Concepts in
Pharmaceutical Development Project Management

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Medical Officer, US FDA

Disclaimer

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.

Introduction

- By way of …
  - Small
  - Medium and
  - Large Pharma

  - the FDA
    - OND\CDER\DNP (Div Neurology Products)
  - Johns Hopkins University, Center for Biotechnology Education

Objectives

- By the end of this lecture, you should be able to:
  - Describe the composition of a drug development team
  - Discuss the role of the Project Manager
  - Discuss the different skill sets needed for the PM position
  - Compare the different tools used by the PM

Recommended Reading

Strategic Project Management at the Project Level

Tony Kennedy*

SmithKline Beecham Pharmaceuticals
Essex, England

I. PROJECT STRATEGY OVERVIEW 1
II. DEVELOPMENT STRATEGY FROM CRADLE TO GRAVE 3
A. Early Development Strategy 3
B. Registration and Life-Cycle Development Strategy 14
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I. PROJECT STRATEGY OVERVIEW

Drug development is not a simple process. If honest, most newcomers to drug development will concede that their initial experience as a project team member for a development project is disconcerting. Unfamiliar technical acronyms fly around the room. Team members with greater development experience and knowledge of the project often dominate the discussion. The new team members probably will be glad to conclude their

Current affiliation: Roche Products Ltd., Welwyn Garden City, England.

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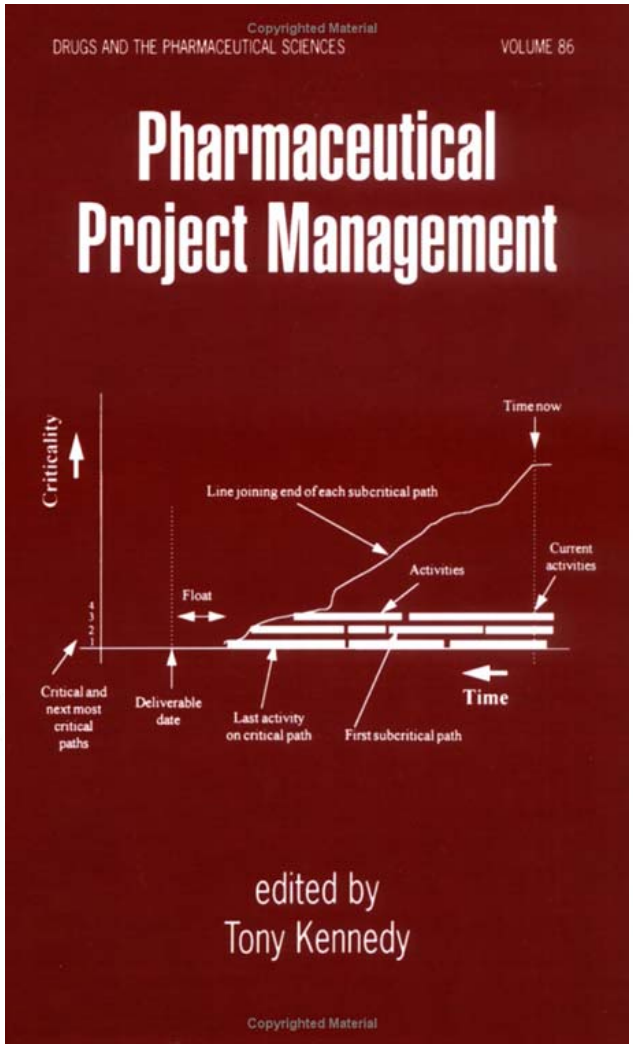


contribution to team discussion and to escape from thei[illegible] team meeting without making fools of themselves. Drug develop[illegible] more comprehensible if the team member has the good fortu[illegible] a project team at its inception rather than, as is often the cas[illegible] acement team member. It is at the initial team meetings that th[illegible] rly development strategy is decided.

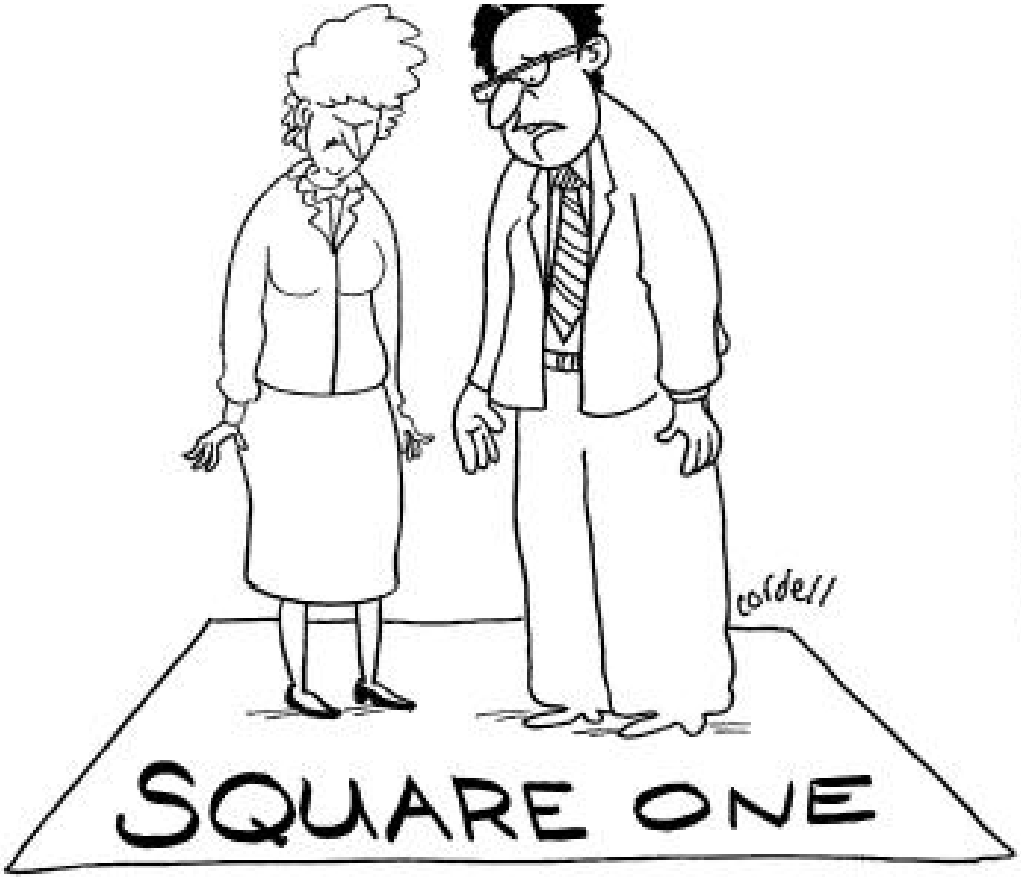
Successful drug development depends on the quality of the development strategy. Ultimately, successful drug development is about translating science into an optimal investment proposal that provides value to a variety of stakeholders and customers. This can be achieved only be establishing a strategy which recognizes who the customers for new medicines are and addresses their needs. This will mean moving increasingly from designing "for" to designing "with" the customer. Health care provided in most countries has experienced significant change in recent years. Probably the greatest change to be faced in the future will be the expectation that new medicines will be not only safe and effective but also cost effective in the overall context of disease management.

Drug development strategy is concerned with establishing clearly set objectives for the development and life cycle management of an asset, recognizing critical hurdles to success, and structuring plans to achieve the best reward/risk for the investment. It requires a range of skill sets which include strong technical knowledge of drug development and understanding of development risk management. Project attrition rates are high, and it is important to understand why and when these can occur. The overwhelming majority of projects fail. A primary objective in drug development, therefore, is to eliminate from development, at the earliest time, projects that offer poor prospects for commercial return. Termination decisions are rarely made with certain knowledge which is why they are so often painful for teams and companies to take. It requires understanding of the importance of the target product profile (TPP) as a strategic tool and the need for its continuous review throughout development. The TPP definition is critical to the design of clinical development strategy. It is also the basis for establishing clear Go/No Go criteria for the compound through development.

It depends on good understanding of planning skills to ensure that alternative development scenarios are recognized and their impacts are fully explored. It also requires business skills to evaluate the investment opportunity integrating the key parameters of risk, time, cost, and return. At the core of all of this is knowledge of the disease area which enables the impact of a new medicine in the total scheme of intervening in the disease state to be assessed. If this analysis is at fault, all else is of little value. In an increasingly

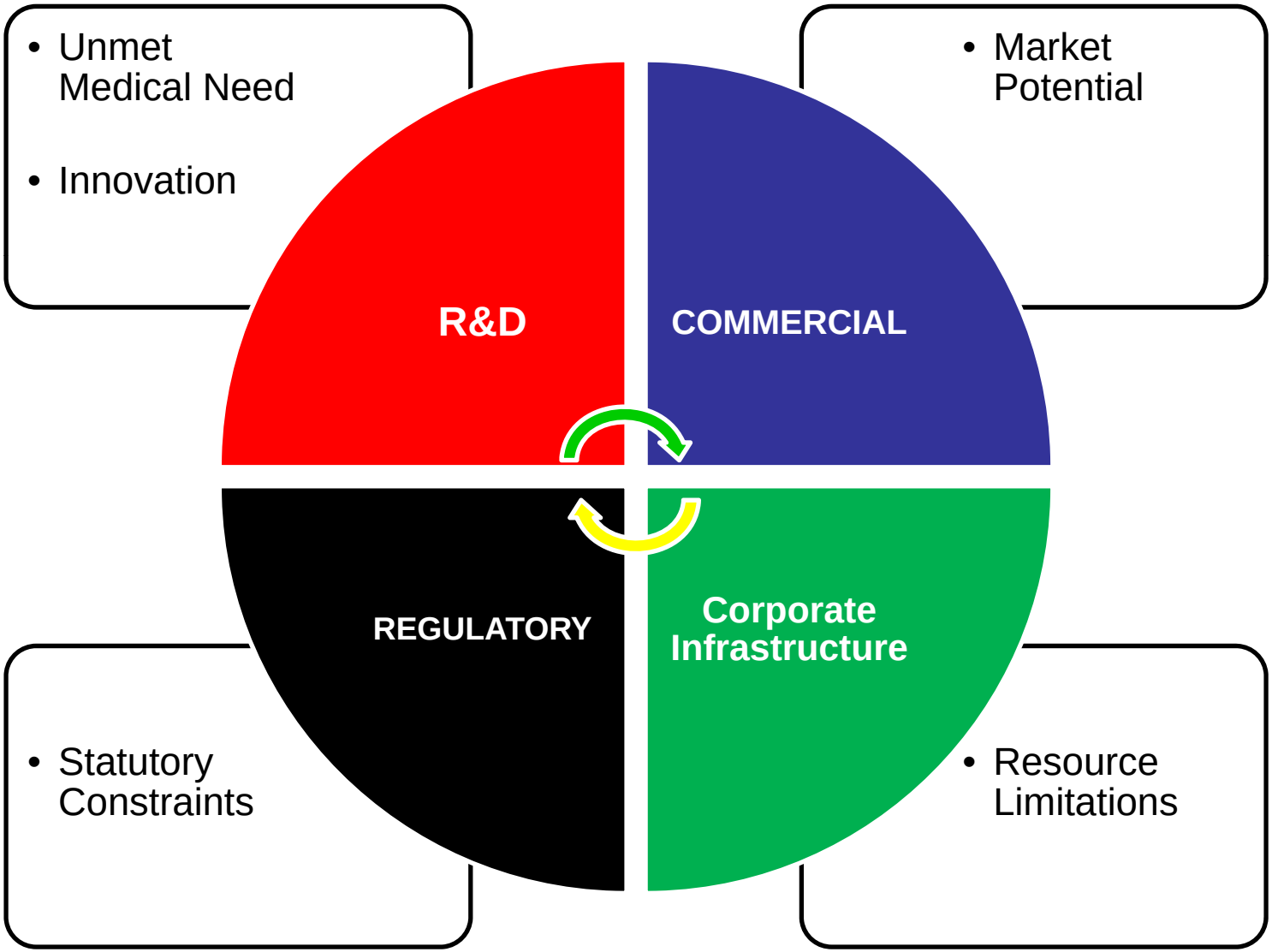
"…is not a simple process"

"..depends on the quality of the development strategy"



"Well, here we are again."

What is Pharmaceutical Development



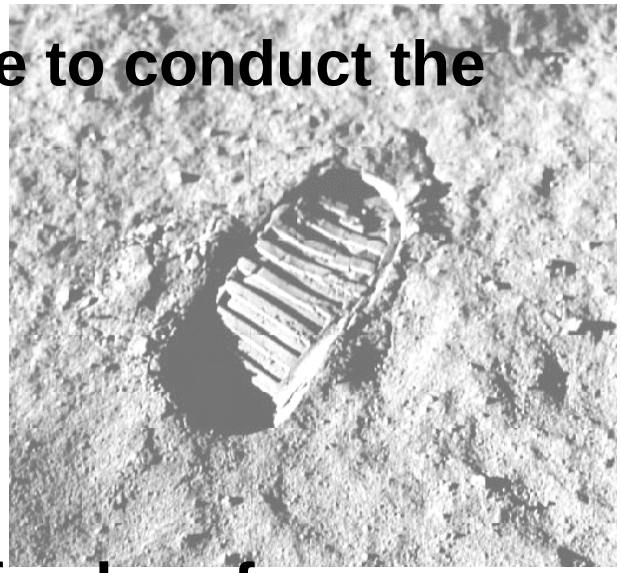
Why of Pharmaceutical Development

- **<u>CMC [21 CFR 312.23(a)(7)]:</u>**

  To assure the proper identification, quality, purity, and strength of the investigational drug.

- **<u>Nonclinical [21 CFR 312.23(a)(8)]:</u>**

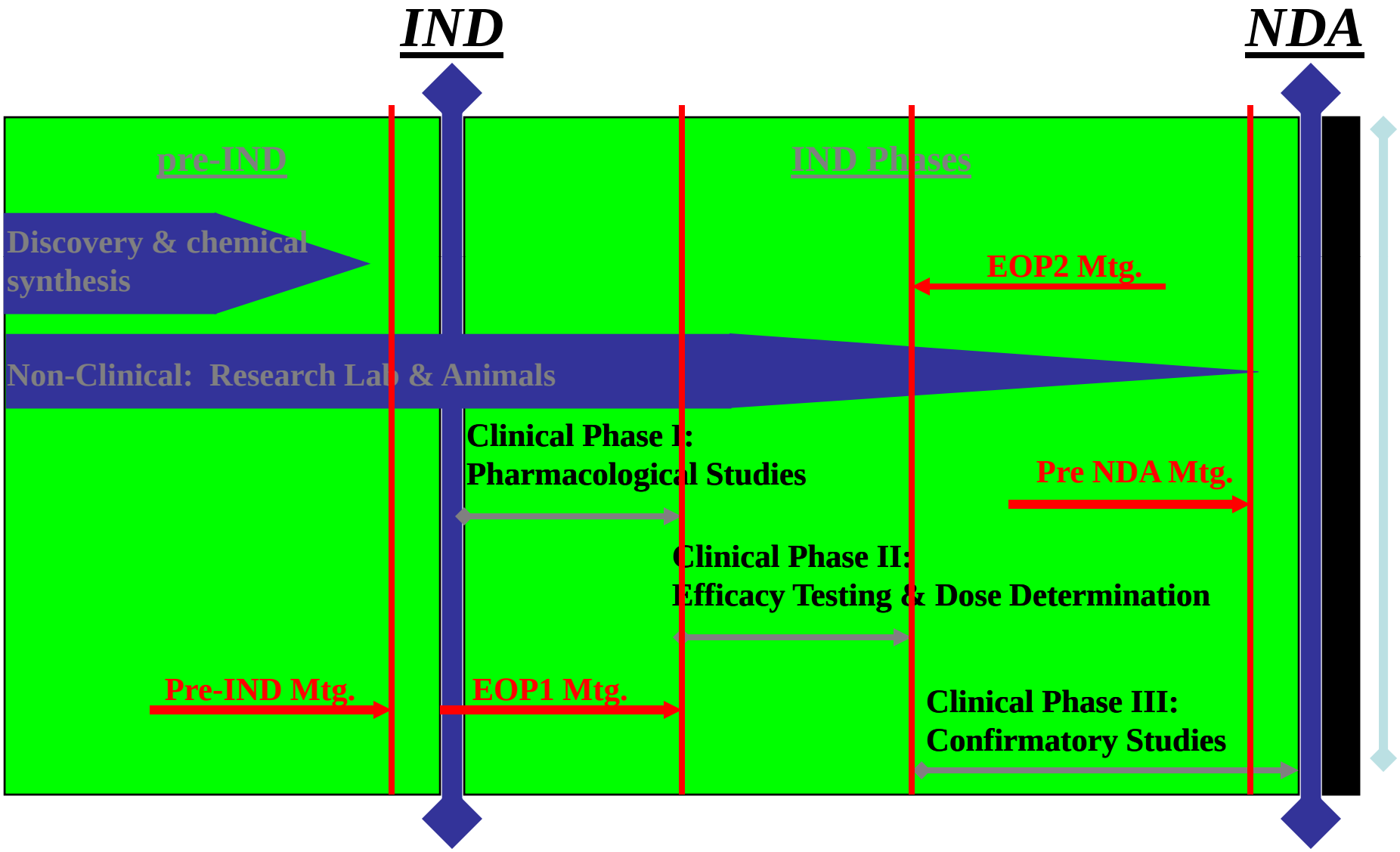
  To assure that it is reasonably safe to conduct the proposed clinical investigations.



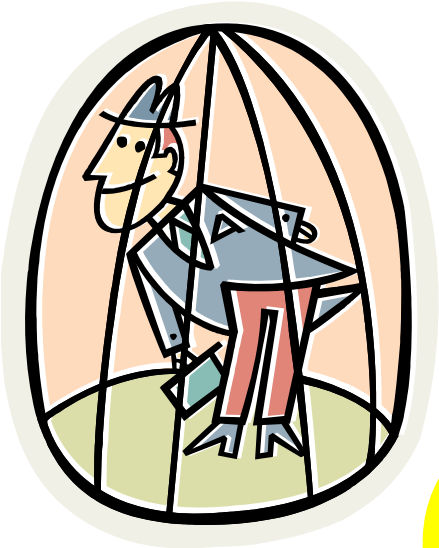
- **<u>Clinical [FD&C Act Sec. 505]:</u>**

  To establish efficacy and safety of a drug for use in humans, in a dose range and schedule that provides an acceptable risk benefit relationship.

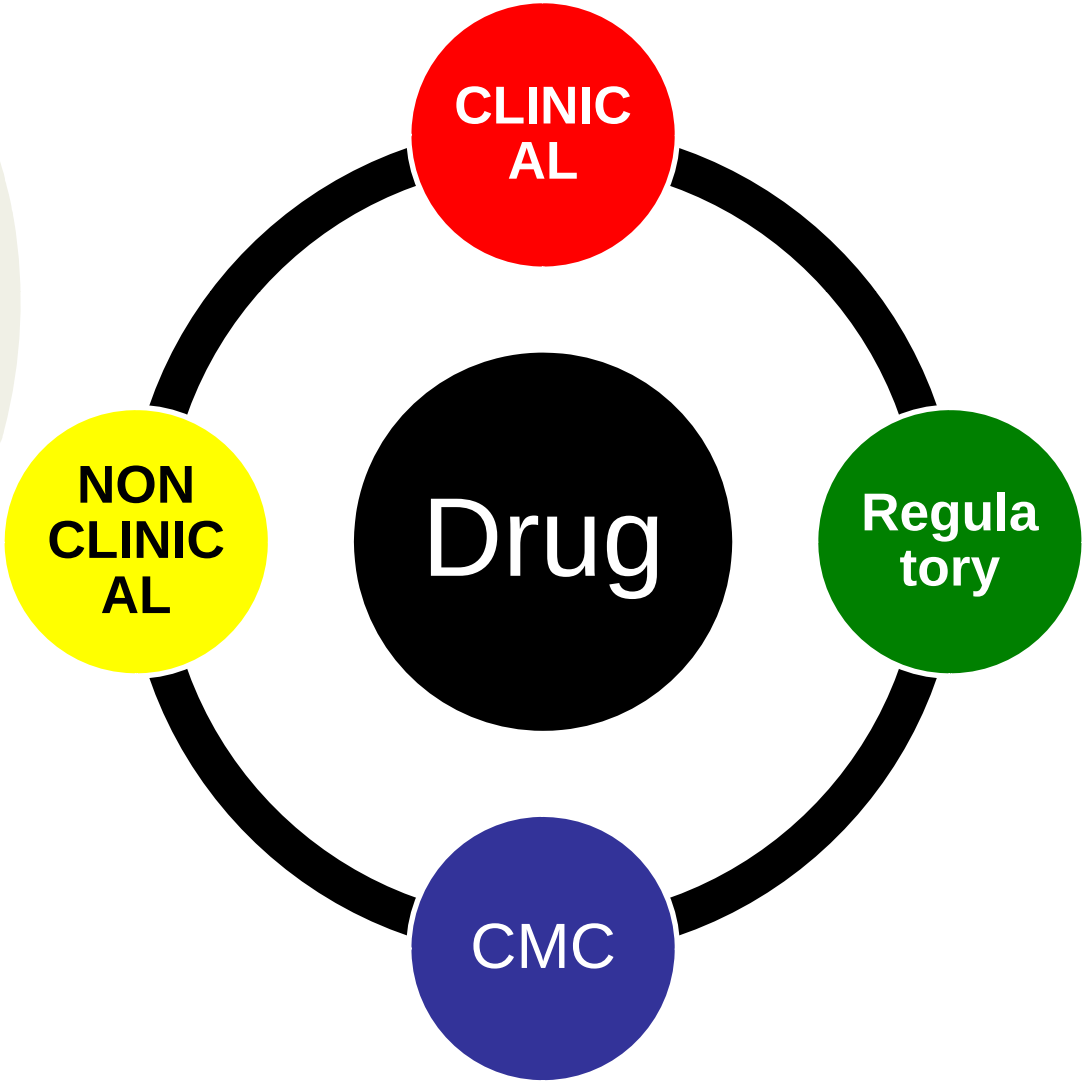
How of Drug Development Process



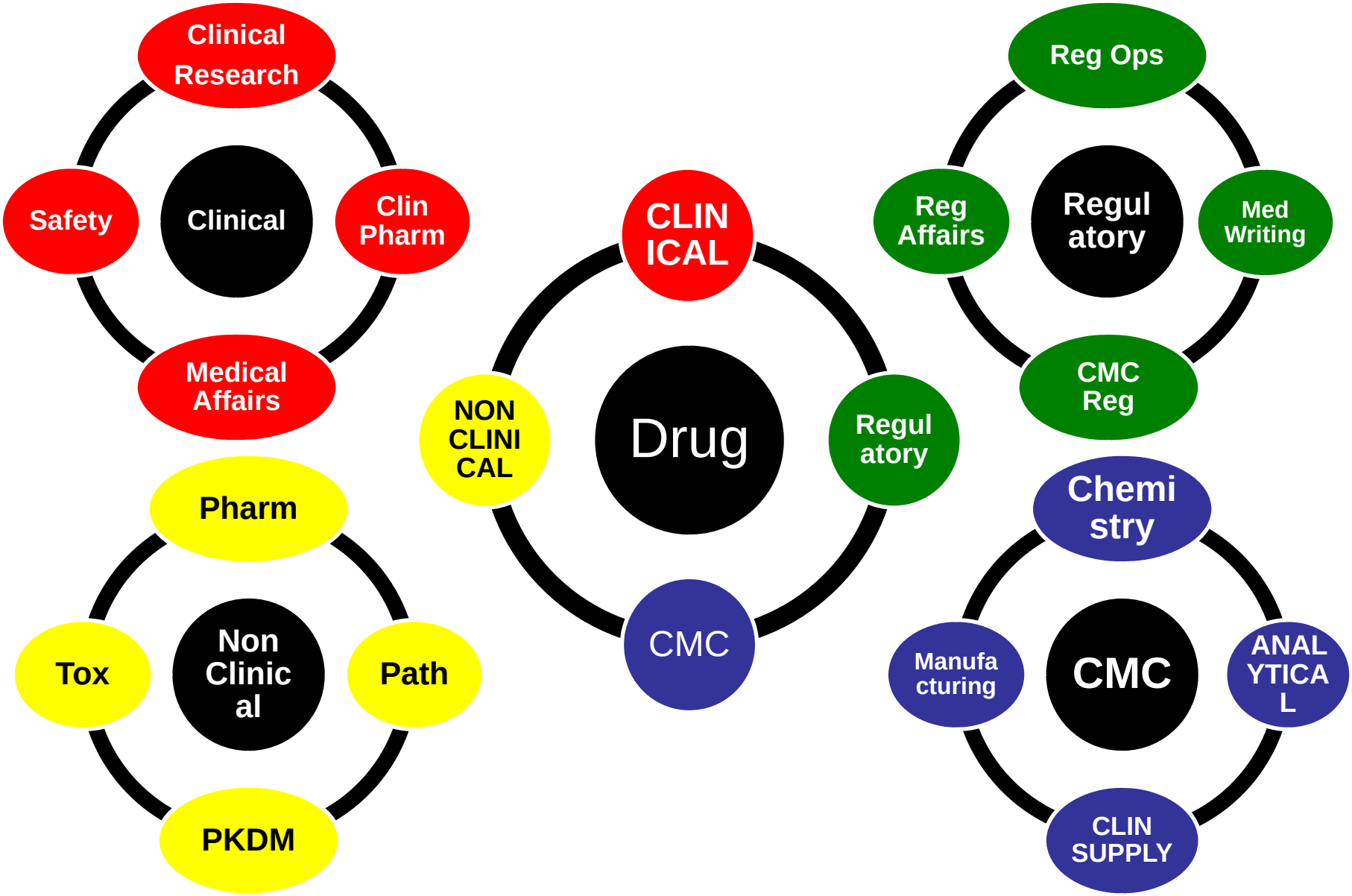
What is a Pharmaceutical Project Team



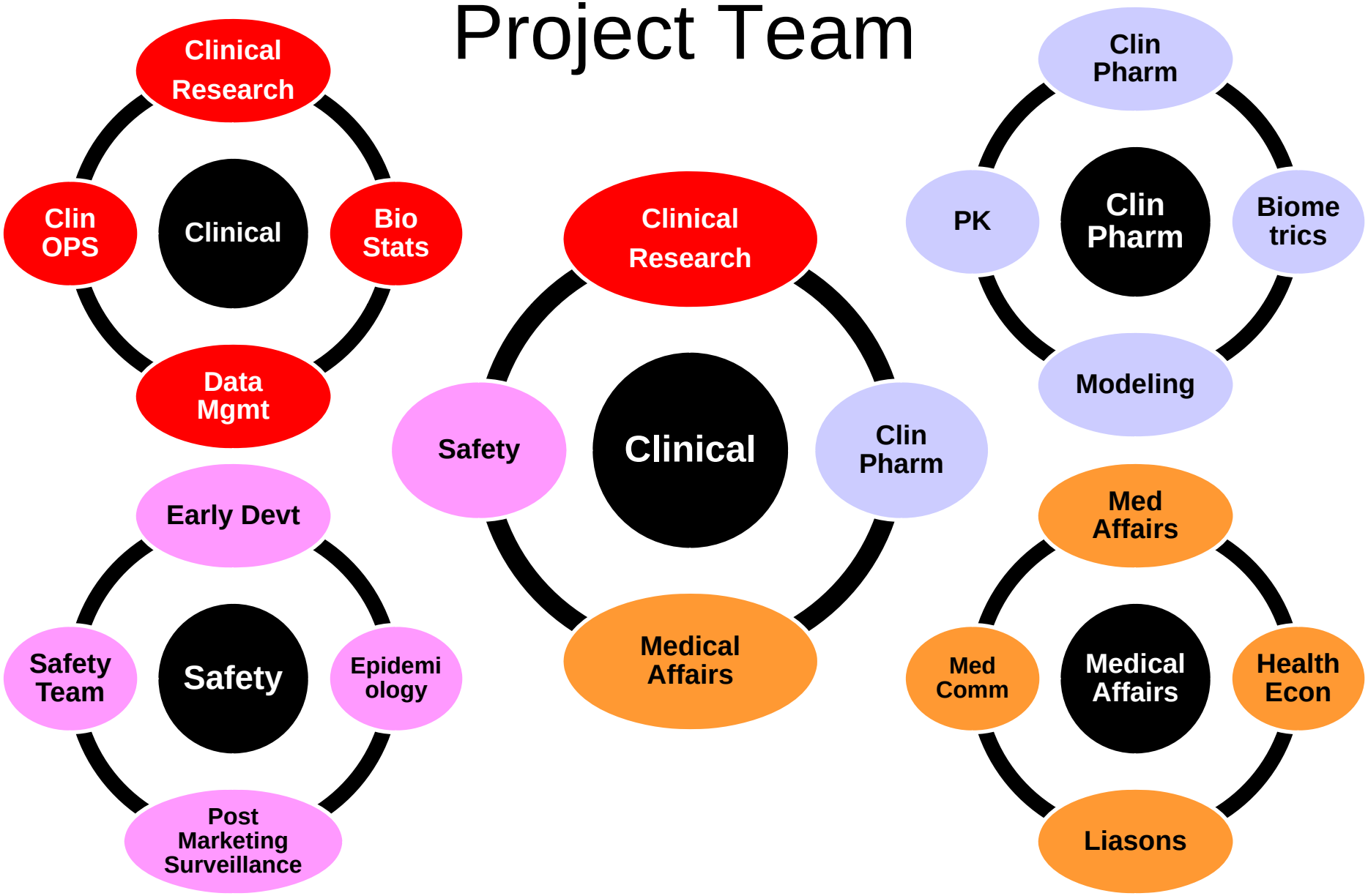
Marketing



The team at the first level

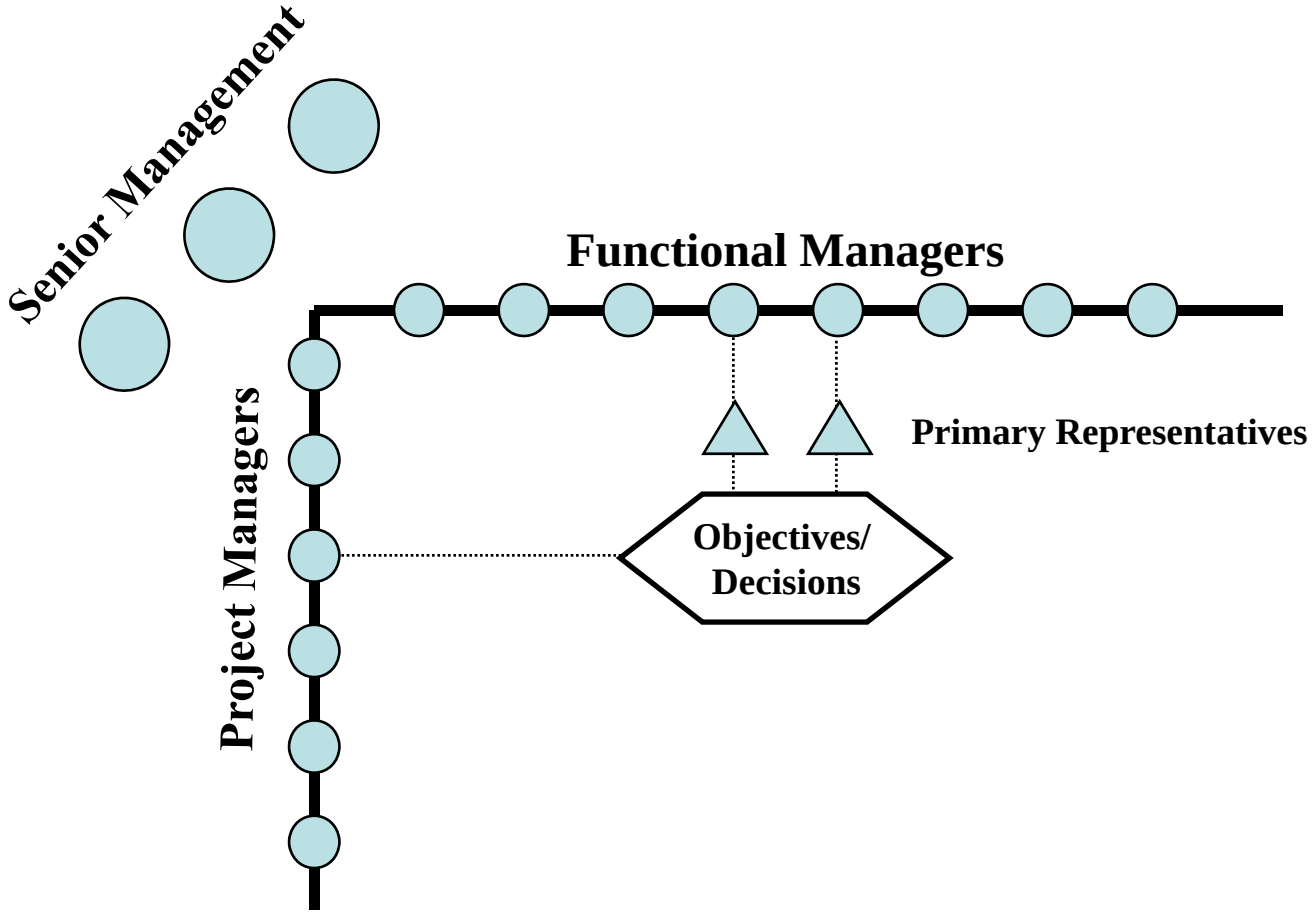


What is a Clinical Development Project Team



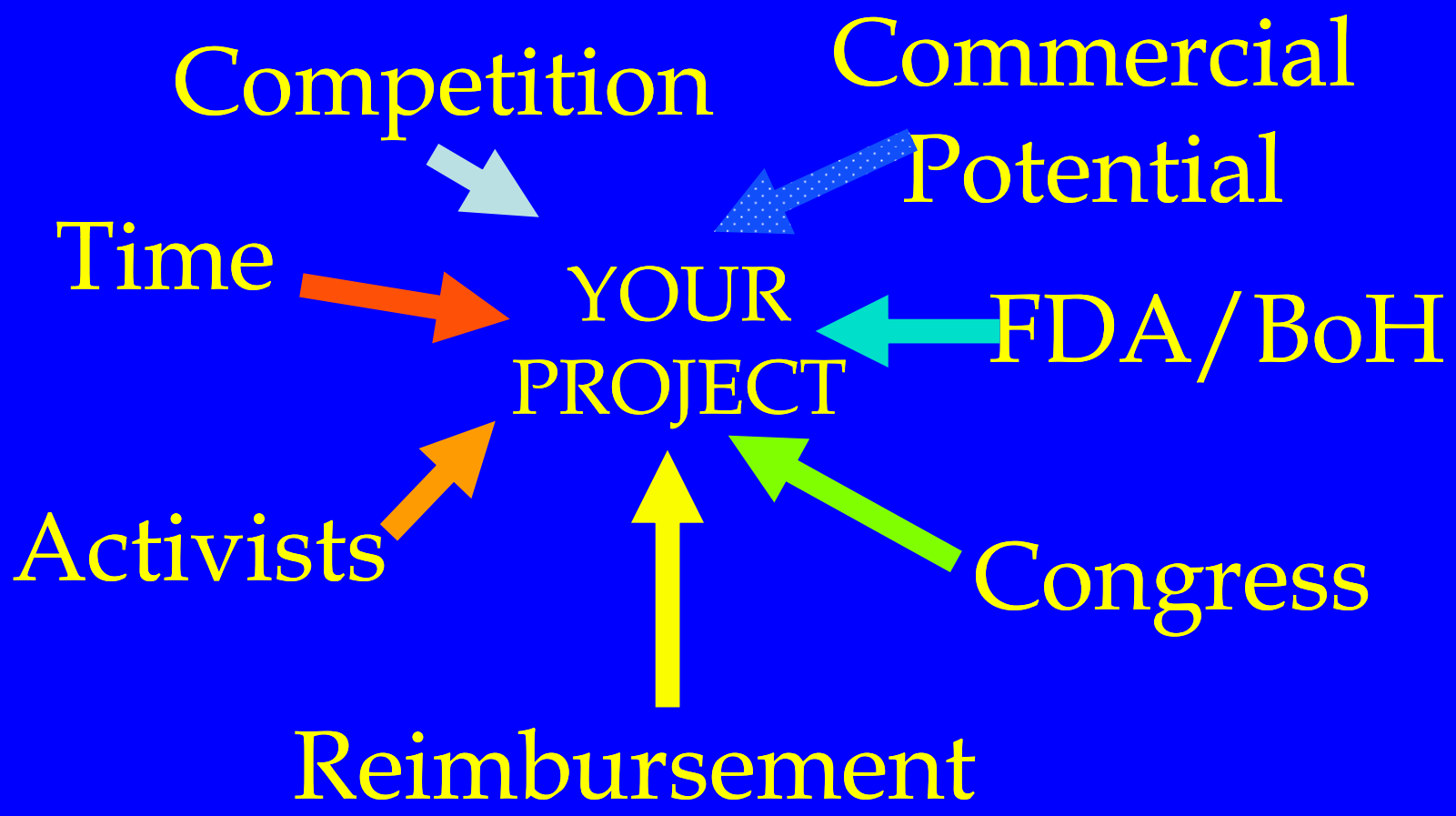
The Matrix Model for Project Teams

- Higher Efficiency and Ownership
- Managing by Influence (No Line Authority)

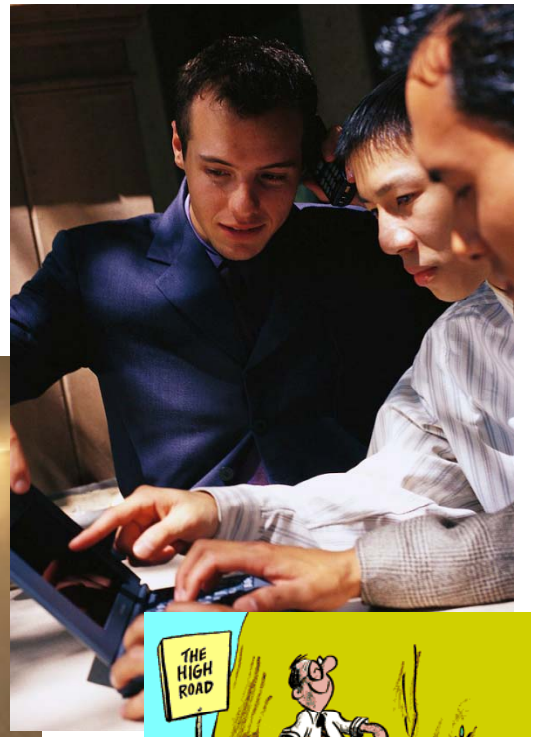


INTERNAL FORCES

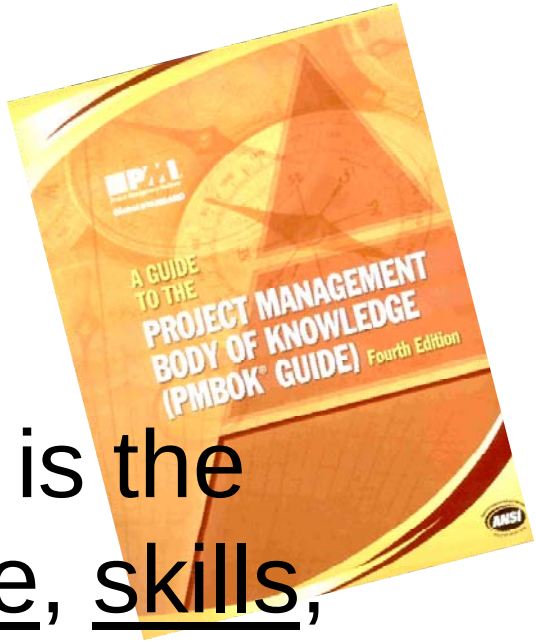
EXTERNAL FORCES



Pharmaceutical Project Management



What is Project Management?



PMBOK

"Project management is the application of knowledge, skills, tools, and techniques to project activities in order to meet or exceed stakeholder needs and expectations from a project."

Cost of Poor Management

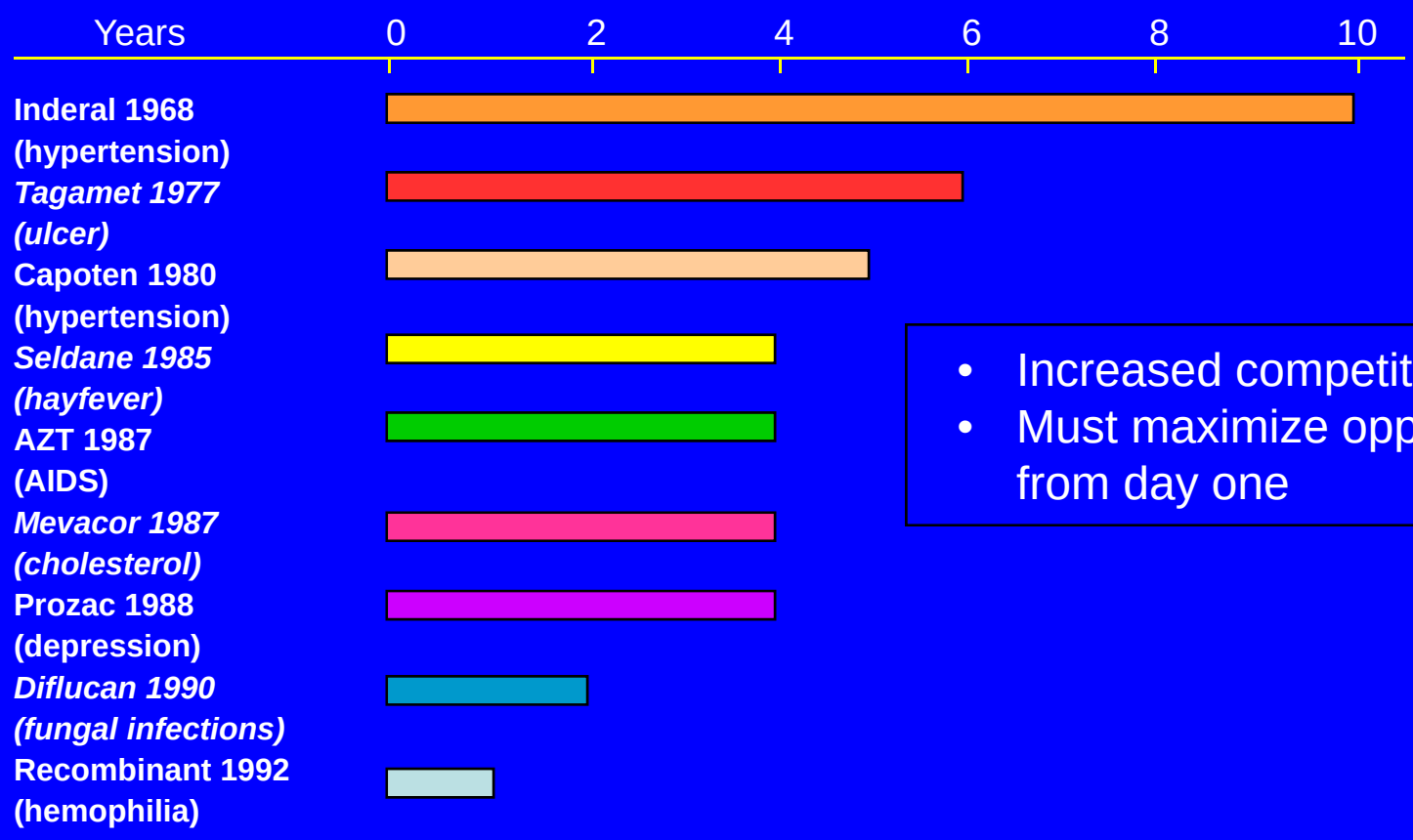
- $ 899 MM/Each New Drug
- Opportunity Costs
- Failed Drugs
- Marketing & Sales Costs
- The Patients are Still Waiting

Benefit of Good Management

- Higher NPVs
- More Products per $
- Identify Losers Sooner
- More Successful Projects
- Faster Reviews

Shrinking time to second in class requires that you get out of the gates fast & hard

Years Between Drug Launch and First Competitor



- Increased competitiveness
- Must maximize opportunity from day one

Source: A.T. Kearney, The Economist 09/20/97

PM EVOLUTION

LINE DRIVEN

PROJECT DRIVEN

Project/Venture

Portfolio P/M

Resource Allocation

Facilitate

Plan/Integrate

Resource Constraints

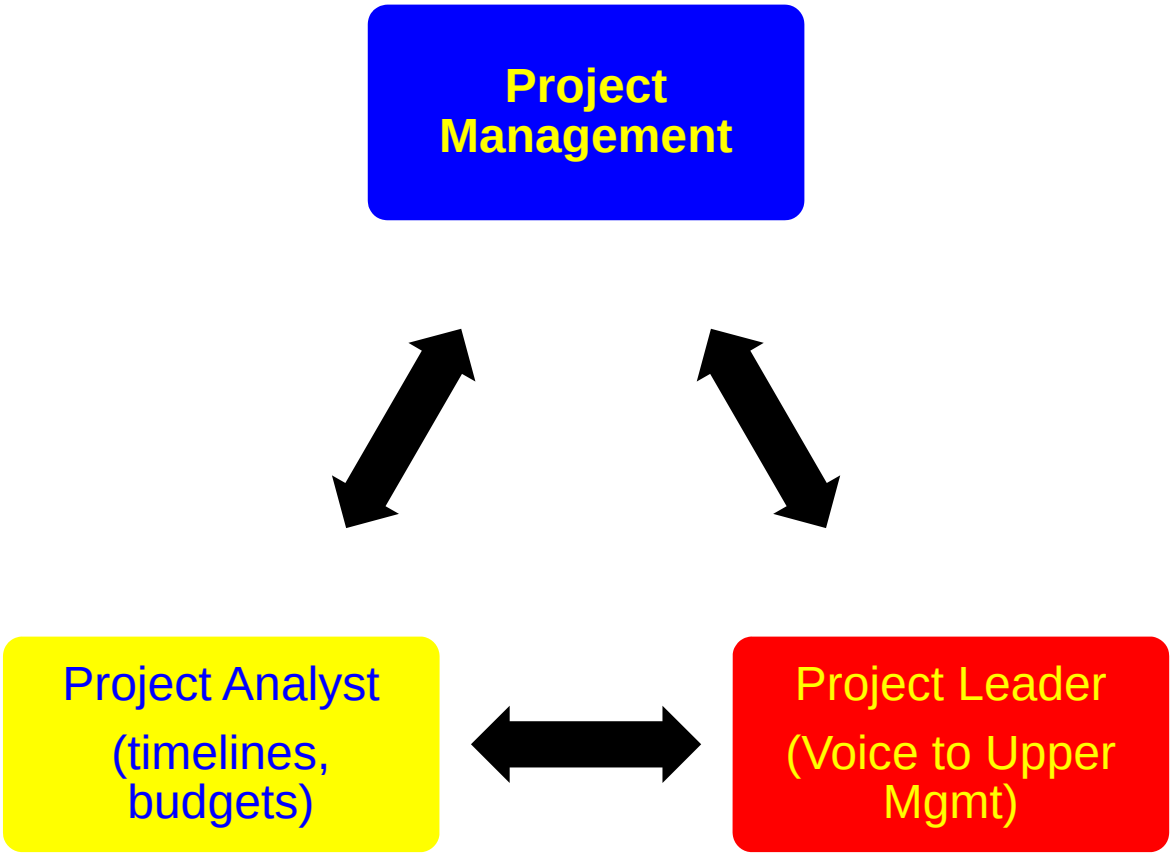
Track

Monitor Status

Notes

1975 1980 1985 1990 1995 2000

The Faces of Clinical Development Project Management



Project Management
Who They Are and What They Do:

From a Project Manager

- Masters of Business Process
- Facilitators of Interpersonal Interaction

What is Project Management?:

- Broad Knowledge
  - Experience
- Interpersonal Skills
- Ability to get the most out of tools / technology
  - Innate analytic
- Communication Techniques
- Facilitating
- Human Factors

What is Project Management?: Knowledge

- Drug development process & benchmarking
- Science/Medicine (therapeutic area)
- Regulations
- Business
- Portfolio management
- Alliance Management
- Risk management
- Project time management
- Project cost management
- Organizational dynamics
- International & corporate culture

What is Project Management?: Interpersonal Skills

- Network planning
- Strategic thinking
- Negotiation
- Meeting management
- Communication (written & oral)
- Conflict management
- Issue resolution
- Contractor management

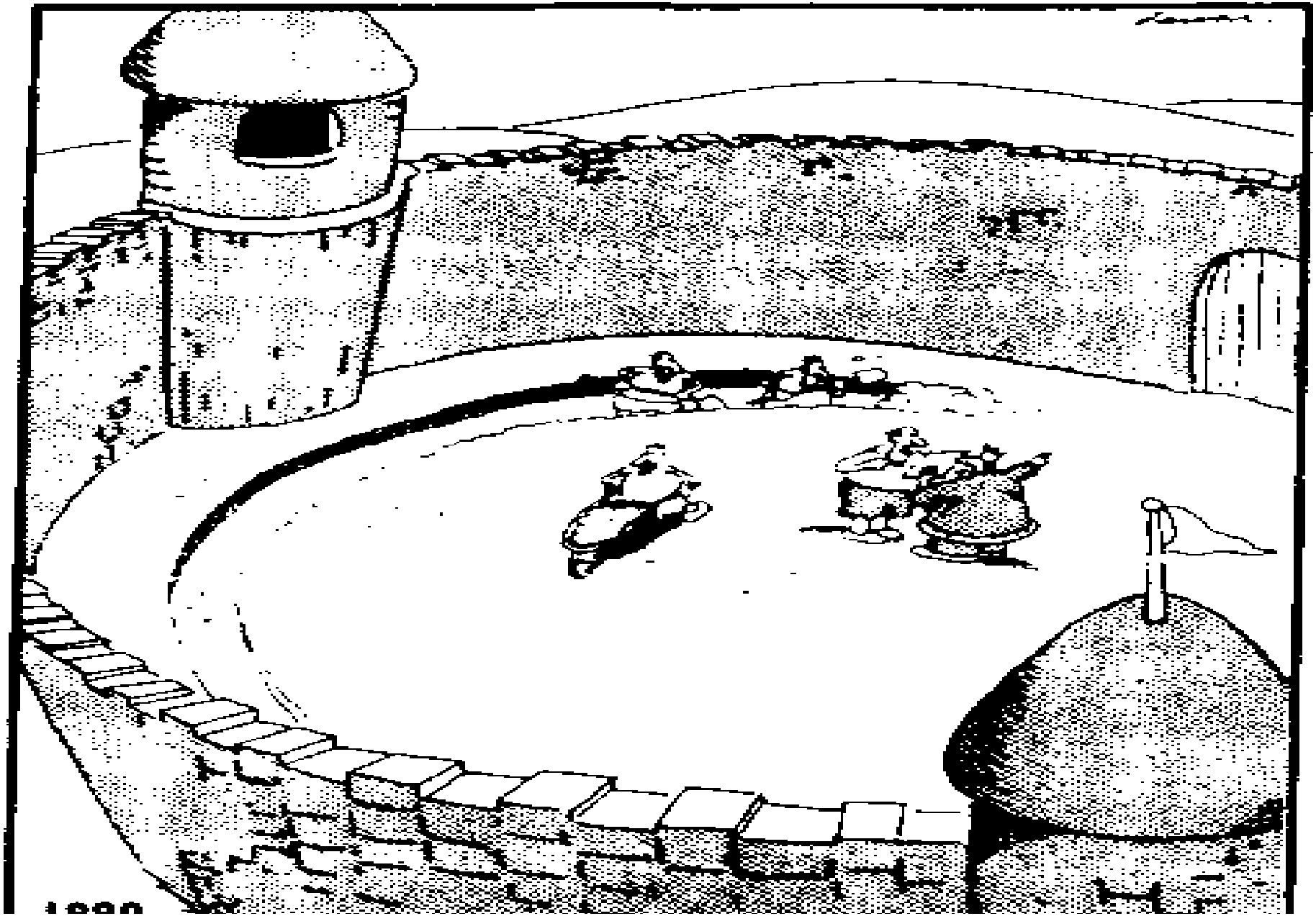
“Sure, we need more research in alchemy, necromancy, and sorcery, but where is the money going to come from?”

What is Project Management?: Tools

- Planning software
- PERT charts
- Gantt (bar) charts
- Dashboards
- Decision trees & network
- Meeting minutes
- Spreadsheets
- e-Mail
- Word processor
- Teleconference
- Videoconference

What is Project Management?: Communication Techniques

- What if analyses
- Critical path analyses
- Brainstorming
- Challenging (devil’s advocate)
- Cajoling
- Nagging
- Begging



Suddenly, a heated exchange took place between the king and the moat contractor!

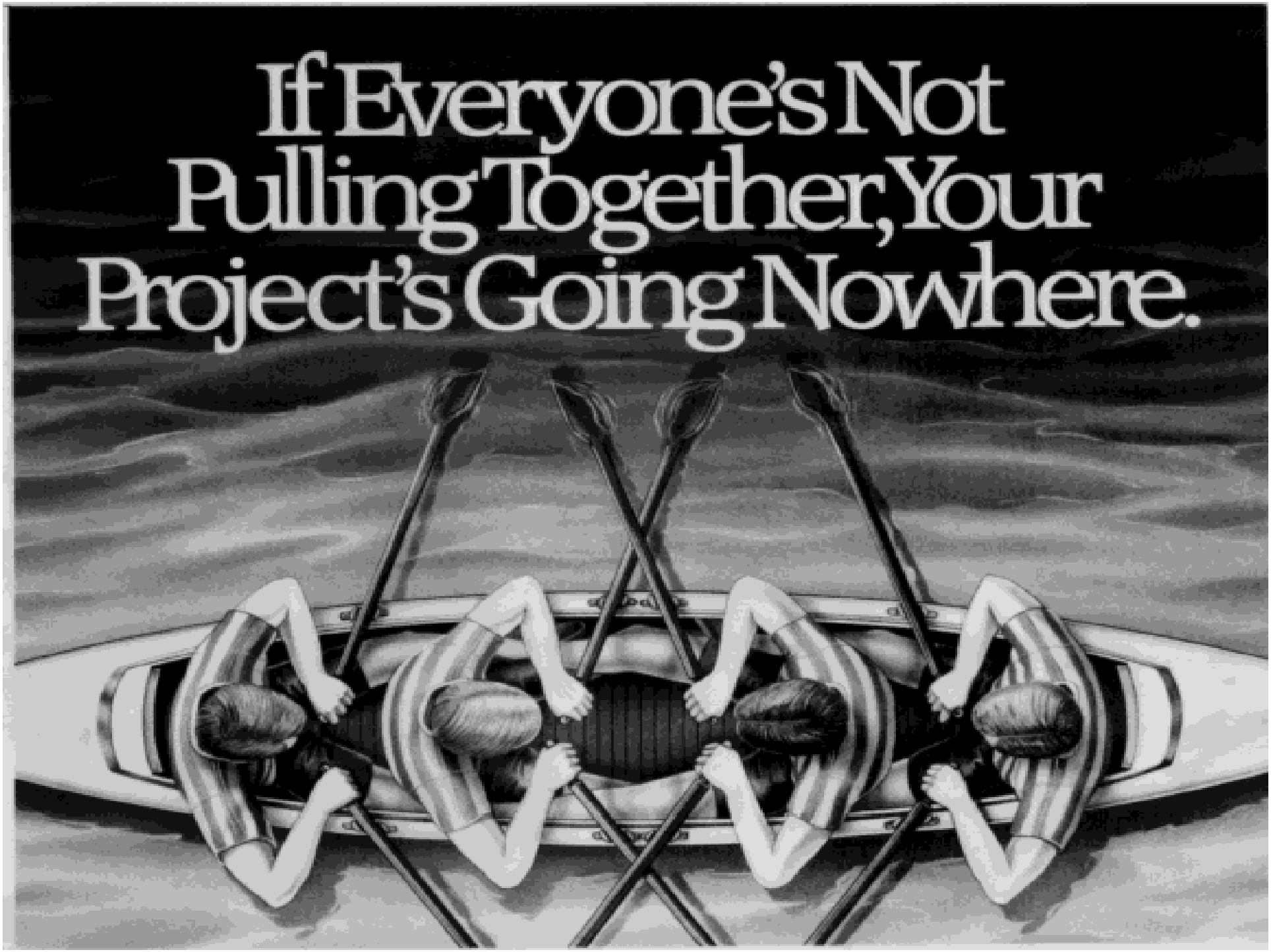
What is Project Management?: Facilitating decisions

- Selecting Clinical Candidates
- Implementing
- Tracking
- Reporting
- Completing /Terminating

Adapted from "How to Keep R&D Projects on Track!"--Robert Szakonyi

What is Project Management?: Human factors

- Leadership
- Team Building
- Matrix/ Heavy-weight Teams
- Communication
- High Performance
- Education


If Everyone's Not
Pulling Together, Your
Project's Going Nowhere.

Tools for the Project Manager

- *Don’t Leave Home Without It!!*
  - *The Team Minutes*
  - *The Target Product Profile*
  - *The Draft Structured Product Label*
  - *The Strategic Development Plan*
  - *The GANNT Chart*
  - *The Probability Analysis*

Team Meeting Minutes

- What they are good for
  - Exquisitely organized progress review
  - Concise communication tool for Senior Management
    - Brings priorities and timelines up front
  - Documentation of accountabilities and responsibilities
  - Drives the agenda of the team meeting

Team Minutes Template

- Issues (Boxed)
  - Things that will cause delay, cost overrun, or that may impact a Go/No-Go decision
  - Background, impact, proposals
- Timelines
  - With key milestones, e.g., final protocol, first patient, database lock, topline data, final report
    - Some Mgmt like planned /projected (while ongoing)/actual
- Financial Summary
- Progress by Dept
  - Nonclinical, Clin Pharm, Clin, Regulatory, CMC, Clinical Supplies
  - More granular, yet **concise** progress report, including finances, timelines, key deliverables met and forthcoming

Target Product Profile

- A contract with the Corporation regarding the desired attributes of the Product
  - Determines estimate of Net Present Value
  - Forms the basis of Go-No Go Criteria
  - Forms the basis of the clinical development plan (CDP;and probably all other DPs) and draft label

Target Product Profiles

Guidance for Industry and Review Staff

Target Product Profile — A Strategic Development Process Tool

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 comments to the Division of Dockets Management (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 Jeanne M. Delasko at 301-796-0900.

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

March 2007
Procedural

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03/09/07

Target Product Profile Awakenol® for the Treatment of Sleeping in 410.651.82 Lectures

ATTRIBUTE	Gold Standard Dontsnuzenol®	Low Case	Base Case	High Case
Dosing and Formulation				
• **Frequency**	BID	BID	QD	QD
• **Food Effect**	Food effect - ↑ Cmax	No Food Effect	No Food Effect	No Food Effect
• **Capsule size**	Size 1 capsule	Size 0 capsule	Size 1 capsule	Size 2 capsule
• **Formulation**	Dry fill	Dry fill	Beads	Bead with IP advantage
Population				
	Adult, Children age 12-16	Adult, Children age 12-16	Adult, Elderly, Children Age 12-16	Adult, Elderly, Children Age 12-16
Efficacy				
• **% Responders** [1]	53	53	60	75
• **Mean change in GPA**	+ 0.04	+0.15	+0.25	+0.35
Safety				
• **Warnings and Precautions**	Black box warning for head spinning and hyperchloremia	Black box warning for head spinning and hyperchloremia	Warning for head spinning or hyperchloremia	No warning for either head spinning or hyperchloremia
Tolerability				
• **Common (>5%) adverse events**	• 10% Nausea • 07% Apathy • 05% Confusion	• 10% Nausea • 07% Apathy • 05% Confusion	• 1-2% less in key AEs	• Clinically significant reduction in key AEs • Reduction in AEs with Superior efficacy
Indications	Falling Asleep in 410.651.82	Falling Asleep in 410.651.82	+ Falling asleep in other JHU courses	+ Falling asleep in any University course

[1] % patients with a score of at least 85 on the Rockville Sleep Scale (RSS)

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.
Any molecules, scientific concepts, or references in this paper are not *necessarily* real. This paper is only distributed to instruct on one way of formatting a TPP

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[1] % patients with a score of at least 85 on the Rockville Sleep Scale (RSS)

The low case may be the

You may not want any of a particular GS attribute, even in the low case

It is not uncommon to incorporate intellectual property positions in the TPP

Differences in numerical results are tricky to assign; be reasonable; What is clinically significant?

Same point as efficacy; This is my common tolerability strategy

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Product Labeling: New Format Highlights Section

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Imdicon safely and effectively. See full prescribing information for Imdicon.

IMDICON® (cholinasol) CAPSULES
Initial U.S. Approval: 2000

WARNING: LIFE-THREATENING HEMATOLOGICAL ADVERSE REACTIONS
See full prescribing information for complete boxed warning.
Monitor for hematological adverse reactions every 2 weeks for first 3 months of treatment (5.2). Discontinue Imdicon immediately if any of the following occur:
- **Neutropenia/agranulocytosis (5.1)**
- **Thrombotic thrombocytopenic purpura (5.1)**
- **Aplastic anemia (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Coronary Stenting (1.2)	2/200X
Dosage and Administration, Coronary Stenting (2.2)	2/200X

----------INDICATIONS AND USAGE----------
Imdicon is an adenosine diphosphate (ADP) antagonist platelet aggregation inhibitor indicated for:
- Reducing the risk of thrombotic stroke in patients who have experienced stroke precursors or who have had a completed thrombotic stroke (1.1)
- Reducing the incidence of subacute coronary stent thrombosis, when used with aspirin (1.2)

Important limitations:
- For stroke, Imdicon should be reserved for patients who are intolerant of or allergic to aspirin or who have failed aspirin therapy (1.1)

----------DOSAGE AND ADMINISTRATION----------
- Stroke: 50 mg once daily with food. (2.1)
- Coronary Stenting: 50 mg once daily with food, with antiplatelet doses of aspirin, for up to 30 days following stent implantation (2.2)

Discontinue in renally impaired patients if hemorrhagic or hematopoietic problems are encountered (2.3, 8.6, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 50 mg (3)

----------CONTRAINDICATIONS----------
- Hematopoietic disorders or a history of TTP or aplastic anemia (4)
- Hemostatic disorder or active bleeding (4)
- Severe hepatic impairment (4, 8.7)

----------WARNINGS AND PRECAUTIONS----------
- Neutropenia (2.4 % incidence; may occur suddenly; typically resolves within 1-2 weeks of discontinuation), thrombotic thrombocytopenic purpura (TTP), aplastic anemia, agranulocytosis, pancytopenia, leukemia, and thrombocytopenia can occur (5.1)
- Monitor for hematological adverse reactions every 2 weeks through the third month of treatment (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence >2%) are diarrhea, nausea, dyspepsia, rash, gastrointestinal pain, neutropenia, and purpura (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact (manufacturer) at (phone # and Web address) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------
- Anticoagulants: Discontinue prior to switching to Imdicon (5.3, 7.1)
- Phenytoin: Elevated phenytoin levels have been reported. Monitor levels. (7.2)

----------USE IN SPECIFIC POPULATIONS----------
- Hepatic impairment: Dose may need adjustment. Contraindicated in severe hepatic disease (4, 8.7, 12.3)
- Renal impairment: Dose may need adjustment (2.3, 8.6, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 5/200X

Product Labeling: New Format Full Prescribing Information

Boxed Warning
1 Indications & Usage
2 Dosage & Administration
3 Dosage Forms & Strengths
4 Contraindications
5 Warnings & Precautions
6 Adverse Reactions
7 Drug Interactions
8 Use in Specific Populations
9 Drug Abuse & Dependence
10 Overdosage
11 Description
12 Clinical Pharmacology
13 Nonclinical Toxicology
14 Clinical Studies
15 References
16 How Supplied/Storage & Handling
17 Patient Counseling Information

Why is Labeling Important

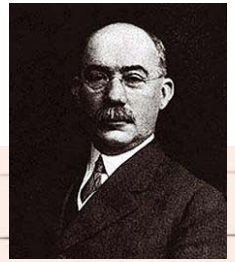
- It is considered the preferred method to convey information about your drug
  - Has profound impact on advertising, claims, compensation
  - Often the first source of information for doctors and consumers
- If you want claims in your label, you need to study it
  - Sometimes things you don’t want get put in, e.g., class labeling

Strategic Development Plan

Adapted from Kennedy's "Pharmaceutical Project Management"

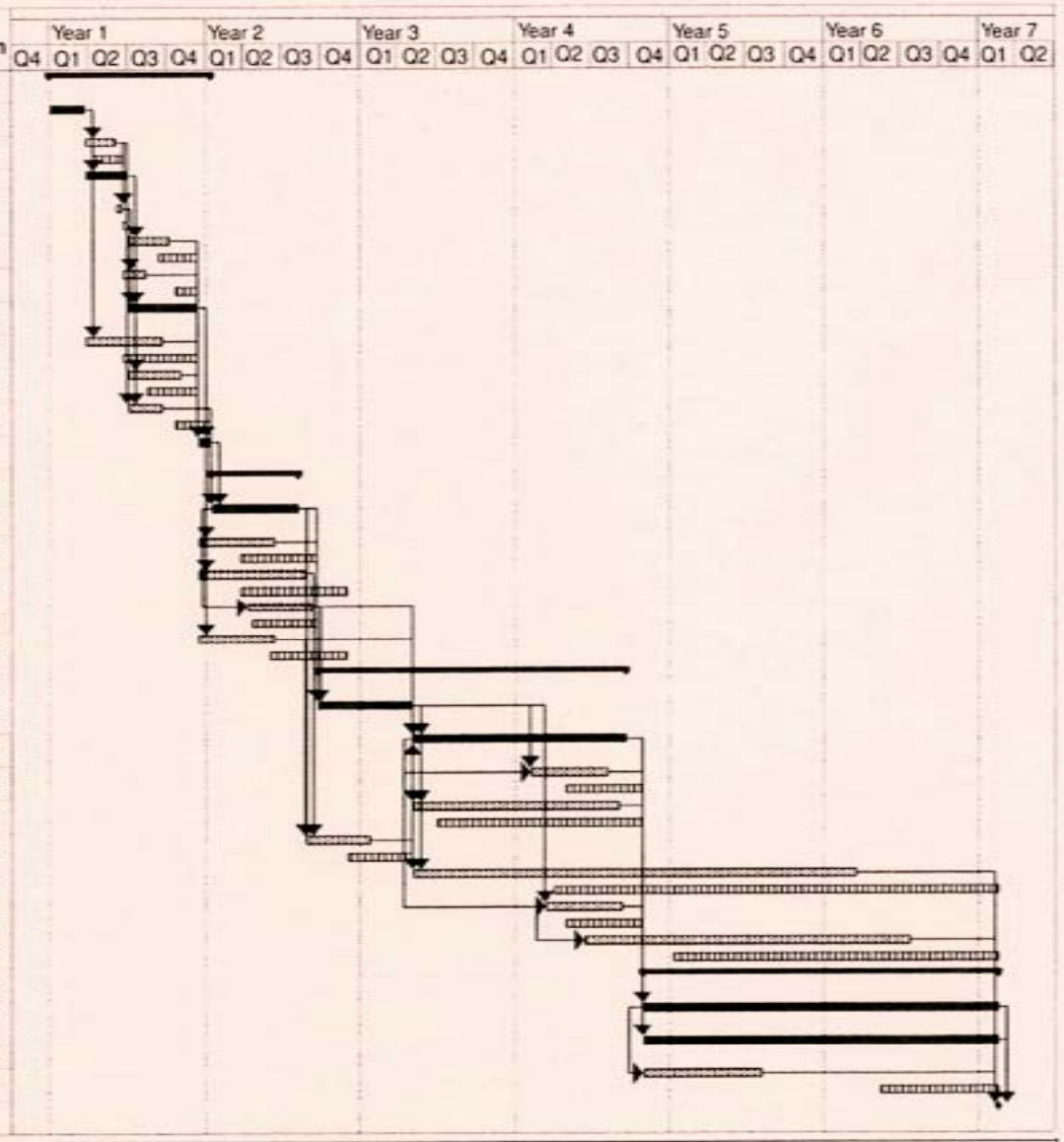
Plan section	Pages	Content	Comment
Executive summary	4	The approval sought (scope of activities, funds, and resources) Development strategy Key risks/risk management Go/no-go checkpoint and criteria High level Gantt chart	A template often used so that the oversight committee has consistent "view" of the projects being presented
Target product profile(s)	2	Refer to Table 3	The detail increases during development phases
Business strategy	5	Market definition Marketing assumptions Pharmacoeconomics strategy	Current and future market structure and constraints to access
Clinical strategy	5	Clinical strategy Clinical studies tabulation Clinical Gantt chart Clinical issues/issue management	High level extract from a functional clinical plan
Regulatory strategy	3	Regulatory strategy Regulatory plan Regulatory risks/risk management	Defines regulatory strategy/plans for the major markets
Technical strategy CMC	3	Drug substance plan Drug product plan Analytics plan Key issues/issue management	The manufacturing strategy for sourcing and supply detailed in functional plans
Scientific summary	4	Scientific rationale Preclinical plan ADME plan Key issues/issue management	High-level status summary and forward activity plan
Development costs	2	Estimated costs by stage Estimated costs by activity type	Standardized analyses for portfolio
Financial analysis	4	5th-yr revenues Financial assessment of project	Standardized analyses for portfolio

Abbreviations: CMC, chemistry, manufacturing and controls; ADME, absorption, distribution metabolism, excretion.



GANNT Chart

ID	Task Name	Duration
1	**Preclinical Phase**	**54 wks**
2	Laboratory API Synthesis and Analysis	12 wks
3	API Physicochemical Evaluation and Preformulation Activities	10 wks
4	GMP Synthesis and Analysis of API	14 wks
5	Preclinical Formulation	2 wks
6	Mutiagencity Studies	14 wks
7	Acute Toxicty Studies	8 wks
8	Repeat-Dose Toxicology Studies	24 wks
9	ADME/PK Evaluation Pre–Phase 1	26 wks
10	Safety Pharmacology Package	18 wks
11	Drug Product Formulation (GMP)	12 wks
12	Regulatory Review (CTA/IND) for Phase 1 Study	4 wks
13	**Phase I**	30 wks
14	Basic Phase I Studies	30 wks
15	Additional tox. (if required), e.g., 3m to support Phase II/III	26 wks
16	Tox. Reproduction: Embryotoxicity (2 Species)	36 wks
17	Drug Product Optimization/Manufacture Phase 2	22 wks
18	API Process Development	26 wks
19	**Phase II**	104 wks
20	Proof-of-Concept Efficacy Trial	32 wks
21	Dose-finding Clinical Trials	72 wks
22	Clinical Pharmacology, e.g., QTc study & interactions	26 wks
23	Long-Term Repeat Dose Toxicology Studies	70 wks
24	Tox. Reproduction: Fertility and Peri/Postnatal	22 wks
25	Carcinogenicity	150 wks
26	Drug Product (Phase 3) Scale-Up and Validation	26 wks
27	Stability of Drug Product (Final Formulation)	110 wks
28	**Phase III**	120 wks
29	Pivotal Phase 3 Efficacy Trials	120 wks
30	Long-Term Safety Evaluation	120 wks
31	Special Population Studies	40 wks
32	Marketing Approval (MAA/NDA) Submission	0 wks



Project: Project plan
Date: 31 Aug '07

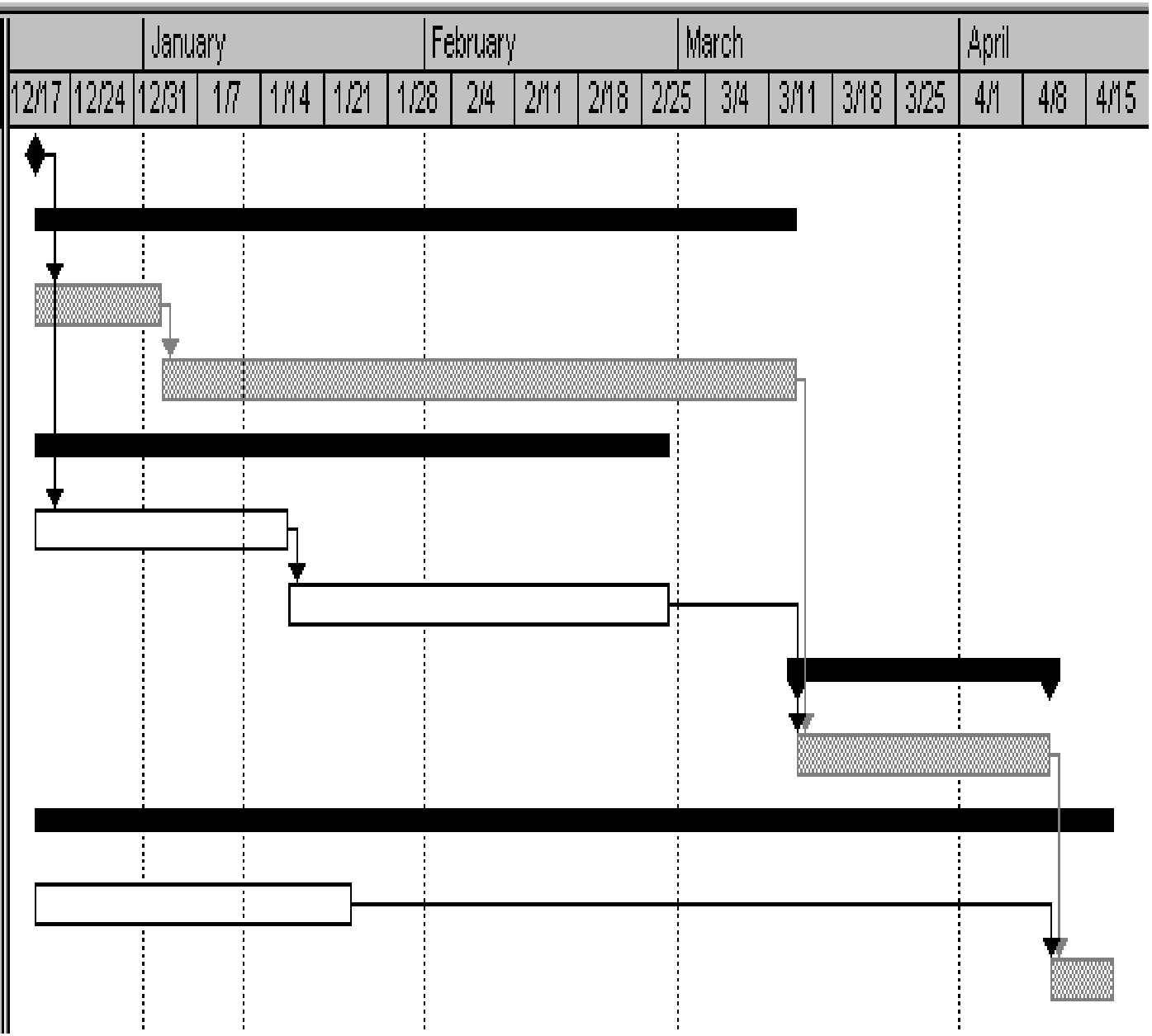
Early Start | Late Start | Critical Task | Milestone | Summary

GANNT Chart

- Allows review of timetables
  - Allows one to double check assumptions
- Identification of resources
- Allows recognition of critical interdependencies
  - e.g., need to clear a product with QA before shipping
  - Forms the basis of Go-No Go Criteria
- Identifies critical path tasks
  - a **critical path** is the sequence of activities which add up to the longest overall project duration. This determines the shortest time possible to complete the project. Any delay of an activity on the critical path directly impacts the planned project completion date. Those activities that can be done at anytime are “not on the critical path”

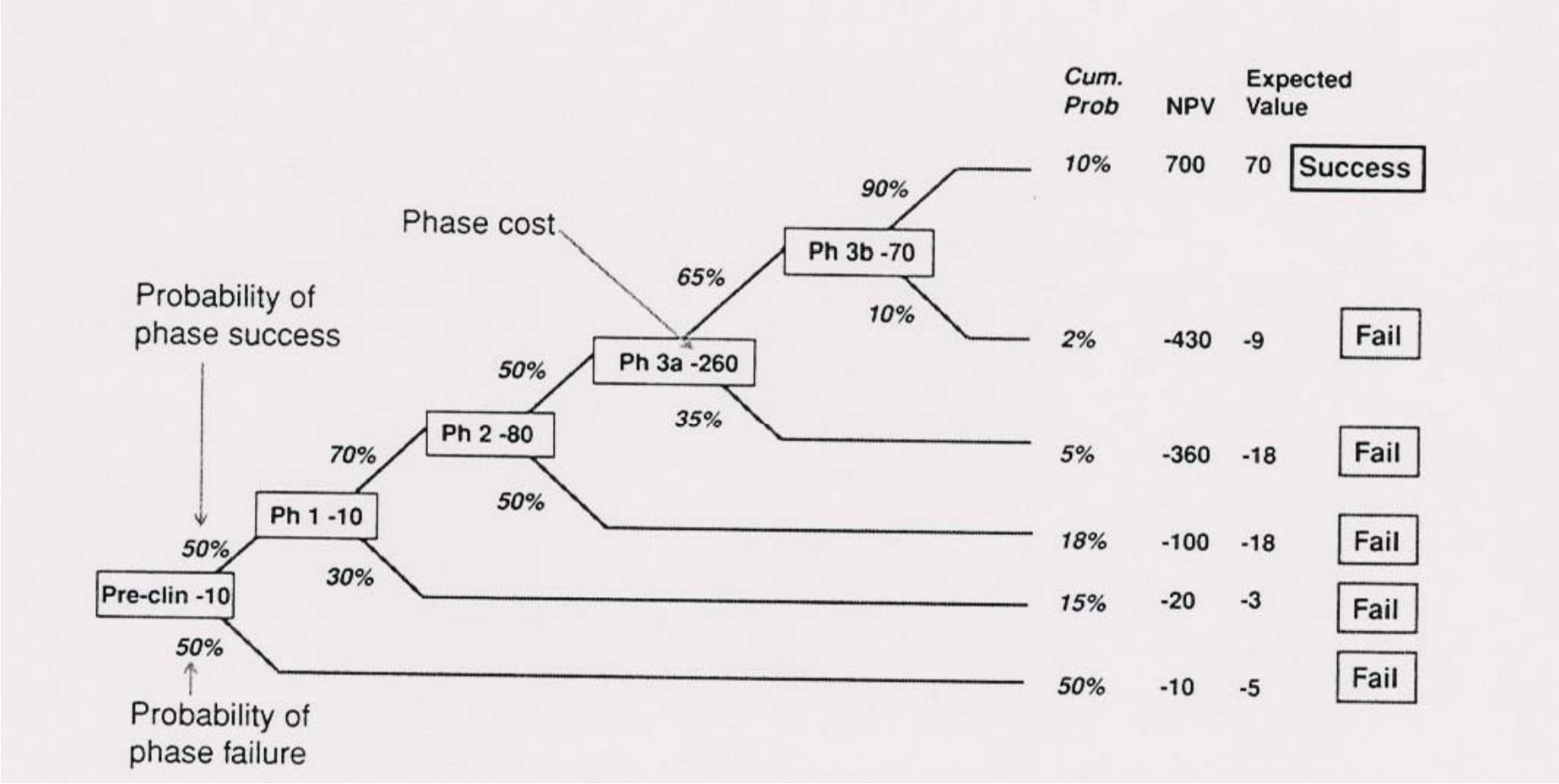
Critical Path Analysis: GANTT Chart

Task Name	Duration
Last Patient Last Visit (LPLV)	0 days
PK Data	**60 days**
Collect Bioanalytical	2 wks
Lock PK Database	10 wks
CRF Data	**50 days**
Collect CRFs	4 wks
Lock CRF Database	6 wks
Analysis	**20 days**
Analyze Data	4 wks
Reporting	**85 days**
Finalize First Draft Report	5 wks
Finalize Report	1 wk



"KIDS! This stop is on the CRITICAL PATH and is scheduled to take exactly 43 minutes! ~ So no slack time!"

Probability Exercises for Project and Portfolio Planning



Summary

- Clinical Development is complex, both in its science and relationships
- The CDPM plays a pivotal role facilitating the planning and execution of CD
- Various tools are at the disposal for organization and communication
- ***Project Leader*** *is the one who takes the reins!*