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)
Objectives

• Clinical Development (CD) as a complex science and set of relationships
  – Review the concept of Clinical Development
  – Discuss the components of the clinical development team
• The role of the CD Project Manager (PM) (CDPM)
• Tools for the CDPM
• How to succeed (and fail) as a CDPM
Recommended Reading

“...is not a simple process”

“...depends on the quality of the development strategy”
"Well, here we are again."
What is Pharmaceutical Development

- Unmet Medical Need
- Innovation

- Market Potential

- Statutory Constraints
- Resource Limitations
Aim of Pharmaceutical Development

- **CMC [21 CFR 312.23(a)(7)]:**
  To assure the proper identification, quality, purity, and strength of the investigational drug.

- **Nonclinical [21 CFR 312.23(a)(8)]:**
  To assure that it is reasonably safe to conduct the proposed clinical investigations.

- **Clinical [FD&C Act Sec. 505]:**
  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.
Drug Development Process

**IND Phases**
- Discovery & chemical synthesis
- Non-Clinical: Research Lab & Animals
- Clinical Phase I: Pharmacological Studies
- Clinical Phase II: Efficacy Testing & Dose Determination
- Clinical Phase III: Confirmatory Studies

**Pre-IND Mtg.**
- Pre-IND Mtg.
- EOP1 Mtg.
- IND Phases
- EOP2 Mtg.

**NDA**
- Pre NDA Mtg.
What is a Pharmaceutical Project Team

Drug

- Clinical
- Regulatory
- Non-Clinical
- CMC
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)

- Senior Management
- Functional Managers
- Project Managers
- Primary Representatives

Objectives/Decisions
INTERNAL FORCES

Evaluation  Team  Turf

Quality  Strategic

Time  Intent

Decision Making  Marketing

Selection  YOUR PROJECT
EXPANDED REIMBURSEMENT
“HCFA Reimbursement For Epogen, Takeover Talk Help Amgen Grow in June”
• “A second increase in the Health Care Financing Administration reimbursement rates for Epogen has aided in increasing the valuation of Amgen in the financial community.”
• “On June 19, HCFA issued a program memorandum to payers that directed payment of claims for Epogen (erythropoietin alfa) in patients whose hematocrit levels reach as high as 37.5%”

“The Pink Sheet” 7/6/98 page 20
On June 24, Gruntal & Co. analyst David Saks predicted that the new reimbursement policy could result in a 10% increase in use; Epogen sales in 1997 were about $1.07 bil. And Amgen’s total revenues were $2.4 bil. Gruntal upgrades Amgen from “buy” to “strong buy.”
Project Management
Value to the Development Process

"OH, YEAH? WELL MY DAD'S EARNED VALUE IS BIGGER THAN YOUR DADS!"

© Knight Associates 2008
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

- Inderal 1968 (hypertension)
- Tagamet 1977 (ulcer)
- Capoten 1980 (hypertension)
- Seldane 1985 (hayfever)
- AZT 1987 (AIDS)
- Mevacor 1987 (cholesterol)
- Prozac 1988 (depression)
- Diflucan 1990 (fungal infections)
- Recombinant VIII 1992 (hemophilia)

- Increased competitiveness
- Must maximize opportunity from day one

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

Project/Venture
Portfolio P/M
Resource Allocation
Facilitate
Plan/Integrate
Resource Constraints
Track
Monitor Status
Notes
The Faces of Clinical Development
Project Management

Project Analyst (timelines, budgets)  Project Leader (Voice to Upper Mgmt)
Duties of the Project Manager

![Diagram showing relationships between Project, Management, and Portfolio]
Project Management
Who They Are and What They Do:

From a Project Manager

• Masters of Business Process
• Facilitators of Interpersonal Interaction

"I'M SORRY, BUT IT SAYS HERE THAT YOU DIDN'T MEET YOUR PROJECT DELIVERABLES."
Project Management of Business Process

- Portfolio Design, Planning & Management
- Planning
- Scheduling
- Resource Allocation
- Human Factors (Teams)
- Decision Making Process
- Process Leadership & Benchmarking
WHAT IS PROJECT MANAGEMENT?

• 1. PORTFOLIO
  – Design & Planning
  – Management
WHAT IS PROJECT MANAGEMENT?

• PLANNING
  – Objectives
  – Strategy
  – Tactics
  – Go/No Go Criteria: Prespecified
  – Integration
  – Budgeting (Finance)
WHAT IS PROJECT MANAGEMENT?

• SCHEDULING
  – Deadlines
  – Velocity
  – Acceleration
  – Tradeoffs
WHAT IS PROJECT MANAGEMENT?

• RESOURCE ALLOCATION
  – Capacity
  – Relative to timing needs?
  – Financial
    • Budget (Forecast)
    • Accounting (Status)
“Sure, we need more research in alchemy, necromancy, and sorcery, but where is the money going to come from?”
WHAT IS PROJECT MANAGEMENT?

6. HUMAN FACTORS
   - Leadership
   - Team Building
   - Matrix/ Heavy-weight Teams
   - Communication
   - High Performance
   - Education
If Everyone’s Not Pulling Together, Your Project’s Going Nowhere.
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?

FACILITATING DECISIONS

Report

Decide

Complete/Terminate

Initiate

Implement

Monitor/Track

Adapted from “How to Keep R&D Projects on Track!” --Robert Szakonyi
WHAT IS PROJECT MANAGEMENT?

- PROCESS LEADERSHIP AND BENCHMARKING
  - Knowledge of the Overall Process
  - Knowing What is Needed Next
  - Knowing How Long it Should Take & How Much It Costs
What is Project Management?:

Interpersonal Quotient

- Broad Knowledge
  - Experience
- Interpersonal Skills
- Ability to get the most out of tools / technology
  - Innate analytic
- Communication Techniques
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
- Monitoring
- Contractor management
What is Project Management?:
Tools of the IQ

- 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!
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 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
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
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 Profile

Typically your “Low Case”

Typically your realistic profile

Typically your “High Case”

Typically your “Gold Standard”

### Exhibit 2 Complexities in Evaluating a Compound (Illustrative)

<table>
<thead>
<tr>
<th>Urology compound drug profiles</th>
<th>Licensing target</th>
<th>Generic on market</th>
<th>On market 5 years</th>
<th>On market 3 years</th>
<th>Launch in 1 year</th>
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<td>Comp A</td>
<td>Comp B</td>
<td>Comp C</td>
<td>Comp D</td>
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<td>Occurrence of dry mouth</td>
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<td>Occurrence of constipation</td>
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<td>42%</td>
<td>30%</td>
<td>12%</td>
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Source: Oliver Wyman analysis.
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
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® (cholinosal) 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)

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).

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
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
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
Strategic Development Plan

Adapted from Kennedy’s “Pharmaceutical Project Management”

<table>
<thead>
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<th>Plan section</th>
<th>Pages</th>
<th>Content</th>
<th>Comment</th>
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<td>Executive summary</td>
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<td>The approval sought (scope of activities, funds, and resources)</td>
<td>A template often used so that the oversight committee has consistent “view” of the projects being presented</td>
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<td>Development strategy</td>
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<td>Key risks/risk management</td>
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<td>Go/no-go checkpoint and criteria</td>
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<td>High level Gantt chart</td>
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<td>Target product</td>
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<td>Refer to Table 3</td>
<td>The detail increases during development phases</td>
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<td>Market definition</td>
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<td>Clinical issues/issue management</td>
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<td>Regulatory strategy</td>
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<td>Regulatory strategy</td>
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<td>Drug substance plan</td>
<td>The manufacturing strategy for sourcing and supply detailed in functional plans</td>
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<td>Scientific summary</td>
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<td>High-level status summary and forward activity plan</td>
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<td>Estimated costs by stage</td>
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Abbreviations: CMC, chemistry, manufacturing and controls; ADME, absorption, distribution, metabolism, excretion.
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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
  • **Critical path** – the sequence of activities that add up to the longest overall project duration. This determines the shortest time possible to complete the project. Any delay 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”
"KIDS! This stop is on the CRITICAL PATH and is scheduled to take exactly 43 minutes! ~ So no slack time!"
## Critical Path Analysis: GANTT Chart

<table>
<thead>
<tr>
<th>Task Name</th>
<th>Duration</th>
<th>Task Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last Patient Last Visit (LPLV)</td>
<td>0 days</td>
<td></td>
</tr>
<tr>
<td>PK Data</td>
<td>60 days</td>
<td></td>
</tr>
<tr>
<td>Collect Bioanalytical</td>
<td>2 wks</td>
<td></td>
</tr>
<tr>
<td>Lock PK Database</td>
<td>10 wks</td>
<td></td>
</tr>
<tr>
<td>CRF Data</td>
<td>50 days</td>
<td></td>
</tr>
<tr>
<td>Collect CRFs</td>
<td>4 wks</td>
<td></td>
</tr>
<tr>
<td>Lock CRF Database</td>
<td>6 wks</td>
<td></td>
</tr>
<tr>
<td>Analysis</td>
<td>20 days</td>
<td></td>
</tr>
<tr>
<td>Analyze Data</td>
<td>4 wks</td>
<td></td>
</tr>
<tr>
<td>Reporting</td>
<td>85 days</td>
<td></td>
</tr>
<tr>
<td>Finalize First Draft Report</td>
<td>5 wks</td>
<td></td>
</tr>
<tr>
<td>Finalize Report</td>
<td>1 wk</td>
<td></td>
</tr>
</tbody>
</table>
Probability Exercises for Project and Portfolio Planning

![Probability Tree Diagram]

- **Cum. Prob:**
  - 10%: 700, Expected Value: 70, Success
  - 2%: -430, Expected Value: -9, Fail
  - 5%: -360, Expected Value: -18, Fail
  - 18%: -100, Expected Value: -18, Fail
  - 15%: -20, Expected Value: -3, Fail
  - 50%: -10, Expected Value: -5, Fail

- **NPV:**
  - Phase 1 (Pre-clin): -10
  - Phase 2: -80
  - Phase 3a: -260
  - Phase 3b: -70

- **Probability of Phase Success and Failure:**
  - Pre-clin: 30%
  - Phase 1: 50%
  - Phase 2: 70%
  - Phase 3a: 65%
  - Phase 3b: 90%

- **Probability of Phase Failure:**
  - Pre-clin: 50%
  - Phase 1: 50%
  - Phase 2: 30%
  - Phase 3a: 35%
  - Phase 3b: 10%
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!