2022 GWCO Congress

Life of a Novel Drug: From Birth To FDA Approval

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SPEAKER DISCLOSURE

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- **Disclosures**
  - Advisory board member for Apellis
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Expected Learning Objectives

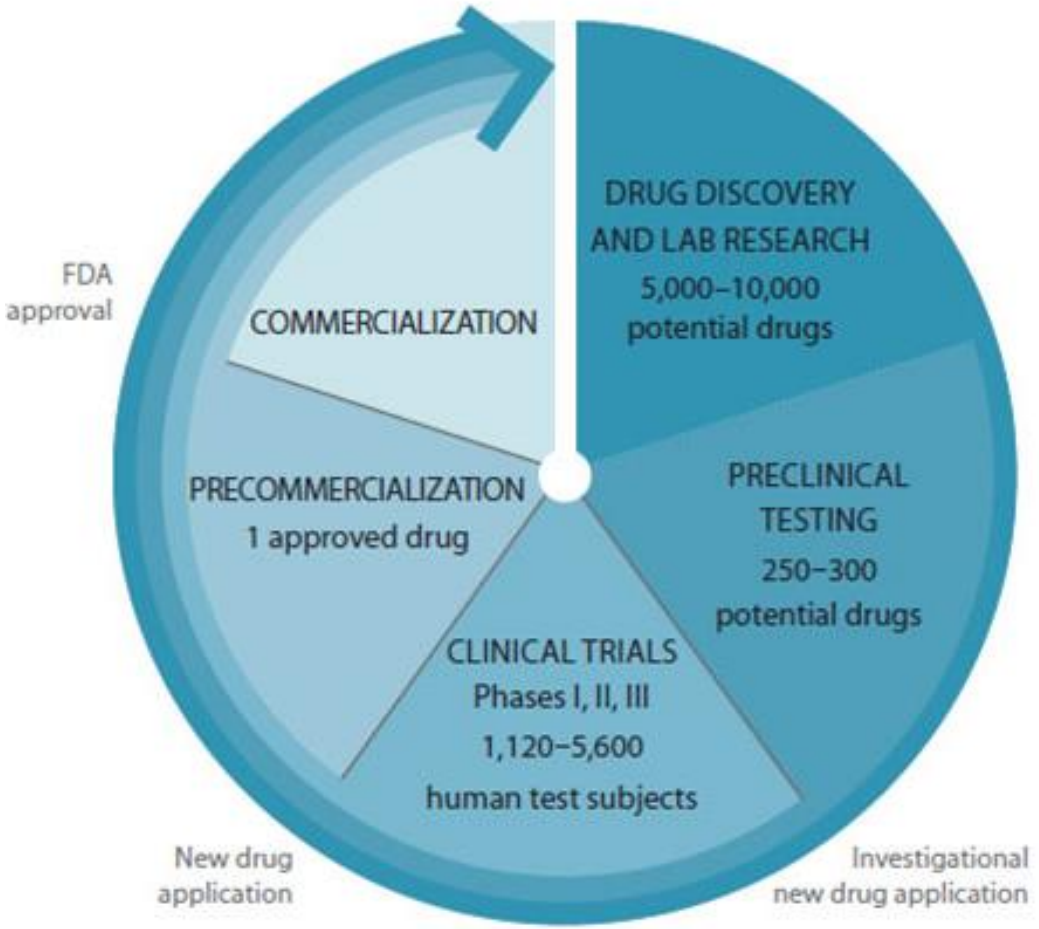
At the end of the session, attendees should be able to:

1. To describe the function of food and drug administration in approval of pharmaceutical
2. To review various steps/phases and the importance of clinical trials
3. To discuss the differences of drug approval and US FDA vs other nations.

INTRODUCTION

The development of a new therapeutic product is a long, complex and expensive process which typically takes 10 to 12 years (and sometimes more) from product identification to commercialization.

NEW DRUG DEVELOPMENT CYCLE



FROM BENCH TO RX PAD

This lifecycle usually involves the following stages:

- **Discovery and Research:** Identification of a target therapy for the diagnosis, cure, mitigation, treatment or prevention of a disease or condition.
- **Development:** This includes the necessary non-clinical research, clinical studies and chemistry, manufacturing and controls (CMC) development to support clinical trials and licensing applications .
- **Regulatory Review and Approval:** Submission of data for regulatory review to demonstrate product safety, efficacy and quality for its proposed indication.
- **Commercialization and Marketing:** Ongoing regulatory compliance through safety reports and other required submissions (e.g., product renewal).

NEW THERAPEUTIC PRODUCT DEVELOPMENT

- Development of a new therapeutic product normally begins with non-clinical testing followed by different phases of human clinical trials in support of the licensing application.
- Chemistry, Manufacturing and Controls (CMC) activities are conducted concurrently to support these studies.
- For every 5000 molecules screened, 5 make it to clinical trials, and usually only 1 becomes an approved new drug.

DISCOVERY AND DEVELOPMENT

- Researchers examine new insights into a disease process, which allows them to design a product to stop the effects of the disease.
- Then, they test molecular compounds to find possible beneficial effects against certain diseases.
- Researchers discover new drugs through existing treatments and new technologies as well.
- Then, they conduct experiments to gather information on how the drug is absorbed, distributed, metabolized, and excreted.
- They also discover its potential benefits and mechanisms of action, the best dosage, the best way to give the drugs, side effects of adverse events, how it affects different groups of people, how it interacts with other drugs and treatments, and its effectiveness compared to other drugs.

DISCOVERY AND DEVELOPMENT

- R&D In the laboratory
  - Insight into various disease and design of products to stop a/o reverse the effects of these conditions
  - Testing molecular compounds
  - Research on unanticipated effects of existing drugs
  - Development of new technologies such as new delivery modalities

PRECLINICAL PHASE

- This preclinical phase of drug development has a *high rate of failure* and involves the identification, synthesis, and purification of a molecule and the determination of potential safety and efficacy.
- The practical application of basic science through translational research leads to drug candidates that undergo initial toxicology studies in nonhuman animals.
- Positive results in the preclinical phase lead manufacturers to filing an investigational new drug application (IDA) with the FDA, which is a prerequisite to testing any product in humans.

PRECLINICAL/NON-CLINICAL STUDIES

- Non-clinical testing (laboratory experimentation and animal investigation) assesses the potential therapeutic effects of a drug substance and demonstrates the reasonable safety of a substance before it can move to human studies.
- It may also include long-term studies (e.g., reproductive and carcinogenicity studies) that are conducted after the clinical trial is initiated.

PRECLINICAL/NON-CLINICAL STUDIES

- Non-clinical studies must be conducted following Good Laboratory Practices (GLP).
- This phase of testing may include *in vitro* and *in vivo* studies to research metabolism (pharmacodynamics [PD] and pharmacokinetics [PK]), safety, toxicity, dosage and efficacy.
- Positive results in the preclinical phase lead manufacturers to filing an investigational new drug application with the FDA, which is a prerequisite to testing any product in humans.

PRECLINICAL/NON-CLINICAL STUDIES

- Preclinical Research Summary
  - Before Human Use, research to assess potential causes of toxicity and serious harm
    - In Vitro Studies
    - In Vivo Studies

PRECLINICAL/NON-CLINICAL STUDIES

FDA requires good laboratory practices (GLP)

- Components of GLP
  - Study conduct
  - Personnel
  - Facilities
  - Equipment
  - Written protocols
  - Operating procedures
  - Study reports
  - A system of quality assurance and oversight for each study

CLINICAL RESEARCH

- Once drug safety is established in preclinical phase, clinical research also known as clinical studies or trials are conducted to establish efficacy
- In designing clinical trials, developers have to consider what they need to accomplish for each of the different Clinical Research Phase
- Investigational New Drug Process (IND) a process before clinical trial research begins

INVESTIGATIONAL NEW DRUG APPLICATION

The IND is the launching point for clinical investigations in the United States and is an essential step along the path toward getting a new drug on the market.

IND Application Must Include:

- Animal study data and toxicology data
- Manufacturing information
- Clinical protocols (study plans)
- Data from any prior human research
- Information about the investigators
- FDA IND Review Team and Study Approval

CLINICAL TRIALS

- The objective of clinical trials is to evaluate the **safety** and **efficacy** of a product in humans.
- A clinical program involves **four phases** and must comply with regional requirements as well as Good Clinical Practices (GCP).
- Phases I to III are conducted to collect **safety** and **efficacy** information in support of the licensing application.
- Phase IV is conducted post-marketing (i.e., once the product reaches the market).

ROLES AND RESPONSIBILITIES

- **Principal Investigator**
  - Also called PI
  - The person(s) in charge of a clinical trial or a scientific research grant.
  - Prepares and carries out the clinical trial protocol (plan for the study) or research paid for by the grant.
  - Responsible for assuring compliance with applicable University IRB policies and procedures, DHHS Federal Policy Regulations, and FDA regulations and for the oversight of the research study and the informed consent process.

ROLES AND RESPONSIBILITIES

- Clinical Trial Site
  - The place where a clinical trial or study is conducted, which must me criteria set forth by regulatory agencies.

ROLES AND RESPONSIBILITIES

- Sub-Investigators and Research Staff
  - Perform tasks as delegated by the Principal Investigator but they do not accept primary responsibility for the research study
  - There may be a number of co-investigators supporting a PI.

SELECTION OF CLINICAL TRIAL PATIENTS

- Through clinical research, specific questions related to a medical product are answered.
- Through these answers, researchers decide who qualifies to participate, how many people will be a part of the study, how long the study will last, a control group, how the drug will be administered, what assessments will be conducted, and how the data will be reviewed.

SELECTION OF CLINICAL TRIAL PATIENTS

- Volunteer recruitment
  - Qualified subjects
  - Informed Consent
    - Declaration of Helsinki
- Inclusion Criterion
- Exclusion Criterion

PHASE I – HUMAN PHARMACOLOGY

- Phase I starts with the initial administration of an investigational product into humans (healthy volunteers, or in patients if for the use of cytotoxic drugs).
- **These studies usually have non-therapeutic objectives.**
- The study design can be open and baseline-controlled or may use randomization and blinding to improve the validity of observations in the study.

PHASE I – HUMAN PHARMACOLOGY

- Phase I clinical trials may include:
  - An estimation of the initial safety and tolerability, including both single- and multiple-dose administration
  - A pharmacokinetics [PK] study
  - Pharmacodynamics [PD] studies, and studies relating drug blood levels to response (PK/PD studies)
  - Early measures of product activity

PHASE I – HUMAN PHARMACOLOGY

- Phase I Summary
  - Purpose: Safety and Dosage
  - 20-100 healthy volunteers or people with the disease
  - Study length usually several months

PHASE II – THERAPEUTIC EXPLORATORY

- Phase II **explores the therapeutic efficacy** in patients, with the designs including concurrent controls and comparisons with the baseline status.
- The patient population is normally selected with narrow criteria.
- A major objective is to determine the dose(s) and regimen to support.

PHASE II – THERAPEUTIC EXPLORATORY

- Phase II Summary
  - Purpose: Efficacy and adverse events
  - Up to several hundred subjects with the disease
  - Several months to 2 years

PHASE III TRIALS

- Phase 3 trials—the large, randomized, controlled clinical trials
- Other objectives may include:
  - Potential study end point evaluations
  - Therapeutic regimens
  - Target populations (e.g., mild versus severe disease)

PHASE III – TRIALS

- Phase III Summary
  - Purpose: Efficacy and monitoring adverse reactions
  - 300-3000 volunteer subjects who have the disease
  - 1 to 4 years

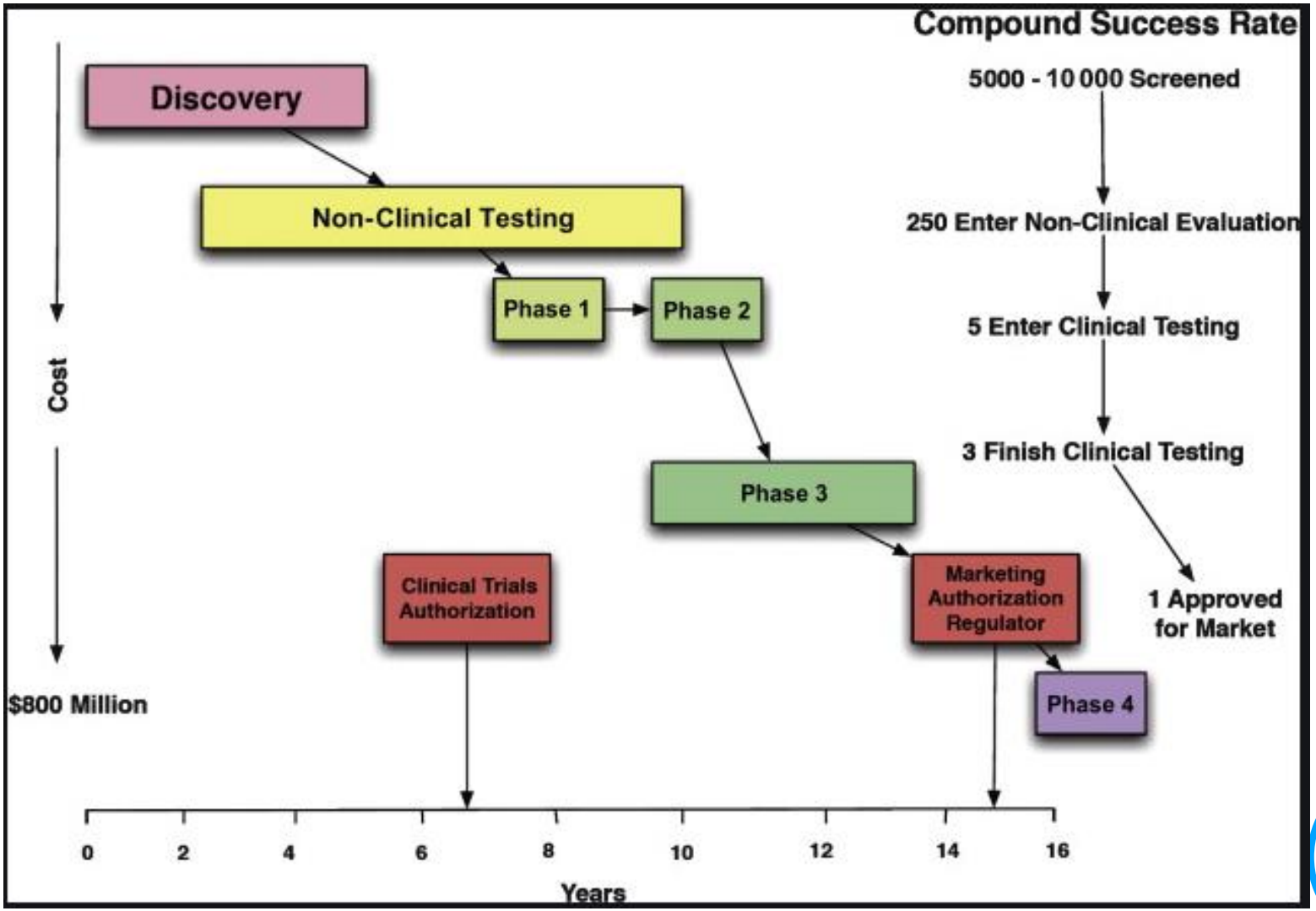
PHASE IV

- **Post-market drug safety monitoring**
- The FDA reviews reports of problems with drugs and can decide to add cautions to the dosage or usage information, as well as other measures for more serious issues.

PHASE IV

- Phase IV Summary
  - Purpose: Safety and efficiency
  - Several thousand volunteers who have the disease
  - Or individual adverse events reports by prescribers

FROM BENCH TO RX PAD



DRUG DEVELOPMENT CHALLENGES

- A lengthy process
- A high degree of uncertainty that a drug will actually succeed
- Increasing costs and pressure on pricing

FDA DRUG REVIEW

- First, a pharmaceutical company submits a drug application that the FDA evaluates for affirmation of efficacy and safety are called pivotal trials.
- The FDA reviews the drug and approves or rejects it.
- Finally, an FDA advisory committee provides their input.

NEW DRUG APPLICATION

The NDA is a formal request made by a Sponsor to market a new drug in the United States. NDAs are typically regulated by FDA's Center for Drug Evaluation and Research (CDER).

NDA Application Must Include:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information
- Process of patent extension
- Data from studies conducted outside of the US
- Institutional review board compliance information
- Direction for use

FDA DRUG REVIEW

- The goal of the FDA is person-centric: to ensure that human drugs in the United States are effective and reasonably safe.
- The Prescription Drug User Fee Act (PDUFA) was developed to streamline the review process of NDAs and BLAs
  - Review deadlines are set by the FDA to accept or reject applications by 10 months following submission for typical applications.
  - Or by 6 months for applications eligible for priority review.
  - Drugs that may qualify for priority review must meet significant therapeutic advancement criteria compared with available treatments.

FDA DRUG REVIEW

- Following approval of a drug, the manufacturer *continues* to monitor adverse effects and clinical benefits, which may be formally evaluated through a **phase 4 clinical trial**.
- Adverse events identified in a clinical setting by physicians or patients are to be reported through the FDA's Adverse Event Reporting System.
- Underreporting is a serious concern, and as a result a system called the Sentinel Initiative was developed to ensure the ability to evaluate data from a large number of individuals using electronic records, insurance registries, and insurance claims.

FDA POST-MARKET DRUG SAFETY MONITORING

- Supplemental application
- INDs for marketed drugs
- Manufacturer inspections
- Drug advertising
- Generic Drugs
- Biosimilars
- Reporting Problems
- Active Surveillance

ACCELERATED APPROVAL

- Accelerated Approval can be applied to promising therapies that treat a serious or life-threatening condition and provide therapeutic benefit over available therapies.
- This approach allows for the approval of a drug that demonstrates an effect on a "surrogate endpoint" that is reasonably likely to predict clinical benefit, or on a clinical endpoint that occurs earlier but may not be as robust as the standard endpoint used for approval.
- This approval pathway is especially useful when the drug is meant to treat a disease whose course is long, and an extended period of time is needed to measure its effect.
- After the drug enters the market, the drug maker is required to conduct post-marketing clinical trials to verify and describe the drug's benefit.
- If further trials fail to verify the predicted clinical benefit, FDA may withdraw approval.

EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

- The Orphan Drug Act (1983) allows maximum flexibility to the design of pivotal trials, including single-arm studies and use of surrogate end points for drugs that treat rare conditions
  - Conditions with fewer than 200,000 individuals affected in the United States
    - Ex: Biallelic RPE65 mutation (cause of Leber's congenital amaurosis)
  - To promote drug development for rare conditions, manufacturers are also eligible for the Orphan Drug Act tax credit which covers 25% of research and development costs and access to grants and additional market exclusivity

EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

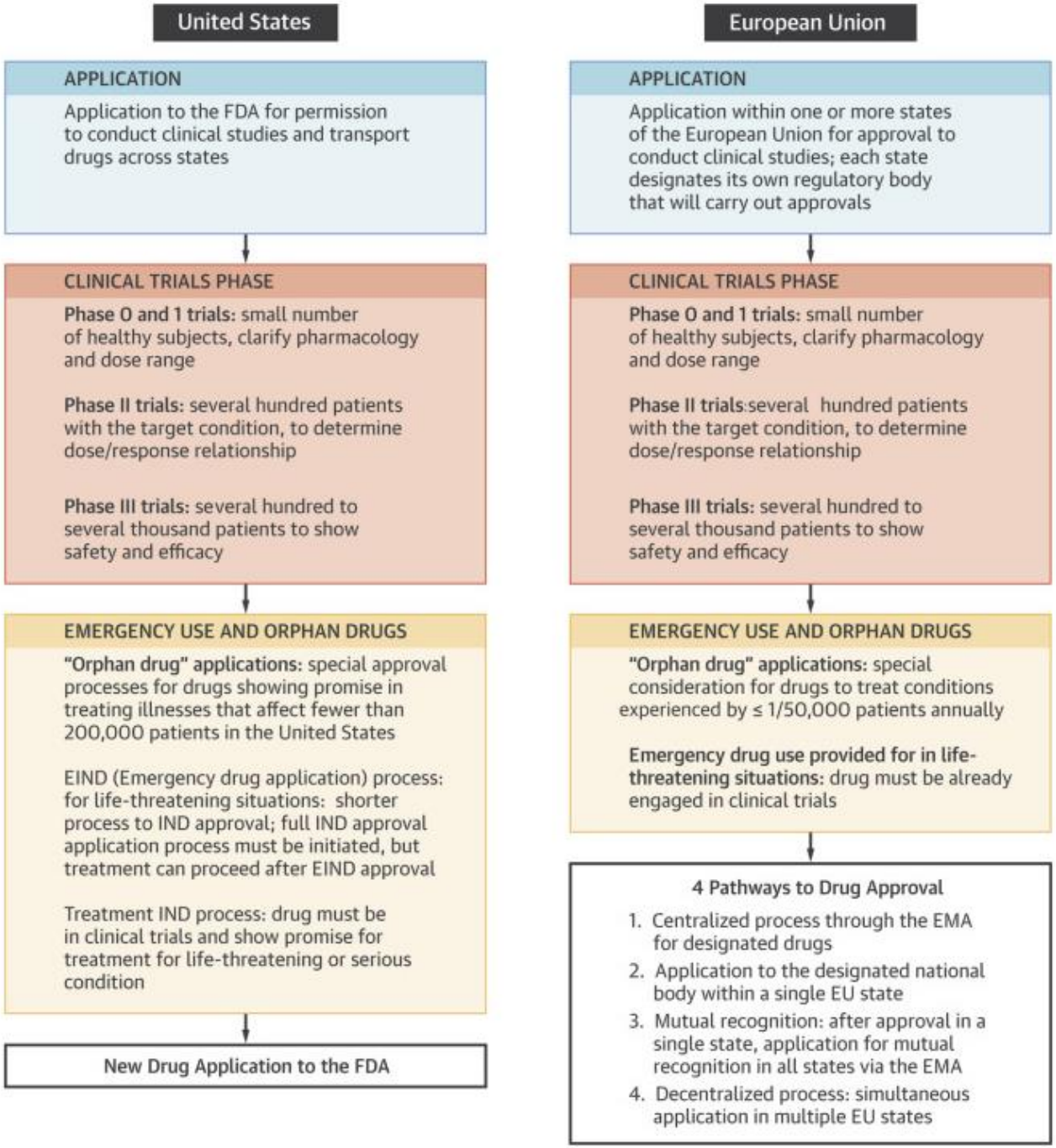
- Fast-track designation (1988) was developed at the height of the AIDS crisis and may be granted to drugs that fill an unmet clinical need.
- Drugs that may qualify include those for conditions with no currently approved treatment
  - Ex. Geographic atrophy
- Drugs that receive this designation may be approved without phase 3 clinical trials.

EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

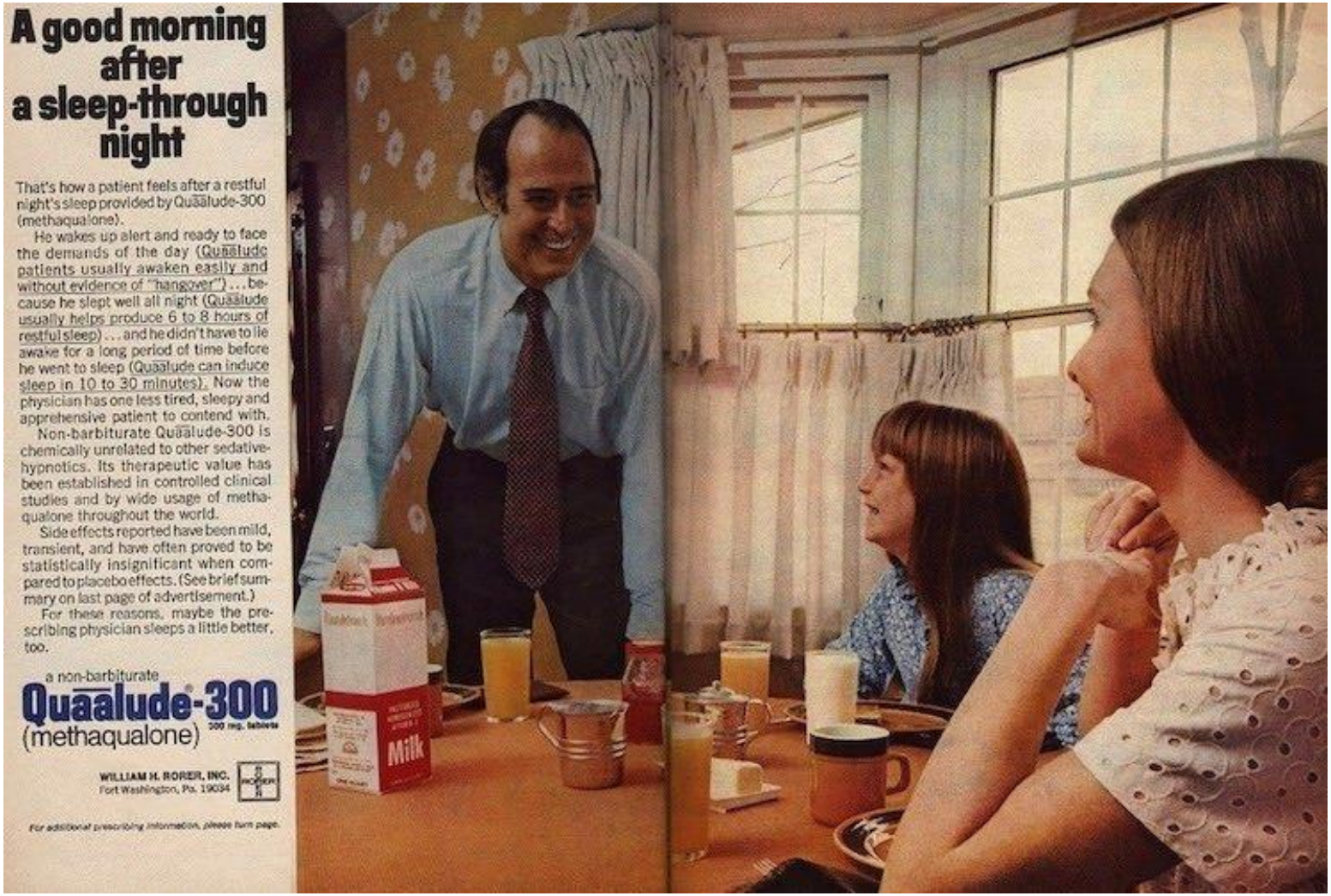
- Accelerated approval (1992) may be granted to drugs based on evaluation of surrogate end points in clinical trials that are "reasonably likely to produce patient benefit" in drugs that fill an unmet clinical need for the treatment of serious conditions, which can shorten the length of pivotal trials.
  - Granted to drugs designed to treat serious conditions when preclinical data indicate significant improvement over current treatments.

EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

- The 21st Century Cares Act was passed by Congress in 2016 to accelerate drug discovery, development, and delivery of new treatments for patients in new ways, including allowing for the modernization of clinical trial design and incorporation of real-world or observational evidence into the FDA's decision-making process.
- It emphasizes the use of the above pathways to expedite drug development and includes 2 new expedited development programs for biologics and devices.


United States
APPLICATION
Application to the FDA for permission to conduct clinical studies and transport drugs across states
CLINICAL TRIALS PHASE
Phase 0 and 1 trials: small number of healthy subjects, clarify pharmacology and dose range
Phase II trials: several hundred patients with the target condition, to determine dose/response relationship
Phase III trials: several hundred to several thousand patients to show safety and efficacy
EMERGENCY USE AND ORPHAN DRUGS
"Orphan drug" applications: special approval processes for drugs showing promise in treating illnesses that affect fewer than 200,000 patients in the United States
EIND (Emergency drug application) process: for life-threatening situations: shorter process to IND approval; full IND approval application process must be initiated, but treatment can proceed after EIND approval
Treatment IND process: drug must be in clinical trials and show promise for treatment for life-threatening or serious condition
New Drug Application to the FDA
European Union
APPLICATION
Application within one or more states of the European Union for approval to conduct clinical studies; each state designates its own regulatory body that will carry out approvals
CLINICAL TRIALS PHASE
Phase 0 and 1 trials: small number of healthy subjects, clarify pharmacology and dose range
Phase II trials:several hundred patients with the target condition, to determine dose/response relationship
Phase III trials: several hundred to several thousand patients to show safety and efficacy
EMERGENCY USE AND ORPHAN DRUGS
"Orphan drug" applications: special consideration for drugs to treat conditions experienced by ≤ 1/50,000 patients annually
Emergency drug use provided for in life-threatening situations: drug must be already engaged in clinical trials
4 Pathways to Drug Approval
1. Centralized process through the EMA for designated drugs
2. Application to the designated national body within a single EU state
3. Mutual recognition: after approval in a single state, application for mutual recognition in all states via the EMA
4. Decentralized process: simultaneous application in multiple EU states

FDA MISTAKES



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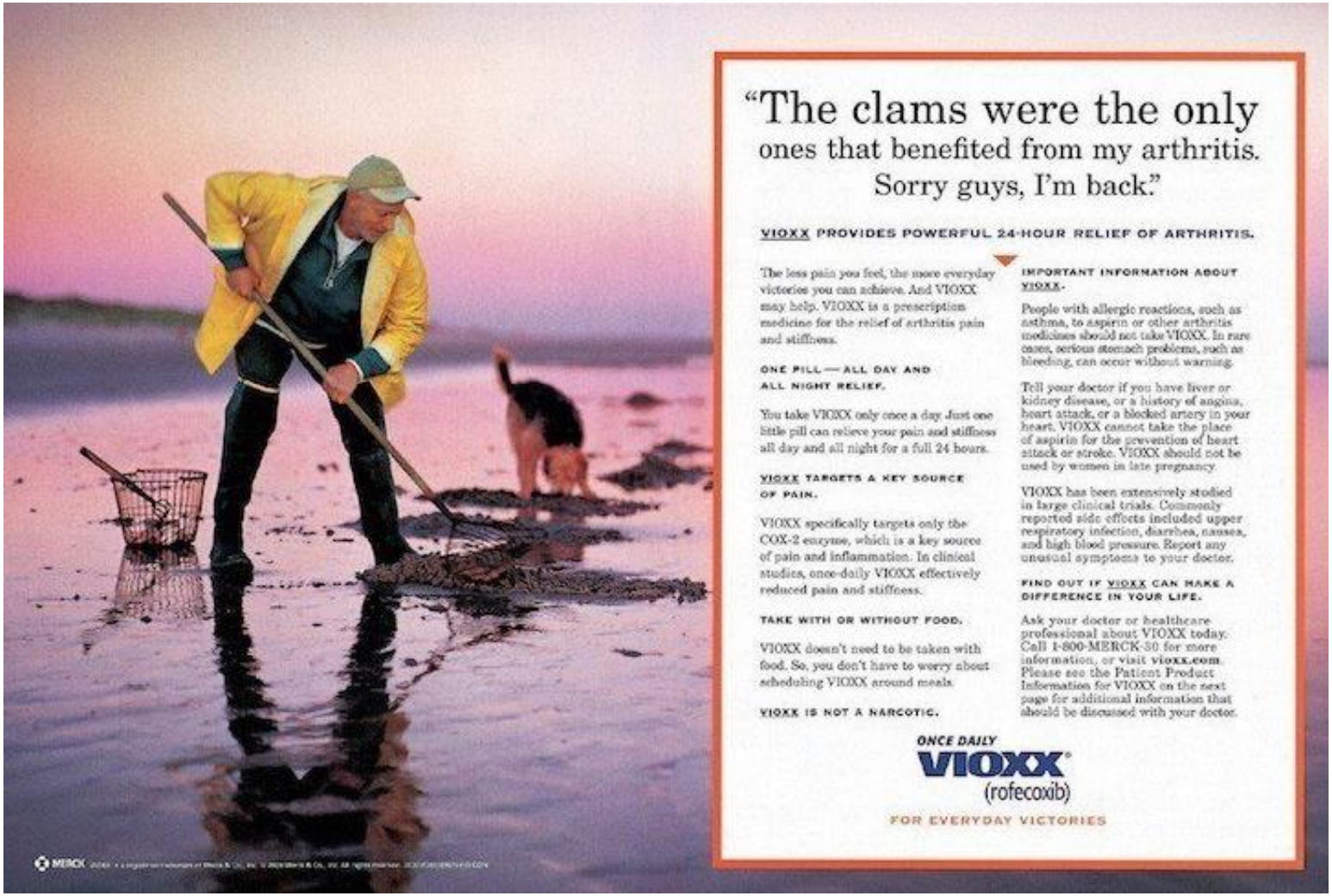
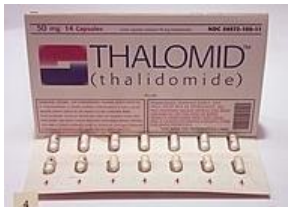


FDA VICTORIES



CONCLUSION

- Overall, the drug development cycle is complex, yet important.
- The goal of the whole process is for researchers to determine if a drug is safe and effective as a treatment for certain conditions.
- But it is vital that biotechnology and pharmaceutical companies come together to consider the causes and trends that bring on these various challenges in order to combat them and introduce beneficial drugs in the supply chain.