

Swiss innovation

in high containment

Metalor Technologies SA, the Swiss precious metals specialist based at Lake Neuchâtel in Switzerland, created its pharmaceuticals business unit in 2003. In 2004, Metalor awarded Foster Wheeler's Basel operation the extended conceptual design for a small-scale API facility for highly potent cytostatic products.

This is a highly innovative project with the whole non-aseptic production taking place inside one isolator divided into five chambers (pressure cascading), with an OEL of <math><0.5\text{ microgram/m}^3</math> and a particle count of ISO 5. The main process equipment consists of two 100-litre glass reactors, one stirred vessel for solution preparation, one pressure filter and one tray dryer, with interconnections by hoses or PVDF piping, all with Tri-clamp® flanges.

Unlike most isolators, which are generally rectangular, this model has a flat T-form so the entire reactor, including legs, could be placed inside. This reduces any sealing requirements to a minimum. The isolator is positioned in the middle of room rather than at the periphery and has windows and gloves fitted at the back, improving view and access to equipment parts.

The wall separating the production and technical areas has windows, so that operators can perform checks without leaving the production area, and visitors can see most of the facility without entering.

Following the success of the conceptual design, Metalor has awarded Foster Wheeler Basel the basic and detailed design and qualification of this exciting project.



Marco Mascarenhas
Manager, Bulk Pharmaceutical Chemicals
Foster Wheeler



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IMPROVING PRODUCTION EFFICIENCY

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.

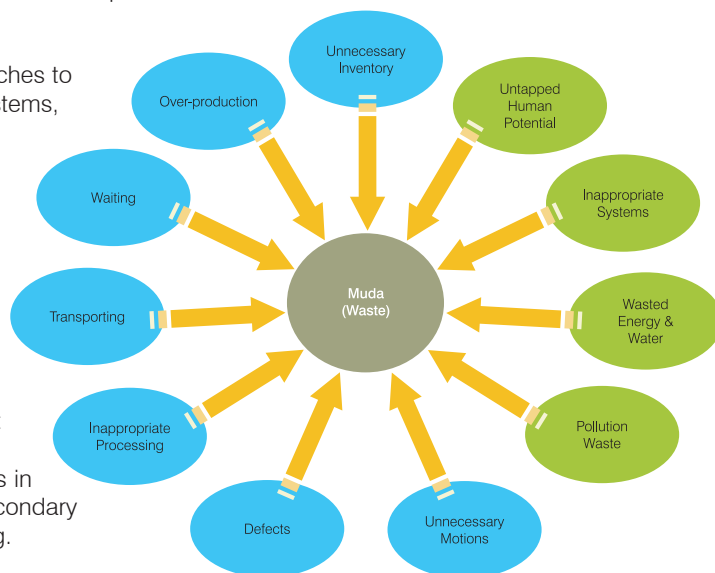
In discussing modern approaches to manufacturing and quality systems, the FDA White Paper draws heavily on *Lean Thinking* that has been implemented for many decades in other manufacturing industries.

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 | 4-5 σ (high manufacturing quality for complex operation) | 4-5 σ (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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IMPROVING PRODUCTION EFFICIENCY

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.

continuous processing

INNOVATIVE TUBULAR STATIC MIXER REACTORS

Choosing the right reactor for the job



Photo courtesy of Sulzer Chemtech

Foster Wheeler engineers are always keen to analyse new process problems and offer ideas and innovative design solutions. Mark Dickson, one of our specialist pharmaceutical process engineers, reviews some of the work he has done recently to develop tubular static mixers for API manufacture.



Chemical reactor design is the cornerstone of any process. Britest and process intensification principles aim towards a process reactor that provides ideal kinetic and thermal conditions for the chemistry, which is difficult to achieve in a batch reactor due to the inherent heat and mass transfer limitations. The ability of a continuous reactor to offer more uniform conditions, whilst providing a narrow residence time distribution, improves reaction yield in compact and intensified equipment, with dramatic impact on layout and capital cost.

There are numerous reactor options available for continuous processing in the pharmaceutical and fine chemical industries. For example, the highly intensified Marbond™ and spinning disc reactors offer excellent heat transfer for short residence time reactions, and oscillatory flow reactors have been proven in single and multi-phase systems and for longer residence time reactions with low exotherms. For moderately exothermic reactions, a jacketed static mixer has the advantages of effective heat transfer, excellent approach to plug flow at low velocity, and relatively low pressure drop, making it a low-cost option for lab development as well as full scale production.

Foster Wheeler has experience of designing static mixer-based reactors to provide a variety of reaction residence times from 1 to 60 minutes in compact reactors less than 10" in diameter and 1 meter in length. This type of reactor can produce plug flow at very low flow rates. Novel equipment designs also ensure the process fluid is always in contact with a cooled surface, which maintains the reactants at the optimum reaction temperature. We combine knowledge of continuous processing with innovative ideas for modelling heat and mass transfer performance of new reactor designs. In addition, static mixer-based equipment can also be used for multiphase reactions and we can provide innovative engineering solutions in the configuration of reactors for multi-stage synthesis.