Challenges & Opportunities in Enterprise-wide Optimization in the Pharmaceutical Industry

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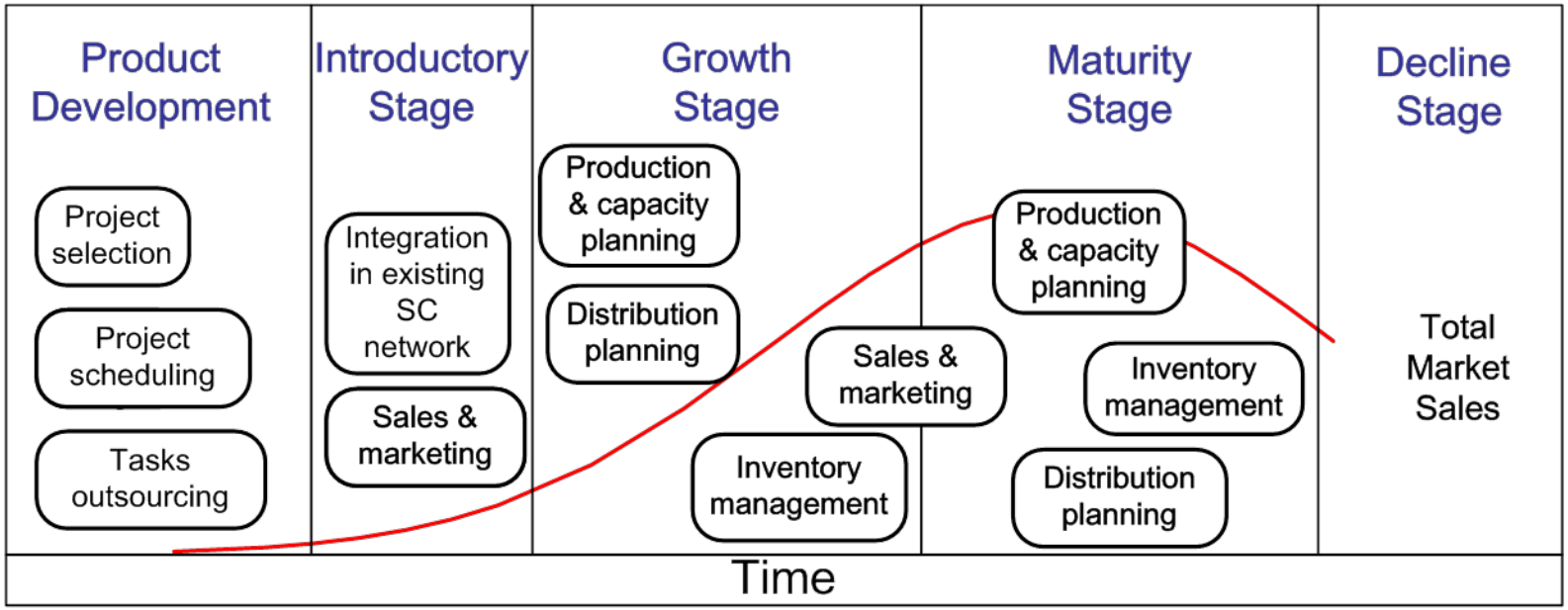
Outline

- Introduction
  - Product Life cycle
  - Pharmaceutical industry characteristics
  - Features of relevant decision problems
- Product development pipeline management
- Capacity Planning
- Supply chain Management
- Directions for Further Research
  - Enhancements / extensions
  - New opportunities & challenges

Product Life Cycle

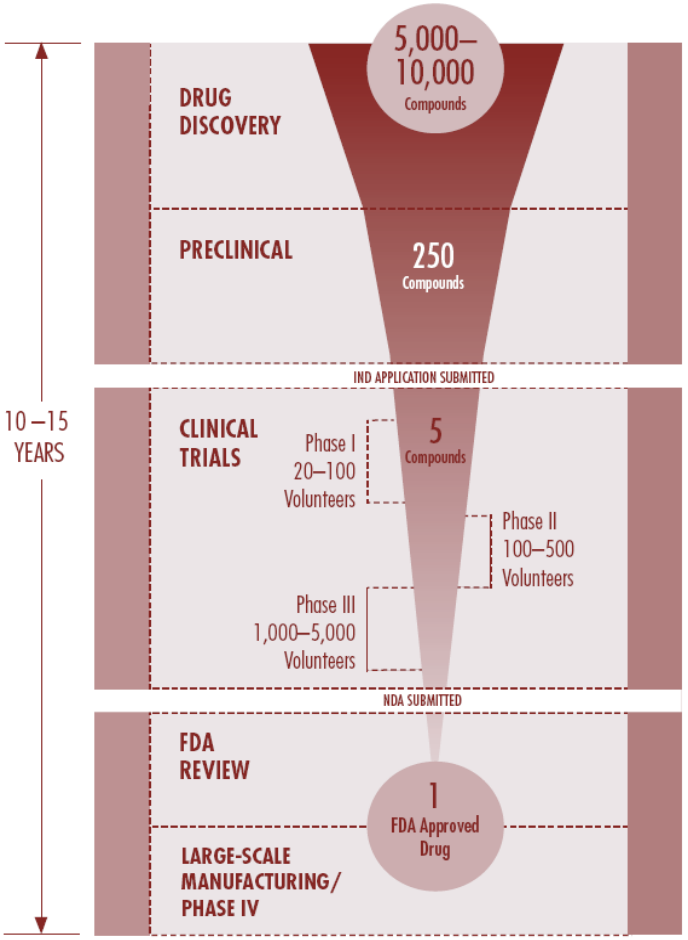


General features

- Details specific to technology sector
- Driven by strategic decisions
- Translated into coordinated tactical and operational plans
- Requires support of multiple corporate functional units
- Complicated by exogenous and endogenous uncertainties
- Product can fail and in-licensing can add new one at any stage

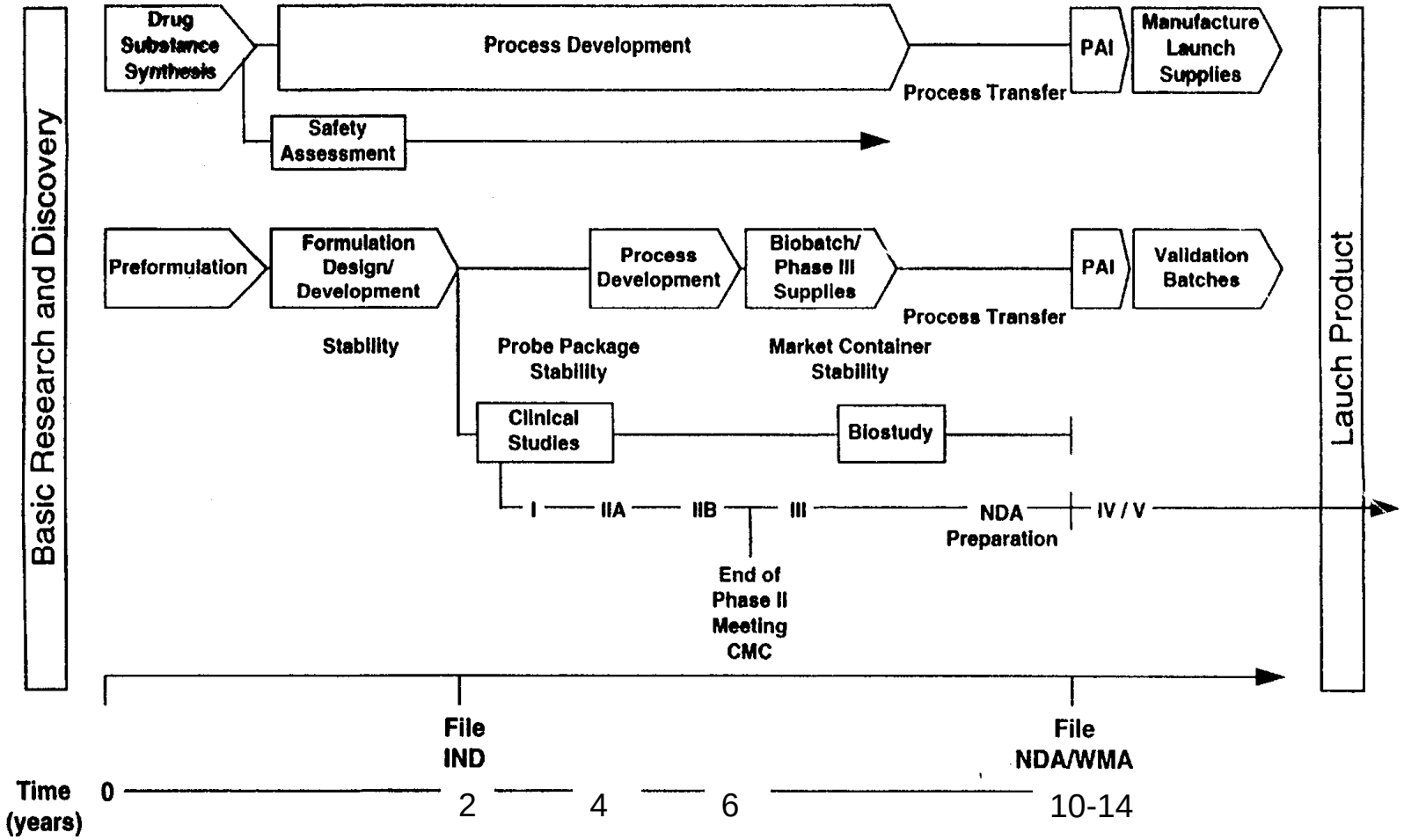
Pharmaceutical Industry Characteristics

- High R&D cost & low success rate
  - 2010 R&D expenditures $67.4 B (~18% sales)
  - 1 in 1000 compounds reach clinical stage
  - 1 in 5 entering trials is commercialized
- High clinical trials cost & extended time
  - $1.3 B cost of new drug;
    Clinical trials ~50% of cost
  - Up to 15 years discovery to launch
- Heavy regulatory burden with regional variations
- Limited product shelf life
- Global business /extended supply chain
- Highly uncertain demands
- Generic competition



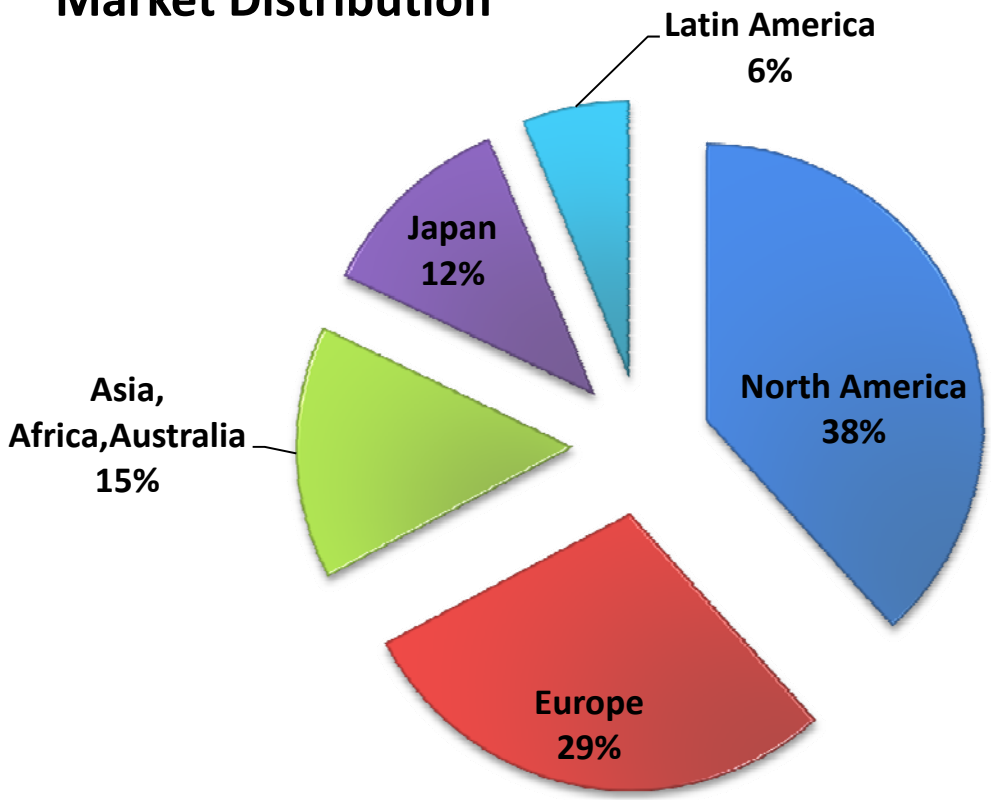
Source: PhRMA (2007)

Product Development Task Sequence



Pharmaceutical Market

Market Distribution



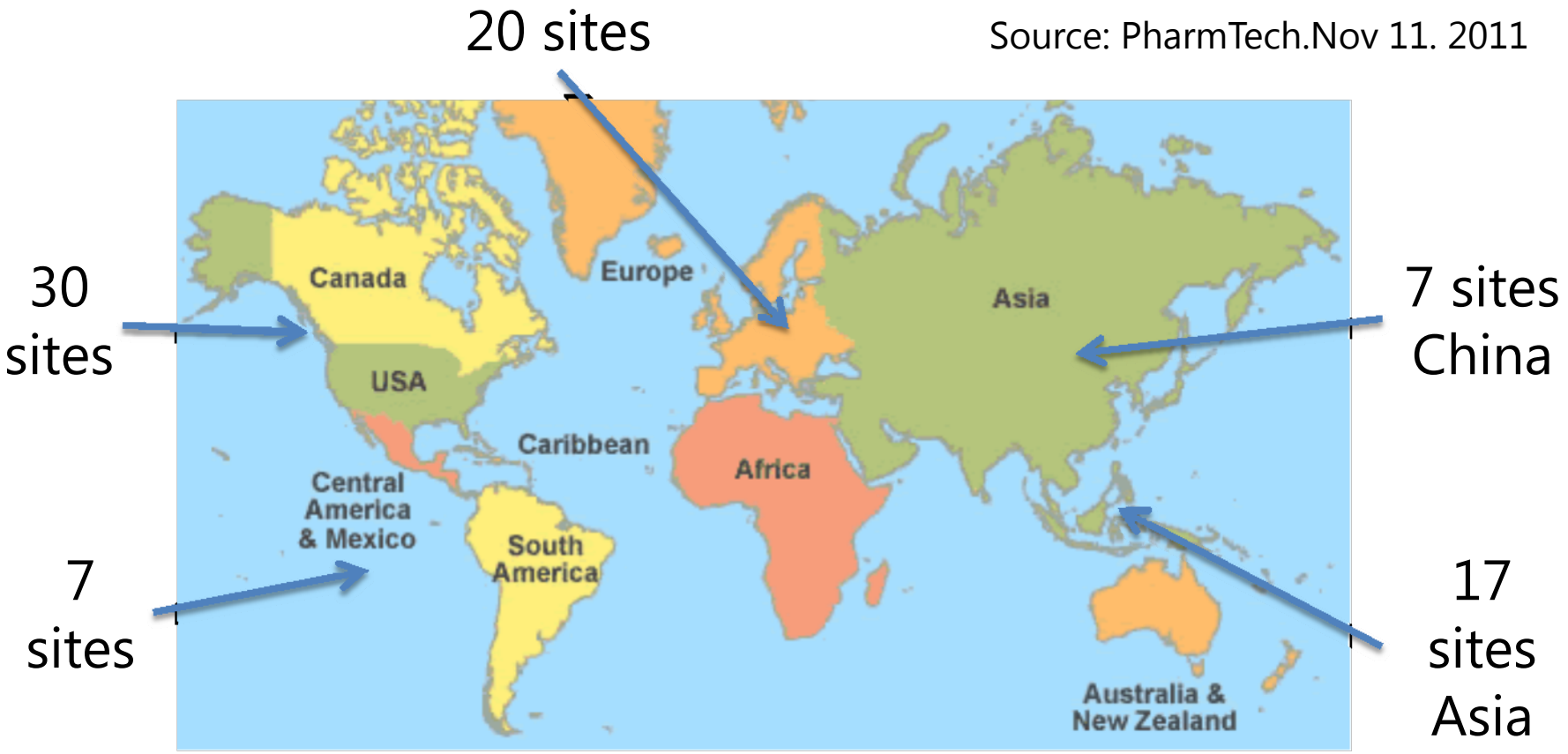
Market Size (2010): $ 856.4 B

Growth Forecast
2011-2015

Region	CAGR %
World	3-6
North America	0-3
Europe	2-5
Asia, Africa, Australia	11-14
Japan	2-5
Latin America	11-14

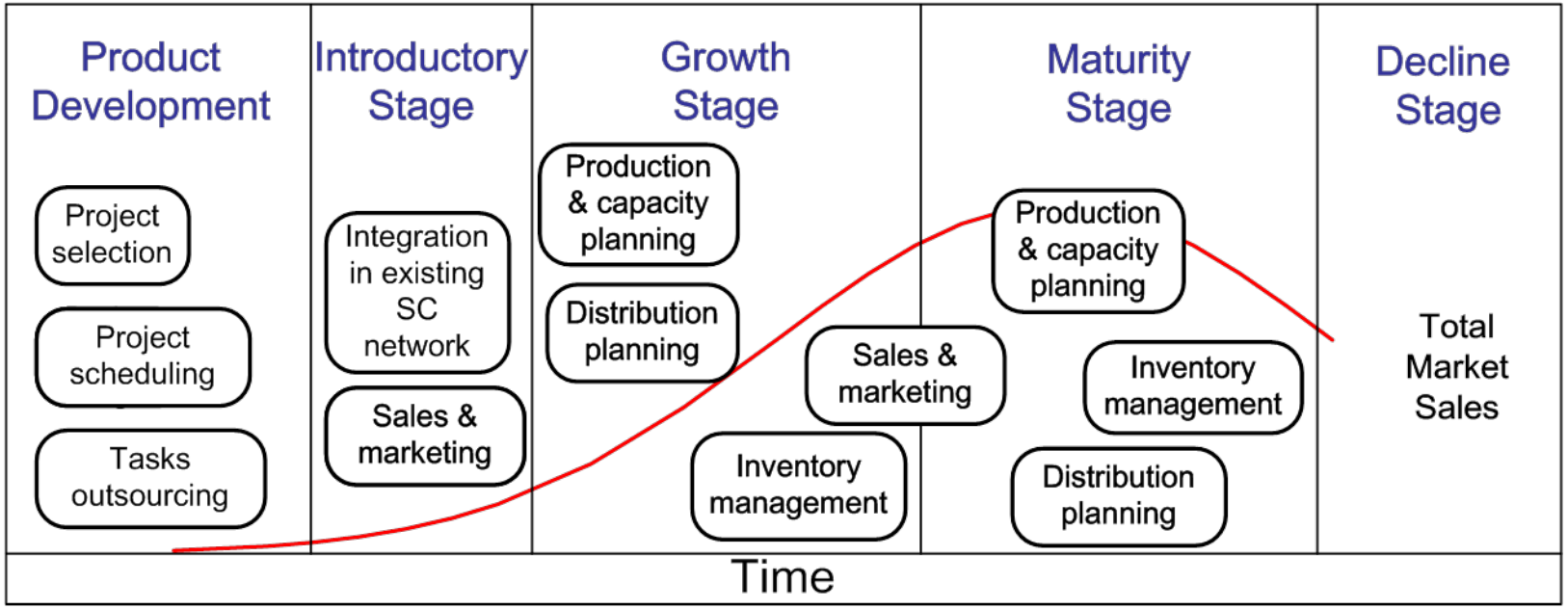
IMS Health, March 2011

Pfizer supply network



Scope: 87 sites, 188 logistics centers, 500 supply partners; 180+ human health products in US; 27 with sales >$50 M

Enterprise Decision Problems over Product Life Cycle

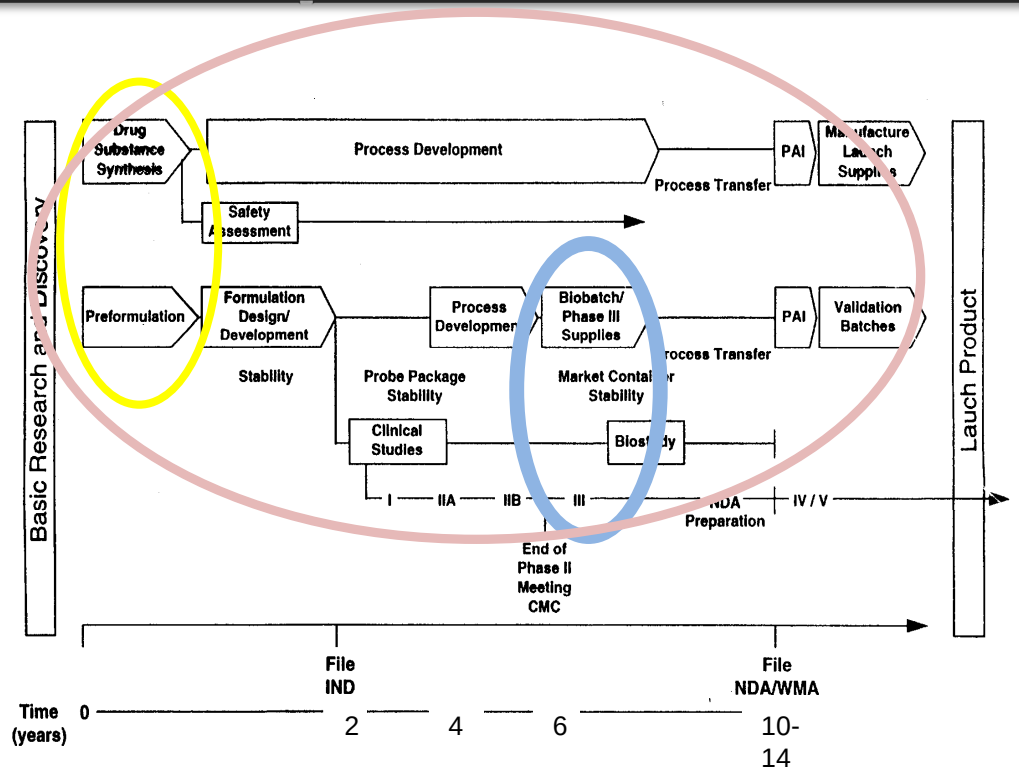


Product Development Pipeline Management

Capacity Planning

Supply Chain Management

Product Development Decision Decomposition



Strategic Decisions

- Selection of candidates
- Prioritization /ordering
- Resource assignment/ reassignment
- Termination of product

Portfolio Selection & Management

Early Phase Testing

- toxicity/stability
- drug delivery options

Clinical Trials Supply Chain Management

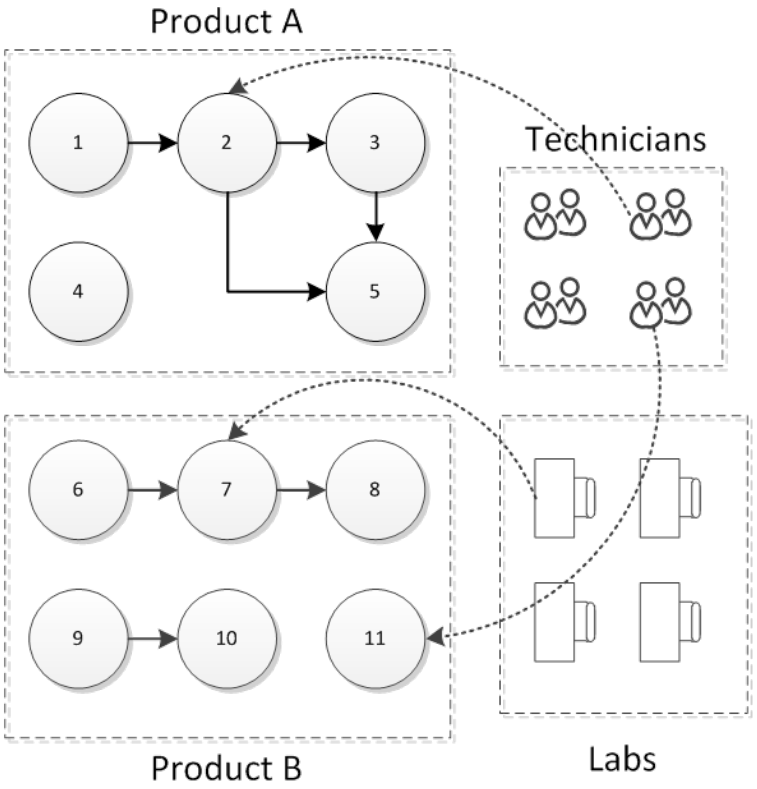
Early Phase Testing

Given:

- A set of potential products
- A set of tests for each product
- Test technological precedence, duration and cost
- Product income as a function of its launching time
- Probability of success of tests

Determine:

- Testing schedule that maximizes eNPV



Problem description
(Source: Jain & Grossmann, 1999)

Early Phase Testing

- Schmidt & Grossmann (1996)
  - An MILP model for testing tasks sequencing
  - Consider no resource sharing among products
  - Trade-off between shorter makespan and higher sales
- Jain & Grossmann (1999)
  - Extension of previous work
  - Simultaneous consideration of resource constraints and task sequencing
  - Option to outsource testing task(s)
  - Rescheduling needed every time product fails test

Portfolio Selection & Execution

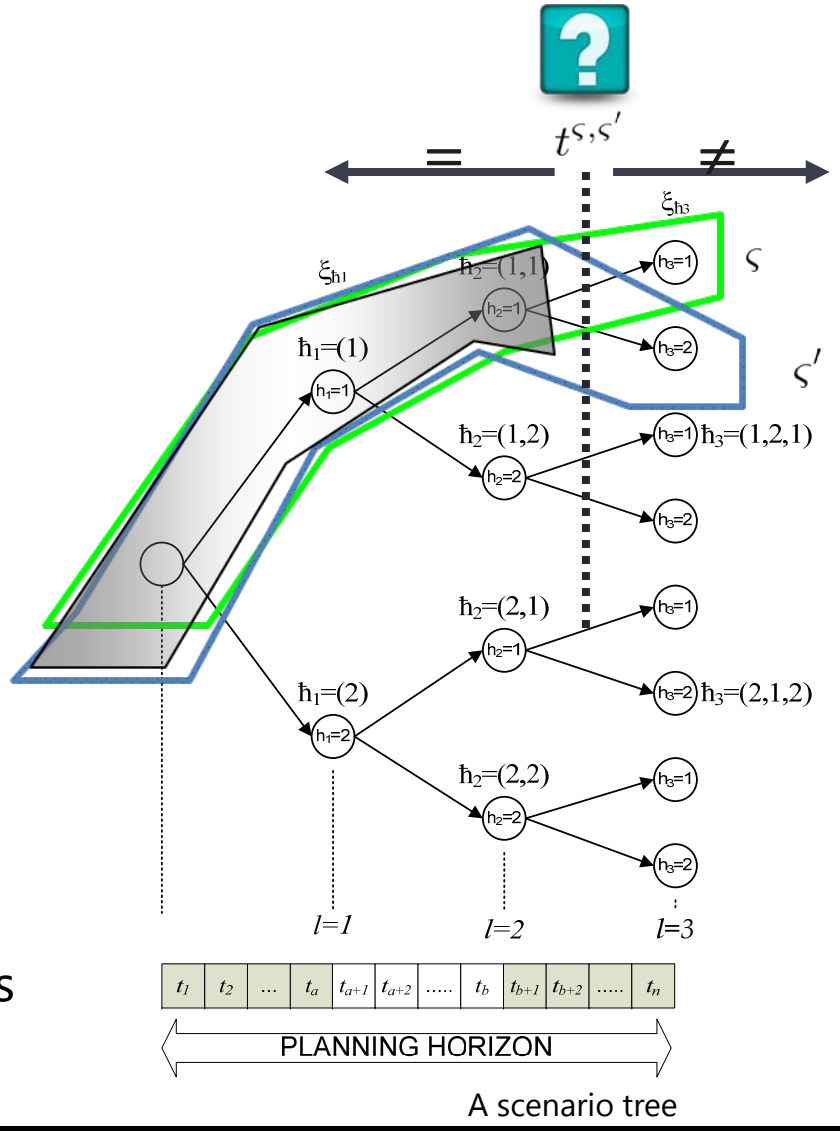
Mathematical programming approaches

- Maravelias & Grossmann (2001)
  - Simultaneous optimizations of test scheduling and design/production planning
  - Two stage stochastic problem considering uncertainties in clinical trials outcome
  - Lagrangian decomposition based algorithm
- Maravelias & Grossmann (2004)
  - Deterministic MILP
  - Consideration of trade-off between
    - higher cost of testing (assignment of more resources, capacity expansions) leading to shorter test duration &
    - higher income due to shorter completion times

Portfolio Selection & Execution

Mathematical programming approaches

- Colvin & Maravelias (2008)
  - Consideration of endogenous uncertainty in clinical trials
  - Multistage stochastic MILP
  - Reduction of the number of non-anticipativity constraints necessary to model indistinguishable scenarios
- Colvin & Maravelias (2009)
  - Consideration of outsourcing
  - Finite horizon approximation to formulate problems using fewer stages

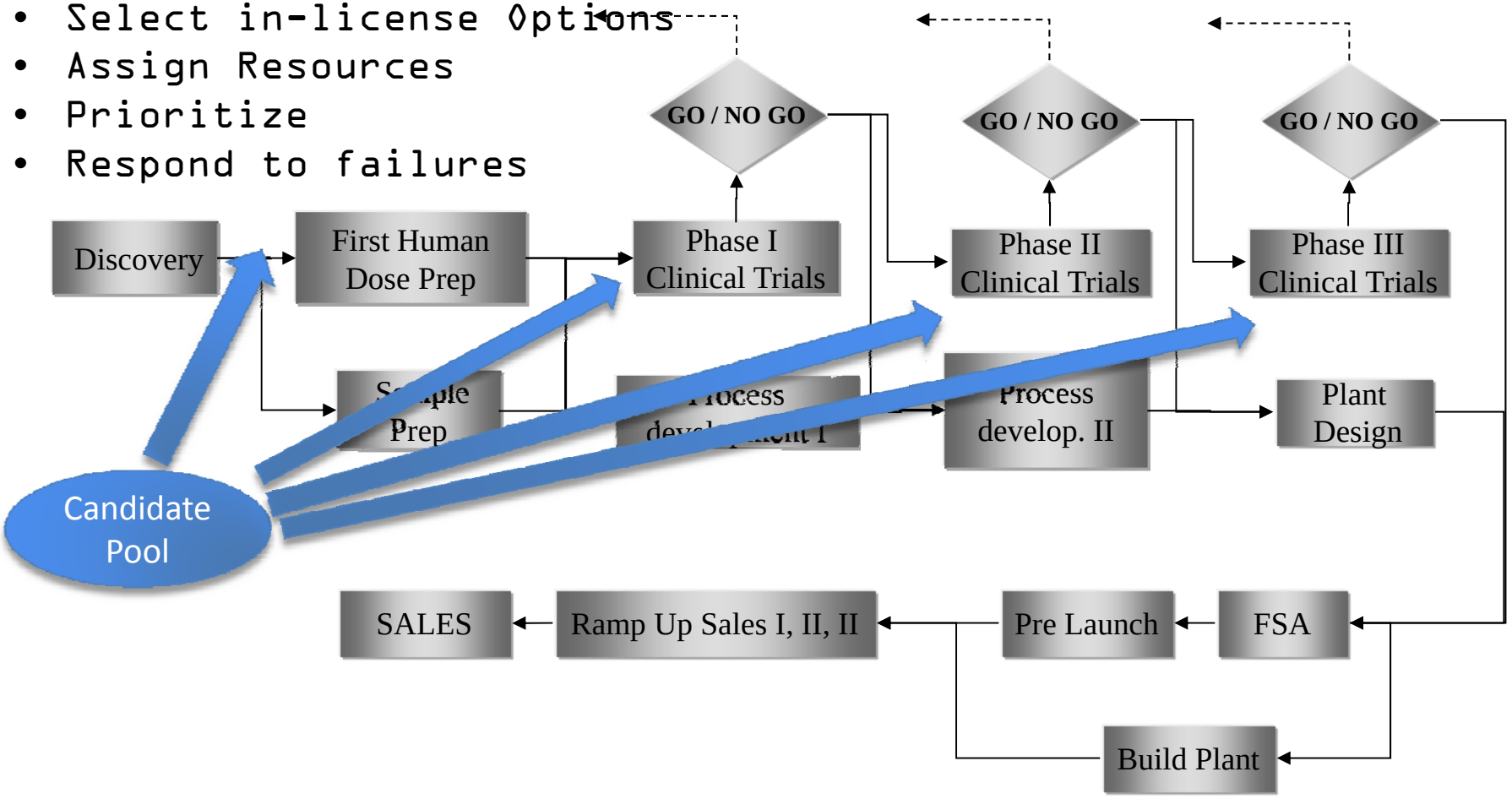


A scenario tree

Product Development Pipeline Tasks & Decisions

Decisions

- Select Products
- Select in-license Options
- Assign Resources
- Prioritize
- Respond to failures



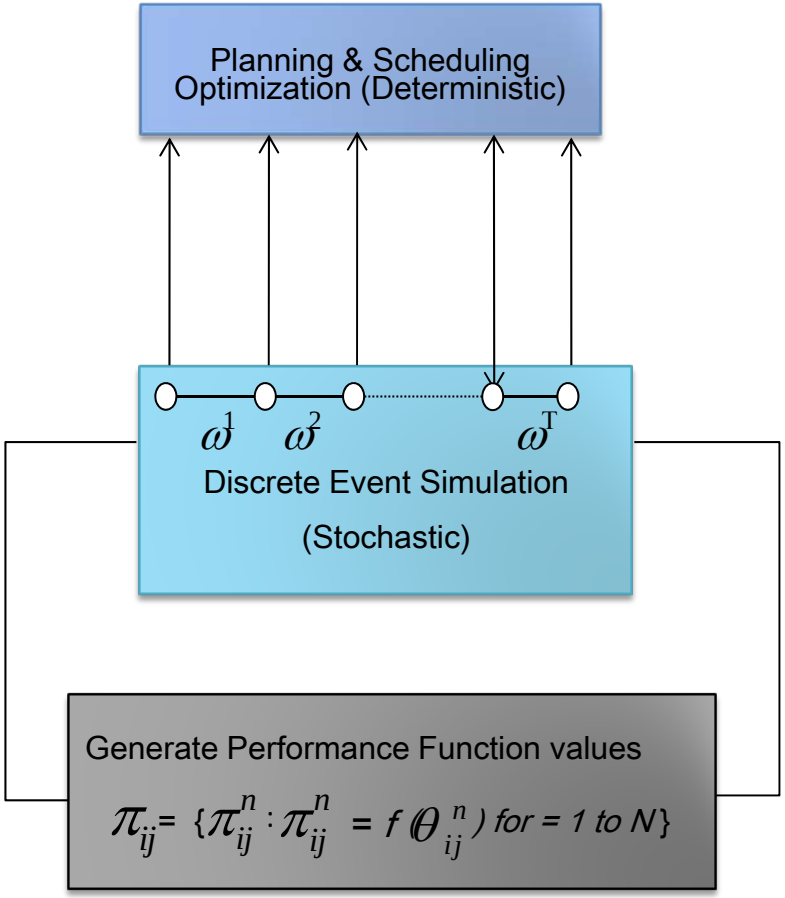
Portfolio Selection & Execution

Simulation based approaches

- Blau et al. (2004)
  - Simulation coupled with genetic algorithm to search for best product portfolio
  - Account for resource, income, and technical interdependencies among different projects
- George & Farid (2008)
  - Multi-objective optimization: expected NPV vs Probability of positive NPV
  - Consideration of project interdependencies

Portfolio Selection & Execution

- Simulation based approaches
  - Subramanian et al. (2001)
    - Utilization of SIM-OPT framework (Simulation using mathematical programming instead of rules for decision making) for R&D project selection
  - Subramanian et al. (2003)
    - Integrate information from simulation to improve optimization solution
  - Zapata & Reklaitis (2010)
    - Use real option analysis & SIM-OPT for valuation of project portfolios
    - Importance of reflecting flexibility to adjust decisions when uncertainties are realized



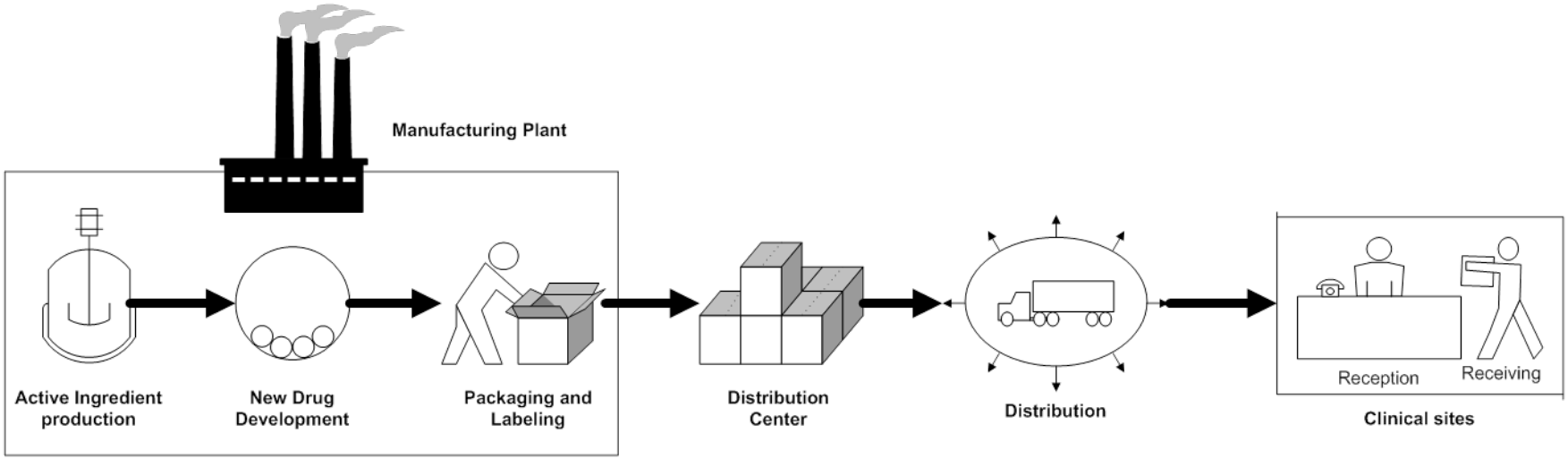
SIM-OPT framework

Valuation of project portfolios
Zapata et al. (2010)

- Comparison between decision tree analysis (DTA) and real options approach (eNPV)
- Case data from Blau et al. (2004)
  - Nine new products (0-8)
  - Comparison of 20 randomly selected portfolios

		ROA approach			
Portfolio	DTA (M$)	Lower bound	Upper bound	Deviation from DTA	
0-6-8	5348.74	2139.00	2139.00	-60.01	-60.01
0-1-4-5	6054.31	2933.55	2905.01	-51.55	-52.02
0-2-4-7	8172.69	3675.17	3675.17	-55.03	-55.03
0-2-5-8	5091.82	1614.18	1443.88	-68.30	-71.64
2-4-5-6-8	8400.29	3610.46	3461.51	-57.02	-58.79
1-2-3-4-6	7370.15	3298.97	3196.04	-55.24	-56.64
0-1-4-6-7-8	10377.5	4469.29	4461.22	-56.93	-57.01
1-2-3-4-5-8	7809.25	3178.72	2703.94	-59.30	-65.38

Clinical Trial Supply Chain



Features

- Finite length horizon (1-2 years)
- Unused inventory at end of trial ➡ wastage
- If right dosage unavailable on patient arrival, patient lost to trial
- Uncertainty in Patient completion of treatment ➡ demand uncertainty
- Uncertainty in manufacturing & distribution channel performance
- Multiple SKU's for each API : dosage levels, placebo, comparator

Clinical Trial Supply Chain

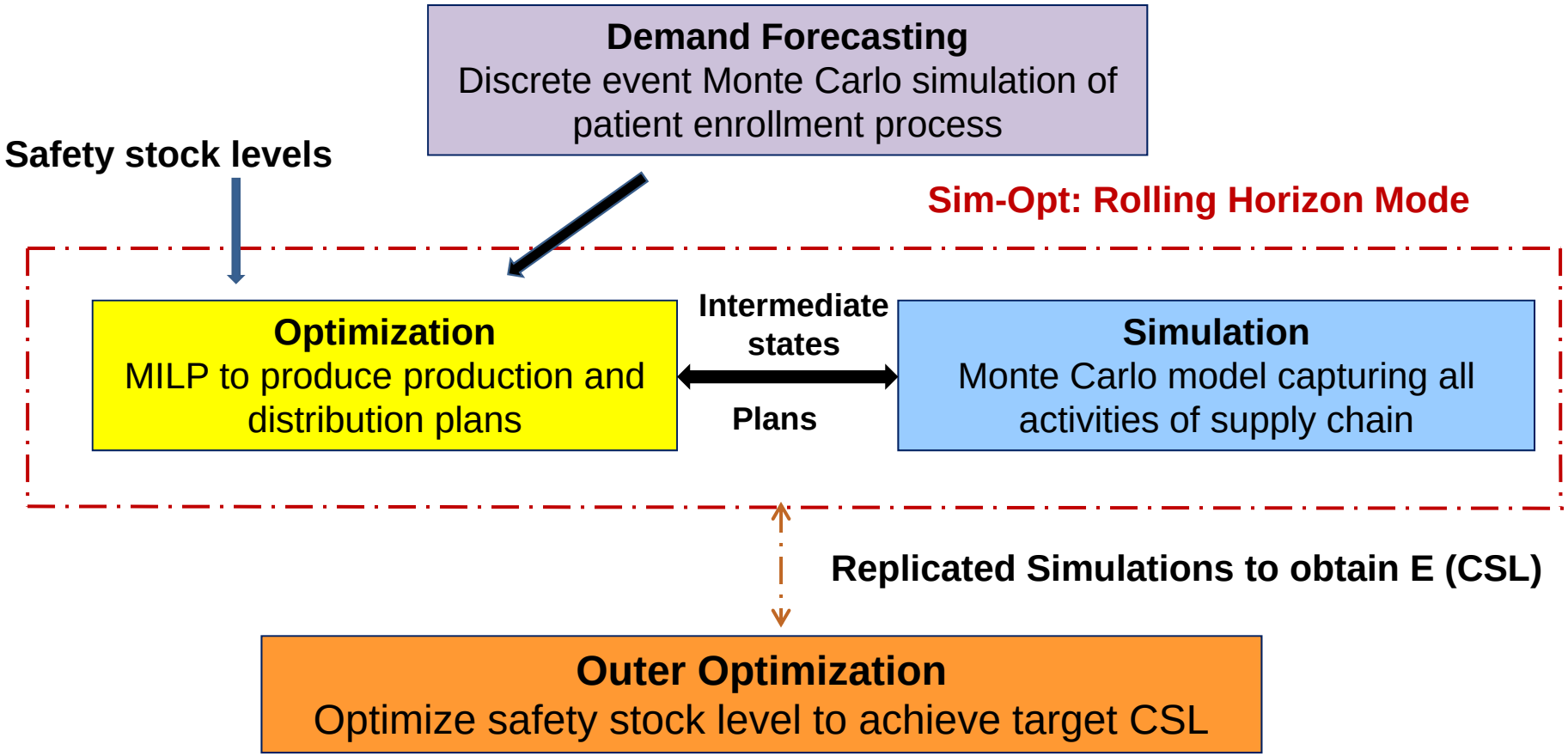
- Kimko and Duffull (2003)
  - Survey statistical models for clinical trial simulation and patient pool selection
- Dowlman et al. (2004) and Peterson et al (2004)
  - Simulation models to evaluate outcomes of pre-defined supply strategy pool
- McGarvey et al. (2007)
  - A discrete event model of patient enrollment
- Abdelkafi et al (2009)
  - Selects best supply plan balancing costs and risk of short supply
  - Uses Bayesian principles to reevaluate supply strategies over time
- Fleischhacker and Zhou (2011)
  - Parameterized Wagner-Within lot sizing model that considers costs of clinical trials failure
- Chen et al (2010)
  - SIM- OPT approach for simulating patient demand
  - Consider the entire CT supply chain

Simulation-based Optimization Approach

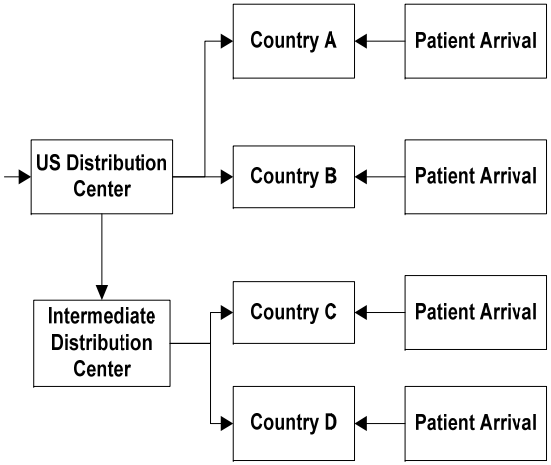
Chen et al. (2011)

Key trade-off: End of trial wastage vs missed patient dosage

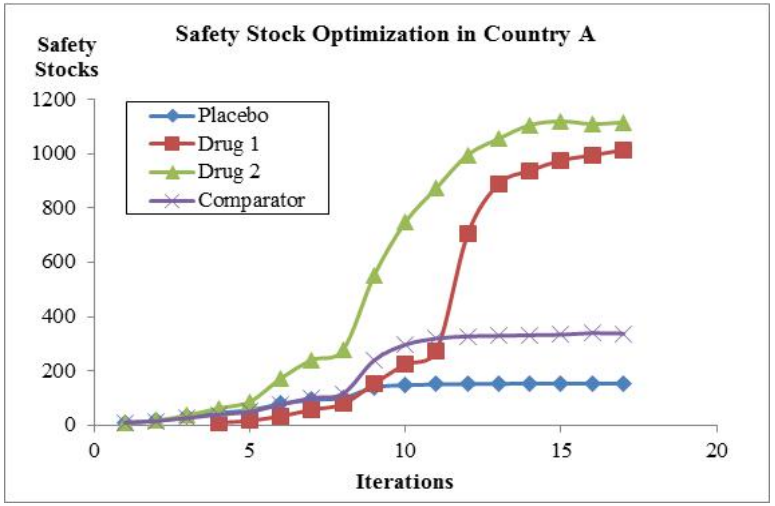
⟺ Safety stock level vs Customer Satisfaction Level (CSL)

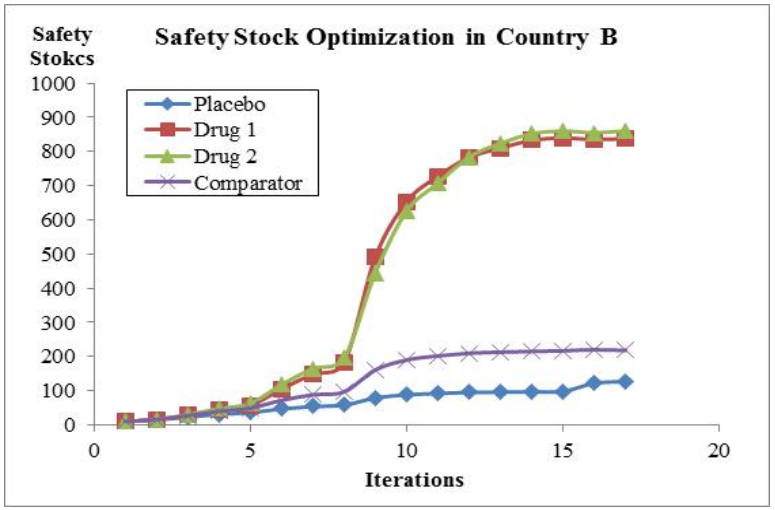


Risk pooling strategy
Chen et al. (2011)



Drug Type	With Risk pooling		Non-Risk Pooling	
	Leftovers	Safety Stock	Leftovers	Safety Stock
US Placebo	1839.7	0	2518.7	281
US Drug 1 Type	1062.2	83	4004.7	1856
US Drug 2 Type	1036.1	60	3653.6	1977
US Comparator	1078.4	10	3927.1	556
EU Placebo	3068.2	384	3253.8	253
EU Drug 1 Type	1592.35	913	3829.9	2039
EU Drug 2 Type	1900.9	934	3297.9	2275
EU Comparator	2986.9	323	3720.4	553





Capacity Planning

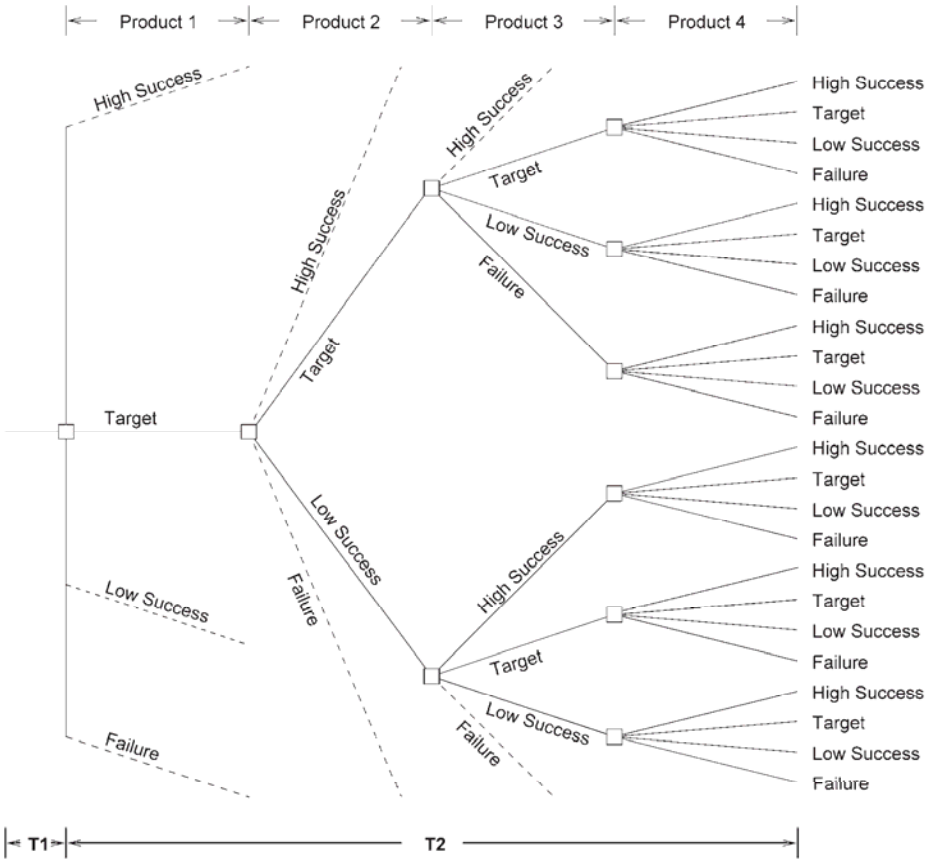
- Given
  - Product requirements & projected demands
  - New product introductions (approval uncertainties)
  - Existing manufacturing & distribution nodes
  - Possible new node locations
  - Possible manufacturing technology alternatives
  - Possible outsourcing alternatives
- Determine
  - Selection of manufacturing & distribution nodes
  - Selection of technologies at sites
  - Network capacity progression over time
  - Optimal Sourcing
- Decision components
  - Strategic level: design/structural decisions
  - Tactical level: production & distribution plans

Literature review

- **Shah (2005)**
  - summarizes the state of the art of SC optimization research
- Papageorgiou et al. (2001)
  - Determine simultaneously product development, capacity/production planning and investment strategy.
  - Consideration of trading structures (Similarly to Fandel & Stammen (2004))
- Gatica et al. (2003) and Levis & Papageorgiou (2004)
  - Extend previous work to a stochastic model considering clinical trials outcomes and demand uncertainty
  - Hierarchical decomposition to address larger problems
- Tsang et al. (2007)
  - Further extend previous study to analyze risk metrics
- Laínez et al. (2009)
  - Selection of technology to be implemented
  - Consideration of financial concerns: Corporate value/Net working capital

Capacity Planning for Multiple Vaccines under uncertainty [Tsang et al. (2007)]

- Manufacturing site with four vaccines for clinical trials
- Consider four demand scenarios as a result of clinical trials outcomes uncertainty
- Develop a two stage MILP model
  - First stage (T1): capacity decisions and portfolio selection
  - Second stage (T1): uncertainty disclosed, planning decisions
- Manufacturing suite construction and scale-up included in the first stage
- Maximizes eNPV

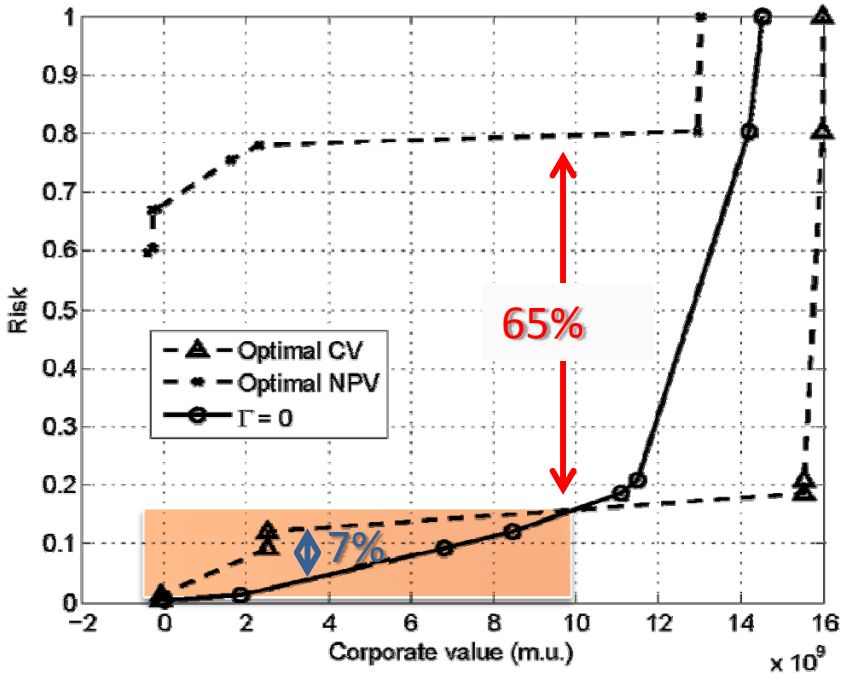


Considered scenario tree

Managing financial risk in the coordination of SC and PDPM [Laínez et al. (2009)]

- Problem statement
  - Which new products to develop considering operational, technological & financial aspects?
  - Expand SC capacity to manufacture new products? Where? By how much?
  - Impact of PDPM decisions on SC echelons activities?
- Proposed approach:
  - Stochastic SC design – planning/ PDPM MILP model with financial considerations
    - Clinical trials outcome endogenous uncertainty (Colvin & Maravelias, 2008)
    - Risk management formulation
  - Objective function: Corporate value

Risk curve



Equations	Binary V.	Continuous V.	CPU Sec.*
59173	2520	52603	148

Supply Chain Management

- Structural decisions handled within capacity planning subproblem
- SCM principally focused on Tactical & Operational level decisions:

Planning decisions to assign production, distribution and inventory resources to respond to demand at medium timeframe

Scheduling decisions on how, where and when to produce in order to satisfy planning targets at short timeframe

Literature review

- Sundaramoorthy and Karimi (2004)
  - MILP model of introduction of new products into existing manufacturing facilities.
  - Includes consideration of outsourcing
- Amaro and Barbosa-Povoa (2008)
  - Sequential approach to planning and scheduling
  - Incorporates reverse flows
- Sousa et al. (2011)
  - MILP formulation for planning of global pharmaceutical SCs
  - Consideration of tax schemes of different regions
  - Decomposition strategies

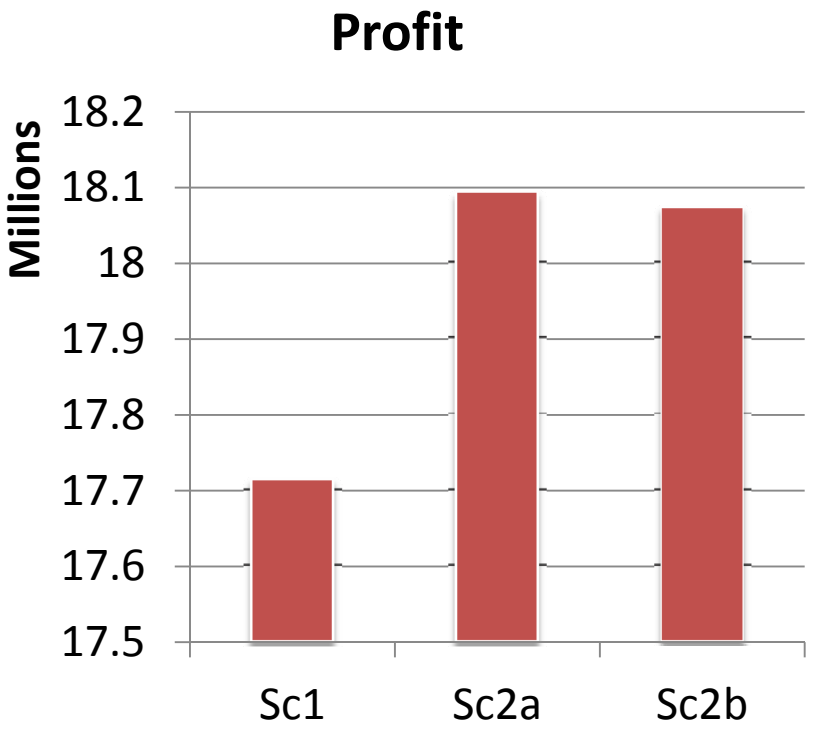
Planning and scheduling of SCs w/reverse flows
Amaro et al. (2008)

Integrated approach for planning and scheduling

- Considers reverse flows: returns of expired products or drug recalls
- Returned material considered as proportion of previous period production
- Develop MILP formulation
- Sequential solution strategy

Pharma case study

- Four drug products, 3 manufacturing sites
- Manufacturing stages: drug production and product customization (Portuguese, Spanish, other ECC markets)
- Three scenarios for recovery
  - SC1: All incinerated
  - SC2a: No minimum recovery requirement
  - SC2b: Minimum requirement for recovery
- Demonstrates advantages of recovery



Economic results for each scenario (Recovery 5% of previous period amount)

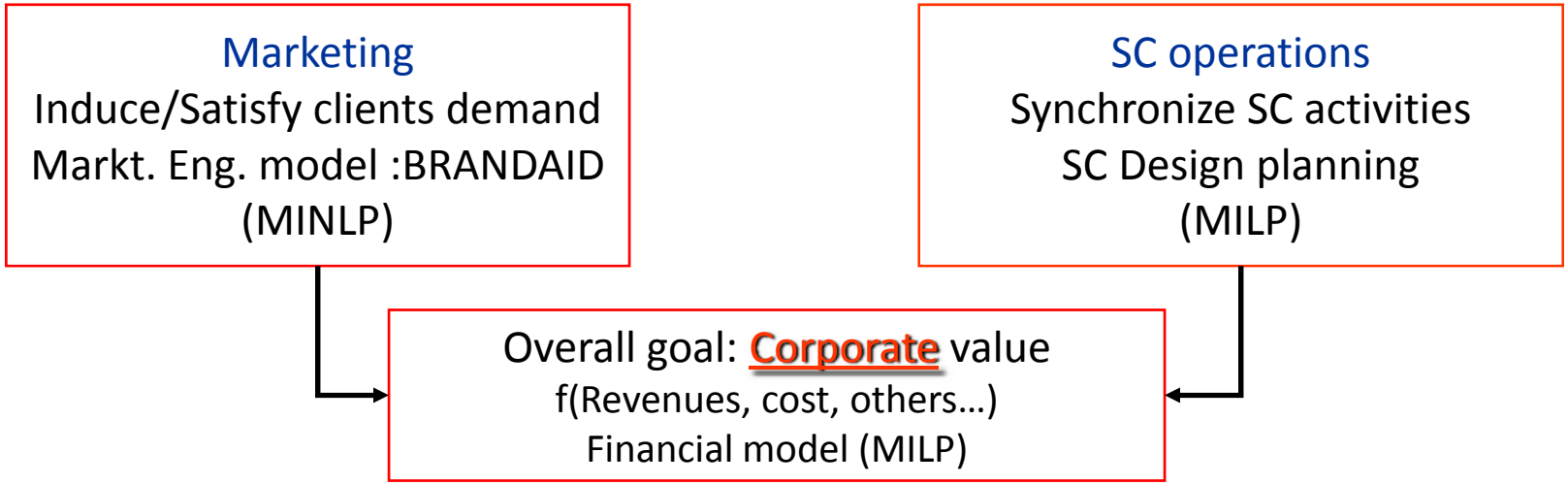
Marketing issues

- Same budget justification as other type of investments
  - In 2006, US pharmaceutical industry
    - R&D → 19% of sales (US$55.2 billions)
    - Marketing → 10% of sales (US$27.3 billions)
- Huge amount of market data → transform it into improved decision making
- Marketing Engineering: systematic translation of data into descriptive/normative model for improved decision making

  (Lilien & Rangaswamy, 2002)
- Opportunity
  - Coordinate marketing efforts to generate demand with capacity planning and supply chain operational plans
  - Meet demands in resource effective manner

Synchronizing Marketing and SC decisions
Laínez et al. (2010)

- An MINLP model integrating SC design/retrofitting, capital budgeting and marketing decisions
- Relevance of correct appraisal of trade-off between induced demand and SC capacity investments required to meet such demand



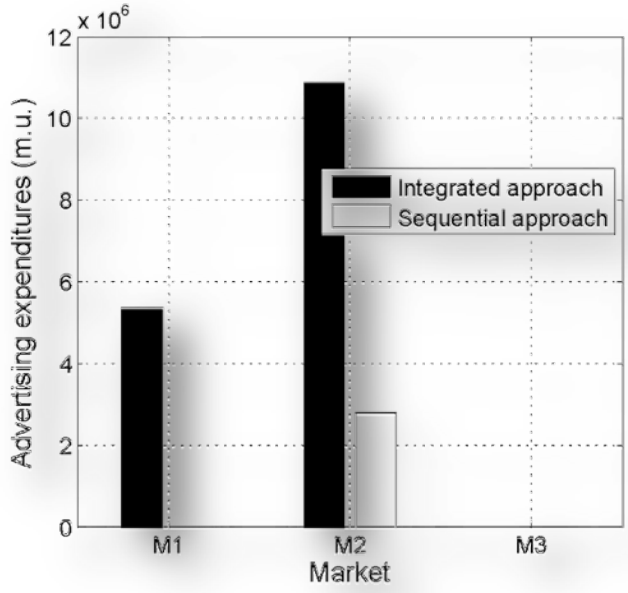
Optimal Solutions

Approach	Revenues	Advertising expenditures	Net revenues	Corporate value	Investment in capacity
Sequential	522.32×10^6	86.11×10^6	436.21×10^6	84.35×10^6	79.77×10^6
Integrated	512.94×10^6	85.15×10^6	427.79×10^6	123.93×10^6	43.42×10^6

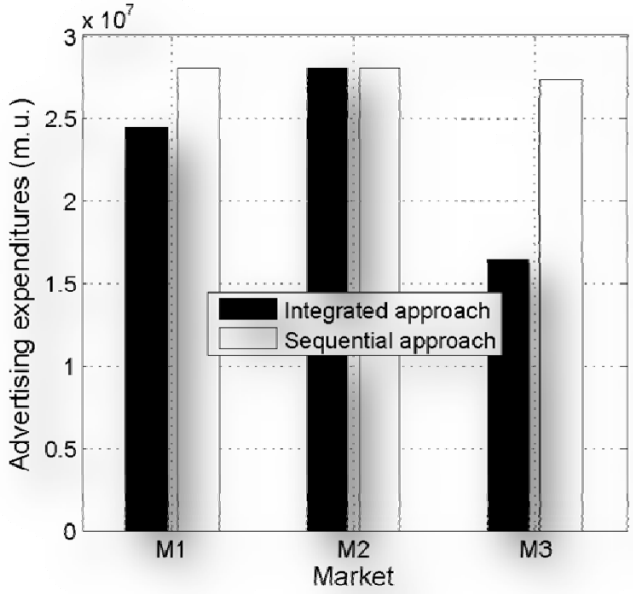
-2% +47%

Induced demand & Advertising expenditures

Product *P1*



Product *P2*



Further Research

- Informatics systems (using ontologies) to support EWO
  - Basis to establish values of uncertain parameters
  - Reduce time for model updating/validation/training
  - Allow intra- and inter-firm benchmarking/comparison
- Product development decisions under interactions/interdependencies among projects
- Clinical trials supply chain
  - Consideration of structure of supply chain (choice of clinics?)
  - Outsourcing alternatives, technology fit & availability constraints
- Capacity planning: re-engineering of network
  - Can model most decision alternatives
  - Key issue: reliable solution of industrial scale problems

Further Research

- Modeling of uncertain parameters and selection of most appropriate scenarios using Bayesian methods
  - Historically based & subjective priors
  - Uncertain parameter distributions
- Use of MIP models & SIM-OPT framework for generalized sensitivity analysis
  - Develop insights about the system
  - Identify critical parameters that limit performance
  - Guidance towards improvements of “optimal” solutions

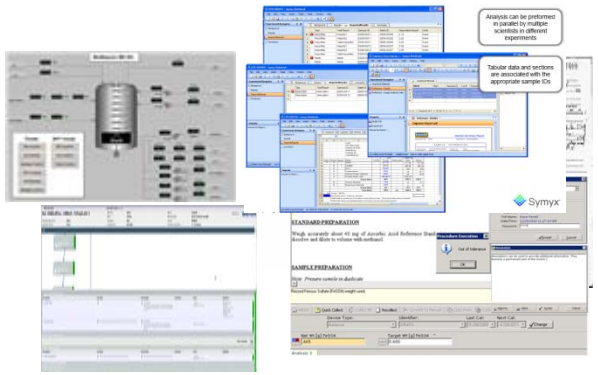
Further Research

- Systems Solutions vs Change management
  - Toyota paradigm: “Technology-Process-People”
  - What business process changes would result from adoption of EWO? Are desirable for effective exploitation of EWO?
  - What new roles are required? What existing roles abandoned?
- Mapping Enterprise Models to Regulatory Framework
  - How do FDA proposals on continuous verification of product quality (real time release) and QbD (flexibility offered by design space) link to and benefit from EWO
  - Can integrated informatics systems and enterprise models help in reducing effort in regulatory compliance

Future Vision

Delivering Business Value from Our Data

Execute



Collect & Store

Analyse

Current

- Paper & electronic sources (no integration)
- Few standards for master data / workflow execution
- No connection with enterprise model

- Little built-in context
- >60% of FTE effort gathering

- Few standards
- Every project is one-off
- **Significant effort (reactive)**

Future

- Electronic sources
- Standards for Master Data & platform recipes

- Integration & built-in context
- NO FTE effort gathering, fully integrated

- Agreed Business Standards
- Data integrated with established Enterprise models – continuous learning/training of model
- **Little effort (proactive)**