Lean Thinking - a $US 90 billion opportunity

"The potential world-wide annual cost saving from production efficiency improvement in the pharmaceutical industry is suggested to be as high as $US 90 billion - equivalent to developing 80-90 new drugs every year."

Huw Thomas
Senior Pharmaceutical Engineer

This dramatic conclusion of the recent FDA White Paper *Innovation and Continuous Improvement in Pharmaceutical Manufacturing* contrasts starkly with the mindset in some areas of the pharma industry that manufacturing, and in some cases development, is no longer a core strategic competency.

When research shows that 90% of manufacturing inefficiencies are locked in during development, then maximizing the efficiency of process development is essential to accelerate time to market, rapidly ramp up to production, enhance acceptance of new products and develop a stronger economic position.

In discussing modern approaches to manufacturing and quality systems, the FDA White Paper draws heavily on *Lean* Thinking that has been implemented for many decades in other manufacturing industries.

Foster Wheeler's Huw Thomas, senior pharmaceutical engineer, presents his opinions based on innovative work carried out at Foster Wheeler and on his experience of using *Lean* tools in process development and secondary pharmaceutical manufacturing.

Waste is the Opposite of Value

The multiple tools and methodologies used to apply *Lean* Thinking are underpinned by a number of core principles.

The central theme of *Lean* Thinking is the elimination of muda (or waste). Taiichi Ohno, creator of the Toyota Production System, originally described seven sources of waste, and four additional sources have since been added to his original list.

Inappropriate Processing: an example

Despite the yield loss (muda) of material in the mother liquor, it is often justified to use crystallization to isolate solid intermediate in API manufacturing on the grounds of purifying the stream prior to the next reaction stage. This is an example of a non-value-adding activity which is unavoidable with present technologies or methods. Taking a wider view of waste would mean adopting new technology, such as optimizing the upstream reactor design and operation to minimize the impurity generation, eliminating the need to use crystallization for intermediate purification.

Pharma is Different - It's Easier than Building Cars!

Some people think that the *Lean* approach will not work because pharma is different, more complex and more regulated than other industries. Whilst this may be true, even a quick overview of recent regulatory thinking shows that the pharma industry has moved towards the systematic, science-based approach that *Lean* Thinking requires.

The table below compares the manufacturing complexity of API manufacturing with automotive manufacturing.

Measurable	Automotive Assembly	API Production Line
Number of components per product	>10,000	typically <10 (number of reagents and raw materials that create product molecules)
Component variation	Each item has multiple degrees of variation (every specification has an associated tolerance)	None in component but some wrong components (impurities) (each reagent molecule component is identical)
Transport	6 axis handling required(complex transport and assembly process - additional source of variation)	Pump
Assembly	Physical assembly required – degree of variation	Self-assembly (variation in assembly process leads to incorrect assembly)
Process capability	4-5σ (high manufacturing quality for complex operation)	4-5σ (poor manufacturing quality despite low complexity)
Cost of poor quality	2-8%	20-25% (poor manufacturing quality despite low complexity)
Multi-purpose plant	>20,000 options (BMW Mini) (production system handles vast range of products – mixed model production)	Dedicated or <5 for MPP (very poor at multi-product production, significant downtime between products)

The comparison reveals that assembly of the API molecule is orders of magnitude less complex than automotive assembly, particularly when considering mixed-model production versus multi-product plants. Conversely, automotive assembly is orders of magnitude more efficient in terms of process capability and cost of manufacturing defects.

This difference is down to two fundamental factors:

- The in-depth scientific understanding of the effect on the final product of changes in the manufacturing process.
- The manufacturing process is designed with minimal possible variability, hence creating minimum variability of the finished product. This inherent 'design for manufacture' is impossible to achieve without the scientific understanding.

Benefits of Applying *Lean* Thinking During Development

The use of *Lean* product development systems has been shown to deliver benefits compared with non-*Lean* systems:

- Time to market reduced by 30% or more
- Product cost reduced by 50%
- Development hours reduced by 45%
- Development time reduced by 24%
- 46% reduction in project team size
- Three-fold reduction in delayed products
- Product achieves normal quality eight times faster

These benefits can be realized in pharma development by focusing on achieving 'design for manufacture', where a lab process can be scaled up to pilot- and full-scale production without the waste-ridden scale-up iterations often currently required at each stage.

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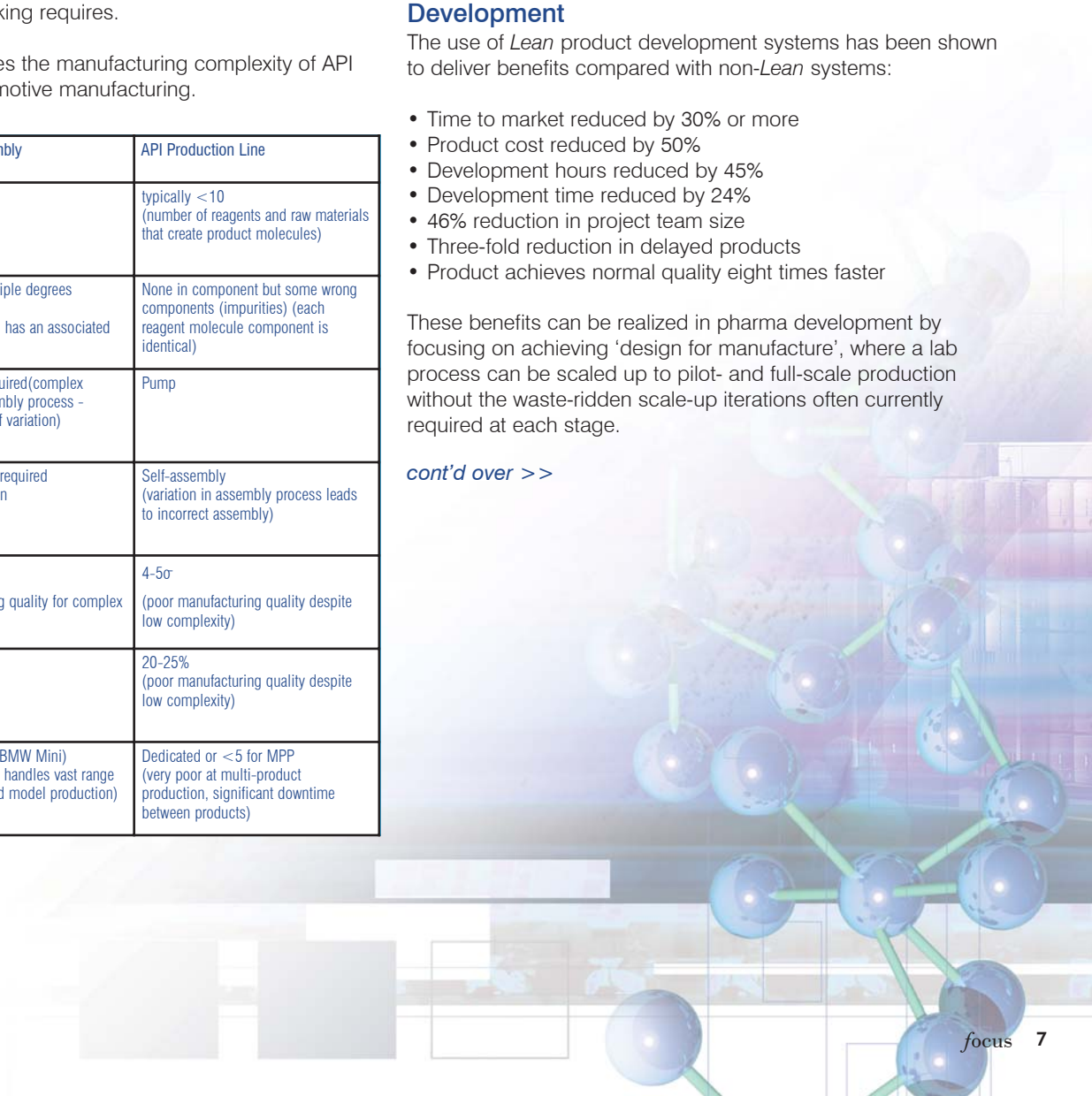

Lean API Manufacturing

Lean Thinking can be applied to many areas of pharma development and manufacturing to gain significant benefit. However some pharmaceutical operating practices are inherently so far removed from the basic *Lean* principles, that the full benefit of *Lean* Thinking will only be achieved by radically changing the whole operational practice.

One example is API manufacture, where plants are typically operated on a batch campaign basis. A plant is configured and operated for a single stage of processing, before being cleaned and reconfigured to carry out the next processing stage. All material produced in the first stage campaign is isolated, dried and packed off for storage before being fed back into the plant during the next stage campaign. This mode of operation is anathema to the *Lean* principle of flow, and locks in vast quantities of waste into the operating cycle. The overall operating cycle of converting raw material into finished products may take many months or even years.

A *Lean* Case Study

Because API manufacturing is such a massive source of waste, Foster Wheeler carried out a paper case study where a recent multi-stage batch plant of under 10 tonnes per year capacity was re-designed following the *Lean* principles at every stage.

The fundamental *Lean* Thinking principles used were:

1 *Science-based approach:*
Chemistry assessed for its suitability to convert to continuous operation.

2 *Making value flow:*
Given that the chemistry was inherently suited for continuous operation, the whole process was configured to flow from raw material to finished product in a single, integrated process.

3 *Quality from a customer's perspective:*
Delivery of final product in a form suitable for direct formulation without further physical processing such as milling.

The summary of the findings of this study are:

Throughput:	Raw material to finished product in <1 day
CAPEX:	>60% reduction in capital cost
OPEX:	Up to 40-fold reduction in utility requirements
Environment Impact:	>80% reduction in plant footprint >7-fold reduction in total effluent >100-fold solvent inventory reduction
Health and Safety:	Elimination of multiple high-containment operator interfaces

Whilst these factors are specific to this plant, data from multiple sources indicates that over 40% of processes are inherently suitable for continuous operation. Achieving the above economic benefits for this proportion of processes represents an enormous economic improvement over current performance.

The *Lean* Future

The pharmaceutical industry can no longer support the waste that has become locked into the manufacturing sector by the current operating model. As the FDA states, the potential annual cost savings from efficient product development and manufacture outweigh the cost of bringing new products to market.

Many other industries have experienced this wake-up call, and many of the companies in these industries have taken on board *Lean* Thinking and have transformed their businesses to survive in the new economic era.

Given the current economic and regulatory pressures, *Lean* Thinking offers a well-proven model to achieve the order of magnitude improvements in development and manufacturing performance that are now being demanded.

Pharma *i*

This article is adapted from a paper, available on our website, *Transforming the Pharma Industry: Lean Thinking Applied To Pharmaceutical Manufacturing* presented by Huw Thomas at the 7th World Congress of Chemical Engineering, held in Glasgow in July 2005.

A copy of Huw's article *The Reality of Small Scale Continuous Processing* (basis of article published Manufacturing Chemist, April 2005), is also on our website.