

# Quality Management Systems Within the Pharmaceutical Industry

Catherine Johnson, RAC

TAP Pharmaceutical Products

# Topics

- Background
  - FDA history, mission, functions
  - Key laws
  - Regulation development
  - Drug development process
- Quality Systems
- Lean Drug Development at TAP

# FDA History

- 1848 Drug Importation Act
- 1862 Lincoln appoints first chemist, beginning the Bureau of Chemistry





**KOPP'S.  
"BABY'S FRIEND"**

CONTAINS EIGHT AND ONE-HALF PER CENT. ALCOHOL-ONE EIGHTH GRAIN SULPHATE OF MORPHINE IN EACH FLUID OUNCE.

Mrs. J. A. KOPP, Sole Prop.  
C. ROBERT KOPP, Mfg. Chemist

**YORK, PA., U. S. A.**

**KING OF BABY SOOTHERS**

SPLENDID FOR  
Wind Colic, Griping in the  
Bowels, Diarrhoea, Cholera,  
Infantum and Teething  
Troubles.

Trial Size, 10c. Large, 25c.

Trade Mark Registered

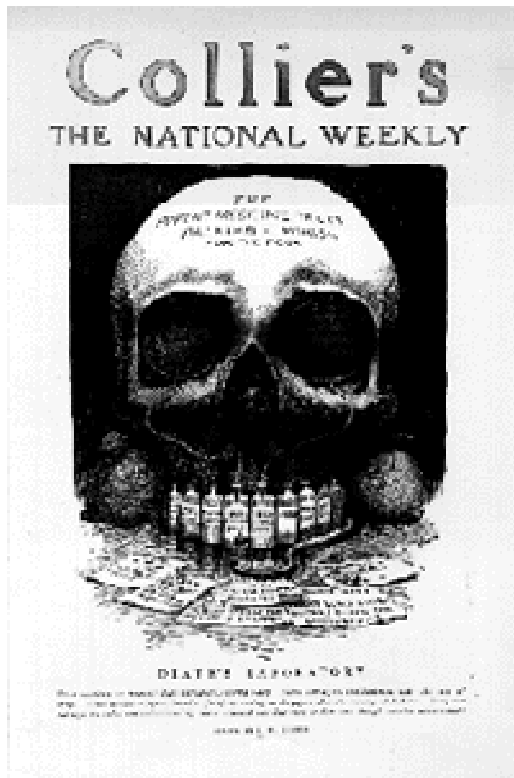
Deodorized Tinct. Opium 1-5 Per Cent.

**TOTT'S  
TEETHING CORDIAL,**

Satisfies the Baby, pleases the Mother, gives rest to both.

# FDA Key Legislation

- 1906 Original Food and Drugs Act passed



# FDA History

- 1927 Food, Drug and Insecticide Administration (1930 name change)
- 1940 Federal Security Agency (FSA)
- 1953 FSA changes to Health, Education and Welfare (HEW)
- 1968 FDA moves to Public Health Services
- 1988 FDA agency of Dept. of Health and Human Services

# Key Legislation

- 1938 The Federal Food, Drug, and Cosmetic Act
  - 1937 Elixir of Sulfanilimide
- 1951 Durham Humphrey Amendment
- 1962 Kefauver-Harris Drug Amendments
  - Thalidomide



Dr. Frances Kelsey, FDA Medical Officer, receives the President's Distinguished Federal Civilian Service Award

# Key Legislation

- 1988 Food and Drug Administration Act
- 1988 The Prescription Drug Marketing Act
- 1992 Prescription Drug User Fee Act
- 1997 Food and Drug Administration Modernization Act

# What the FDA Regulates

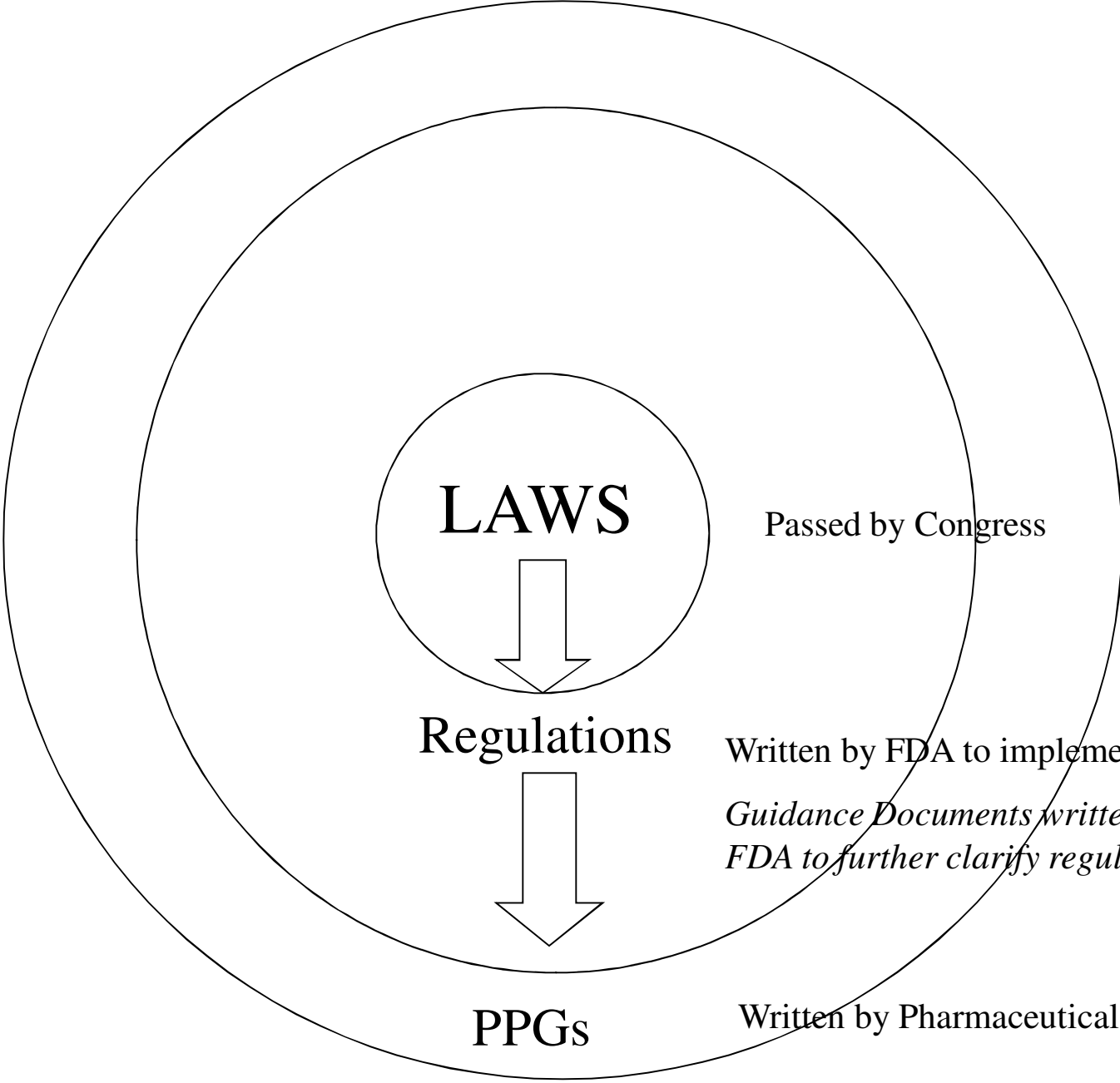
- Biologics
- Cosmetics
- Drugs
- Foods
- Medical Devices
- Radiation-Emitting Electronic Products
- Veterinary Products

# What the FDA Does Not Regulate

- Advertising
- Alcohol
- Consumer Products
- Drug Abuse
- Health insurance
- Meat and Poultry
- Pesticides
- Restaurants and Grocery Stores
- Water

# FDA's Mission

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.



**LAWS**

Passed by Congress

**Regulations**

Written by FDA to implement laws

*Guidance Documents written by  
FDA to further clarify regulations*

**PPGs**

Written by Pharmaceutical Co.

How does a law come to be?

## How Does a Regulation Come to Be?

Publish in Federal Register: Advance Notice Proposed Rulemaking  
or Notice of Intent to Publish a Proposed Rule



Publish Proposed Rule: (Comment period 60 days to 1 year)



Agency analyzes comments: (may call for further comments)



Publish the interim or final regulation                      or  
Abandons intention to publish rule



The final rule is announced in the Federal Register  
with the effective date

## How Does a Guidance Document Come to Be?

Publish notice in Federal Register announcing the draft and inviting comments



Post the draft guidance document on the internet



Agency reviews comments and revises draft as appropriate



Announces the issuance of the final guidance or re-issue a new draft



Implement the new guidance once discussions are complete

# Getting a New Drug to Market

## The Process

# What it Takes to Get a Drug to Market

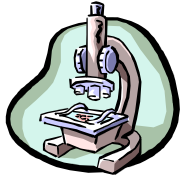
- Scientists, physicians, engineers and other researchers
- 10-15 years
- \$ 800 million – 1.2 billion

# Drug Development

- Discovery
- Non-clinical
- Pre-IND meeting
- IND Submission
- FDA Review of IND
- Clinical Investigations
- End of Phase 2 Meeting
- USAN Naming
- Pre-NDA Meeting
- NDA Submission
- FDA Review of NDA
- NDA Approval
- Post-marketing

# Major Milestones for Drug Development

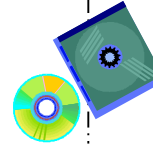
Discovery



IND



NDA

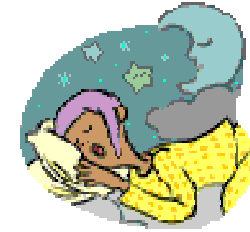


NDA Approval



Pre-IND

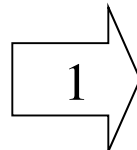
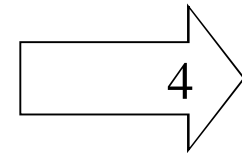
Pre-NDA



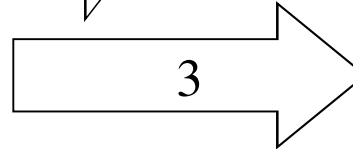
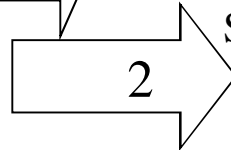
Finalize labeling

Phase 4 commitments

Clinical Studies



Clinical Studies



FDA Review



Reports

AE

Annual Report

CMC



Toxicology

Pharmacology



# Drug Development Process

Pre-clinical

**Discovery**

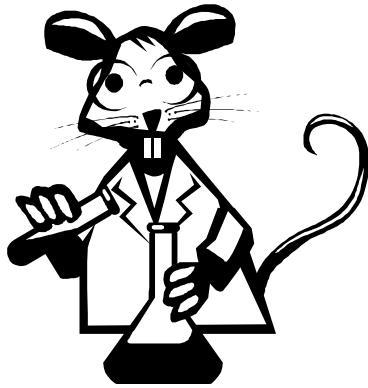


**Synthesis and Purification**

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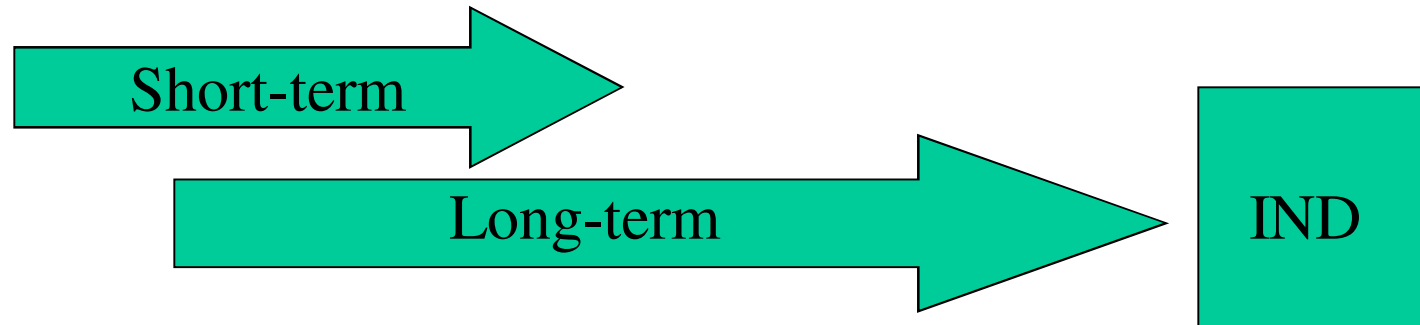
*Working toward 21 CFR 211 - Good Manufacturing Practices*

# Drug Development Process



Pre-clinical

**Animal testing**



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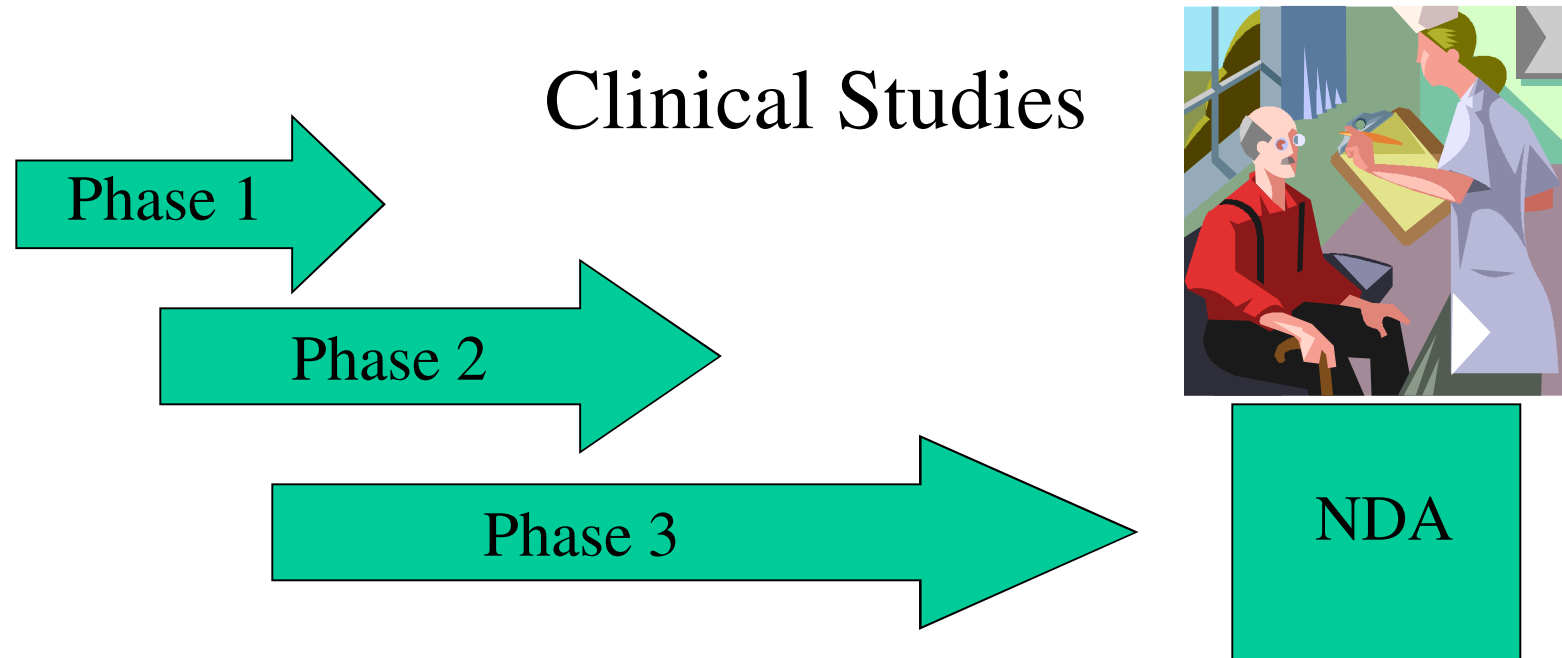
21 CFR 58 Good Laboratory Practices

FDA and ISO Guidance Documents

# Investigational New Drug Application (IND)

- Introductory Info
- Investigational Plan
- Investigator's Brochure
- Protocol
- Investigator's Info
- Chemistry, Manufacturing & Controls
- Non-clinical Pharmacology and Toxicology
- Previous Human Use

# Drug Development Process



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21 CFR Part 312 – IND Regulations      ICH E6 GCP Consolidated Guidance

21 CFR Part 50 – Protection of Human Subjects Regulations

21 CFR Part 56 – Institutional Review Board Regulations

# New Drug Application (NDA)

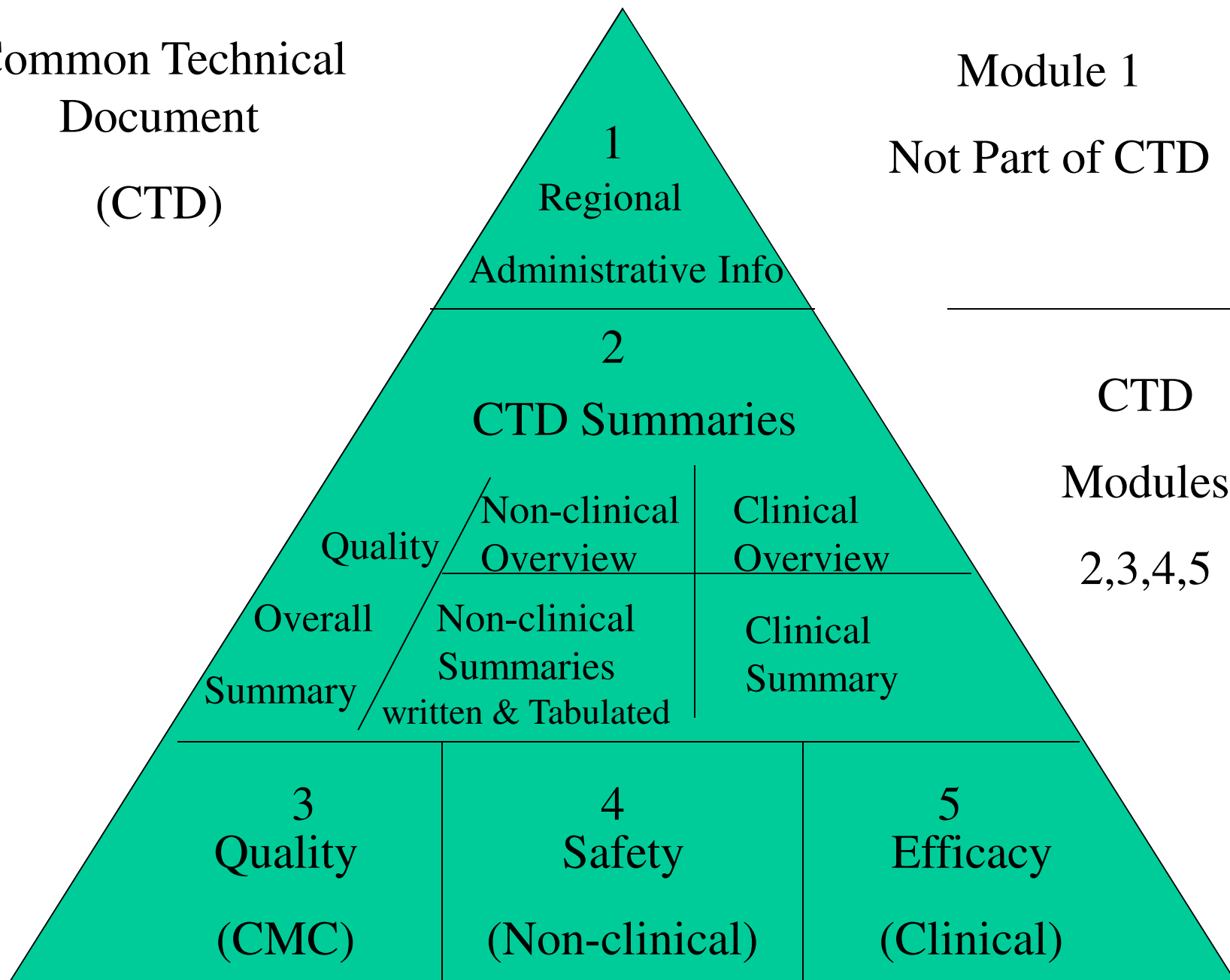
- Application form
- Index
- Summaries
- CMC
- Non-clinical
- Pharmacokinetics & Bioavailability
- Microbiology
- Clinical reports
- Case Report Forms
- Statistical Section
- Samples and Labeling
- Patent Information
- Financial Disclosure

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21 CFR 314 - Application for FDA approval to market a new drug

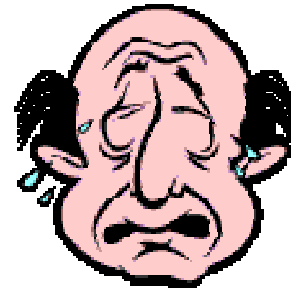
Common Technical Document (CTD)

Module 1  
Not Part of CTD



# Drug Development Process

- Approval Letter
- Approvable Letter
- Not-Approvable Letter



# Post-Marketing Activities

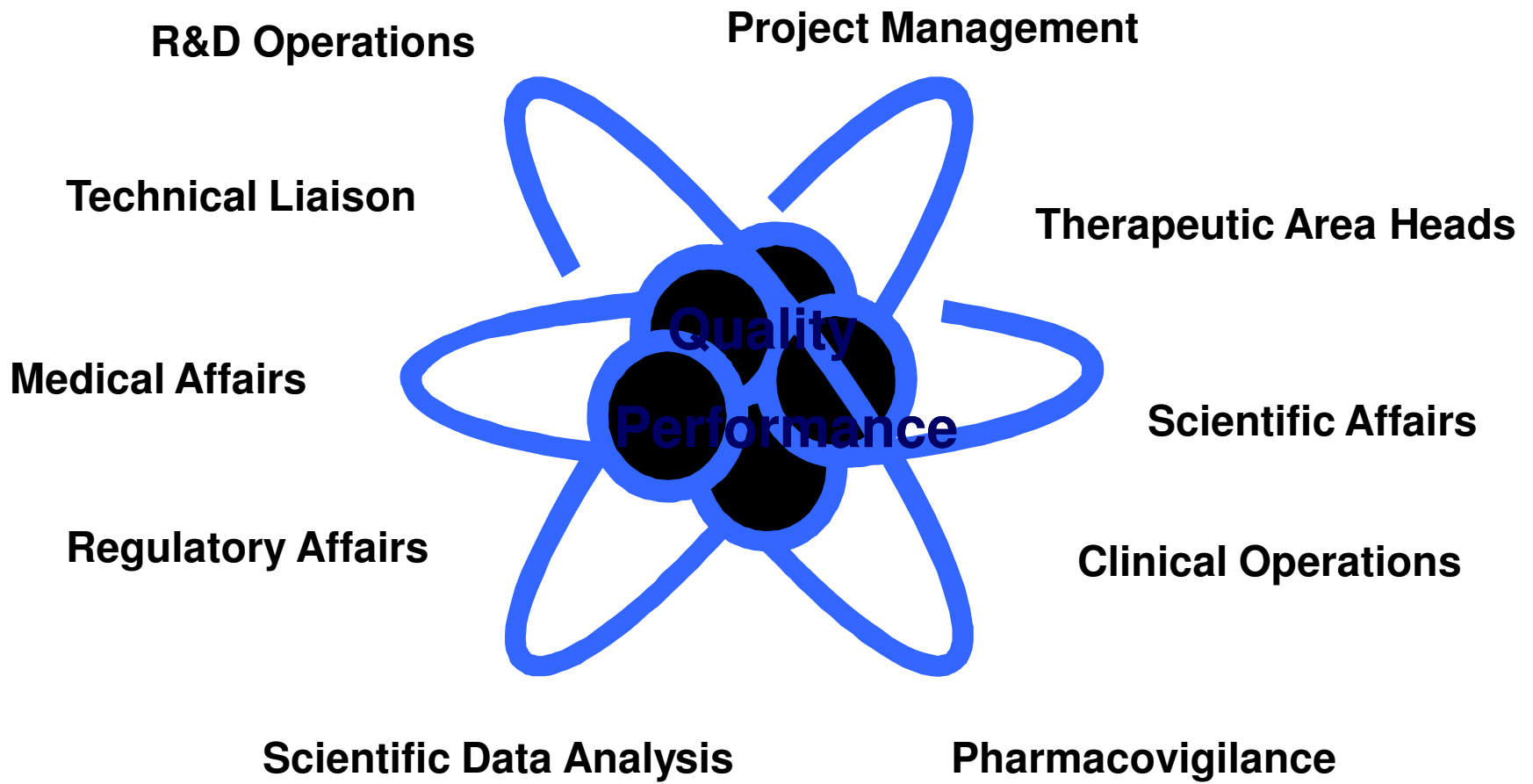
- Adverse Events
- Periodic Adverse Event reports (quarterly 3 yrs)
- Annual Report

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21CFR 314.80: Post-marketing reporting of Adverse events

21CFR 314.81: Other post-marketing reports

# QMS Structure at TAP R&D



# LEAN DRUG DEVELOPMENT

# Study Initiation

- Subject enrollment cannot start until study initiation activities are completed
- Phase III study has typically 500 – 1000 subjects
- Multiple sites involved
- The longer the start-up time for the study, the later the completion date of the study

# Study Initiation at TAP

- Prepare Protocol Synopsis
- Select sites to conduct clinical trial
  - Identify potential sites
  - Conduct Pre-study Site visits
- Complete contracts for scope of work
  - CDA, Site Agreement (Contracts)
- Collect essential documents from sites
  - 1572 , CVs, Financial Disclosure Certifications, etc.
- Acquire required approval
  - IRB approval: Protocol, Informed Consent Template, Sites

# Study Initiation

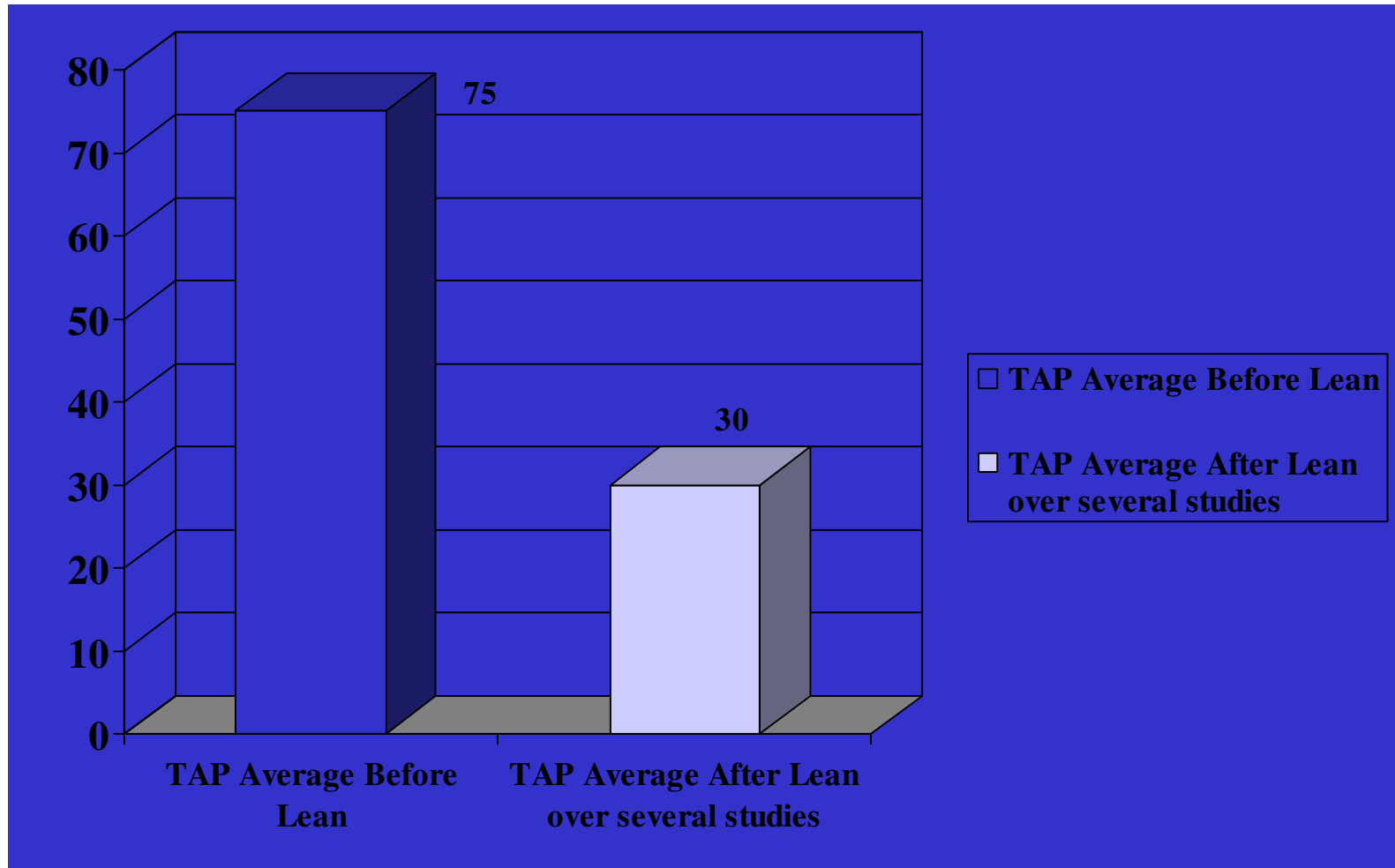
3 key sub-processes reviewed:

- Number of days required to execute 75% of Investigator Contracts
- Protocol Approval to Study Start
- Tracking and Processing of Essential Documents

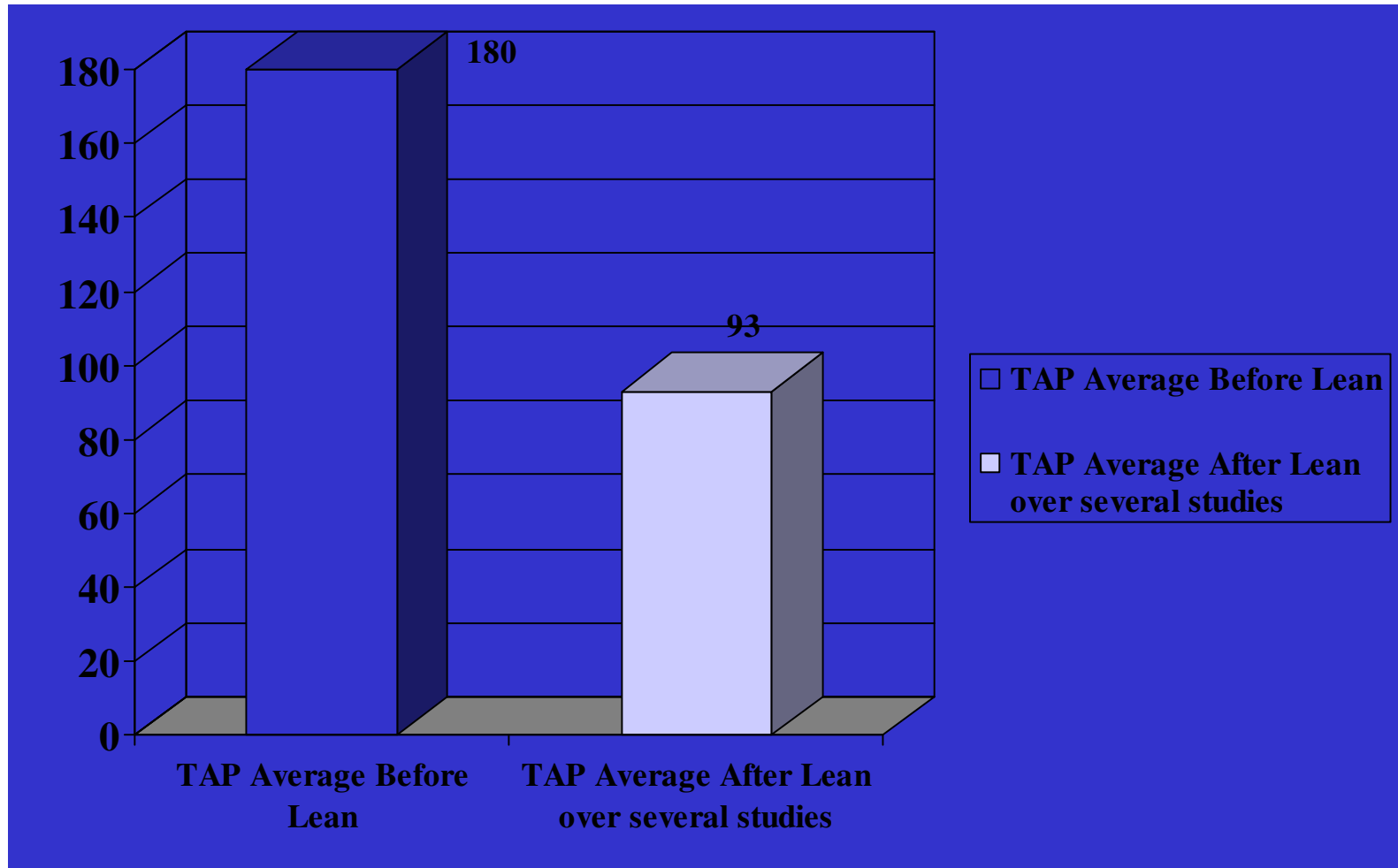
Goal was to reduce cycle time while maintaining or improving quality and service level

# Study Initiation Results

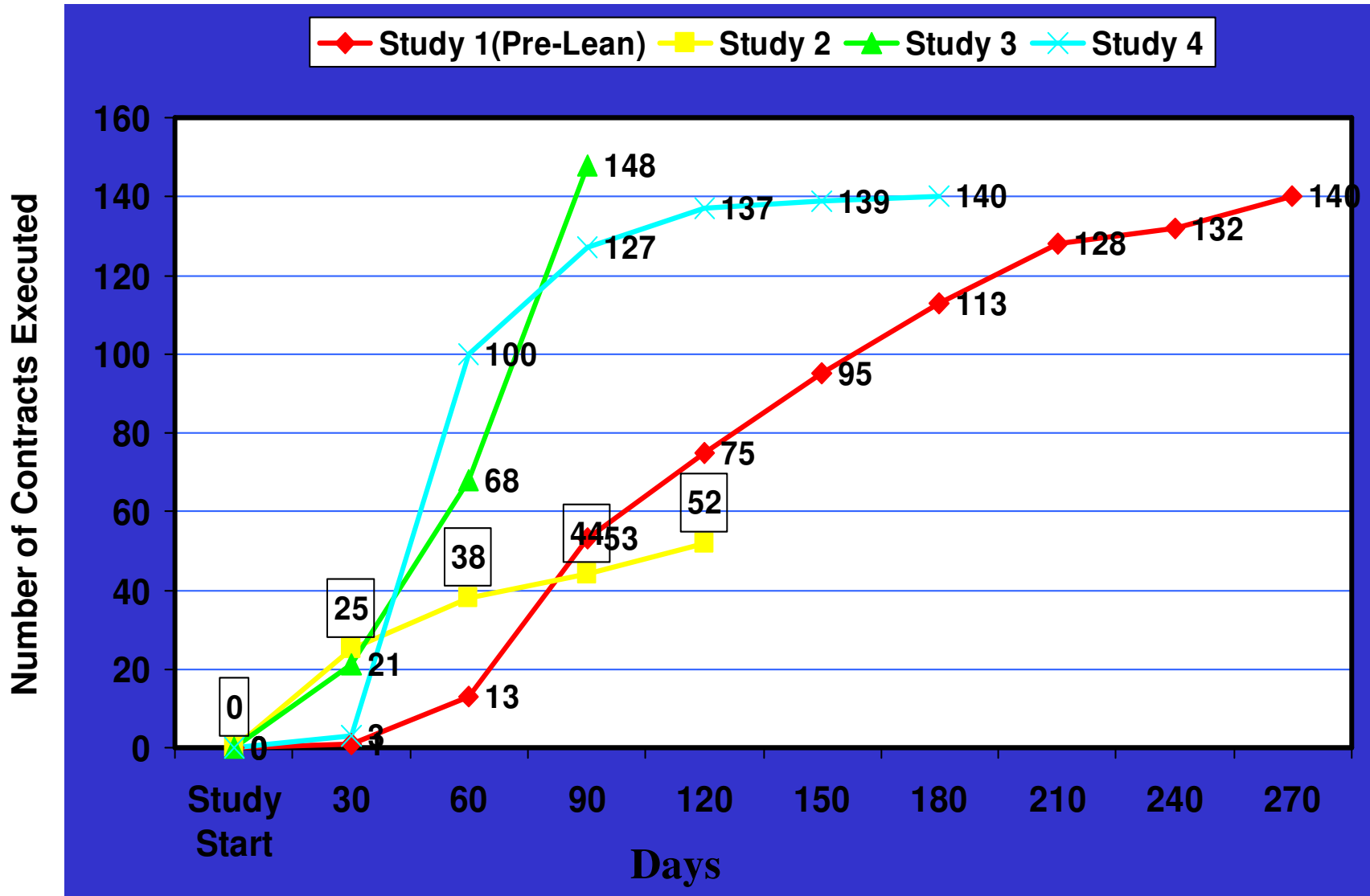
# Days to Execute Investigator Contracts



# % of Investigator Contracts Executed

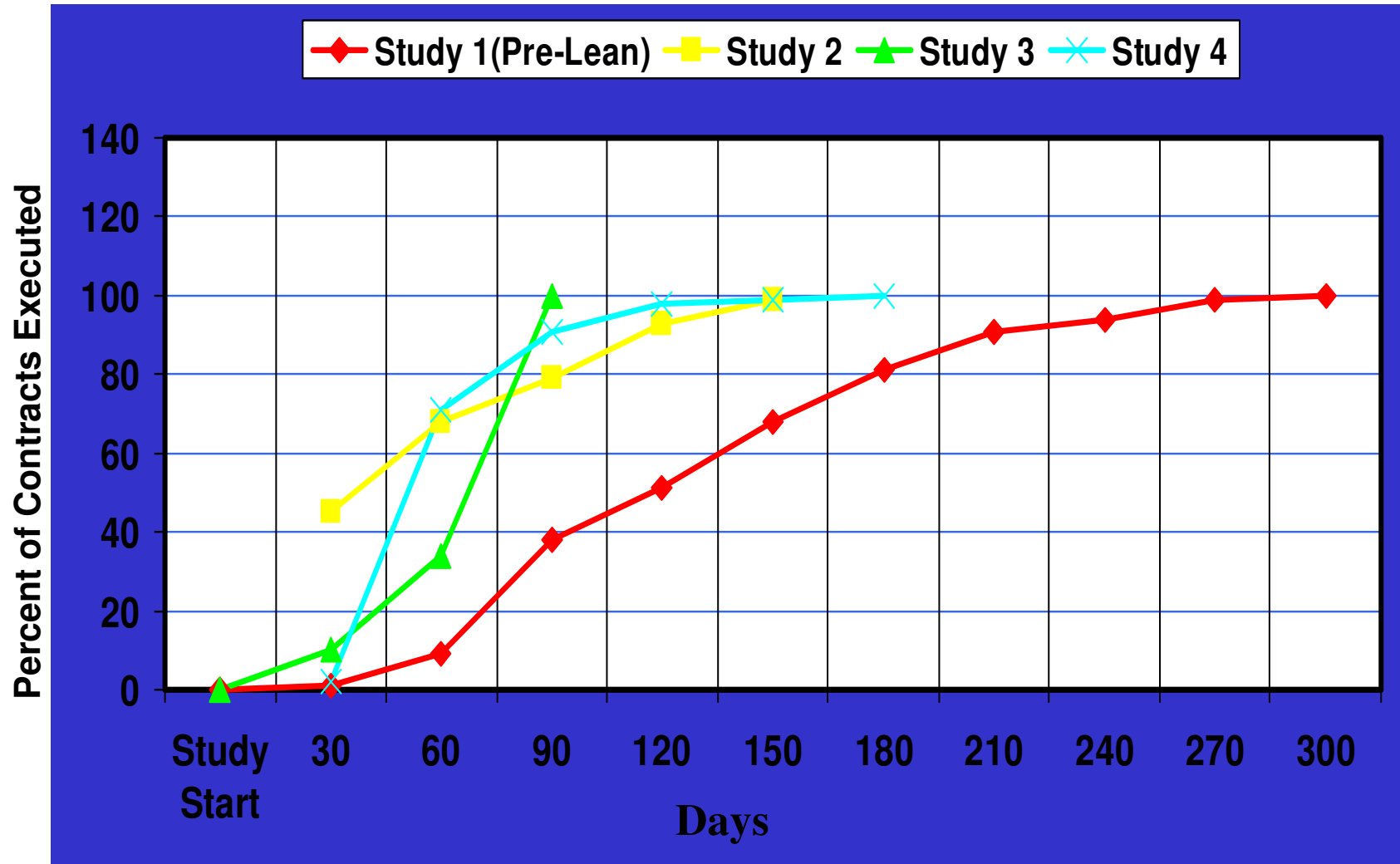


# Days to Execute Investigator Contracts



Note: Study start is 30 days prior to Investigator Meeting

# Percent of Contracts Executed



Note: Study start is 30 days prior to Investigator Meeting

# Examples of Addressing Waste

Contract Development

Protocol Review

Informed Consent Review

Tracking Essential Documents

# Examples of Waste and Improvement Action Study Initiation Process

- Waste
  - Site contract development process resulted in long lead times due to inefficient processes between TAP's Legal and Clinical Operations areas
- Process Improvement
  - Developed a standard template for Investigator contracts
  - Clinical Operations' central tracking system facilitated prioritization of site contract work

# Examples of Waste and Improvement Action Study Initiation Process

- Waste
  - Site contract development process resulted in long lead times due to inefficient processes between TAP's Legal and Clinical Operations areas (cont.)
- Process Improvement
  - Developing a Master Service Agreement for investigators conducting several studies
  - Allow for non-proprietary synopsis to be distributed without a CDA to prospective investigators

# Examples of Waste and Improvement Action Study Initiation Process

- Waste
  - Multiple Protocol Review cycles
- Process Improvement
  - Developed an eSystem (TAP's eDOC) to allow on-line and simultaneous access of protocol by multiple reviewers
  - Instituted Protocol Review Committee which eliminated multiple reviews by final approvers

# Examples of Waste and Improvement Action Study Initiation Process

- Waste
  - Sample Informed Consent Form (ICF) goes through multiple reviews, revisions, annotations and changes
- Process Improvement
  - Developing an ICF template incorporating central IRB style/format based on cross-functional TAP input

# Examples of Waste and Improvement Action Study Initiation Process

- Waste
  - Clinical Operations used separate (per study) Excel spreadsheets
    - To track address, essential documents, etc.
    - Especially inefficient and prone to errors in cases where an investigator was in more than one study
- Process Improvement
  - Now utilizing a single source Clinical Trial Management System (CTMS) to track investigators and documents across compounds and studies

# What Have We Learned?

- Pharma R&D can use Lean
- Need to invest in a Lean Structure to support this initiative
- Need to over-communicate internally to alleviate fears

# What Have We Achieved?

- Standardized activities across many processes
- Optimized floor plan
- Developed Value Stream maps for key processes
- Cycle Time reduction achieved
- Addressed inefficient activities freeing up time to improve overall productivity

# THANK YOU

Catherine Johnson  
Quality Performance Manager  
TAP Pharmaceutical Products Inc.  
675 North Field Drive  
Lake Forest, IL 60045  
847-582-2684

