

2022 GWCO Congress



Life of a Novel Drug: From Birth To FDA Approval

Roya Attar, OD, MBA, FAAO

SPEAKER DISCLOSURE

- **Assistant Professor & Director of Optometric Services at the University of Mississippi Medical Center Dept of Ophthalmology**
- **Disclosures**
 - Advisory board member for Apellis
 - Advisory board member for Visus Pharmaceuticals



Expected Learning Objectives

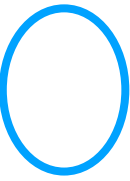

At the end of the session, attendees should be able to:

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.

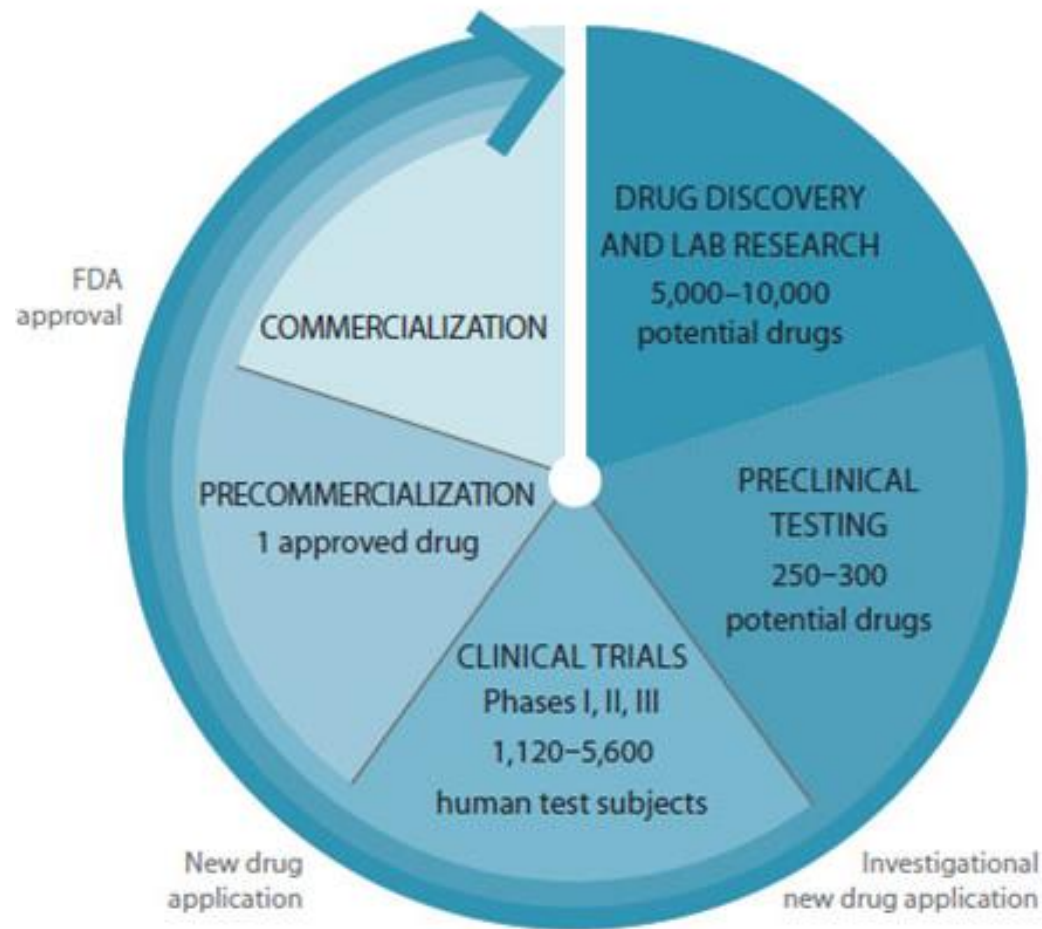


INTRODUCTION

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.



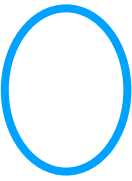
NEW DRUG DEVELOPMENT CYCLE





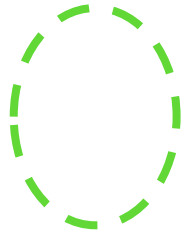
FROM BENCH TO RX PAD

This lifecycle usually involves the following stages:

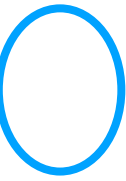
- **Discovery and Research:** Identification of a target therapy for the diagnosis, cure, mitigation, treatment or prevention of a disease or condition.
 - **Development:** This includes the necessary non-clinical research, clinical studies and chemistry, manufacturing and controls (CMC) development 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

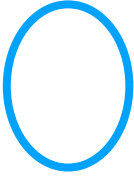


- Development of a new therapeutic product normally begins with non-clinical testing followed by different phases of human clinical trials in support of the licensing application.
- Chemistry, Manufacturing and Controls (CMC) activities are conducted concurrently to support these studies.
- For every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





DISCOVERY AND DEVELOPMENT


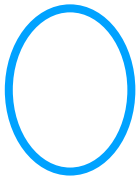
- Researchers examine new insights into a disease process, which allows them to design a product to stop the effects of the disease.
 - Then, they test **molecular compounds** to find possible beneficial effects against certain diseases.
 - Researchers discover new drugs through existing treatments and 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



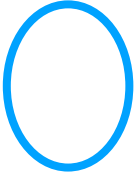
R&D In the laboratory

- 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

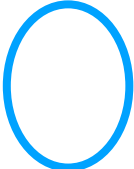


- This preclinical phase of drug development has a *high rate of failure* and involves the identification, synthesis, and purification of a molecule and the determination of potential safety and efficacy.
 - The practical application of basic science through translational research leads to drug candidates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



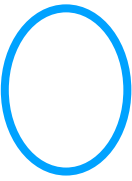
PRECLINICAL/NON-CLINICAL STUDIES



- 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.
- 

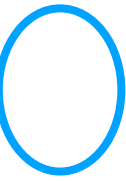


PRECLINICAL/NON-CLINICAL STUDIES



Preclinical Research Summary

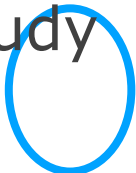
- Before Human Use, research to assess potential causes of toxicity and serious harm
 - In Vitro Studies
 - In Vivo Studies






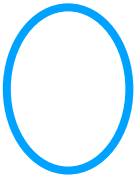
PRECLINICAL/NON-CLINICAL STUDIES

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
- 
- 

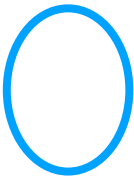


INVESTIGATIONAL NEW DRUG APPLICATION



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.

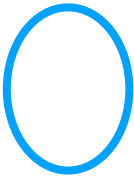
IND Application Must Include:

- 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



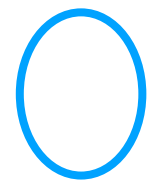
- The objective of clinical trials is to evaluate the safety and efficacy of a product in humans.
 - A clinical program involves four phases and must comply with regional requirements as well as Good Clinical Practices (GCP).
 - Phases I to III are conducted to collect safety and efficacy information 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.

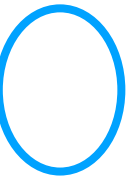




ROLES AND RESPONSIBILITIES

• Clinical Trial Site

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

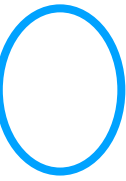




ROLES AND RESPONSIBILITIES

• 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.

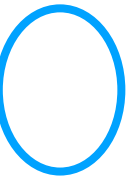




SELECTION OF CLINICAL TRIAL PATIENTS



- 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.
- 





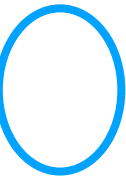
SELECTION OF CLINICAL TRIAL PATIENTS

➤ Volunteer recruitment

- Qualified subjects
- Informed Consent
 - ❖ Declaration of Helsinki

➤ Inclusion Criterion

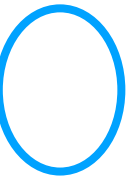
➤ Exclusion Criterion





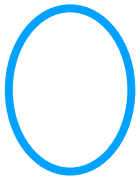
PHASE I – HUMAN PHARMACOLOGY

- 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

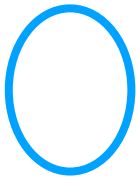
- Phase I clinical trials may include:
 - An estimation of the initial safety and tolerability, including both single- and multiple-dose administration
 - A pharmacokinetics [PK] study
 - Pharmacodynamics [PD] studies, and studies relating drug blood levels to response (PK/PD studies)
 - Early measures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



PHASE I – HUMAN PHARMACOLOGY


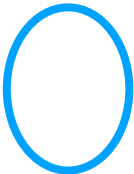


• Phase I Summary

- 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.
- 
- 

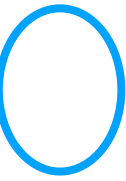


PHASE II – THERAPEUTIC EXPLORATORY



Phase II Summary

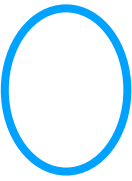
- Purpose: Efficacy and adverse events
 - Up to several hundred subjects with the disease
 - Several months to 2 years
- 





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)
- 

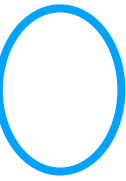


PHASE III – TRIALS



Phase III Summary


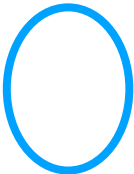
- Purpose: Efficacy and monitoring adverse reactions
 - 300-3000 volunteer subjects who have the disease
 - 1 to 4 years
- 





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.
- 
- 

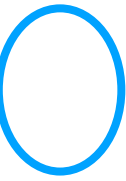


PHASE IV

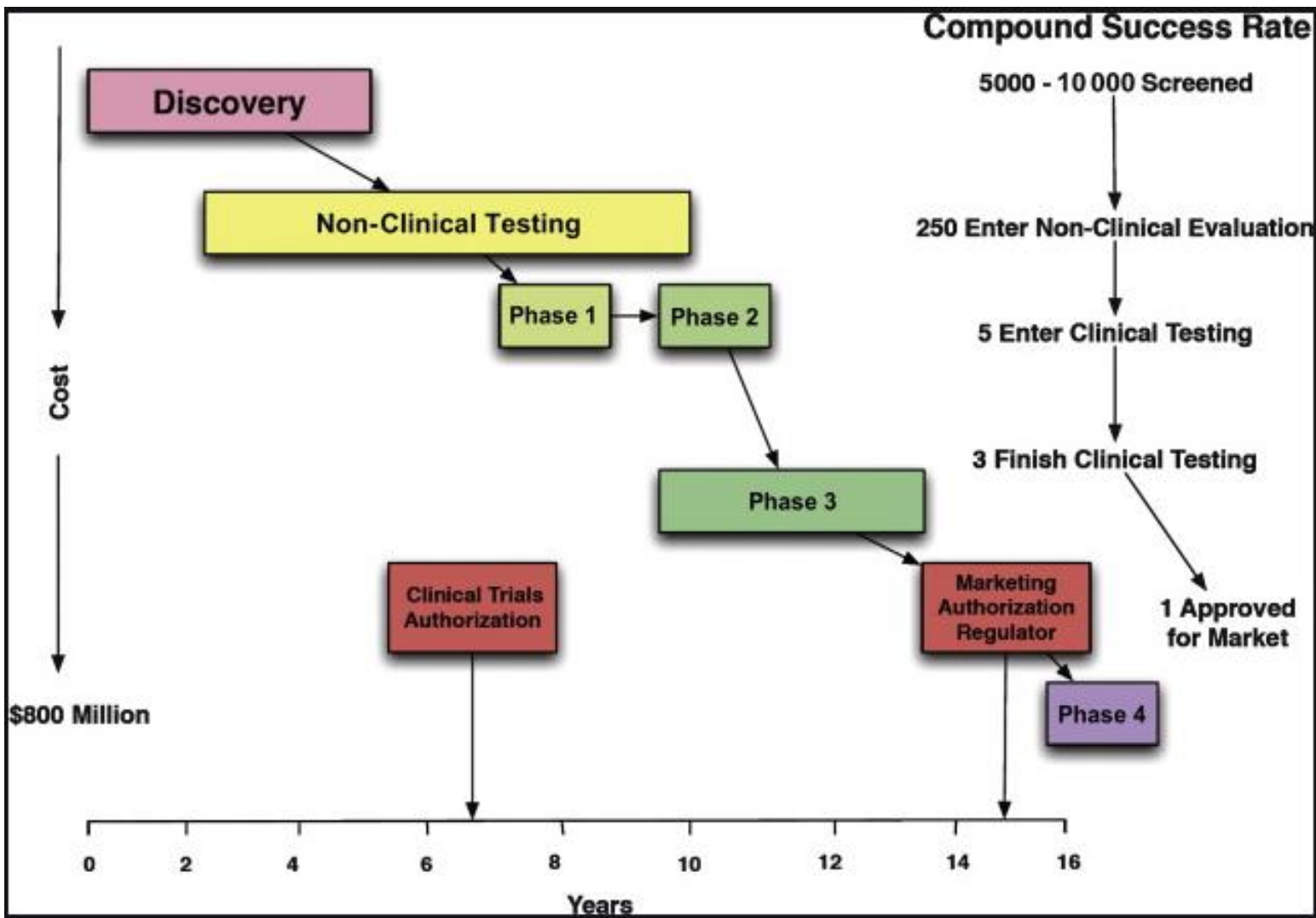


Phase IV Summary

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


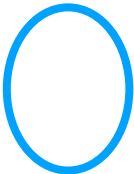


FROM BENCH TO RX PAD



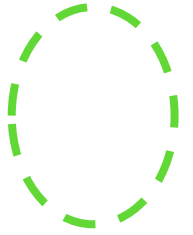



DRUG DEVELOPMENT CHALLENGES

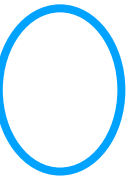
- A lengthy process
 - A high degree of uncertainty that a drug will actually succeed
 - Increasing costs and pressure on pricing
- 
- 



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.
- 

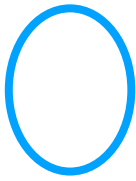




NEW DRUG APPLICATION

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).

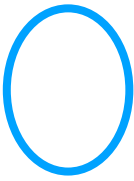
NDA Application Must Include:

- 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

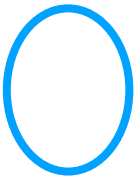


- The goal of the FDA is person-centric: to ensure that human drugs in the United States are effective and reasonably safe.
 - The Prescription Drug User Fee Act (PDUFA) was developed to streamline the review process of NDAs and BLAs
 - Review deadlines are set by the FDA to accept or reject applications 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.
- 



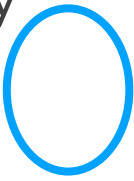
FDA POST-MARKET DRUG SAFETY MONITORING



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

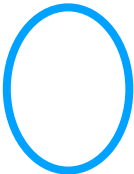


ACCELERATED APPROVAL

- 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.
- 



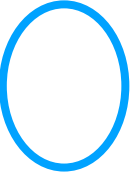
EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

- 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
- 




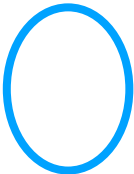
EXPEDITED PATHWAYS TO DRUG DEVELOPMENT



- 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.
- 

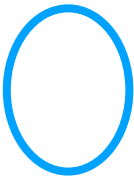


EXPEDITED PATHWAYS TO DRUG DEVELOPMENT

- 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 Cures 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 $\leq 1/50,000$ patients annually

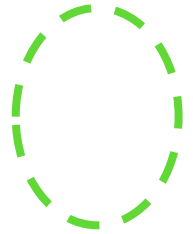
Emergency drug use provided for in life-threatening situations: drug must be already engaged in clinical trials



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



A good morning after a sleep-through night

That's how a patient feels after a restful night's sleep provided by Quaalude-300 (methaqualone).

He wakes up alert and ready to face the demands of the day (Quaalude patients usually awaken easily and without evidence of "hangover")... because he slept well all night (Quaalude usually helps produce 6 to 8 hours of restful sleep)... and he didn't have to lie awake for a long period of time before he went to sleep (Quaalude can induce sleep in 10 to 30 minutes). Now the physician has one less tired, sleepy and apprehensive patient to contend with.

Non-barbiturate Quaalude-300 is chemically unrelated to other sedative-hypnotics. Its therapeutic value has been established in controlled clinical studies and by wide usage of methaqualone throughout the world.

Side effects reported have been mild, transient, and have often proved to be statistically insignificant when compared to placebo effects. (See brief summary on last page of advertisement.)

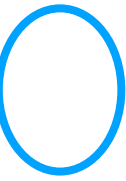
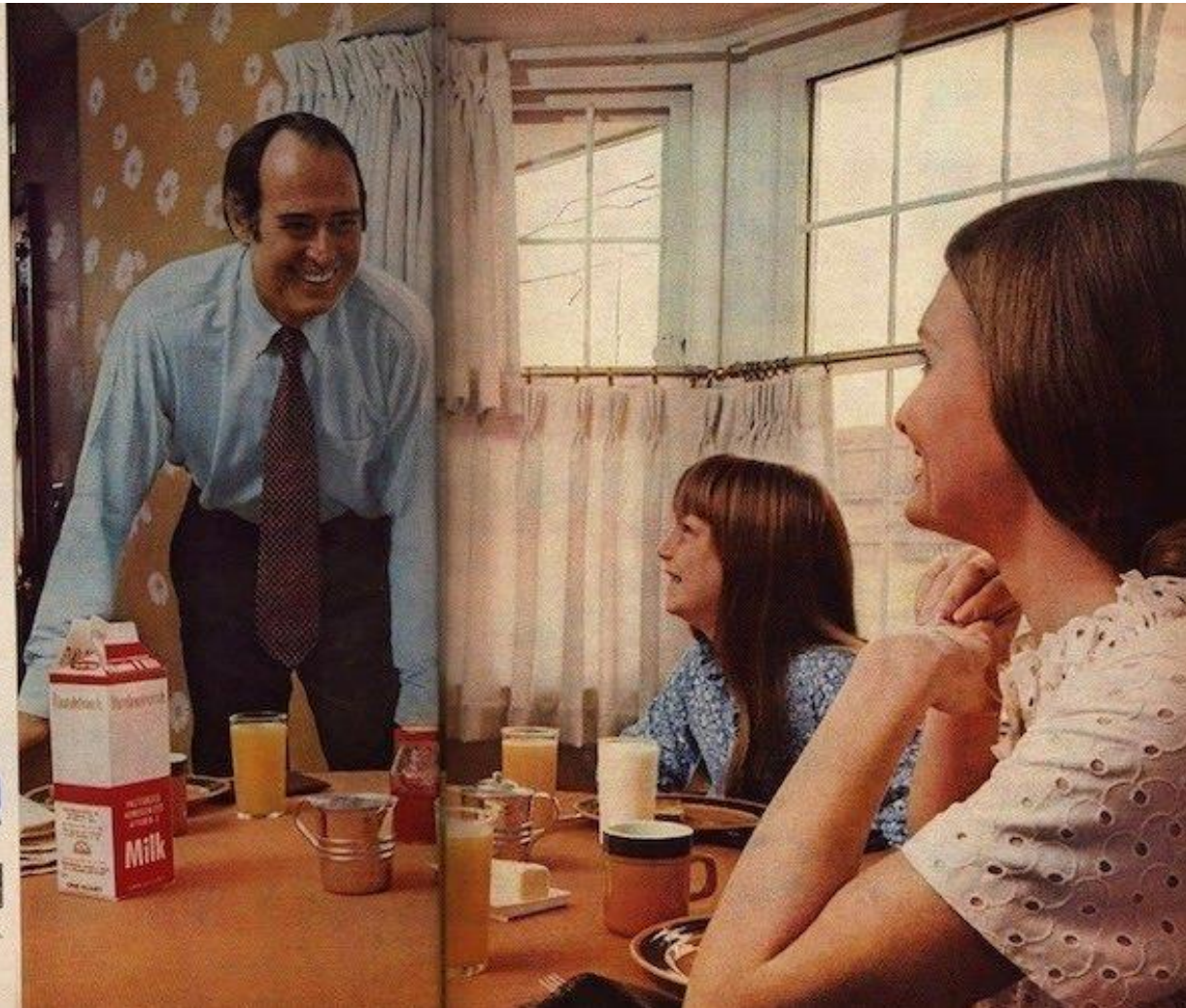
For these reasons, maybe the prescribing physician sleeps a little better, too.


a non-barbiturate
Quaalude-300
(methaqualone) 300 mg. tablets

WILLIAM H. ROPIER, INC.
Fort Washington, Pa. 19034



For additional prescribing information, please turn page.





FDA MISTAKES



**DARVON
LIFTS THE BURDEN
OF PAIN**

A non-narcotic analgesic with the potency of codeine

DARVON (Dextro Propoxyphene Hydrochloride, Lilly) is equally as potent as codeine yet is much better tolerated. You will find it helpful in any condition associated with pain. Because Darvon is non-narcotic, it is safe to use in chronic conditions requiring long-term therapy. Side effects are minimal. The usual adult dose is 32 mg. every four hours or 60 mg. every six hours as needed. Available in 32 and 60-mg. tablets.

DARVON COMPOUND (Dextro Propoxyphene and Acetylsalicylic Acid Compound, Lilly) combines the antipyretic and anti-inflammatory benefits of "A.S.A. Compound" with the analgesic properties of Darvon. Thus, it is useful in relieving pain associated with occurrence of chronic disease, such as neuralgia, neuritis, or arthritis, as well as acute pain of traumatic origin. The usual adult dose is 1 or 2 tablets every six hours as needed.

Each Tablet "Darvon Compound" provides:

"Darvon"	32 mg.
Acetylsalicylic Acid	160 mg.
"A.S.A." (Acetylsalicylic Acid, Lilly)	327 mg.
Caffeine	32.4 mg.

*A.S.A. Compound (Acetylsalicylic Acid and Acetylsalicylic Compound, Lilly)

POLIO VACCINE

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

FDA MISTAKES

"Really?"

Yes...

desPLEX[®]

to prevent ABORTION, MISCARRIAGE and
PREMATURE LABOR

*recommended for routine prophylaxis
in ALL pregnancies . .*

96 per cent live delivery with **desPLEX**
in one series of 1200 patients⁴—
— bigger and stronger babies, too.¹

No gastric or other side effects with **desPLEX**
— in either high or low dosage^{3,4,5}

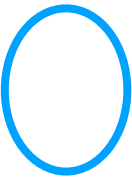
(Each **desPLEX** tablet starts with 25 mg. of diethylstilbestrol, U.S.P., which is then ultramicronized to smooth and accelerate absorption and activity. A portion of this ultramicronized diethylstilbestrol is even included in the tablet coating to assure prompt help in emergencies. **desPLEX** tablets also contain vitamin C and certain members of the vitamin B complex to aid detoxification in pregnancy and the effectuation of estrogen.)

For further data and a generous
trial supply of **desPLEX**, write to:
Medical Director

REFERENCES

1. Canalis, E. M., et al.: *Am. J. Obst. & Gynec.* 65:1299, 1953.
2. Gitman, L., and Kaplowitz, A.: *N. Y. St. J. Med.* 50:2833, 1950.
3. Karnaky, K. J.; Smith, M. J. 45:1166, 1952.
4. Peilo, E. P.: *Mind Times* 82:921, 1954; *Am. J. Surg.* 87:95, 1954.
5. Bass, J. W.: *J. Natl. M. A.* 43:30, 1951; 43:225, 1953.

GRANT CHEMICAL COMPANY, INC., Brooklyn 26, N.Y.



VIOXX PROVIDES POWERFUL 24-HOUR RELIEF OF ARTHRITIS.

IMPORTANT INFORMATION ABOUT VIOXX.

ONE PILL—ALL DAY AND
ALL NIGHT RELIEF.

Tell your doctor if you have liver or kidney disease, or a history of angina, heart attack, or a blocked artery in your heart. VIOXX cannot take the place of aspirin for the prevention of heart attack or stroke. VIOXX should not be used by women in late pregnancy.

VIOXX has been extensively studied in large clinical trials. Commonly reported side effects included upper respiratory infection, diarrhea, nausea, and high blood pressure. Report any unusual symptoms to your doctor.

FIND OUT IF **YIOXX** CAN MAKE A
DIFFERENCE IN YOUR LIFE.

Ask your doctor or healthcare professional about VIOXX today. Call 1-800-MERCK-30 for more information, or visit viox.com. Please see the Patient Product Information for VIOXX on the next page for additional information that should be discussed with your doctor.

VIOXX IS NOT A NARCOTIC.

ONCE DAILY
VIOXX®
(rofecoxib)

FOR EVERYDAY VICTORIES

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.
- 