Food and Drug Administration and Drug Development

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Background and Career

Education

- BS Biology, BS Laboratory Science
- Ph.D. Pharmaceutical Sciences (Pharmacokinetics)

Career

- Pharmacokinetic Reviewer, Division of Biopharmaceutics, CDER, Food and Drug Administration
- Mid 90's departed FDA, went into Regulatory Affairs
- Several companies during my career, start-up, small, medium, big-pharma
- Big Pharma Novartis 14 years
- Retired after 35+ years in Pharma
- Consulting

Agenda

- Evolution of Drug Regulations
- Food and Drug Administration
- Drug Development
- Benefit: Risk Assessment

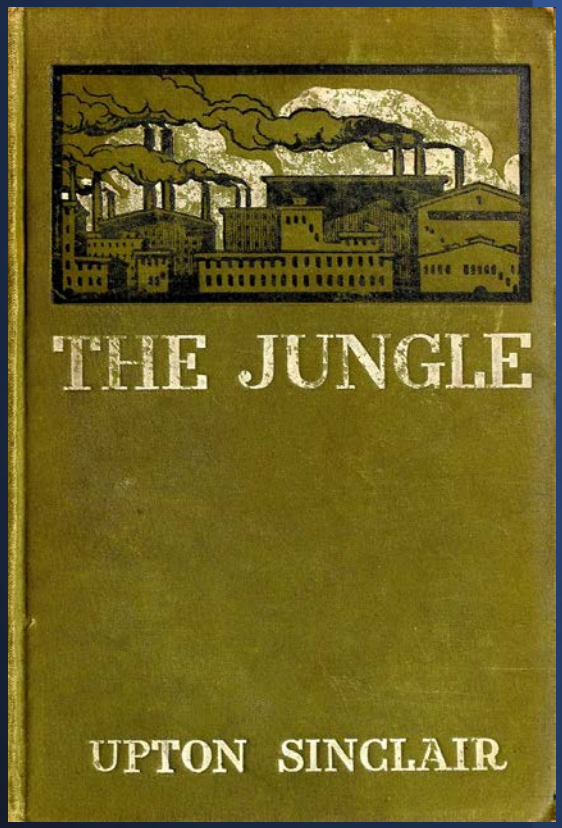
Evolution of Drug Regulations

Prior to 1906

- Unregulated consumer market
- Caveat emptor “may the buyer beware”
- “Snake oils” labeled and marketed to treat and cure ailments and diseases
- No evaluation as to safety or effectiveness

“The Jungle” Upton Sinclair

- Published February 1906
- Described unsanitary practices and health violations in the meat packing industry
- Sparked public outcry
- **In response**, June 30, 1906, Congress passed Pure Food and Drug and Meat Inspection Act
  - First Consumer Protection law to regulate food and drug industries
  - Required foods and drugs to be properly labeled, for meat to be inspected, and meatpacking plants to maintain sanitary standards
  - Establish Bureau of Chemistry, within Department of Agriculture, to oversee enforcement (In 1930, renamed the Food and Drug Administration (FDA)



Author	Upton Sinclair
Country	United States
Genre	Political fiction
Publisher	Doubleday, Page & Co.
Publication date	February 26, 1906
Pages	413

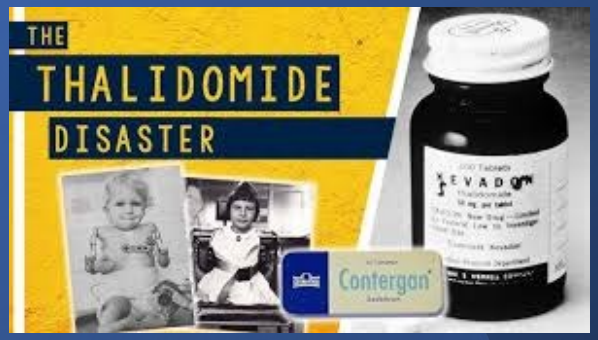
Elixir Sulfanilamide Disaster

- Sulfanilamide (Massengill), tablet and powder, used to treat streptococcal infections
- June 1937, sponsor's chemist dissolved sulfanilamide in diethylene glycol (anti-freeze) to make an elixir which was Distributed US-wide
- Fall 1937, >100 deaths in 15 states reported due to ethylene glycol toxicity
- **In response**,
  - in 1938, Congress passed Federal Food, Drug, and Cosmetic Act (FD&C Act) which increased FDA's authority to regulate drug safety

Bottles of elixir sulfanilamide

https://en.wikipedia.org/wiki/Elixir_sulfanilamide

Thalidomide



- Late 1950s, thalidomide prescribed in Europe in for morning sickness (brandname Contergan and Thalomid)
- NDA submitted to FDA to market thalidomide in the US
- FDA Medical Reviewer Frances Kelsey refused to approve because of 1) insufficient safety data and 2) anecdotal clinical evidence
- In 1957, Germany and Australia linked thalidomide to severe birth defects—hands and feet projecting directly from the shoulders and hips—that eventually shown to involve >10,000 babies
- Thalidomide never marketed in the US
- **In response** in 1962, Congress passed Kefauver-Harris amendments to the FD&C Act, requires manufacturers to
  - provide effectiveness of drug products prior to being marketed
  - conduct adequate and well-controlled clinical studies

https://en.wikipedia.org/wiki/Thalidomide

Regulation Milestones

- 1906 Pure Food and Drugs Act
  - stipulates food had to be “pure and unadulterated”
- 1938 FD&C Act
  - stipulates drugs had to be shown to be safe
- 1962 Kefauver-Harris Drug Amendments
  - stipulates sponsors had to provide evidence of both safety and efficacy of a NEW DRUG before it can be marketed

“The history of drug regulation is built on tombstones”

Michael Harris

Food and Drug Administration (FDA)

- Commissioner Robert Califf, MD
- **Mission : To protect the public's health**
- White Oak Campus Silver Spring, MD
- Regulates ~25% of the US market
  - Pharma, Food, Cosmetic, Medical Devices, OTC, Veterinary manufacturers, Tobacco products
- Approx 18,000 scientists, reviewers, auditors
- Budget $6.5 billion (2022)

How does the FDA enforce the law?
Act versus Code of Federal Regulations (CFR)

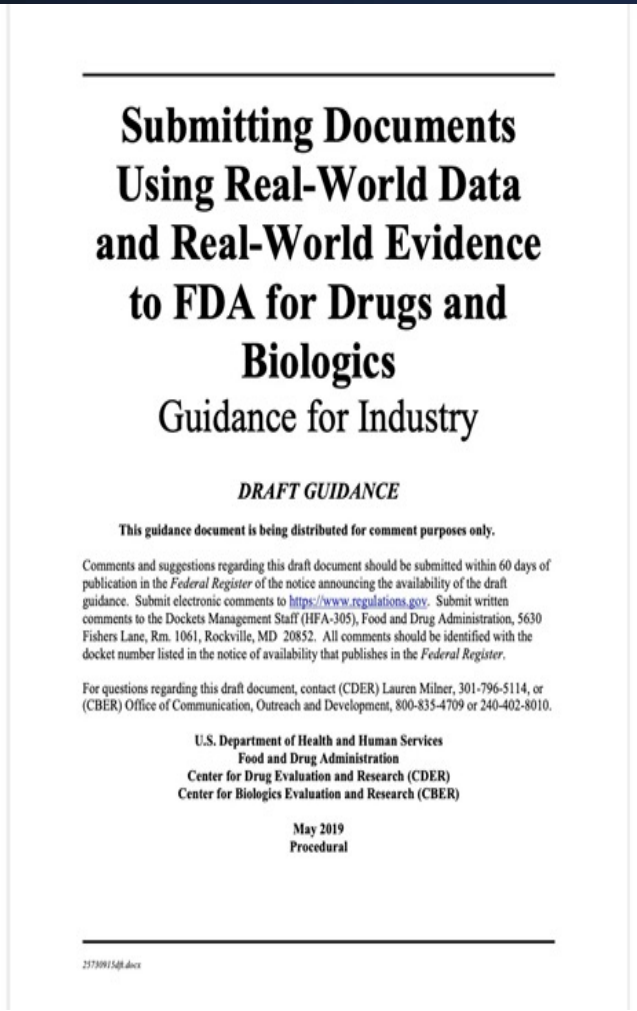
- Food Drug & Cosmetic Act (FD&C Act)
  - Broad legislation passed by Congress
  - Outlines general principles and rules of law
- Code of Federal Regulations
  - Created by Agencies
  - Specifies rules as to requirements to be followed to implement the Act

21 Code of Federal Regulations (CFR) Reserved for rules of the FDA

- CFR 312 PART 312—INVESTIGATIONAL NEW DRUG APPLICATION
  - This part contains procedures and requirements governing the use of investigational new drugs (IND), including procedures and requirements for the submission to, and review by, the FDA of IND's.

- CFR 314.105 APPROVAL OF AN NDA
  - This part sets forth procedures and requirements for the submission to, and the review by, the FDA of applications and abbreviated applications to market a new drug under section 505 of the Federal Food, Drug, and Cosmetic Act, as well as amendments, supplements, and postmarketing reports to them.

FDA Guidance for Industry



Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Lauren Milner, 301-796-5114, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

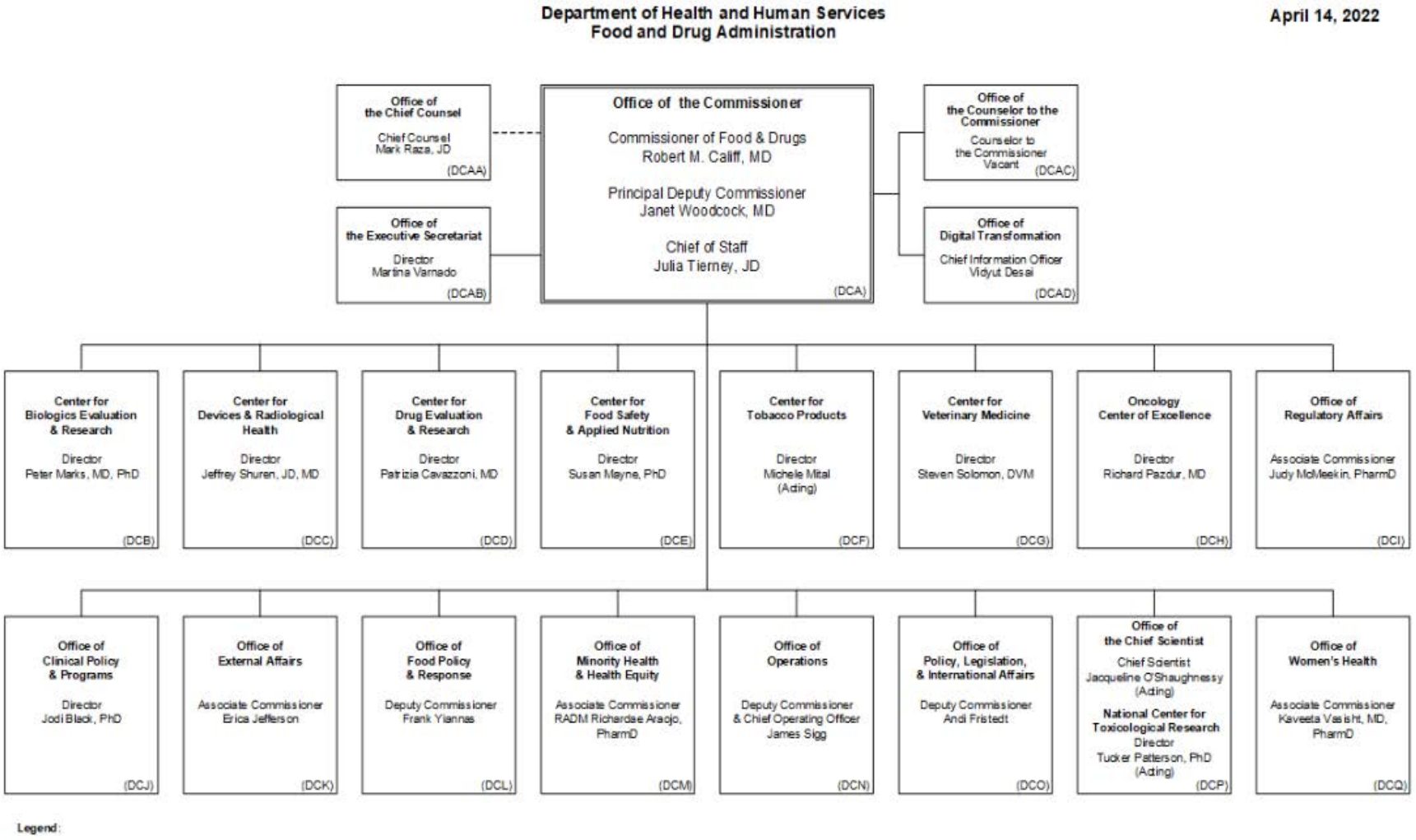
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2019
Procedural

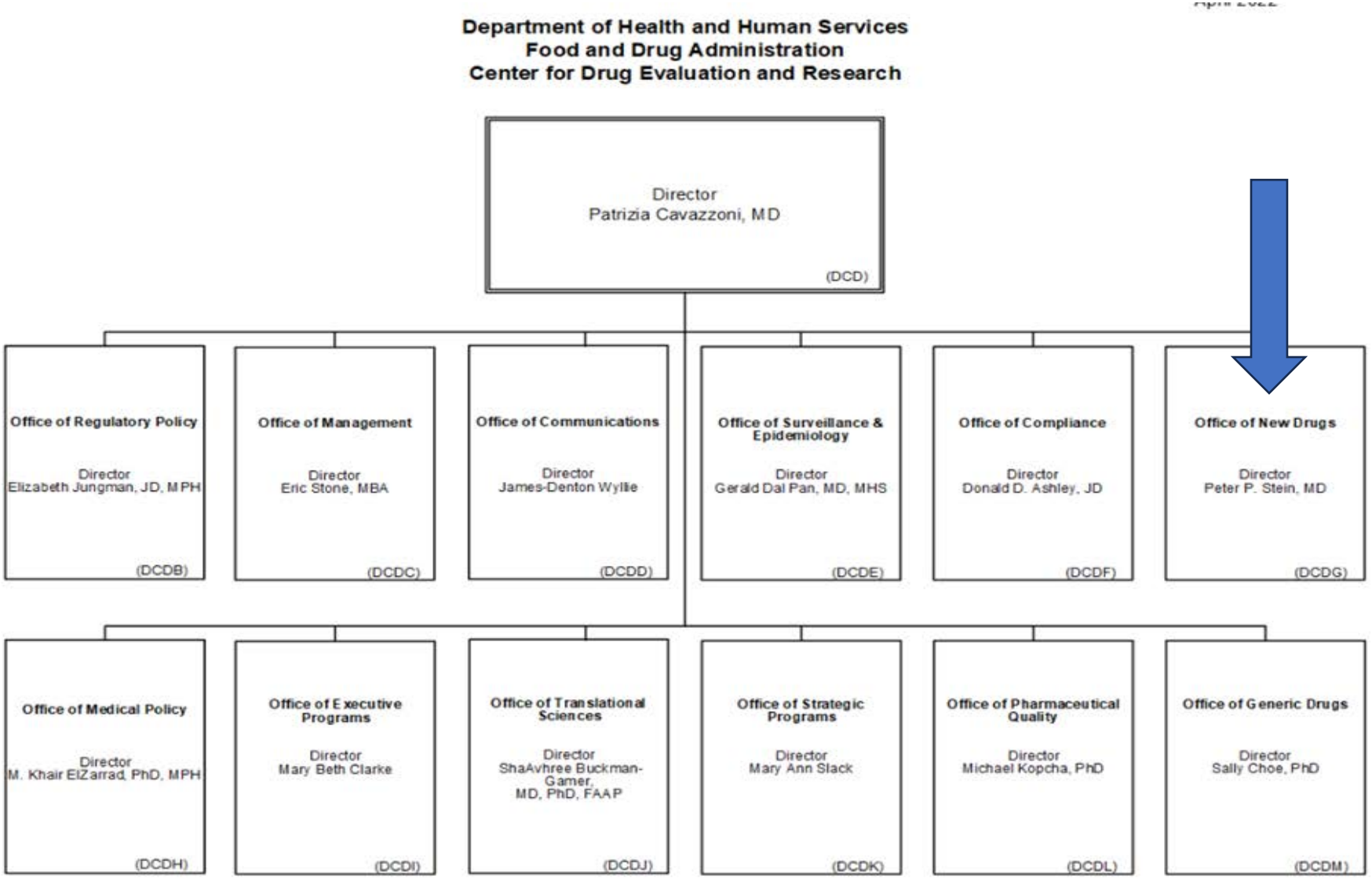
- Guidance for Industry issued by FDA on specific topics
- Represents FDA's current thinking on a topic
- Published in Federal Register for public comment before finalized which are posted at https://www.fda.gov/industry/fda-basics-industry/guidances
- Majority of guidances contained in 3 categories:
  - clinical/medical
  - pharmaceutical quality/CMC
  - procedural.
- Do not bind FDA or sponsor

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

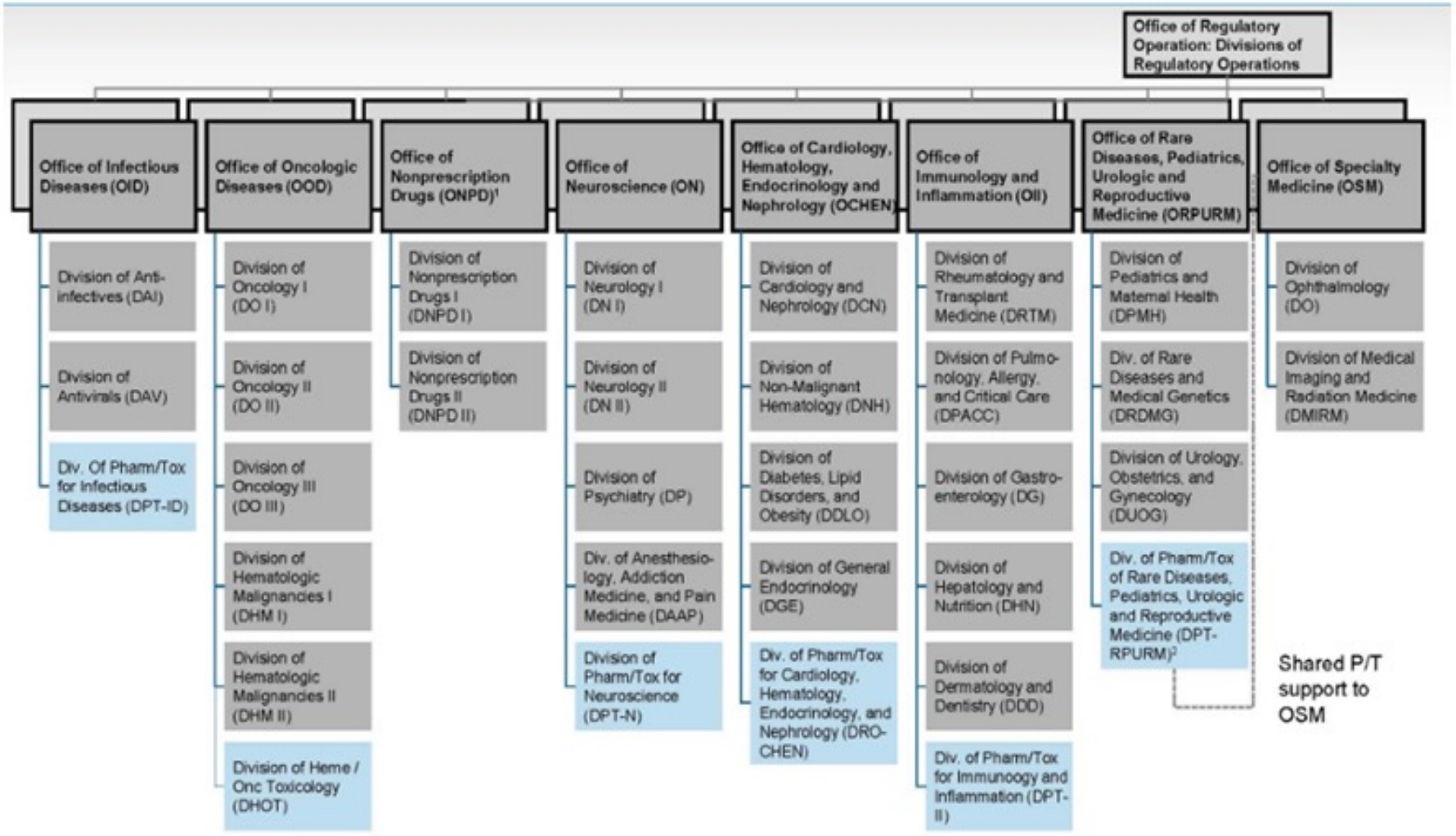
FDA Organization Chart



Center for Drug Evaluation and Research



Office of New Drugs composed of Review Divsions



Divisions' Review Team

- FDA does not conduct Clinical Studies (responsibility of sponsors)
- Analyzes study results and looks for possible issues with data, such as weaknesses of study design or statistical analyses
- Evaluates benefit: risk
- Review Team Composition
  - Project Managers (Primary FDA communicator to Sponsor's Regulatory Affairs contact)
  - Medical Reviewers
  - Biostatisticians
  - Clinical Pharmacology/Pharmacokinetic Reviewers
  - CMC
  - Toxicology reviewers
  - Device reviewers
  - Interdisciplinary Review Team for consultation ie cardiology
  - GXP inspectors for manufacturing sites and study sites

Drug Development

Start to End

Drug Development Process

STEP 1 : Discovery and Drug Development:

- Pure Science: Identifies potential receptors for a NEW DRUG to bind (agonist/antagonist) and poses hypothesis NEW DRUG that targets this receptor will have X effect
- Drug Chemist initiates synthesis of NEW DRUG
- Translational Science: Conducts investigation with NEW DRUG to determine if hypothesis is true or not

STEP 2 : If true, then Preclinical Research: NEW DRUG undergoes *in vitro* and *in vivo* animal testing to investigate drug safety and mechanism of action (GLP), if safe and has in vivo effect then

STEP 3 : Clinical Research: NEW DRUG tested on people to ensure they are safe and effective. (GCP)

PHASE 1	PHASE 2	PHASE 3
Purpose: Pharmacokinetics • Safety and dose PK determination of NEW DRUG • Study Participants 20–100 HV • Length of Ph1 - Several months • Approximately 70% of drugs move to next phase	Purpose: Dose Ranging • Efficacy and side effects of low, medium, high dose range of NEW DRUG • Study Participants Up to several hundred people with disease/ condition • Length of Ph2 - Months to 2 years • Approximately 33% of drugs move to next phase	Purpose: 2 Pivotal well-controlled trials to show Efficacy and Safety of NEW DRUG • Study Participants 300–3,000 volunteers who have disease or condition • Length of Ph3 - 1 to 4+ years • Approximately 25– 30% of drugs move to submission

STEP 4 : NEW DRUG NDA SUBMITTED: FDA review teams reviews submitted NEW DRUG data and decides to approve or not to approve (12-month review)

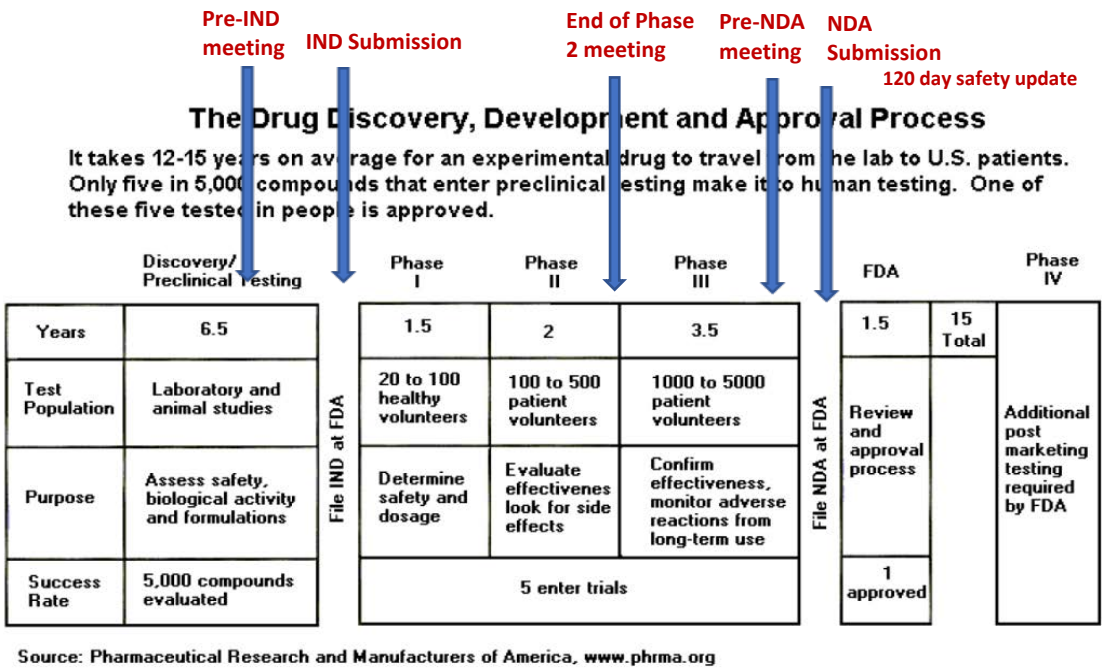
STEP 5 : IF APPROVED

- FDA and drug sponsor continues to monitor NEW DRUG safety once available in the market for use by the public.
- Additional Phase 4 studies may be performed after the NEW DRUG is approved

Start Drug Discovery to Finish Approval

Avg Duration 12-15 years

Milestones Patent filed — IND filed 30 Day review — NDA submitted - 12 months review



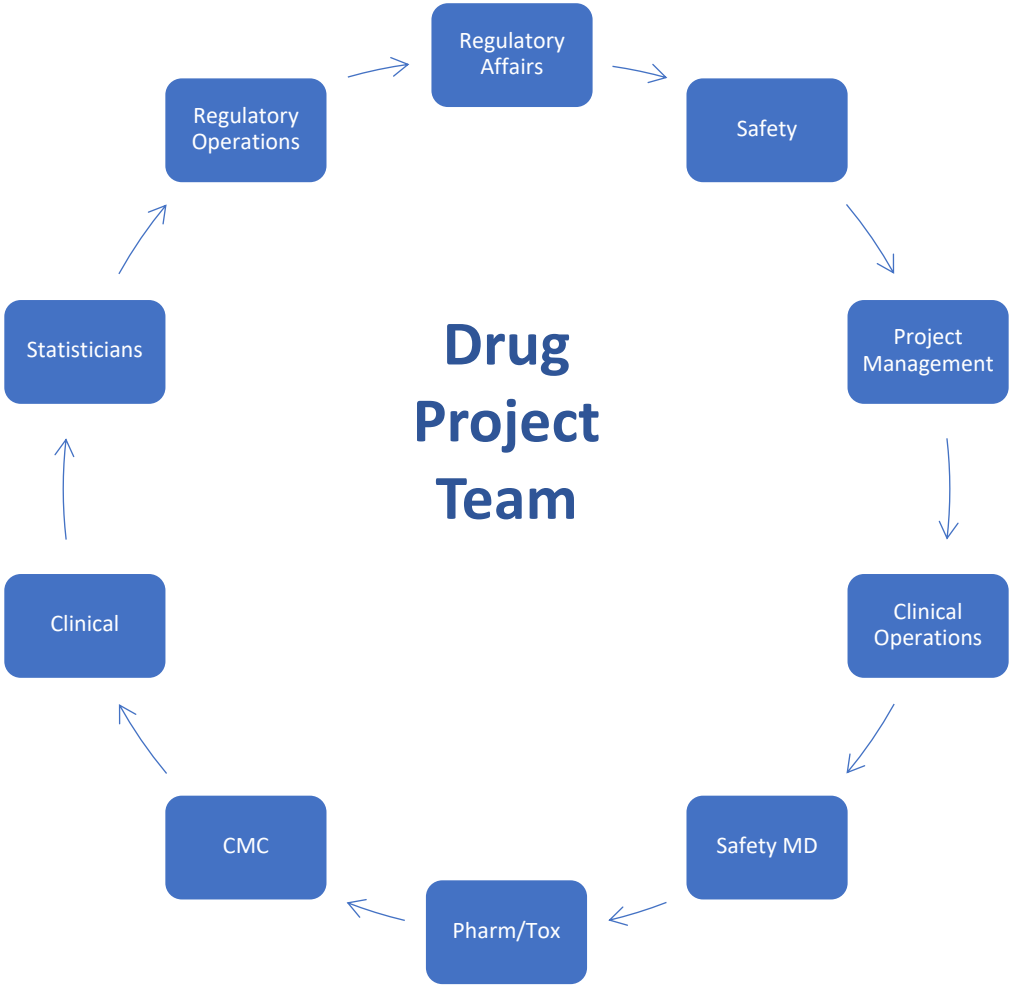
Source: Pharmaceutical Research and Manufacturers of America, www.phrma.org

Post Approval Activities

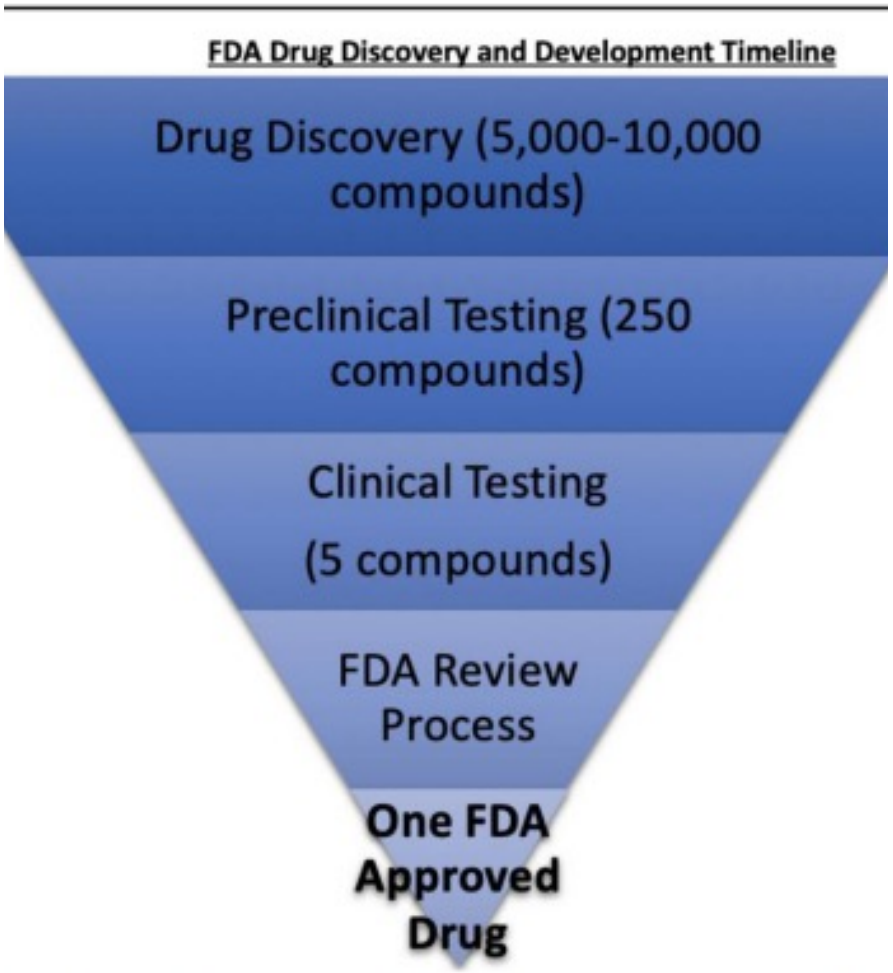
- Advertising and promotional
- Distribution
- Detailing
- Reimbursement
- Safety reporting
- Phase IV studies
- Annual Reports

Clock is ticking Patent term 20 years which starts when patent is filed

Who is doing the work?
Sponsor Drug Development Project Team



- Project Team Line Functions
  - Regulatory Affairs + Reg Ops
    - Liaise with FDA
    - Prepare submissions
    - Leads teams in preparation of Briefing Books
  - Statisticians
  - Project management
  - Clinical Operations
  - Pharmacology/Toxicology
  - CMC
  - Clinical / Safety



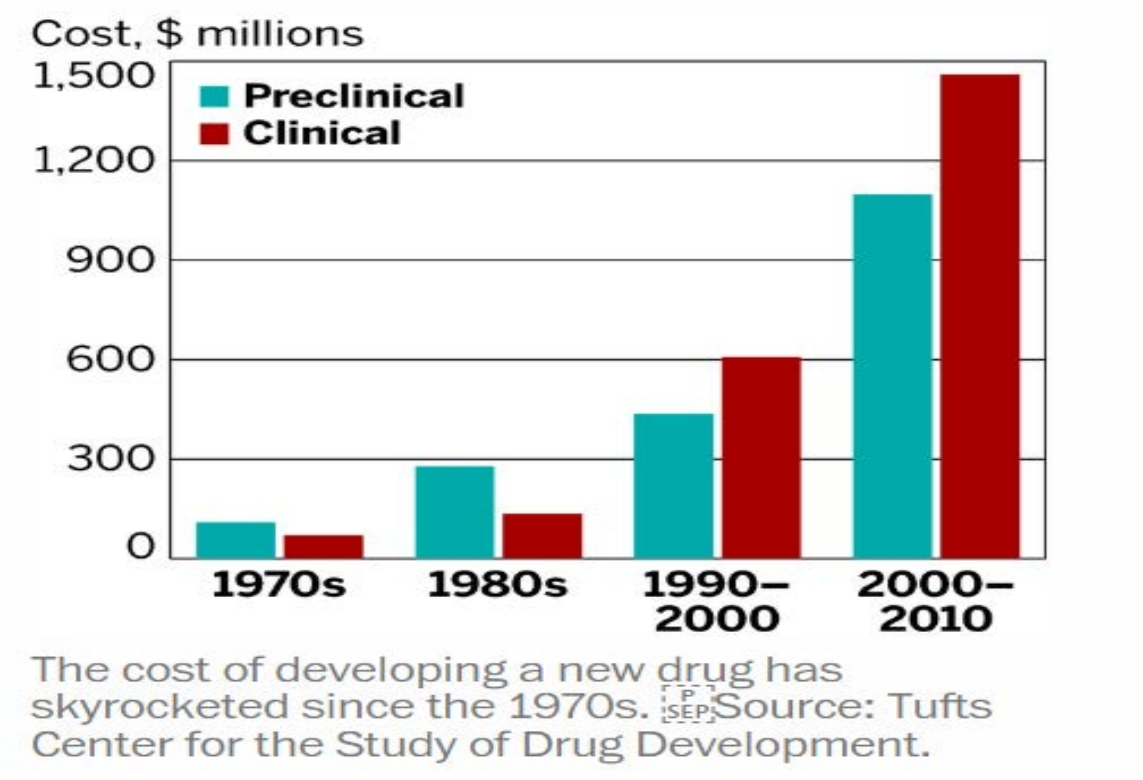
FDA Drug Discovery and Development Timeline. Thou
didate compounds are screened to eventually result in
pproved drug. This process takes on average 10–12 yea

What are the odds of a NEW DRUG going all the way from Discovery to Approval?

Cassidy et al. Infectious Agents and Cancer (2020) 15:73

Significant increase In Cost to bring NEW DRUG to market

- Cost approaching $3 billion (Rick Mullin November 20, 2014)



Mullin R; Chemical & Engineering News Volume 92, Issue 47; Nov 2014

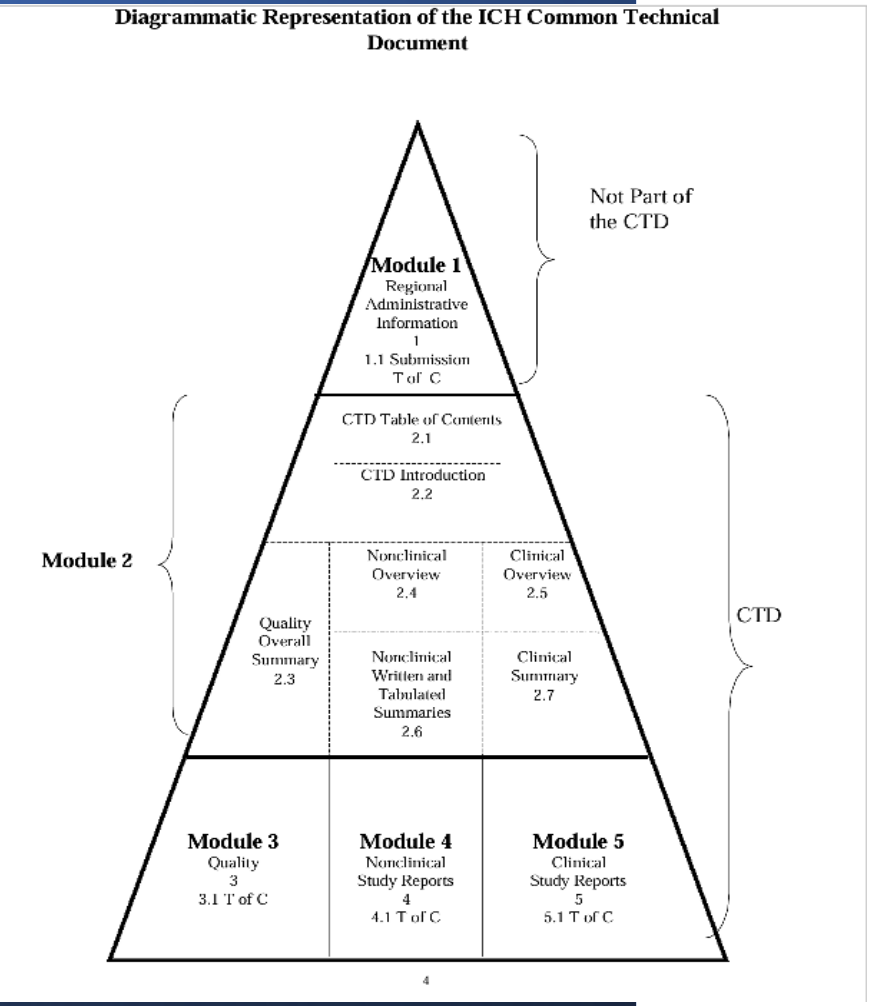
FDA Review

After NDA is submitted to the FDA

New Drug Application

- Submitted electronically Via FDA Electronic Submissions Gateway
- 12-month review
- During review
  - Reviewers ask Questions, reanalysis, additional data
  - At end of the review, labeling negotiations over package insert

Common Technical Document (e-CTD)



- Composed of 5 modules (sections)
  - Module 1 : Region-specific information
  - Module 2: Summary tables
    - CMC, PC, Clinical
  - Module 3: CMC data
    - DS
    - DP
  - Module 4: Nonclinical study reports
  - Module 5: Clinical study reports

The Comprehensive [e-CTD] Table of Contents Headings and Hierarchy

https://www.fda.gov/media/76444/download

Defining NEW DRUG Risk : Benefit
4 Questions

 **How serious is the disease/condition to be treated by the NEW DRUG?**	**<u>Serious, life threatening, or unmet medical need?</u>**
 **What are benefit(s) or advantages of the NEW DRUG compared to currently approved therapies?**	What is NEW DRUG value proposition compared to approved drug(s)? Is its efficacy superior? Better safety? More convenient?
 **If there is potential harm (risk), how big is the harm relative to the disease?**	Severe side effects of NEW DRUG for cancer is acceptable (nauseous, hair loss, bone marrow toxicity) but not for NEW DRUG for nonlife threatening indications such as allergic rhinitis
 ***Are there safer alternatives already approved?***	*If there are approved drugs that are safer or more effective, then if NEW DRUG has weaker efficacy with questionable safety, then may be strongest argument against approval*

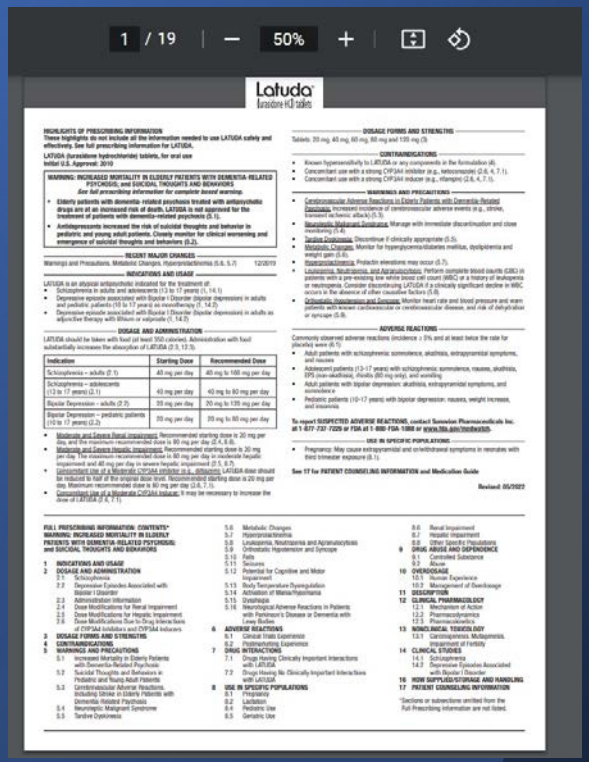
Case Study: Thalidomide
Benefit : Risk Assessment

	Morning sickness during pregnancy	Multiple myeloma
How serious is the illness/condition/ syndrome being treated ie life threatening, unmet?	Not serious Not life threatening	Unmet Serious Life threatening
Risk: How big is the harm of an AEs/SAEs?	Fetal toxicity Neuropathy Deep vein thrombosis Pulmonary embolism	Fetal toxicity Neuropathy Deep vein thrombosis Pulmonary embolism
Benefit: What is the benefit?	Marginal reduction in nausea and vomiting	Extends life overall response rates of 46%-67% for relapsed and refractory disease
Patient population	Pregnant women otherwise healthy	Multiple myeloma patients not healthy
Safer options available?	Diet	No
Approved or not approved?	**No**	**Yes approved in combination with the steroid dexamethasone 2006**

Risk: Benefit Evaluation and Probability of Approval

Efficacy : Drug vs Control p < 0.05 Safety: Drug ≥ Control Probability of Approval Very good	Efficacy : Drug vs Control p > 0.05 Safety : Drug ≥ Control Probability of Approval 0
Efficacy : Drug vs Control p < 0.05 Safety: Drug < Control Probability of Approval depends on indication • Unmet Medical Need • Life Threatening • Magnitude of effect • Can Risk Be Managed • Can Drug Be Stopped and Safety Reversed 	Efficacy : Drug vs Control p > 0.05 Safety : Drug < Control Probability of Approval 0

- 25% probability to end up in green – POA approaching 100%
- 25% probability to end up in yellow – POA depends on if the Benefit outweighs the Risk?
- 50% probability to end up in red – POA 0%



Package Insert

- Once FDA Review of NDA is completed
- Drug is approvable
- FDA Focus is on package insert (PI)
  - Contains summary of essential scientific information needed for safe and effective use of the drug
  - Is to be informative, accurate and not promotional
  - Living document that is updated when new information such as safety or new indications becomes available
  - *Prescribing Information Resources For Industry*
  - https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources

The Result

A Drug

- Time: From research to FDA approval – average 15 years
- Investment: $1 - 2+ billion
- Human capital: 1000s+ over years
- Time to recoup investment – average 7 – 10 years (depending on approval)
- When development started, No guarantee of success

Jet Airliner

- Time: approx. 1 year
- Estimated cost: $350 million
- Time to recoup investment: when jet is sold
- When manufacturing started, completed jet will be available

What has the partnership of Scientist, Pharma, and FDA Accomplished?

- Novel Receptors identified
- Deadly infections treated
- Childhood diseases eradicated by vaccination
- Chronic conditions such as diabetes, hypertension, schizophrenia managed
- Diseased organs can be replaced and maintained with immunosuppressants
- Joints replaced with artificial devices
- Inside of body imaged with CT, MRI
- Cancer treatments (poisons) replaced with more targeted, less debilitating therapies

OUTCOME Average life span and Quality of Life (***QoL)*** increased significantly over the decades

Fair Balance

- Good news
  - Previously untreatable disorders such as hemophilia, sickle-cell are now treatable by gene therapies which have the power to cure serious, even fatal, diseases
- Bad news
  - Cost of drugs
    - Average cost of gene therapy is millions/dose
    - Costs treating chronic conditions for decades exploding
- As health care cost explode, societal challenges are
  - Who will pay for innovative treatments at these prices?
  - Who will have access?

Options

Options	Opposed by
Option #1 Inflation Reduction Act permits Medicare, for first time, to negotiate prices of certain high-cost drugs that lack competition. Goes into effect in 2026	PhRMA
Option #2 Universal Health Insurance single payer in which costs are shared by society	Private Health Insurance
Option #3 Outcomes-based pricing which refunds some or all of treatment's cost if results don't last	PhRMA
Outcome #4 Rationing and/or only those with wealth have access	Patients/Parents/Society

As science evolves, think what's possible but also what needs to be fixed

If pursuing a career in pharma, Dan's thy shall

1. Remember Clinical studies are scientific experiments
2. Follow the data and remember FDA's motto "In God we trust, but others need to show data"
3. Statisticians are critical in designing clinical studies
4. Remember KISS Principle – Keep clinical study design Simple as complicated study designs impacts time and costs
5. Remember before initiating the next trial, learn from the last trial, pressure test I/E requirements and study related assessments with potential investigators and trial participants
6. Remember pharmacokinetic profile of NEW DRUG is foundational to understanding the drug
7. Don't forget CMC and ensure CMC is in sync with the Phase of development
8. Remember when considering PE ensure it is appropriate for the indication and has agreement with FDA

Dan's thy shall
(Part 2)

9. Avoid amending ongoing trials which increases complexity and costs
10. Use milestone meetings with FDA wisely to obtain input from the key customer
11. Remember oversight of the clinical site is critical
12. Efficacy is measurable but Safety is in the "eyes of the beholder"
13. Remember data speaks for itself
14. It is not a "true" negotiations as FDA as all the power in granting the approval
15. Remember the responsibility we have in asking patients to enroll in a trial of an unproven drug
16. Be totally transparent with the FDA
17. Be totally transparent with the FDA
18. Be totally transparent with the FDA

Questions ?

CASE STUDY

BRIDGING STRATEGY

M. DANIEL GORDIN, PH.D.

CASE STUDY

AN EXPERIMENTAL DRUG THAT IS AN IMMEDIATE RELEASE (IR) DOSAGE FORM WAS ADMINISTERED BID IN THE PHASE 2 DOSE RANGING STUDY. THE RESULTS OF THE PH2 STUDY SHOWED THE EXPERIMENTAL DRUG WAS EFFECTIVE WITH AN ACCEPTABLE SAFETY PROFILE.

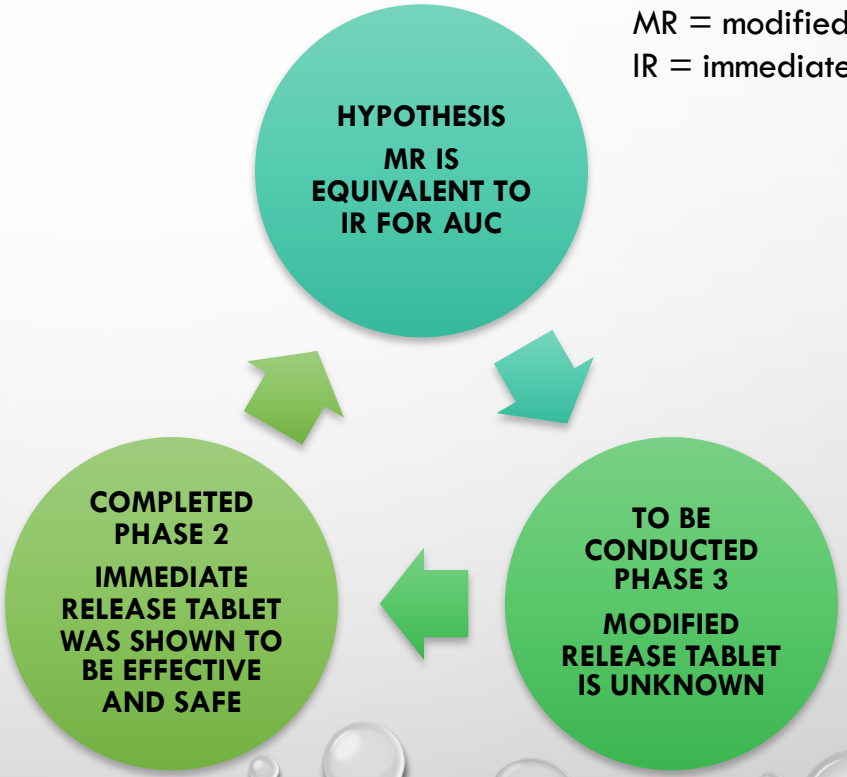
FOLLOWING THE STUDY, MARKETING INDICATED THAT MARKET RESEARCH INDICATED THAT TO BE COMPETITIVE WITH THE APPROVED BID COMPETITOR, QD ADMINISTRATION WAS NEEDED. REGULATORY WAS REQUESTED TO DEVISE A WINNING REGULATORY STRATEGY TO SUPPORT THE SWITCH FROM THE BID IR FORMULATION TO A QD MODIFIED RELEASE (MR) TABLET WHICH IS *HOPED* TO BE USED IN PHASE 3.

QUESTIONS

1. WHAT APPROACH SHOULD BE USED TO DETERMINE IF THE MR TABLET CAN BE USED IN PHASE 3?
2. WHAT STUDIES WOULD YOU RECOMMEND TO THE PROJECT TEAM BE CONDUCTED WITH THE MR TABLET TO DETERMINE IF THE MR CAN REPLACE THE IR FOR USE IN THE PHASE 3 PIVOTAL STUDIES?

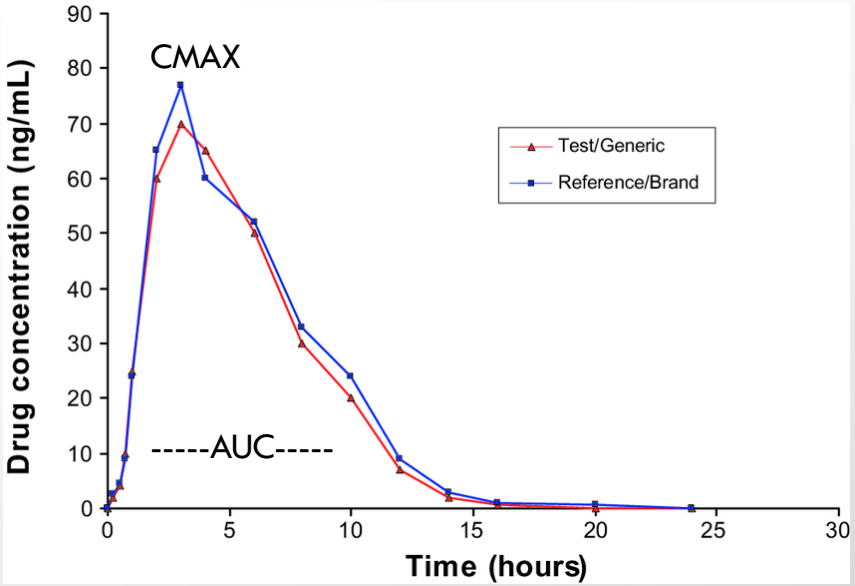
STRATEGY

MR = modified release
IR = immediate release



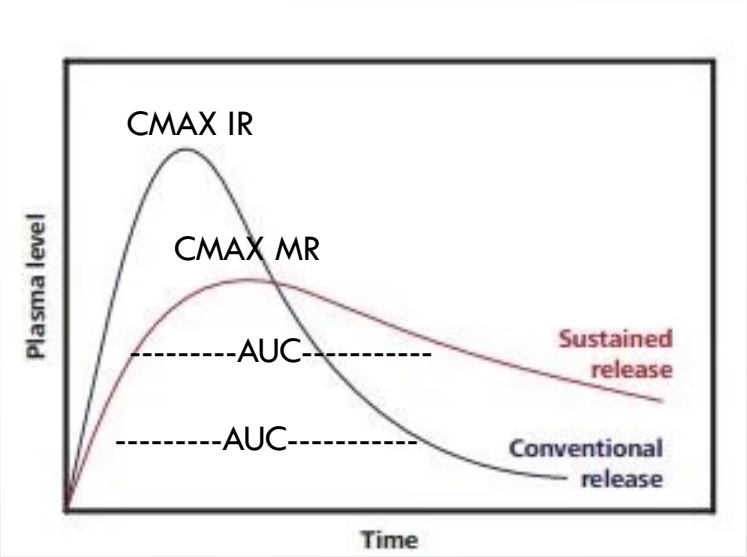
PHARMACOKINETICS (PK) 101
AUC AND CMAX

- AREA UNDER THE CURVE (AUC)
  - MEASURES EXTENT OF DRUG ABSORPTION FROM THE FORMULATION OVER TIME
- MAXIMUM CONCENTRATION (CMAX)
  - MEASURES RATE OF ABSORPTION AS TO HOW FAST THE DRUG IS ABSORBED FROM THE GI TRACT INTO THE BLOOD



MR PK COMPARED TO IR PK

- MODIFIED RELEASE (MR) FORMULATION
  - DESIGNED TO PROLONG RELEASE OF DRUG FROM DOSAGE FORM
  - MR CMAX < IR CMAX
  - AUC EXPECTED TO BE WITHIN 80-125% FOR AUC
- HIGH FAT MEALS MAY AFFECT MR FORMULATION DRUG RELEASE (FOOD EFFECT)
- DELAY IN MR TABLETS FROM GI TRACT



IR TO MR ASSUMPTIONS

- DRUG HAS LINEAR KINETICS
- TECH OPS PROVIDES TEST RESULTS THAT SHOWS MR FORMULATION HAS PASSED
  - STABILITY (GUIDANCE FOR INDUSTRY Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS NOVEMBER 2003)
  - IN VITRO DISSOLUTION TESTING FOR MR RELEASE (GUIDANCE FOR INDUSTRY EXTENDED-RELEASE ORAL DOSAGE FORMS: DEVELOPMENT, EVALUATION, AND APPLICATION OF IN VITRO/IN VIVO CORRELATIONS SEPTEMBER 1997)

OPTIONS TO CONSIDER

OPTION 1

REPEAT PH2 STRATEGY

- REPEAT PHASE 2 WITH MR FORMULATION
- ADVANTAGE
  - DEFINITIVE OUTCOME IF IT WORKS
- DISADVANTAGE
  - SIGNIFICANT DELAY WITH REPEATING PHASE 2 STUDY AND DELAY START OF PHASE 3

OPTION 2

BRIDGING

- COMPARE IR FORMULATION TO MR FORMULATION
- ADVANTAGE
  - DELAY IS CONSIDERABLY LESS THAN REPEATING A PHASE 2 STUDY
- RISK
  - OUTCOME MAYBE GIVE A FALSE POSITIVE IF NOT TESTED RIGOROUSLY

REGULATORY'S RECOMMENDATION

- WHAT STRATEGY WOULD YOU RECOMMEND TO BRIDGE MR FORMULATION TO IR FORMULATION?

  IF TECH OPS PROVIDES IN VITRO RESULTS THAT SHOWS MR IS VIABLE THEN RECOMMEND BRIDGING STRATEGY

- WHAT STUDIES WOULD YOU RECOMMEND TO THE PROJECT TEAM BE CONDUCTED WITH THE MR TABLET PRIOR TO INITIATING THE PHASE 3 PIVOTAL STUDIES?

  NEXT SLIDE

- WHAT DO YOU SAY TO SKEPTICS?

  SUGGEST THAT THE BRIDGING STRATEGY PROPOSAL CAN BE SUBMITTED TO THE FDA FOR REVIEW AND COMMENT BEFORE INITIATING THE WORK, HOWEVER, EXPECT AT LEAST A 6-MONTH DELAY

BRIDGING STRATEGY STUDIES TO BE CONDUCTED

BE STUDY

- TWO-ARM, SINGLE DOSE, RANDOMIZED STUDY COMPARING MR FORMULATION (TEST) AGAINST IR PHASE 2 FORMULATION (REFERENCE)
- OBJECTIVE: TO DETERMINE THE EQUIVALENCE OF THE MR TO IR FOR AUC
- HEALTH VOLUNTEERS
- DRAW TIMED BLOOD SAMPLES FROM 0 TO 24 HRS
- TWO ONE-SIDED T-TEST, 90% CONFIDENCE INTERVAL BETWEEN 80 - 125% FOR CMAX AND AUC

FOOD EFFECT STUDY

- TWO-ARM, SINGLE DOSE, RANDOMIZED STUDY COMPARING MR FORMULATION FASTED (REFERENCE) AGAINST MR FED WITH HIGH FAT MEAL (TEST)
- OBJECTIVE: TO DETERMINE IF HIGH FAT MEAL CAUSES DOSE DUMPING
- HEALTH VOLUNTEERS
- DRAW TIMED BLOOD SAMPLES FROM 0 TO 24 HRS
- TWO ONE-SIDED T-TEST, 90% CONFIDENCE INTERVAL BETWEEN 80 - 125% FOR CMAX AND AUC

MULTIPLE DOSE STUDY

- TWO-ARM, RANDOMIZED, MULTIPLE DOSE, STUDY COMPARING MR FORMULATION 7 DAYS QD DOSING
- OBJECTIVE: TO DETERMINE IF PK CHANGES AFTER MULTIPLE DOSING
- HEALTH VOLUNTEERS
- DRAW TIMED BLOOD SAMPLES FROM 0 TO 24 HRS ON DAY 1, CMINS, AND 0-24 HRS ON DAY 6
- TWO ONE-SIDED T-TEST, 90% CONFIDENCE INTERVAL BETWEEN 80 - 125% FOR DAY 1 CMAX AND AUC AND DAY 6 AUC AND CMAX

BRIDGING STRATEGY
BEST POSSIBLE OUTCOME

BE STUDY

- AUC WITHIN 80-125% CI
- CMAX NOT WITHIN 80-125% CI
- CONCLUSION
  - EQUIVALENT FOR AUC
  - NOT FOR CMAX (BY DESIGN)

FOOD EFFECT STUDY

- AUC FOOD AND AUC FED WITHIN 80-125% CI
- CMAX FOOD AND CMAX FED WITHIN 80-125% CI
- CONCLUSION
  - NO FOOD EFFECT
  - CAN BE ADMINISTERED WITH FOOD

MULTIPLE DOSE STUDY

- DAY 1 AUC 0-24 TO DAY 6 AUC 0-24 WITHIN 80-125% CI
- DAY 1 CMAX TO DAY 6 AUC WITHIN 80-125% CI
- CONCLUSION
  - NO DOSE DUMPING
  - NO DELAYED RELEASE WITH QD DOSING FOR 7 DAYS

FINAL THOUGHTS

- IDEAL TO AVOID DOSE SIGNIFICANT FORMULATION CHANGES AFTER PHASE 2
- FIRST THINGS FIRST CHECK FDA WEBSITE FOR GUIDANCE DOCUMENT
  - GUIDANCE FOR INDUSTRY SUPAC-MR: MODIFIED RELEASE SOLID ORAL DOSAGE FORMS SCALE-UP AND POSTAPPROVAL CHANGES: CHEMISTRY, MANUFACTURING, AND CONTROLS; IN VITRO DISSOLUTION TESTING AND IN VIVO BIOEQUIVALENCE DOCUMENTATION (SEPTEMBER 1997 CMC 8)

- TECH OPS NEEDS TO PROVIDE THE NECESSARY DATA TO SUPPORT IR TO MR
- CMC AMENDMENT AND STUDY PROTOCOLS TO BE SUBMITTED
- DEVELOPMENT DELAY>12 MONTHS DUE TO SETTING UP CONDUCTING STUDIES, ANALYZING THE RESULTS FROM 3 BRIDGING STUDIES
- BRIDGING STRATEGY IS NOT "ONE SIZE FITS ALL"
  - CAN ONLY BE CONSIDERED WITH
    - SOLID DOSAGE FORMS
    - DRUGS WITH LINEAR KINETICS
  - CANNOT BE CONSIDERED WITH
    - BIOLOGICS (MAB)
    - CELL THERAPIES
- ENSURE THERE IS A BACKUP PLAN
  - IF BE AND/OR MULTIPLE DOSE STUDY FAIL, THEN IR BID DOSING IS FALL BACK