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

Eoin McManus

Eli Lilly and Company

March 2016

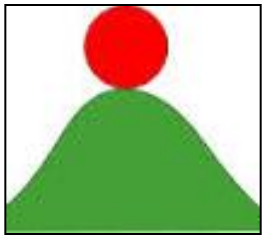
Agenda

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?

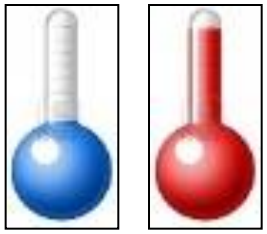
Fast reactions

Energetic reactions

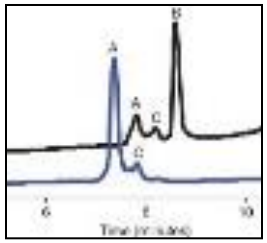


Unstable intermediate

High Pressure



Extreme Temperatures



Control Strategy

High Volume

Low Volume

High Containment

Environmental

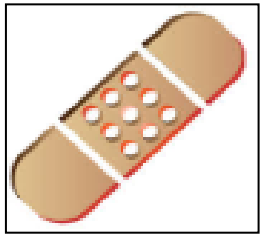
Hazardous Materials

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

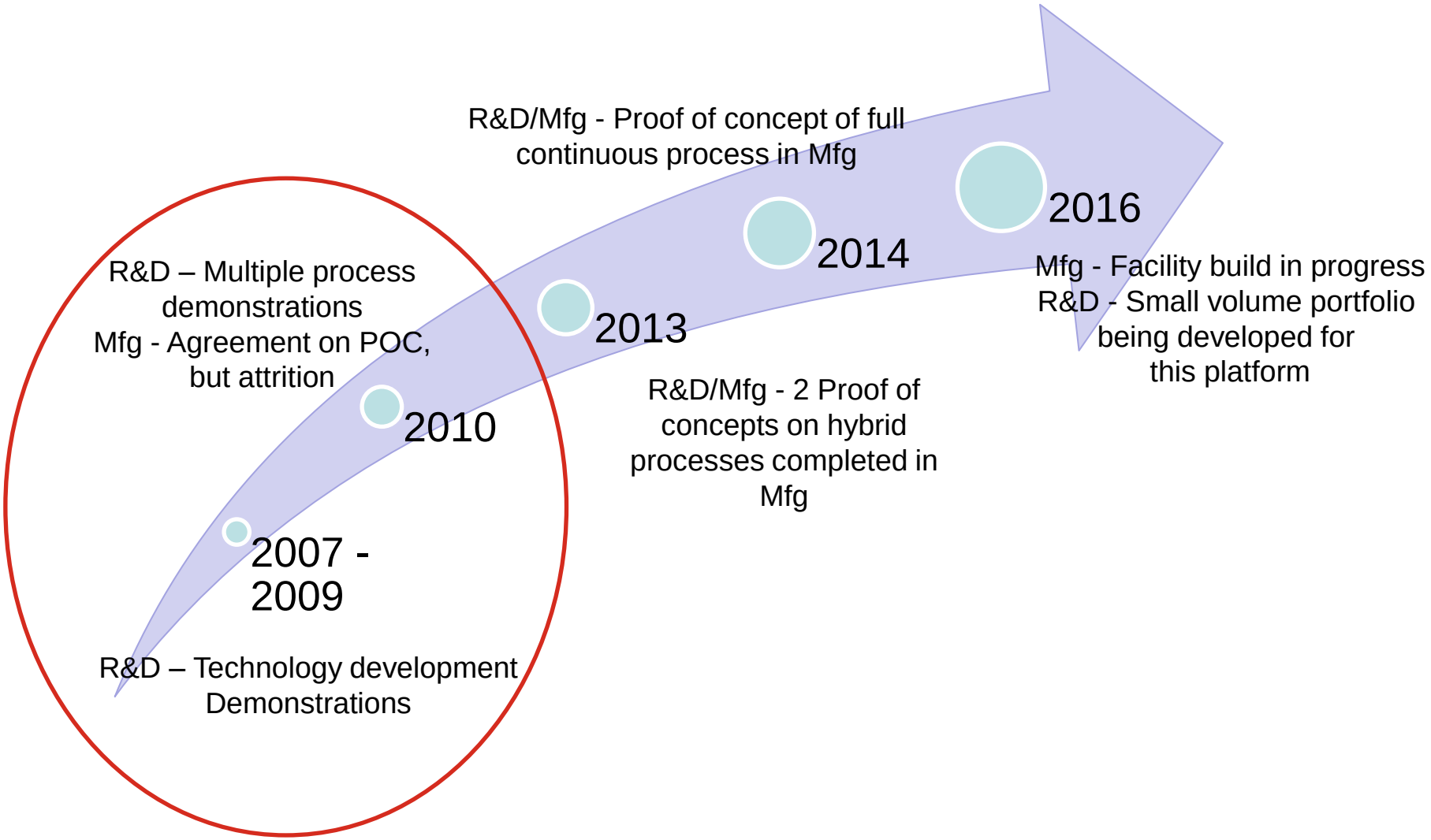
-Containment

-Smaller volumes

-Lower reagent amounts

-Neat reactions

Timeline for API continuous at Lilly



Phase 1 : Platform development in R&D

Platform Technologies for Continuous Reactions

80L PFR

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

6L CSTR

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

200L Pipes in Series
Demo model only
(Production Scale)

Platforms for Continuous Workup/Isolation

Counter-current
Liquid-liquid Extraction

Continuous Crystallization

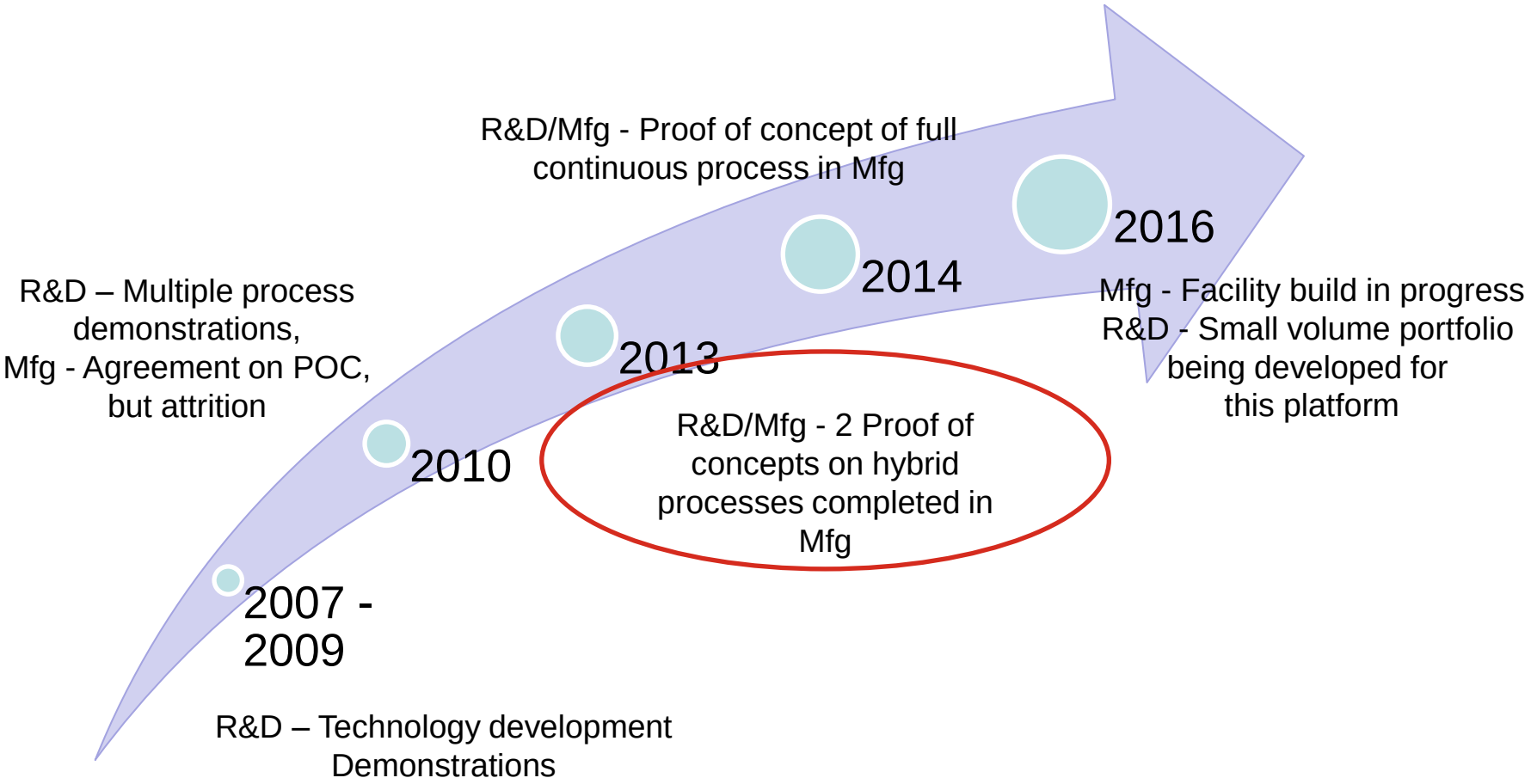
Distillation

Continuous Crystallization +
In-line Slurry Milling

Intermittent Flow Rotary Evap

Packed Bed
for Adsorption
& Reaction

Timeline for API continuous at Lilly



Phase 2: Proof of concept within manufacturing (Hybrid process)

Proofs of concept in Lilly Manufacturing

Project A

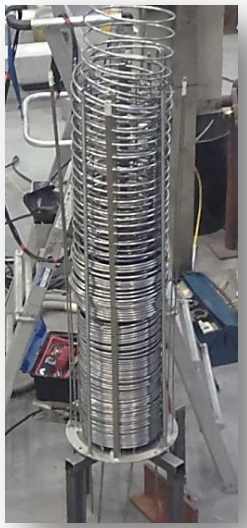
API cost reduction of >30%
Robust Pd removal
Green chemistry reduces waste

Registration Stability
120 kgs

Project B

Eliminated $20M spend on H_2 bunker
Safer alternative to batch
Green chemistry

Registration Stability
1800 kgs



Project C

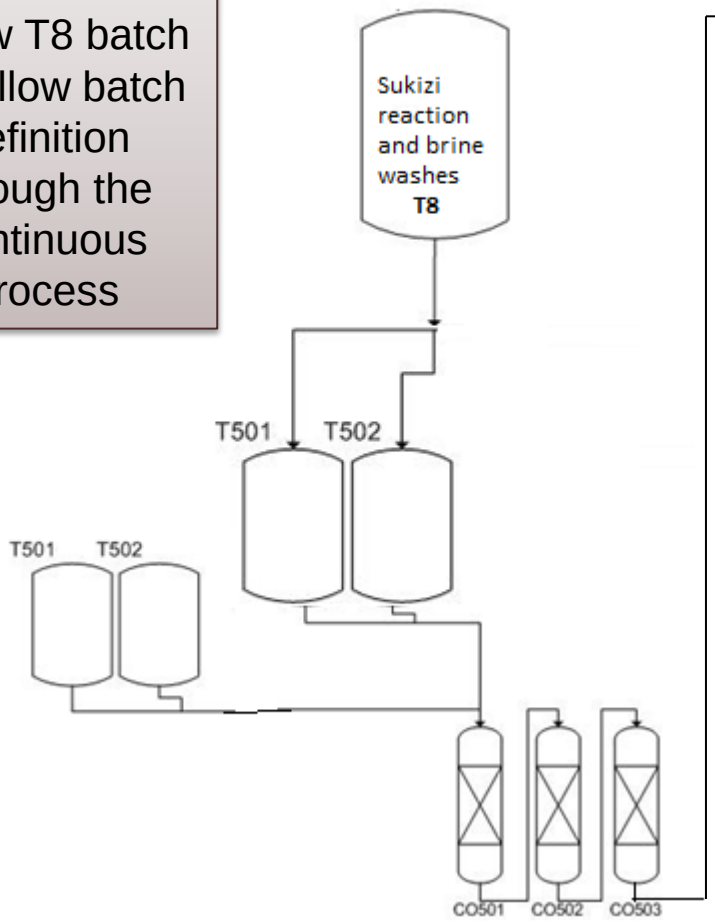
Development time reduced
Tech transfer req'd half the time
Green chemistry reduces waste

Pre-registration stability
150 kgs

Case Study: Continuous Unit Operations – Thermal PFR and adsorption

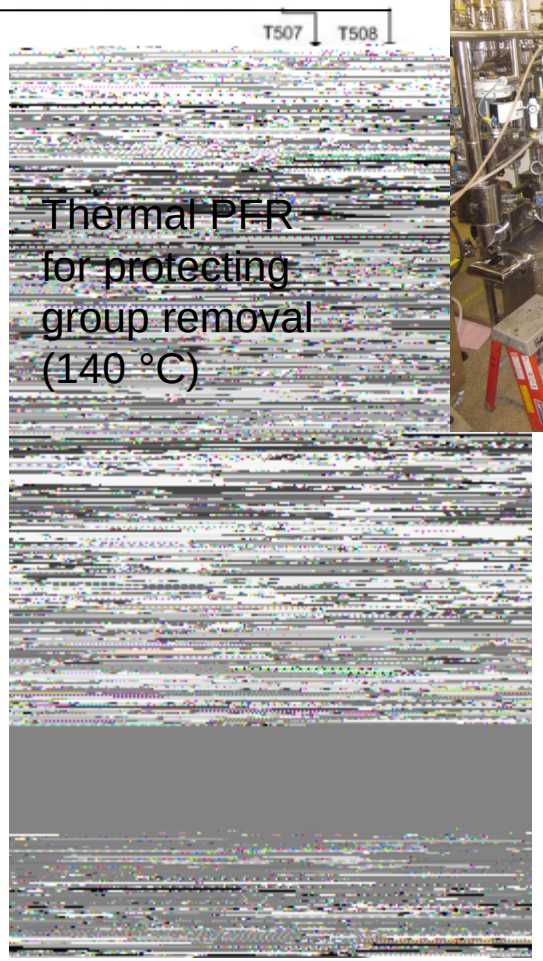
The filling of the feed tanks with a new T8 batch will allow batch definition through the continuous process

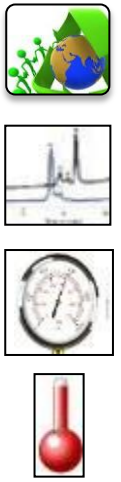
Palladium Adsorption



Packed bed column for Pd removal

De-BOC reaction





Realized Cost Savings

Process Element	Quality and Technical Rationale	Benefits for Primary Stability Campaign	Commercial Processing Benefits
Column Pd removal process	•Minimizes use of expensive resin to remove Pd catalyst •Robustness of impurity control	↓ API cost (6%)*	↓ API cost (10%)*
Plug flow reactor	•Readily achieves desired high temperature •Enables elimination of tech to final crystallization step	↓ cycle time: 2 weeks ↑ Overall yield 10%	↓API Cost (15%)*

*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)*

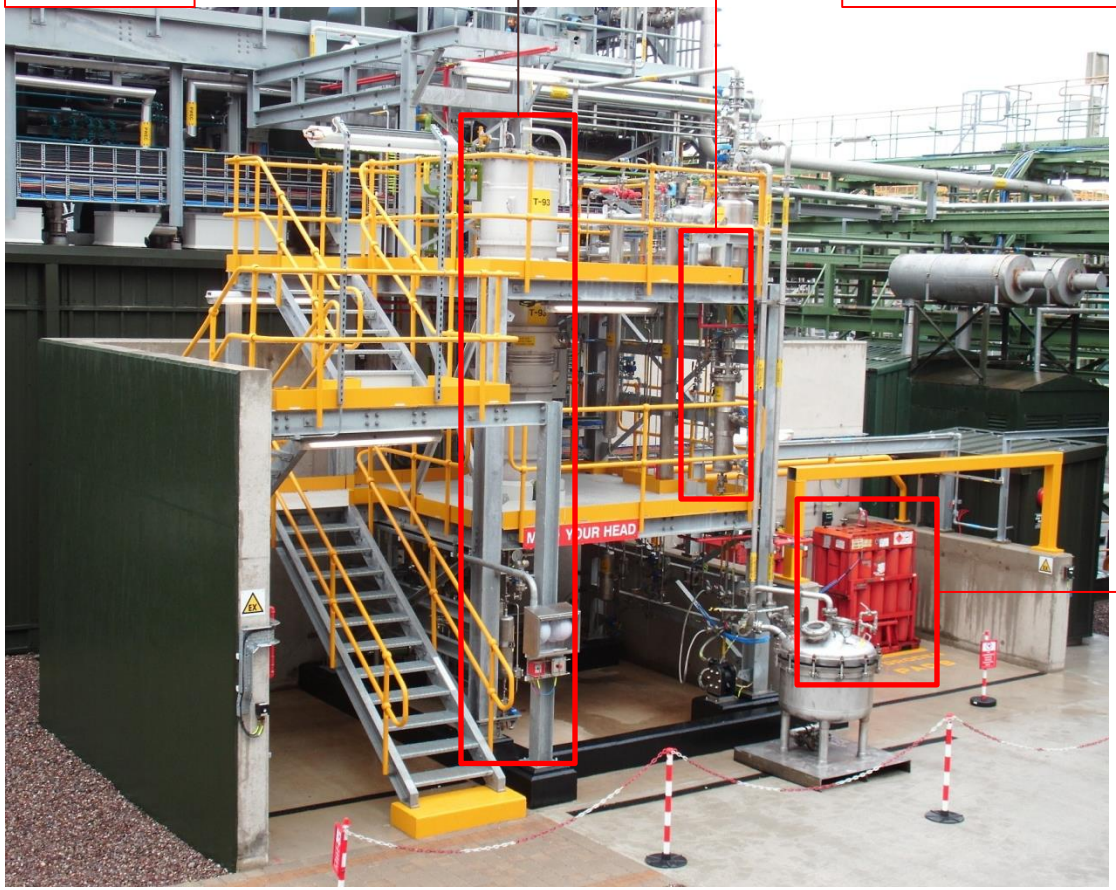
- *High Pressure Hydrogenation has a superior safety profile* vs. batch alternatives
  - Runs as a *low risk operation*
  - All hydrogen is kept outside of the building
  - 380 L pipes-in-series reactor – Lilly design

- *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

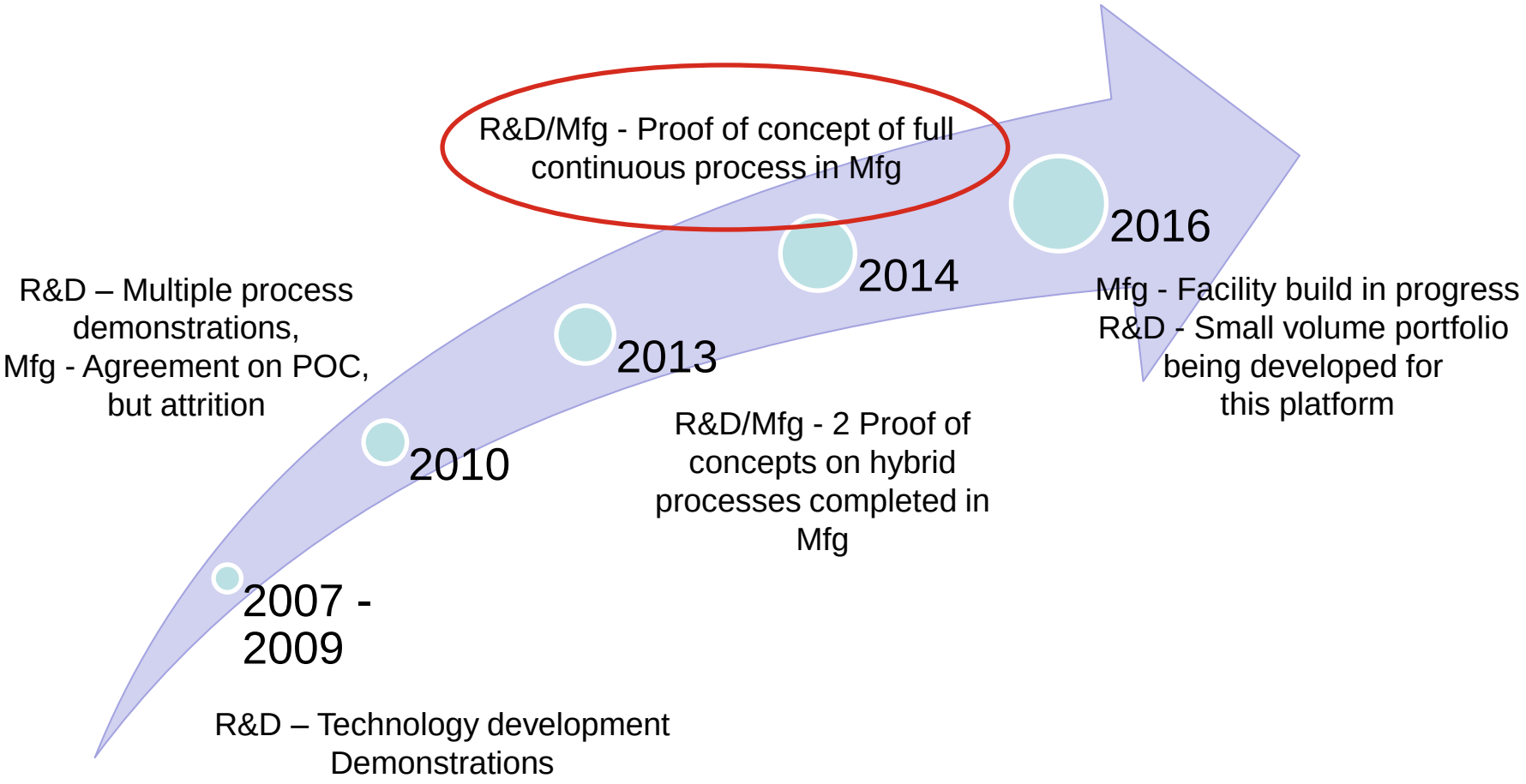
Safety & Capital Cost Benefits

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

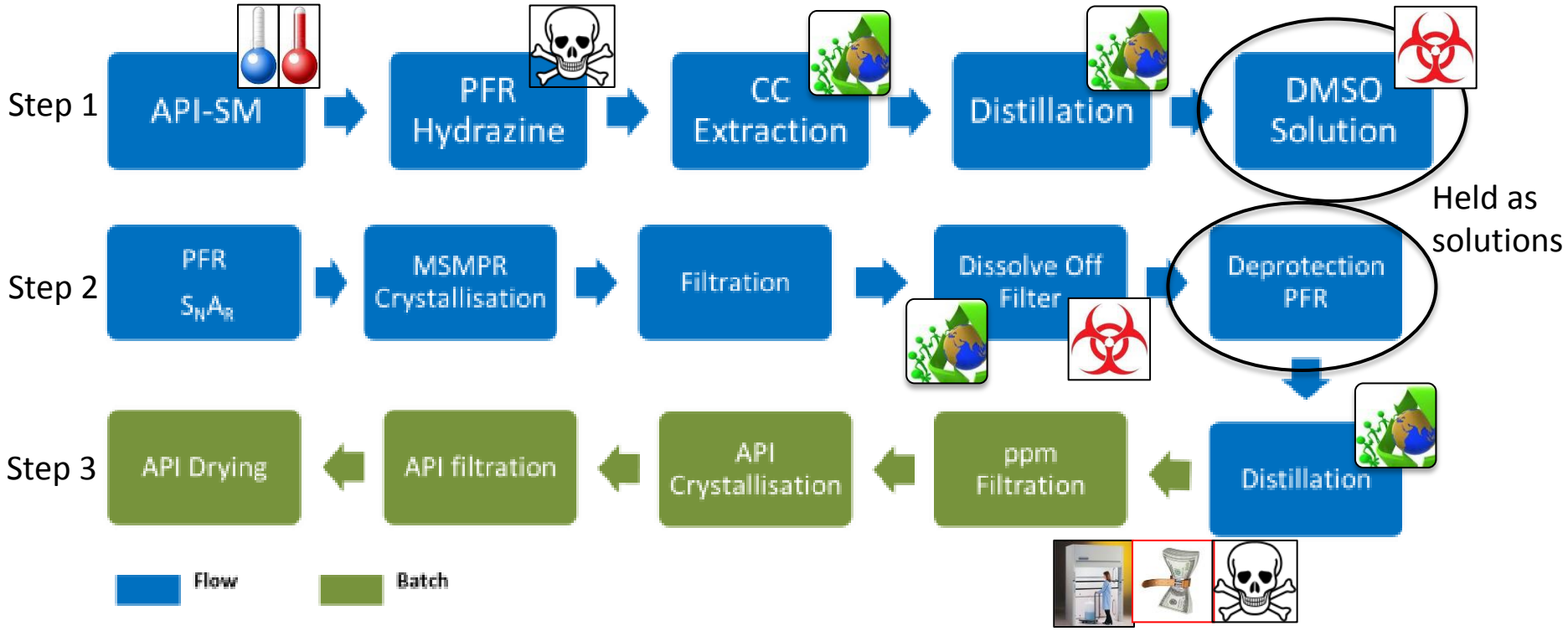
Timeline for API continuous at Lilly



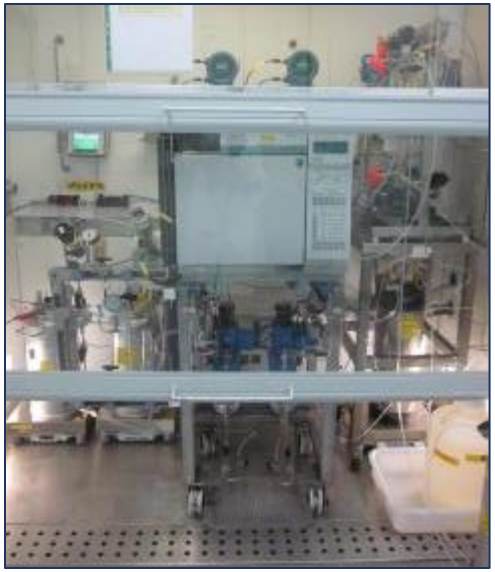
Phase 3: Proof of concept Small Volume Continuous

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



cGMP Campaign: Step 1



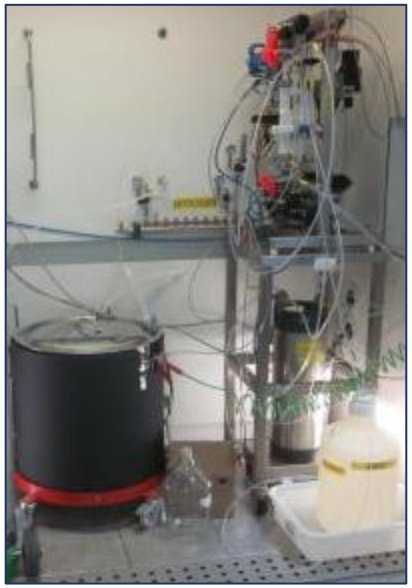
Reaction + Monitoring

Continuous Extraction

Automated Distillation

- 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.

cGMP Campaign: Step 2



Reaction + Monitoring

Continuous Crystallization

Filtration Dissolution

Reaction + Monitoring + Pumps

- 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.

cGMP Campaign: Step 3

Distillation

Holding Tank

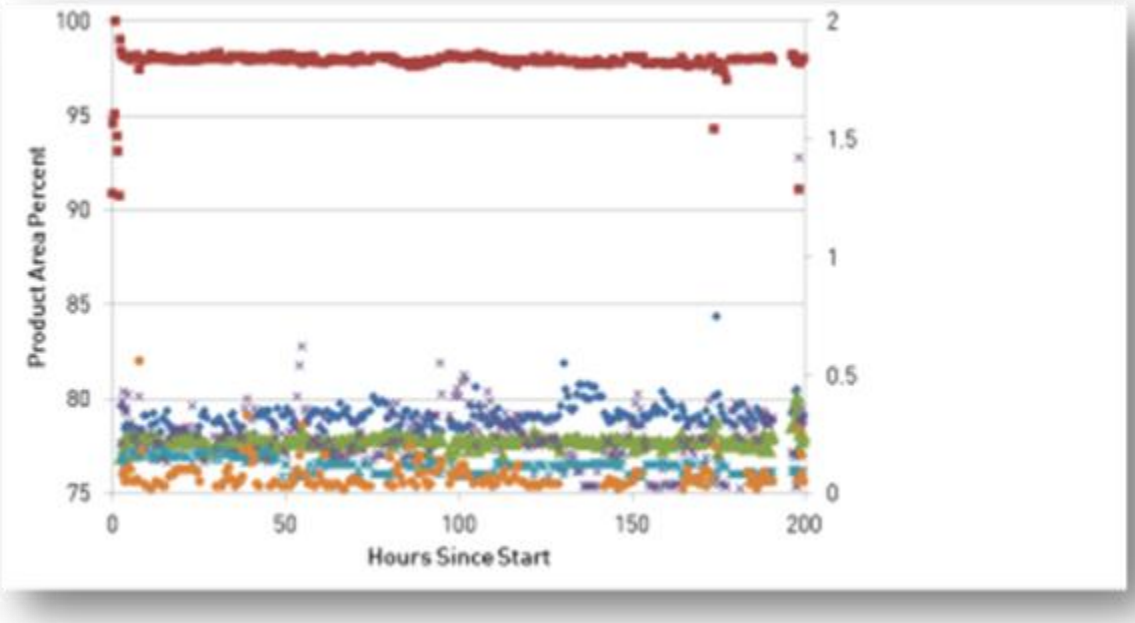
Batch Crystallization

Drying

- 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

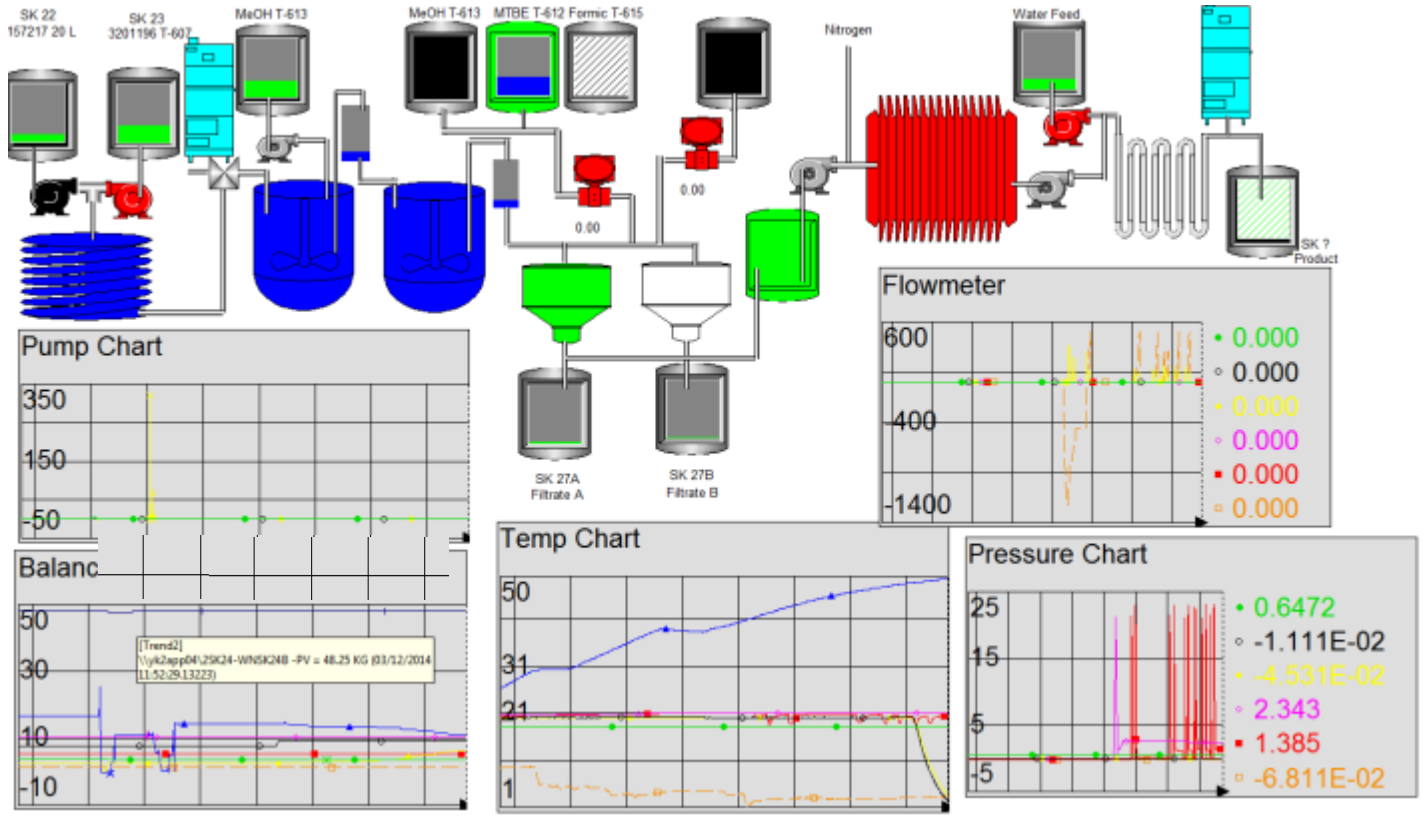


uPLC response corresponded to temperature for reactor.

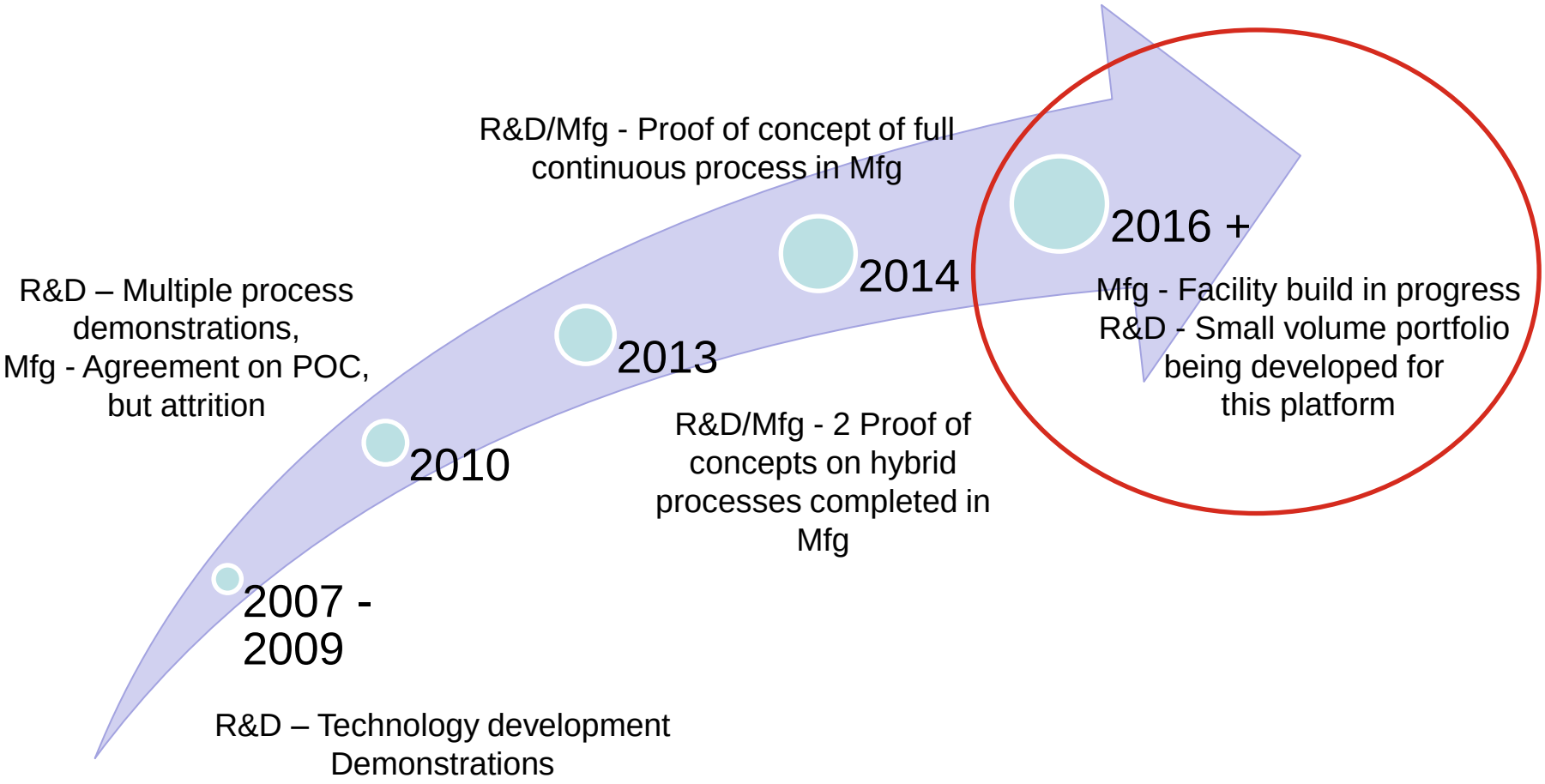
Monitored to ensure impurities remained at acceptable levels.

Process Monitoring

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

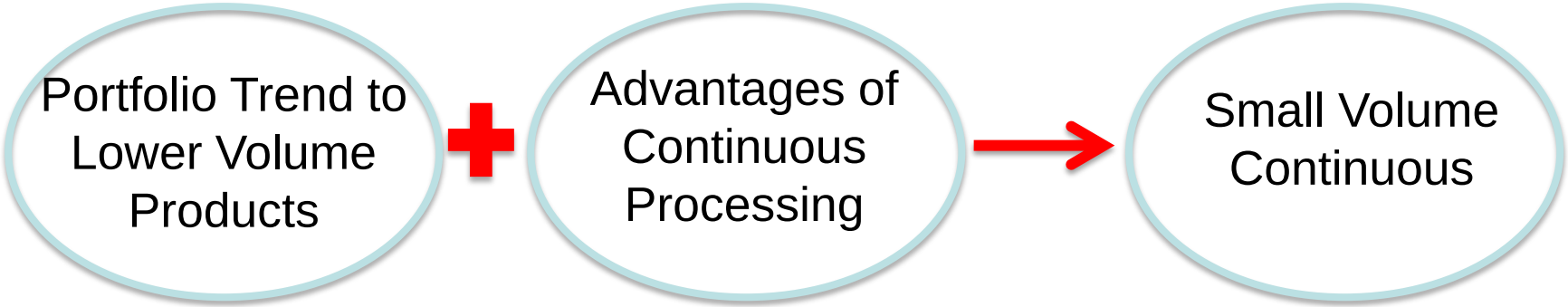


Timeline for API continuous at Lilly



Phase 4: Small Volume Continuous platform implementation

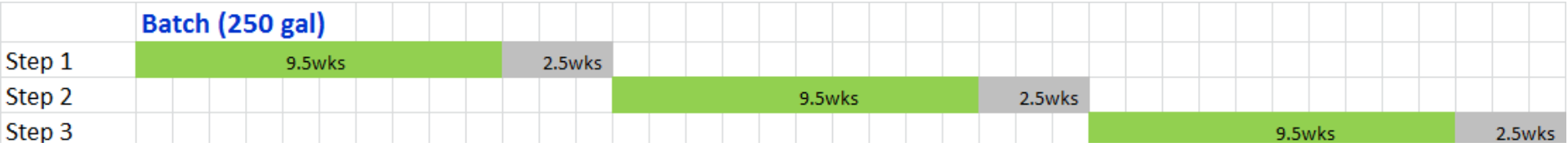
Why Small Volume Continuous ?



- 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 Lillys post-FHD portfolio has a projected API volume of less than 1500 Kgs/yr
- Fully continuous processes at these scales allows 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

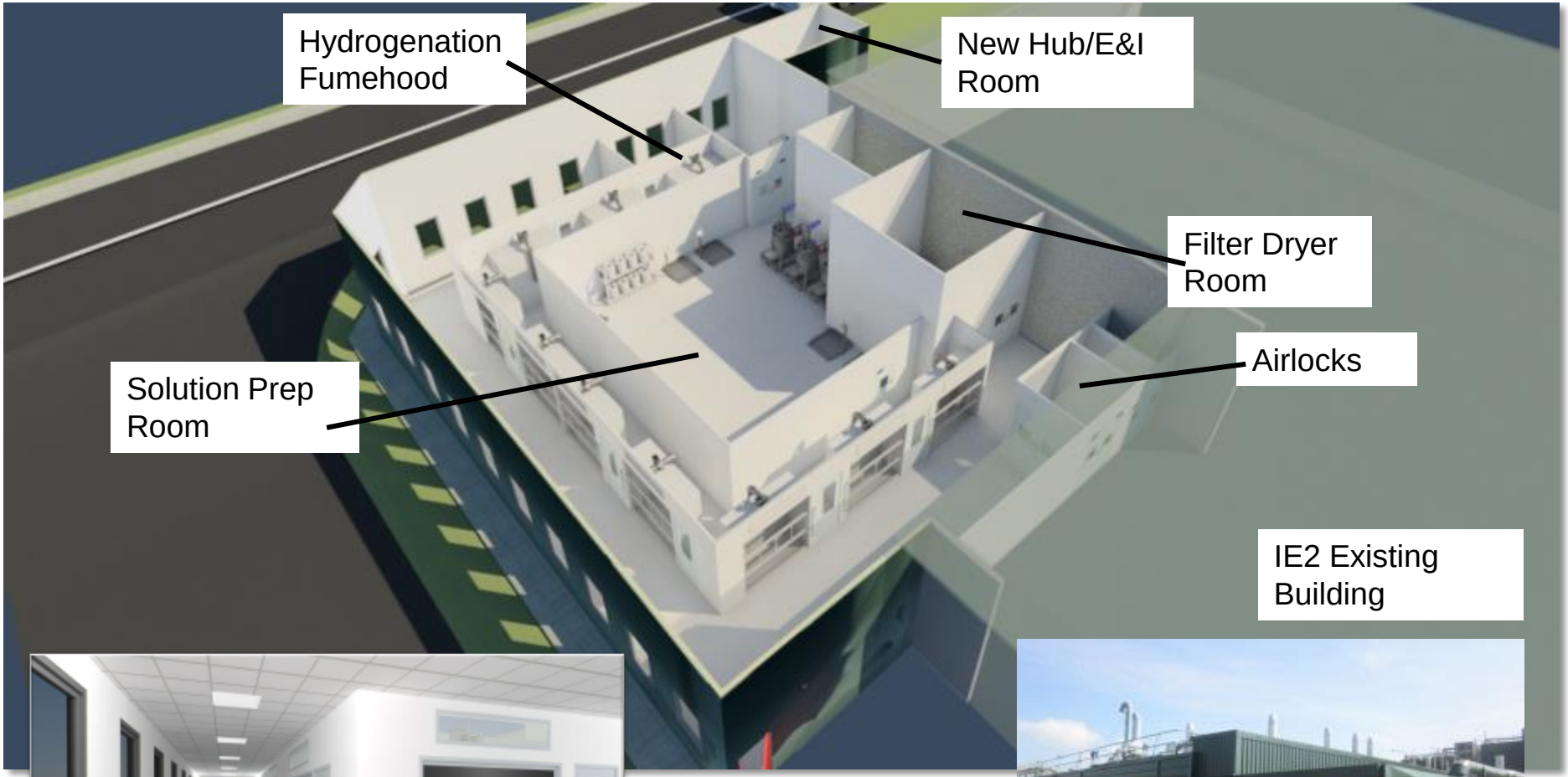
As an example, consider producing 400 kg of API via a batch process:



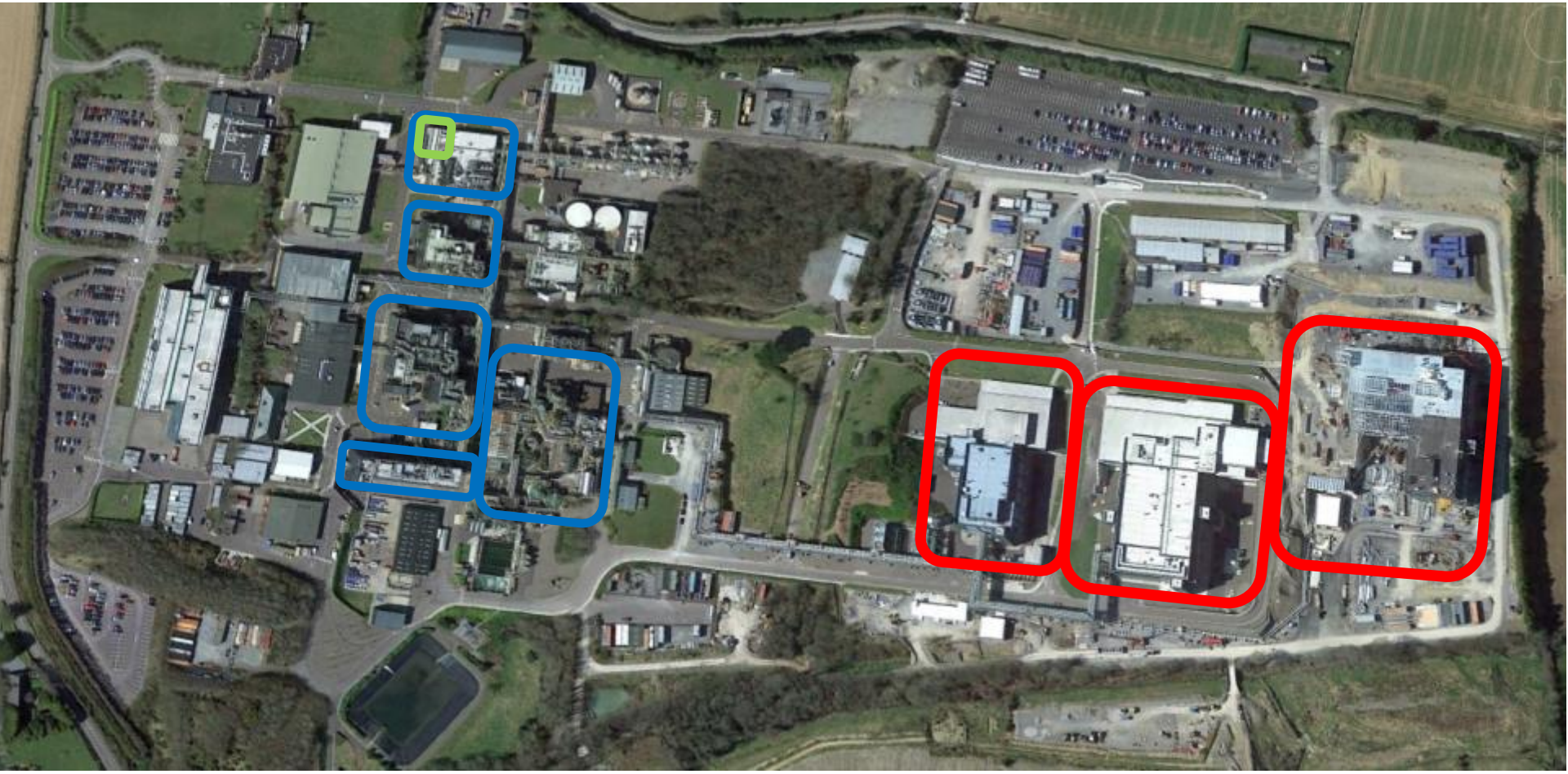
Batch throughput is 6 kg/day; average of Kinsale campaigns

Using a fully continuous process where all the steps are running simultaneously:

IE2 SVC Facility – Operational in 2017



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)

Overall Learnings

- 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