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

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Foundations of Computer Aided Process Operations (FOCAPO)

Savannah, January 2012
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

<table>
<thead>
<tr>
<th>Product Development</th>
<th>Introductory Stage</th>
<th>Growth Stage</th>
<th>Maturity Stage</th>
<th>Decline Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project selection</td>
<td>Integration in existing SC network</td>
<td>Production &amp; capacity planning</td>
<td>Production &amp; capacity planning</td>
<td>Total Market Sales</td>
</tr>
<tr>
<td>Project scheduling</td>
<td>Sales &amp; marketing</td>
<td>Distribution planning</td>
<td>Inventory management</td>
<td></td>
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<tr>
<td>Tasks outsourcing</td>
<td></td>
<td></td>
<td>Distribution planning</td>
<td></td>
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</tbody>
</table>

**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

- Drug Substance Synthesis
- Safety Assessment
- Preformulation
- Formulation Design/Development
- Stability
- Process Development
- Probe Package Stability
- Clinical Studies
- Biobatch/Phase III Supplies
- Market Container Stability
- Biostudy
- Process Transfer
- PAI
- Manufacture Launch Supplies
- PAI
- Validation Batches
- Time (years)
  - File IND
  - File NDA/WMA
  - 0
  - 2
  - 4
  - 6
  - 10-14
### Pharmaceutical Market

#### Market Distribution

- **North America**: 38%  
- **Europe**: 29%  
- **Asia, Africa, Australia**: 15%  
- **Japan**: 12%  
- **Latin America**: 6%

**Market Size (2010)**: $856.4 B

#### Growth Forecast 2011-2015

<table>
<thead>
<tr>
<th>Region</th>
<th>CAGR %</th>
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<tbody>
<tr>
<td>World</td>
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<tr>
<td>North America</td>
<td>0-3</td>
</tr>
<tr>
<td>Europe</td>
<td>2-5</td>
</tr>
<tr>
<td>Asia, Africa, Australia</td>
<td>11-14</td>
</tr>
<tr>
<td>Japan</td>
<td>2-5</td>
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<tr>
<td>Latin America</td>
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*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

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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

Diagram:
- Discovery
- First Human Dose Prep
- Sample Prep
- Process development I
- Phase I Clinical Trials
- GO / NO GO
- Phase II Clinical Trials
- GO / NO GO
- Phase III Clinical Trials
- GO / NO GO
- Plant Design
- Build Plant

SALES
Ramp Up Sales I, II, II
Pre Launch
FSA

Candidate Pool
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

\[ \pi_{ij} = \{ \pi_{ij}^{\theta} : \pi_{ij}^{\theta} = f(\theta_{ij}^{\theta}) \} \text{ for } \theta = 1 \text{ to } N \]
• 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

<table>
<thead>
<tr>
<th>Portfolio</th>
<th>DTA (M$)</th>
<th>ROA approach</th>
<th>Deviation from DTA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower bound</td>
<td>Upper bound</td>
</tr>
<tr>
<td>0-6-8</td>
<td>5348.74</td>
<td>2139.00</td>
<td>2139.00</td>
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<tr>
<td>0-1-4-5</td>
<td>6054.31</td>
<td>2933.55</td>
<td>2905.01</td>
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<td>0-2-4-7</td>
<td>8172.69</td>
<td>3675.17</td>
<td>3675.17</td>
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<td>0-2-5-8</td>
<td>5091.82</td>
<td>1614.18</td>
<td>1443.88</td>
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<td>2-4-5-6-8</td>
<td>8400.29</td>
<td>3610.46</td>
<td>3461.51</td>
</tr>
<tr>
<td>1-2-3-4-6</td>
<td>7370.15</td>
<td>3298.97</td>
<td>3196.04</td>
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<tr>
<td>0-1-4-6-7-8</td>
<td>10377.5</td>
<td>4469.29</td>
<td>4461.22</td>
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<tr>
<td>1-2-3-4-5-8</td>
<td>7809.25</td>
<td>3178.72</td>
<td>2703.94</td>
</tr>
</tbody>
</table>
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)

Demand Forecasting
Discrete event Monte Carlo simulation of patient enrollment process

Optimization
MILP to produce production and distribution plans

Simulation
Monte Carlo model capturing all activities of supply chain

Sim-Opt: Rolling Horizon Mode

Outer Optimization
Optimize safety stock level to achieve target CSL

Replicated Simulations to obtain E (CSL)
Risk pooling strategy
Chen et al. (2011)

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>With Risk pooling</th>
<th>Non-Risk Pooling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Leftovers</td>
<td>Safety Stock</td>
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<tr>
<td>US Placebo</td>
<td>1839.7</td>
<td>0</td>
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<tr>
<td>US Drug 1 Type</td>
<td>1062.2</td>
<td>83</td>
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<tr>
<td>US Drug 2 Type</td>
<td>1036.1</td>
<td>60</td>
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<tr>
<td>US Comparator</td>
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<td>10</td>
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<tr>
<td>EU Placebo</td>
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<td>384</td>
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<tr>
<td>EU Drug 1 Type</td>
<td>1592.35</td>
<td>913</td>
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<tr>
<td>EU Drug 2 Type</td>
<td>1900.9</td>
<td>934</td>
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<tr>
<td>EU Comparator</td>
<td>2986.9</td>
<td>323</td>
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</table>
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

<table>
<thead>
<tr>
<th>Equations</th>
<th>Binary V.</th>
<th>Continuous V.</th>
<th>CPU Sec.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>59173</td>
<td>2520</td>
<td>52603</td>
<td>148</td>
</tr>
</tbody>
</table>
Supply Chain Management

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

- Strategic
  - Planning decisions to assign production, distribution and inventory resources to respond to demand at medium timeframe
- Tactical
  - Scheduling decisions on how, where and when to produce in order to satisfy planning targets at short timeframe
- Operational
Literature review

  - 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 $\rightarrow$ 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

Marketing
Induce/Satisfy clients demand
Markt. Eng. model : BRANDAID (MINLP)

SC operations
Synchronize SC activities
SC Design planning (MILP)

Overall goal: Corporate value
f(Revenues, cost, others...)
Financial model (MILP)
Optimal Solutions

<table>
<thead>
<tr>
<th>Approach</th>
<th>Revenues</th>
<th>Advertising expenditures</th>
<th>Net revenues</th>
<th>Corporate value</th>
<th>Investment in capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential</td>
<td>522.32x10^6</td>
<td>86.11x10^6</td>
<td>436.21 x10^6</td>
<td>84.35x10^6</td>
<td>79.77 x10^6</td>
</tr>
<tr>
<td>Integrated</td>
<td>512.94x10^6</td>
<td>85.15x10^6</td>
<td>427.79 x10^6</td>
<td>123.93x10^6</td>
<td>43.42 x10^6</td>
</tr>
</tbody>
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-2%       +47%

Induced demand & Advertising expenditures
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

**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

**Future**
- Electronic sources
- Standards for Master Data & platform recipes
- Integration & built-in context
- NO FTE effort gathering, fully integrated

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

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