Design and Implementation of a Small Footprint Continuous API facility for Portfolio Commercialization

Eoin McManus
Eli Lilly and Company
March 2016
Agenda

1. Drivers for Continuous API
2. Phase 1: Platform Technologies & Reactions
3. Phase 2: Proof of concept with Manufacturing
4. Phase 3: Proof of concept Small volume continuous
5. Phase 4: Construction of Novel Facility
6. Overall Learnings
What are the Drivers for Applying Continuous Processing?

- Fast reactions
- Energetic reactions
- Unstable intermediate
- High Pressure
- Extreme Temperatures
- Control Strategy

- High Volume
- Low Volume
- High Containment
- Environmental
- Hazardous Materials
- Quality

- Capability Build
- Established Capability
- Accelerate Supply Chain
- Enable Route
- Route Re-design
Realized Benefits of Continuous at Lilly

**Improved Speed**
- Automated DOEs
- Eliminate unit ops
- Streamline tech transfer
- Rapid prototyping

**Lower Cost**
- Better synthetic routes
- New capabilities & added capacity
- Deferred capital investment
- Increased throughput

**Improved Quality**
- Real-time analytical
- Steady State
- Equipment is engineered to process
- Less material at risk

**Improved HSE**
- Reduced waste
- Containment
- Smaller volumes
- Lower reagent amounts
- Neat reactions
Timeline for API continuous at Lilly

Phase 1: Platform development in R&D

- 2010: R&D – Multiple process demonstrations
  Mfg - Agreement on POC, but attrition
- 2013: R&D/Mfg - Proof of concepts on hybrid processes completed in Mfg
- 2014: R&D/Mfg - 2 Proof of concept of full continuous process in Mfg
- 2016: Mfg - Facility build in progress
  R&D - Small volume portfolio being developed for this platform
Platform Technologies for Continuous Reactions

Plug Flow Reactors (PFRs)
1. High or low temperature and pressures with all liquid reagents and product
2. High pressure hydrogenation, carbonylation, aerobic oxidation with liquid + gas reagents
3. Azide formation, thermal cyclization and deprotections, cryogenic reactions
4. Packed bed reactions

Continuous Stirred Tank Reactors (CSTRs)
1. Low or high temperature and pressure with solids in flow
2. Organometallic reactions including Grignards
3. Biphasic coupling reactions or sequestered catalyst

80L PFR  6L CSTR
Platforms for Continuous Workup/Isolation

- Counter-current Liquid-liquid Extraction
- Distillation
- Intermittent Flow Rotary Evap

Continuous Crystallization

Continuous Crystallization + In-line Slurry Milling

Packed Bed for Adsorption & Reaction
Phase 2: Proof of concept within manufacturing (Hybrid process)
Proofs of concept in Lilly Manufacturing

**Project A**
- API cost reduction of >30%
- Robust Pd removal
- Green chemistry reduces waste

**Registration Stability**
- 120 kgs

**Project B**
- Eliminated $20M spend on H₂ bunker
- Safer alternative to batch
- Green chemistry

**Registration Stability**
- 1800 kgs

**Project C**
- Development time reduced
- Tech transfer req’d half the time
- Green chemistry reduces waste

**Pre-registration stability**
- 150 kgs
The filling of the feed tanks with a new T8 batch will allow batch definition through the continuous process.

**Palladium Adsorption**

- Sukizzi reaction and brine washes T8
- T501, T502
- CO501, CO502, CO503

**De-BOC reaction**

- Thermal PFR for protecting group removal (140 °C)
- Packed bed column for Pd removal
### Realized Cost Savings

<table>
<thead>
<tr>
<th>Process Element</th>
<th>Quality and Technical Rationale</th>
<th>Benefits for Primary Stability Campaign</th>
<th>Commercial Processing Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column Pd removal process</td>
<td>• Minimizes use of expensive resin to remove Pd catalyst • Robustness of impurity control</td>
<td>↓ API cost (6%)*</td>
<td>↓ API cost (10%)*</td>
</tr>
<tr>
<td>Plug flow reactor</td>
<td>• Readily achieves desired high temperature • Enables elimination of tech to final crystallization step</td>
<td>↓ cycle time: 2 weeks</td>
<td>↓ API Cost (15%)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ Overall yield 10%</td>
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</tbody>
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*Cost reductions are based on R&D costing models and are relative to the all batch process used in pivotal campaign. R&D’s costing models and are used to help guide process development.*
Case Study: Safety and High Volume Drivers for a Reductive Amination

- **High projected peak volume (>100,000 kg/year)**

- **High Pressure Hydrogenation has a superior safety profile** vs. batch alternatives
  - Runs as a *low risk operation*
  - All hydrogen is kept outside of the building
  - 380 L pipes-in-series reactor – Lilly design

- **It is a green alternative to the previous approach which used stoichiometric sodium triacetoxyborohydride (STAB).**
  - Avoids the use of 1.2 million kg of STAB over the lifetime of the product
  - *Catalysis* – Just 0.001 eq of catalyst used with option to recover and recycle the metal.

- **Significant cost savings in $/kg API**

Material Comparison in 2 metric ton Campaign (Kinsale, Ireland 2013): 983 kg STAB vs 1.1 kg Ir catalyst
Pipes in Series Reactor for Hydrogenations

380 L Reactor – Kinsale IE2 facility
1. Safety
   • >99% liquid filled reactor with segmented flow of hydrogen vs. batch where 30% of headspace is hydrogen
   • 50X less hydrogen in the system at any point in time

2. Capital Avoidance
   • Batch: 2500L autoclave rated to 1000 psig and bunker = $30MM
   • Continuous: 850L plug flow pipe system = $2MM
   • $28MM potential CapEx savings

3. Other factors can heighten cost risk
   • Uncertainty around approval of the drug
   • Uncertainty around peak demand of API
   • Uncertainty around long term use beyond the lifecycle of the product
Phase 3: Proof of concept Small Volume Continuous
Small Volume Continuous Demonstration at GMP Manufacturing Facility

- Asset was low volume oncolytic perfect for SVC concept
- Continuous process reduced cost by 57% and waste by 62%; also eliminated 2 crystallizations and reduced handling of potent compounds

Step 1
API-SM → PFR Hydrazine → CC Extraction → Distillation → DMSO Solution

Step 2
PFR → MSMPR Crystallisation → Filtration → Dissolve Off Filter → Deprotection PFR

Step 3
API Drying ← API filtration ← API Crystallisation ← ppm Filtration ← Distillation

Flow Batch
• This entire step occupied 3 standard size walk-in fume hoods.
• Continuous unit operations significantly reduced hydrazine concentration in reaction and allowed its removal to ppm levels.
• On-line analytical verified that operations were in a state of control.
• Ran for over 200 hours at 3.3 kg/day.
This entire step occupied 3 standard size walk-in fume hoods.
On-line HPLC units were run simultaneously to monitor the purity of each reaction.
Ran for over 200 hours at 3.3 kg/day.
Distillation conducted semi-continuous feeding into holding tank
Final crystallization with filtration and drying of low OEL compound performed batch
5 GMP batches isolated
Process Analytical Technology

- Used on-line uPLC (Waters PATrol) after each reaction, this was crucial to monitoring the health of the process.
- Refractive index utilized to measure axial dispersion and good indication of steady-state

uPLC response corresponded to temperature for reactor.
Monitored to ensure impurities remained at acceptable levels.
Process Monitoring

- Data historian (PI) for monitoring
- Scripts were running to send alerts to personnel when something should be checked.
Timeline for API continuous at Lilly

- **R&D – Technology development Demonstrations**
  - 2007 - 2009

- **R&D – Multiple process demonstrations, Mfg - Agreement on POC, but attrition**
  - 2010

- **R&D/Mfg - 2 Proof of concepts on hybrid processes completed in Mfg**
  - 2013

- **R&D/Mfg - Proof of concept of full continuous process in Mfg**
  - 2014

- **Mfg - Facility build in progress**
  - 2016 +

**Phase 4: Small Volume Continuous platform implementation**
Why Small Volume Continuous?

- Small Volume Continuous is the concept of fully continuous processes operating at rates of 3-10 kg/day to deliver material quantities less than 1500 kgs/yr.

- >75% of Lilly's post-FHD portfolio has a projected API volume of less than 1500 Kgs/yr.

- Fully continuous processes at these scales allow for the following benefits:
  - Enhanced plant productivity
  - Reduction in capital investment
  - Fast start/stop decisions
  - Wider p/T operating space afforded with continuous platforms
  - Risk reduction since process is developed/demonstrated at commercial scale.
Material Throughput Advantage of Continuous over Traditional Batch Processes

As an example, consider producing 400 kg of API via a batch process:

Batch throughput is 6 kg/day; average of Kinsale campaigns

Using a fully continuous process where all the steps are running simultaneously:
IE2 SVC Facility – Operational in 2017

- Hydrogenation Fumehood
- New Hub/E&I Room
- Filter Dryer Room
- Airlocks
- IE2 Existing Building
- Solution Prep Room
- New Hub/E&I Room
- Filter Dryer Room
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Reshaping the Irish Landscape
Program for Small Volume Continuous Platform

Regulatory
- Engage early with HPRA/FDA:
  - Facility
  - Control strategy
  - CTD format

Quality
- Q systems
- Production standards

Process
- Control strategy
- PAT/Analytical strategy

Facility / Equipment
- SVC Facility
- Commercial standard
- PAI ready
- Equipment evolution

Business Processes
- IT / Data integrity
- Supply chain
- Capacity model

Significant program to enable Small Volume Continuous platform
Priority initiative in parallel to Facility delivery 2015-2017
API Accomplishments to Date

Lilly manufacturing:
• 2 registration stability campaigns in 2013
• 2 clinical trial campaigns including 1 SVC demonstration in 2014
• 1 validation campaign in 2015

External manufacturing:
• 2 clinical trial campaigns in 2013
• 2 validation campaigns in 2015

Regulatory activity:
• 1 Type C meeting with FDA in 2013
• Several End of Phase 2 (EOP2) with FDA meetings since 2013
• 1 NDA submission with FDA in 2016 and 1 further submission planned
  (for processes with continuous unit ops)
Continuous processing has many benefits, but business case has evolved over time

Each major internal partner (R&D, Manufacturing, Quality, Regulatory etc.) had a different driver

Leadership and trust needed

Close partnership between R&D and Manufacturing

Proof of Concepts invaluable to gain alignment
  – Each also had individual business case

Portfolio attrition delayed manufacturing POCs
  – Selected ‘high probability of next campaign’

Regulatory feedback lagged implementation

Third party network is essential
Acknowledgements

Derek Berglund
Scott May
Marty Johnson
Jen Groh
Tim White
Paul Collins
Bret Huff
Ciara Hood
Kinsale Ireland Operations Staff