Pharmaceutical Manufacturing – the Quiet Revolution

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Pharma Manufacturing

API or Drug Substance (primary manufacture)
- chemistry, biochemistry or fermentation

Drug Product (Secondary manufacture)
- Formulation with excipients – Blending and mechanical processing

Labelling and Packaging
Pharma… a Success Story

- Worldwide sales in 2014 expected to top $1 trillion
- Incalculable benefits in terms of lives saved
- Major industry for the UK
  - UK had 14.9 per cent share of world exports (2012)
  - 80.7 per cent of UK firms in the sector are classed as innovative
  - £13.34 billion of current price GVA in 2013, approximately 0.8% of the total economy
  - 9% of the manufacturing economy
Sectoral Pressures (UK)

- Margins under pressure
- Business models challenged
  - Small molecule diminishing returns
  - Shift from MNC discovery-based to generics
- Reputational problems
- Decline in UK in last few years

- Commoditisation is taking root, impacting on business models, supply chain management and manufacturing strategy
Looks can Deceive...

Motor industry
Toyota’s failure rate <30ppm

Drug product manufacture
Failure rate c 6.7% (3 sigma)
How did things get like this?

**History**
- Batch processing the accepted paradigm
- No incentive to change when margins high

**The Business**
- Always urgency for commercial, patent or patient-centred reasons
- Driven by stock markets and market access

**Randomness**
- Varying product effectiveness
- Poor process reproducibility and control

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ICES
What are the pharma industry’s manufacturing problems?

• Manufacturing
  • Product shortages
  • Product recalls
  • Inefficient supply chains

• Impacting on manufacturing
  • Drug research effectiveness
  • Increasing drug potency
  • Commoditisation
  • High attrition rates during long product trials
  • Separation of primary and secondary, often for tax or market access reasons
  • The products are really hard to make well
MANUFACTURING ISSUES
Product Shortages – drugs unavailable to meet demand

Source USFDA 2012
Reasons for Shortages

Primary reason for supply disruption %

- Factory improvement: 35%
- Manufacturing problems: 31%
- Discontinued product: 14%
- API shortage: 8%
- Other material shortage: 6%
- Increased demand: 4%
- Loss of site: 2%

Source: USFDA 2012
Recalls – in the US

• “Of the Class I recalls from 2004 to 2011,
  – 34 % affected more than 100,000 units of a drug
  – 64 % of recalled drugs had been distributed nationwide.
• 40 % of the recalls were because of contaminated drugs
• 25 % of the drugs were recalled for having the wrong doses or release mechanisms.
• The rest were the result of product mix-ups or mislabeling
• Large in size and strongly linked to manufacturing

Joshua Gagne, Brigham and Women’s Hospital
UK voluntary recalls

• In last 20 cases (c 2 years)
  – 5 from mislabelling
  – 8 from observed contamination / impurity
  – 4 from manufacturing problems
  – 1 from fraud (counterfeiting / illegal transport)
  – 1 from portfolio change
  – 1 from logistics problems
• ie 85% with a manufacturing element
# Cash to Cash Cycle (2008-11)

<table>
<thead>
<tr>
<th>Sector</th>
<th>C2C Cycle (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemical (BASF, DOW DuPont)</td>
<td>77</td>
</tr>
<tr>
<td>Consumer Products (Colgate, Kimberley Clarke, P&amp;G, Unilever)</td>
<td>18</td>
</tr>
<tr>
<td>Electronics (Apple, LG, Motorola, Samsung)</td>
<td>5</td>
</tr>
<tr>
<td>Pharma (Abbott, Amgen, Lilly, Merck, Pfizer)</td>
<td>179</td>
</tr>
</tbody>
</table>

\[ \text{C2C} = \text{days of Inventory} + \text{days of debtors} - \text{days of credit} \]

Source: A Mayer, Supply chain insights LLC
Other supply chain concerns

• Epidemic response
  – How can we respond to an epidemic that grows over 2-3 months if the drug supply chain is 6 months long?
• Supply into multiple, different regulatory frameworks
• Changing face of prescription and medication access
ISSUES IMPACTING MANUFACTURE
Attrition

- A new drug may fail at any clinical trial stage or indeed post trials
- The process takes around 2 years per stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Fail Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>35.5%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>67.6%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>39.9%</td>
</tr>
<tr>
<td>FDA approval</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

- Conclusion that high early stage investment in manufacture only sensible in reusable assets like utilities and infrastructure

Data: Hay M et al Nature biotechnology 2014
The Patent Cliff

- Current sales values of drugs coming off patent
- Product will likely be in competition with generic forms
- Manufacturing is involved in the response and may be an opportunity not a problem

Sanofi $8.1 million
Novartis $7.7 million
Roche $7.2 million
AZ $6.7 million
Lilly $6.0 million

http://moneymorning.com/
SEEKING A MANUFACTURING-LED SOLUTION
Visions for the future

- Continuous instead of batch
- Monitored and Controlled
- Modular / Distributed
Typical *continuous* bulk chemical plant
Low waste (<1%)
Low cost
High energy efficiency
Robust quality performance
Most of the engineering going into the plant is for processing

Typical batch chemical plant
High waste (90%)
High cost
Low energy efficiency
Moderate quality performance
Much of the engineering going into the plant is infrastructure
Visions for the future…

• Manufacturing solutions have to bring
  – Robust processing
  – Efficient and clean processing
  – Cost-effective processing
  – Enabling leaner supply chains

• They also have to be
  – Agile (capacity planning)
    • Rapid installation, commissioning, validation
    • Rapid and economical process design
  – Flexible (dealing with product attrition cost-effectively)
  – Enable collateral benefits in reducing the burden of infrastructure costs
  – Consistent with regulatory needs
  – ie enable implementation of better manufacturing options in a way that doesn’t compromise business needs
The important focus is NOT only the manufacturing supply chain but also

How is the manufacturing supply chain assembled?
What drives Pharma Supply Chain design?

• The chemists and pharmacists in process development (!)
  – They influence
    • Chemistry/process
    • Manufacturing technology
    • Process scalability
    • Likely outsource partners

• The available manufacturing plant (in and out of company)
  – Little time to design and build a new “traditional” plant
  – Much manufacturing in pre-existing plant
Linear vs Convergent routes

At 75% yield per stage
Linear gives c.4.2% overall yield
Convergent gives c.10.6% yield
A Desirable Model

This can only be agile and flexible with step changes in the capability to design processes and plants.
CAPABILITY CHALLENGES TO ENABLE THE CHANGE
Scope of the Problem

• To enable new manufacturing approaches we need to be better at…
  – Science challenges
    • Understanding (where we don’t have the predictive science to design or control well)
  – Systems challenges
    • Process design challenges
    • Plant design and performance challenges
    • Supply chain design and operational challenges
## Some Science Challenges

<table>
<thead>
<tr>
<th>Area</th>
<th>Gap / Issue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product attributes - relationship to product performance</td>
<td>Primarily pharmacokinetics / biology</td>
</tr>
<tr>
<td>Relationship between processing and drug product attributes</td>
<td>Insufficient understanding to design and control process with a high level of confidence</td>
</tr>
<tr>
<td>Impact of API and excipient properties on drug product process and product attributes</td>
<td>Insufficient understanding to predict the impact of raw material variation</td>
</tr>
<tr>
<td>Solids and slurry handling</td>
<td>Mixing (and avoiding demixing or segregation during processing and transport)</td>
</tr>
<tr>
<td>Effective separation and purification methods</td>
<td>Targeted separations from complex mixtures of similar molecules at low cost</td>
</tr>
<tr>
<td>Efficient synthesis of actives</td>
<td>Current synthetic routes massively inefficient (chemistry and biochemistry)</td>
</tr>
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</table>
## Some Systems Challenges

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<tr>
<td>Process design</td>
<td>Simulation is restricted by available science to link properties to causal prediction</td>
</tr>
<tr>
<td>The business case</td>
<td>Complex technoeconomic arguments around the investment case are not fully defined or even appreciated</td>
</tr>
<tr>
<td>Managing risk of innovative equipment design, gathering understanding</td>
<td>In an empirical sector (“seeing is believing”) need better ability to run at lab to pilot scale and to gather rich data early</td>
</tr>
<tr>
<td>Supply chain design</td>
<td>Design of better supply chains with limited data availability</td>
</tr>
<tr>
<td>Supply chain</td>
<td>Using supply chain characteristics to inform technology choice</td>
</tr>
<tr>
<td>Operations</td>
<td>Detection of outlier states – eg accidental contamination “needle in a haystack”</td>
</tr>
<tr>
<td>Organisational</td>
<td>Fragmentation leads to resistance at handovers and lack of whole system overview</td>
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The Business Case

• There are multiple relevant lifecycles in pharma
  – Product (Discovery, testing, marketing, off-patent, retirement)
  – Process/plant (Trials materials, manufacturing, second generation process/plant)
  – Facility (Construct, operate, modify, close)
• Typically owned by different parts of the organisation and probably under different budgets
• How should a business case be posed against that backdrop?
The Business Case

• A case based on single project ROI alone is at a disadvantage vs traditional processing
  • Existing capital assets and supply chain infrastructures
  • Decision and financial infrastructures assume existing manufacturing approach
  • Currently the main decisions are
    – GO / NO GO and
    – In-house vs outsource
• Hanging strategic technology projects on (small) individual projects doesn’t work
  – But a strategic manufacturing technology change is a massive risk
Organisational resistance to adoption of innovative technology

Product life cycle – Business Unit
A simple series of staged investments

Stage 1
Initial route development

Stage 2
Route enhancement

Stage 3
Scale-up + Tech Trans

2nd generation
Modified manufacture

Manufacturing project

Process development capability
Why work hard with only 10% chance of success?

Process development resources
Why invest in novel equipment when plants don’t have?

Manufacturing capability
Why develop capability when almost all plants batch?

Manufacturing infrastructure
What is case for novel infrastructure when nobody can tell me what?

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The road so far...

Companies explore the potential for change

Implementation of one or more continuous processes

Evangelism hits a roadblock – the business case is not clear at an individual process level, but development capabilities continue to show potential

New supply chain level arguments emerge - this is a strategy to step changes in business capability

Regulatory authorities are brought on board as allies
The Next Key Challenge

- Accessing the full range of benefits available rather than single benefits
  - Steady state supply chain performance important but also want things like
  - Flexibility and agility of supply
  - Reduced costs of infrastructure / services
  - Reduced risk of loss of supply via contamination
  - Lower time and resource need for process development
  - Simplified operation for deployment in emerging markets
Conclusions

• The problem of changing the way we make pharmaceuticals is immensely complex and difficult
• There will be a lot of problems along the way
• There are enormous opportunities if we are successful
Thanks to – A*Star and colleagues at ICES, CMAC, GSK, AZ, Pfizer, Novartis and Merck

I am inclined to attach some importance to the new system of manufacturing; and venture to throw it out with the hope of its receiving a full discussion among those who are most interested in the subject.

Charles Babbage 1791-1871