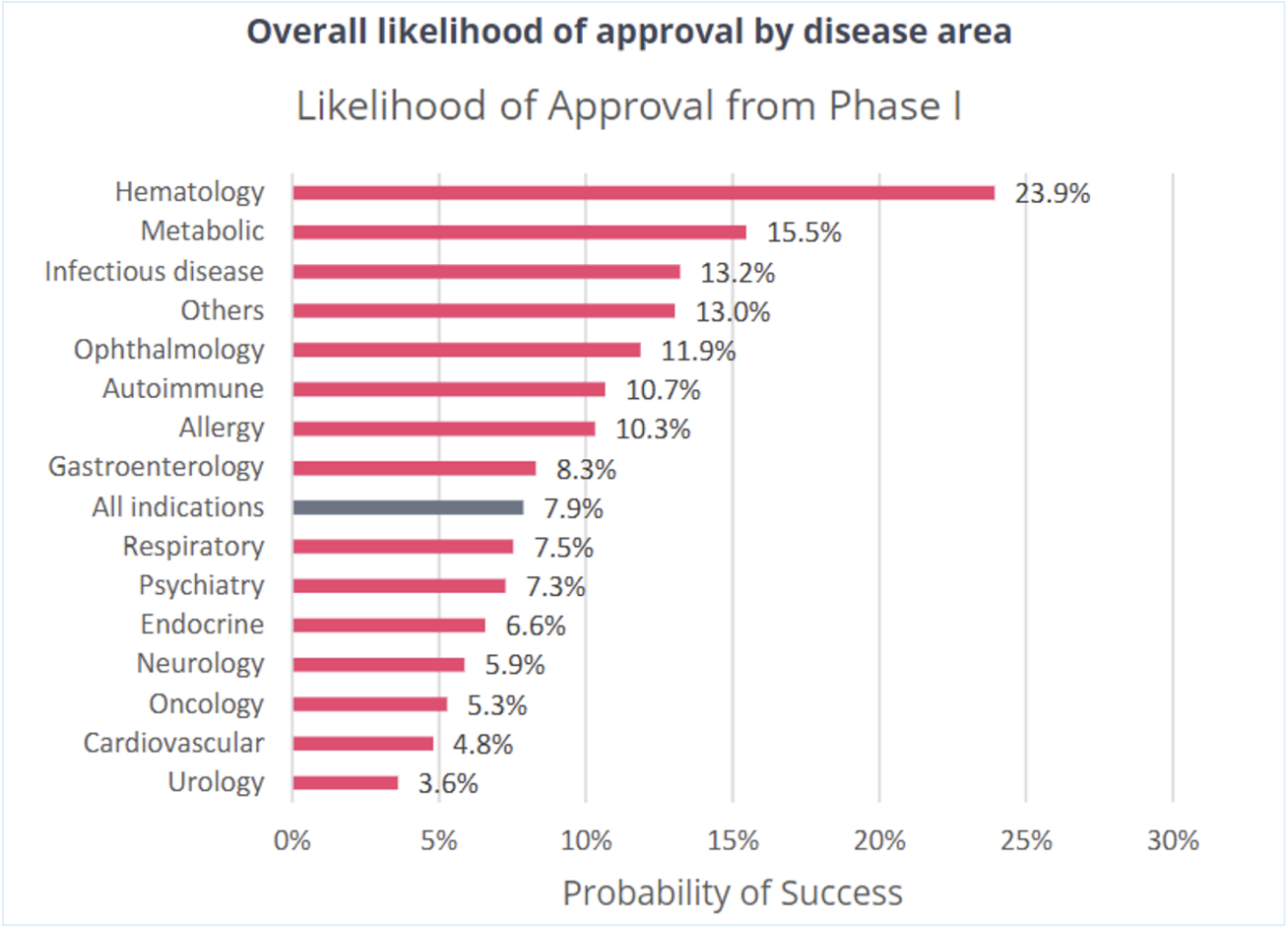


Overall success rate from Phase 1 to approval = 7.9%

*New Drug Application; †Biologics license application

Data source: BIO, PharmaIntelligence, & QLS. (2021, February). Clinical Development Success Rates and Contributing Factors 2011–2020. Retrieved December 4, 2024, from https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf

Success Rate for Drug Approval, by Disease Area



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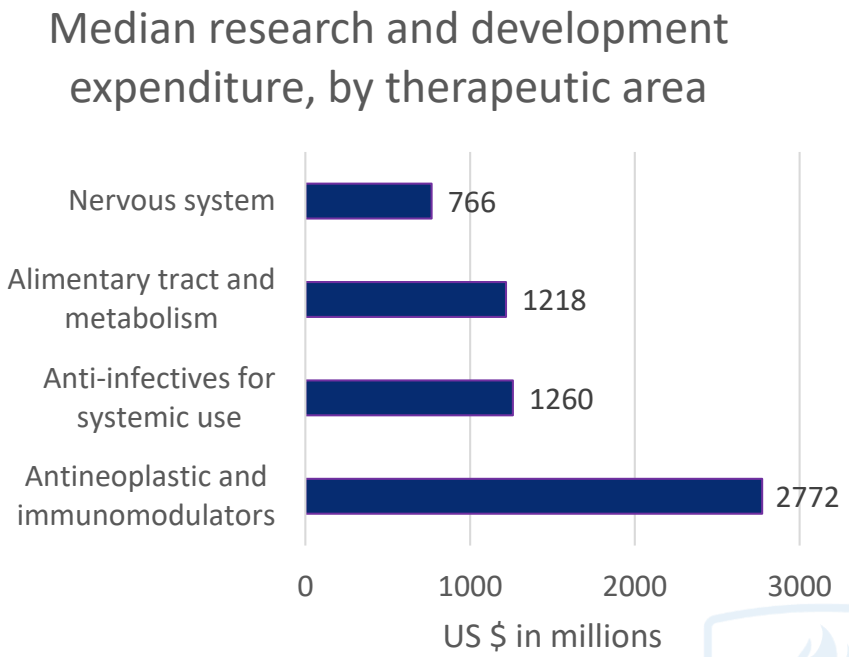
Time for Drug Approval

- On average, it takes 14 years to go from target identification to first drug approval
  - The time for clinical trials has increased in the last decade
- It is important to get innovative and effective medicines to patients quickly
- FDA has devised pathways to expedite approval—accelerated pathway, fast-track designation
  - Optimize tension between access and safety/effectiveness

Source: Martin, L., Hutchens, M., & Hawkins, C. (2017). Trial watch: Clinical trial cycle times continue to increase despite industry efforts. *Nature Reviews. Drug discovery, 16*(3), 157. https://doi.org/10.1038/nrd.2017.21

Cost to Develop a New Drug

- How much do pharmaceutical companies spend on research and development to bring a single drug to the market?
  - Median cost is $1.1 billion
  - Mean cost is $1.6 billion
- Cost varies by therapeutic categories
  - Highest for anticancer and immunomodulators



Data source: Wouters, O. J., McKee, M., & Luyten, J. (2022). Errors in source data for study of drug development costs. *JAMA, 328*(11), 1110. https://doi.org/10.1001/jama.2022.14317

Summary

Lecture Summary

- **Overview of drug development:** five steps of the drug approval process
- **Regulatory agencies around the world:** although different agencies, the goal is approving safe and effective drugs
- **The Food and Drug Administration:** different agencies within the FDA to approve different types of products, e.g., drugs vs. biologics
- **Key FDA regulations:** evolution in regulations in last century to promote drug development
- **Drug approval in numbers:** drug approval success rate; cost and time to get new drugs in the market
- **FDA trailer:** nice video summarizing drug approval process
  - https://www.youtube.com/watch?v=fZ-Msidi7EE **(an active link appears in the Online Library section of the lecture page)**