The Economic Impact of QbD and other Considerations on Formulation Development

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## Pharmaceutical Industry Trends

- **R&D:** new excipients/formulations for difficult drugs, complex drug combinations and release profiles

- **Technology Transfer from R&D to Manufacturing:** more predictable product scale-up, early commitments to final formulation and process

- **Manufacturing & QC:** process economies, improved quality, rationalization of plant and equipment, analysis and benchmarking

- **Regulatory:** increased scrutiny of CMC sections, pre-approval inspection report cards

- **Clinical Development:** compressed development and regulatory approval timelines, especially 505(b)2 filings
Rapid, high quality, low-cost formulation development and manufacturing desired

Reduce reliance on “processing” of formulations
- Granulations can often be avoided
  - Densification and increased particle size for flow
  - Achieve content uniformity through dry blending

Reduce excipient numbers
- Simplify DOE
- QA/QC benefits
- Simplify stability trials
- Streamline inventory management

Increased production rates, throughput, and yields
- Lower cost of production leads to improved access to medicine.
What Drives Cost?

- Marketing
- IT
- Maintenance
- Regulatory
- Equipment
- Process
- Excipients
- R&D
- Energy
- Quality
- Labor
- API
Some Pharma Economic Facts

- Pharma industry globally is roughly $1 Trillion industry.
- USA is the world’s biggest consumer of prescription drugs, ~$340B
  - Followed by EU, then Japan
- Only 15% (3 out of 20) of approved drugs produce enough revenue to cover development costs.
- You need a big success, the “blockbuster” in order to survive.
  - Strategy is changing from high volume, endemic focus to higher value, niche markets (cancer, lifestyle, etc.)
- At the end of the day, pharma is a business and must be treated as such.
Fundamental Economic Rules in Pharmaceutical Industry

**Branded drugs must get to market quickly.**
- Patent clock starts ticking as an NME
- Sacrifice in sales revenue comes at maturity

**Generic drugs must control COGs**
- Every penny is valuable to the generics producer

**Biologics**
- High R&D costs
- Low COGs
- Highly profitable
How does excipient selection affect revenue?

Actives dictate excipients.
Excipients dictate processes.
Processes dictate COGs.
COGs impact revenue.
## Excipient Impact on Market Segment

<table>
<thead>
<tr>
<th>Segment</th>
<th>Production efficiency</th>
<th>Batch size</th>
<th>Appearance</th>
<th>Speed to market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branded</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generic</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>OTC</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Direct Compression Tablet Manufacture Unit Operations

Minimize processing steps and reduce cost
**Process Comparison**

**Man hours**
- Approximately 40 man hours dedicated to direct compression process
- Approximately 72 man hours dedicated to wet granulation
- 180% cost increase in man hours alone.

**Energy Costs**
- Significant energy cost associated with spray drying operation
# Comparative Process Cost

<table>
<thead>
<tr>
<th>Process</th>
<th>Relative Production Cost/Batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct compression blending and tableting</td>
<td>1</td>
</tr>
<tr>
<td>Fluidized bed granulation and tableting</td>
<td>1.5</td>
</tr>
<tr>
<td>High shear granulation and tableting</td>
<td>2.2</td>
</tr>
<tr>
<td>Hot melt extrusion or other complex process</td>
<td>2.4 +</td>
</tr>
</tbody>
</table>

* Based on typical cost of 0.5 million tablet batch. Processing costs vary with batch size, equipment and formulation characteristics.
Fig. 1 COGS% for different types of companies
Sensitivity of Generics Market Sector to COGs

**IVAX Corporation**

- **COGS%**
- **Operating Income**
- **R&D**

**Par Pharmaceuticals**

- **COGS%**
- **Operating Income**
- **R&D**
Are Manufacturing Costs Significant to Total Operational Costs and Expenditures?

Cost distribution: 16 large pharma companies

Sales: > $300 billion

Costs: ~ $250 billion

<table>
<thead>
<tr>
<th>Manufacturing Costs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel</td>
<td>$22.5 Bn</td>
<td>24%</td>
</tr>
<tr>
<td>Operations</td>
<td>$22.5 Bn</td>
<td>24%</td>
</tr>
<tr>
<td>Raw Materials</td>
<td>$45 Bn</td>
<td>49%</td>
</tr>
<tr>
<td>Excipients</td>
<td>$1-2 Bn</td>
<td>~2%</td>
</tr>
</tbody>
</table>

Raymond H. Scherzer April 2002
Computer Modeling

- Developed software program that analyzed cost of formulation and process
- Inputs for type of process, ingredients, labor, packaging, batch size, etc.
- Considered conversion to DC formula with high functionality ingredients.

Output of savings:
- Packaging size reduction + “trickle down effect”
- Batch size improvement
- Labor, energy savings
- QA/QC costs
- Speed
Case study

Customer used high functionality excipients to switch from wet granulation to direct compression.

- Granulation and numerous blending steps eliminated

Saved over $1M

Energy, labor?

Where was the savings?

Tyvek

Bottom line – streamline your processes.
The formulator’s customer is manufacturing.

Focus on the process.
- Excipients are cheap.
- Labor can only be cut if you fire someone.
- The process is ~50% of the COGs component.

Minimizing equipment, steps, and components in a process minimizes total cost.

Simple, but robust. Therefore there is a need for QbD.
Economics of QbD

Pharmaceutical industry lags in Quality Systems behind other industries.

As of 2008, only 20 submissions included QbD elements (<10%).

By 2011, submissions with QbD increased to 50.

QbD is being thrust into the pharmaceutical landscape.

Does it have an ROI?
In 2009, McKinsey Group determined that QbD could reduce costs if properly implemented.

COGs can be reduced 10-20%

Process and Product Development (PPD) can be reduced by 20-30%
  – Includes pharm dev, pharm sci, process development and technical development

Stated that QbD could be implemented for as little as $200K or as much as $1M.
Compiled all financial figures by analyzing 2012 Annual Reports

- Revenues, earnings, Sales and General Admin (SGA), COGs, R&D Costs, Taxes

Broke them out into market sectors

- Branded, generic, biotech

Determined that PPD is approximately 15% of R&D costs

Only one generics company was in top 12 so searched out three others.
Compiling Current Data

Re-established COGs as percent of revenue
- Branded pharma – 26%
- Generic – 50%
- Biotech – 14%

Re-establish R&D Cost as percent of revenue
- Branded Pharma – 19%
- Generic – 7%
- Biotech – 22%

From R&D, we can determine PPD

Applied McKinsey model to this information.
Basic Cost Benefit Analysis

- Top 12 pharma revenue: $241B
- Top 12 pharma COG: $60B
- Top 12 pharma R&D: $43B

- Saving 10% on COG: $6B
- Saving 20% on PPD (which is 15% of R&D): $1.3B

- Total Savings is 3% ($7.3/$241)

What about the cost? What about the market?
Assessing the cost of QbD

Interviewed QbD experts from industry.

Few could quantify costs
  – Generally agreed with savings proposal by McKinsey
  – CMC sections grow appreciably
    • FDA reviewers have to review additional data
    • Delays can ensue causing significant losses downstream

Some companies now have QbD Departments

Additional experimentation is required

Many adopt a ‘wait and see’ approach

Use QbD elements at critical stages
  – Have to consider the high cost of high failure rates
  – Wait until Phase IIb
Quantifying the Cost of QbD

Determining cost is difficult and highly varied.

Labor allocation has to be increased.

Other areas impacted
- Process re-design
- Design space
- Control strategies
- Process strategies
- PAT implementation

Able to quantify a number of FTE (full time employee) hours

Able to quantify some additional equipment cost
- Whether lab or production
Not broken? Don’t fix it.

Existing products face no additional QbD cost
  – Don’t touch what the FDA has already approved
  – Generics already have high COGs
    • Any changes are immediately scrutinized.

QbD aspects will only be applied to existing products if
  – There is a compelling reason – IT IS BROKEN!
  – Scheduled re-design, re-location, revision...

Otherwise the approach is SUPAC.

Newer products will receive QbD throughout the product life cycle.
Putting together the Cost Model

Compared R&D spend to number of approvals over a time period
  – Average R&D life is 15 years
  – Effective Patent Life (EPL) is 12 years.

Average annual R&D spend per drug approved is $413M per year per company.

With an average model drug using $413M R&D and other factors determined previously, we can build a model.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average R&amp;D cost</td>
<td>$413M</td>
</tr>
<tr>
<td>Average COGs</td>
<td>$578M</td>
</tr>
<tr>
<td>Product revenue at peak sales</td>
<td>$2,197M</td>
</tr>
<tr>
<td>Peak Sales Curve Factor</td>
<td>75%</td>
</tr>
<tr>
<td>- Accounts for starting sales at 0, ramp up in sales to maturity.</td>
<td></td>
</tr>
<tr>
<td>Potential regulatory delay</td>
<td>4 months</td>
</tr>
<tr>
<td>Additional employees</td>
<td>5 at $100K each</td>
</tr>
<tr>
<td>Equipment cost</td>
<td>$800K</td>
</tr>
<tr>
<td>Branded Product</td>
<td>Lifetime Savings</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Average R&amp;D per year</td>
<td>$413 M</td>
</tr>
<tr>
<td>Average COGS per year</td>
<td>$578 M</td>
</tr>
<tr>
<td>PPD as a percent of R&amp;D</td>
<td>15%</td>
</tr>
<tr>
<td>PPD Savings</td>
<td>20%</td>
</tr>
<tr>
<td>COGS Savings</td>
<td>10%</td>
</tr>
<tr>
<td>R&amp;D Life</td>
<td>15 Years</td>
</tr>
<tr>
<td>Effective Patent Life (EPL)</td>
<td>12 Years</td>
</tr>
<tr>
<td>Peak Sales Curve Factor</td>
<td>75%</td>
</tr>
<tr>
<td>Potential Delay</td>
<td>0.3 Years</td>
</tr>
<tr>
<td>Annual Product Sales at Peak</td>
<td>$2,197 M</td>
</tr>
<tr>
<td>Number of Employees</td>
<td>5</td>
</tr>
<tr>
<td>Cost per Employee</td>
<td>$100 K</td>
</tr>
<tr>
<td>Equipment</td>
<td>$800 K</td>
</tr>
<tr>
<td>Total</td>
<td>$879 M</td>
</tr>
<tr>
<td>Net Savings</td>
<td>$379 M</td>
</tr>
<tr>
<td>Net Revenue</td>
<td>$19,287 M</td>
</tr>
<tr>
<td>Savings</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
Delays turned out to be the most critical component regarding return on investment in QbD.

- Delays exceeding 5.25 months resulting in a loss.
- Doubling labor from 5 employees to 10 only resulted in a 0.1% reduction in ROI.
- Capital equipment investment has no impact.

Bottom line – time to market is paramount for branded products.
Lifetime R&D support for generic products drops precipitously, only $1M per year per company.

R&D lifetime also drops to 5 years as companies want to invest as little as possible.

However, drug life span increases to 20 years.

Revenue may only be $15M per product due to increase competition and dilution of the market.

Fewer FTEs required.
   — Reduced to 2 FTEs.
## Generic Product Cost/Benefit Analysis

<table>
<thead>
<tr>
<th>Generic Product</th>
<th>Lifetime Savings</th>
<th>Lifetime Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average R&amp;D per year</td>
<td>$1.0 M</td>
<td>$150 K</td>
</tr>
<tr>
<td>Average COGS per year</td>
<td>$7.5 M</td>
<td>$15 M</td>
</tr>
<tr>
<td>PPD as a percent of R&amp;D</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>PPD Savings</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>COGS Savings</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>R&amp;D Life</td>
<td>5 Years</td>
<td></td>
</tr>
<tr>
<td>Product Life Expectancy</td>
<td>20 Years</td>
<td></td>
</tr>
<tr>
<td>Annual Product Sales at Peak</td>
<td>$14.9 M</td>
<td></td>
</tr>
<tr>
<td>Number of Employees</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cost per Employee</td>
<td>$100 K</td>
<td>$5 M</td>
</tr>
<tr>
<td>Equipment</td>
<td>$500 K</td>
<td>$500 K</td>
</tr>
<tr>
<td>Total</td>
<td>$15.1 M</td>
<td>$5.5 M</td>
</tr>
<tr>
<td>Net Savings</td>
<td>$9.6 M</td>
<td></td>
</tr>
<tr>
<td>Net Revenue</td>
<td>$298 M</td>
<td></td>
</tr>
<tr>
<td>Savings</td>
<td>3.2%</td>
<td></td>
</tr>
</tbody>
</table>
COGs turned out to be the overall driving factor for generics

- Reducing COG savings from 10% to 5% resulted in an overall drop to 0.7% in total savings
- Must achieve 3.5% savings in COGs to break even

PPD savings had little impact due to significant reduction in R&D costs.

Labor component had much bigger impact.

- Increasing to 5 FTE’s, savings reduced to 0.7%

Equipment now impacts the equation.

Bottom line – “Cost is King” in generics
## Biotech Product Cost/Benefit Analysis

<table>
<thead>
<tr>
<th>Biotech Product</th>
<th>Lifetime Savings</th>
<th>Lifetime Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average R&amp;D per year</td>
<td>$246 M</td>
<td>$111 M</td>
</tr>
<tr>
<td>Average COGS per year</td>
<td>$159 M</td>
<td>$190 M</td>
</tr>
<tr>
<td>PPD as a percent of R&amp;D</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>PPD Savings</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>COGS Savings</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>R&amp;D Life</td>
<td>15 Years</td>
<td></td>
</tr>
<tr>
<td>Effective Patent Life (EPL)</td>
<td>12 Years</td>
<td></td>
</tr>
<tr>
<td>Peak Sales Curve Factor</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Potential Delay</td>
<td>0.2 Years</td>
<td>$352 M</td>
</tr>
<tr>
<td>Annual Product Sales at Peak</td>
<td>$1,918 M</td>
<td></td>
</tr>
<tr>
<td>Number of Employees</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Cost per Employee</td>
<td>$100 K</td>
<td>$13.5 M</td>
</tr>
<tr>
<td>Equipment</td>
<td>$800 K</td>
<td>$800 K</td>
</tr>
<tr>
<td>Total</td>
<td>$301 M</td>
<td>$366 M</td>
</tr>
<tr>
<td>Net Savings</td>
<td>-$65 M</td>
<td></td>
</tr>
<tr>
<td>Net Revenue</td>
<td>$16,910 M</td>
<td></td>
</tr>
<tr>
<td>Savings</td>
<td>-0.4%</td>
<td></td>
</tr>
</tbody>
</table>
Biotech QbD

Data limited on biotech
- Number of products supported and cost per product.

Biotech exhibits a higher R&D cost and lower cost of goods compared to traditional pharma.
- Not nearly as skewed as generics
- Expected this to react very similar to branded pharma

Delaying approval by more than 7 weeks resulted in negative ROI.

Very sensitive to time!
What’s not captured?

QbD is an insurance policy – real cost associated with QbD, but benefits that will never have to be quantified
- Lost batches and cost of failure – never happen
- More flexibility, better control
- Improved efficacy and safer medicine

Conversely, may implement QbD in products that never reach markets
- Failure in the clinic
- Cost realized, but never recouped

Owe quality to the market – patients and caregivers expect quality
- “It’s the right thing to do.”
Summary

Considering the economics of formulation

- Process is largest consumer of COGs
  - Labor and energy are secondary
  - Excipients mean nothing
- Simplicity in numbers saves money

QbD economics

- Needs to be evaluated in Phase II
- For branded and biotech, do everything possible to minimize regulatory delay
- For generic products, COGs savings is critical.
  - Nimble and flexible products to keep costs low.