



# Continuous Manufacturing of Small Molecule Pharmaceuticals

## The Ultra Lean Way of Manufacturing

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# Agenda

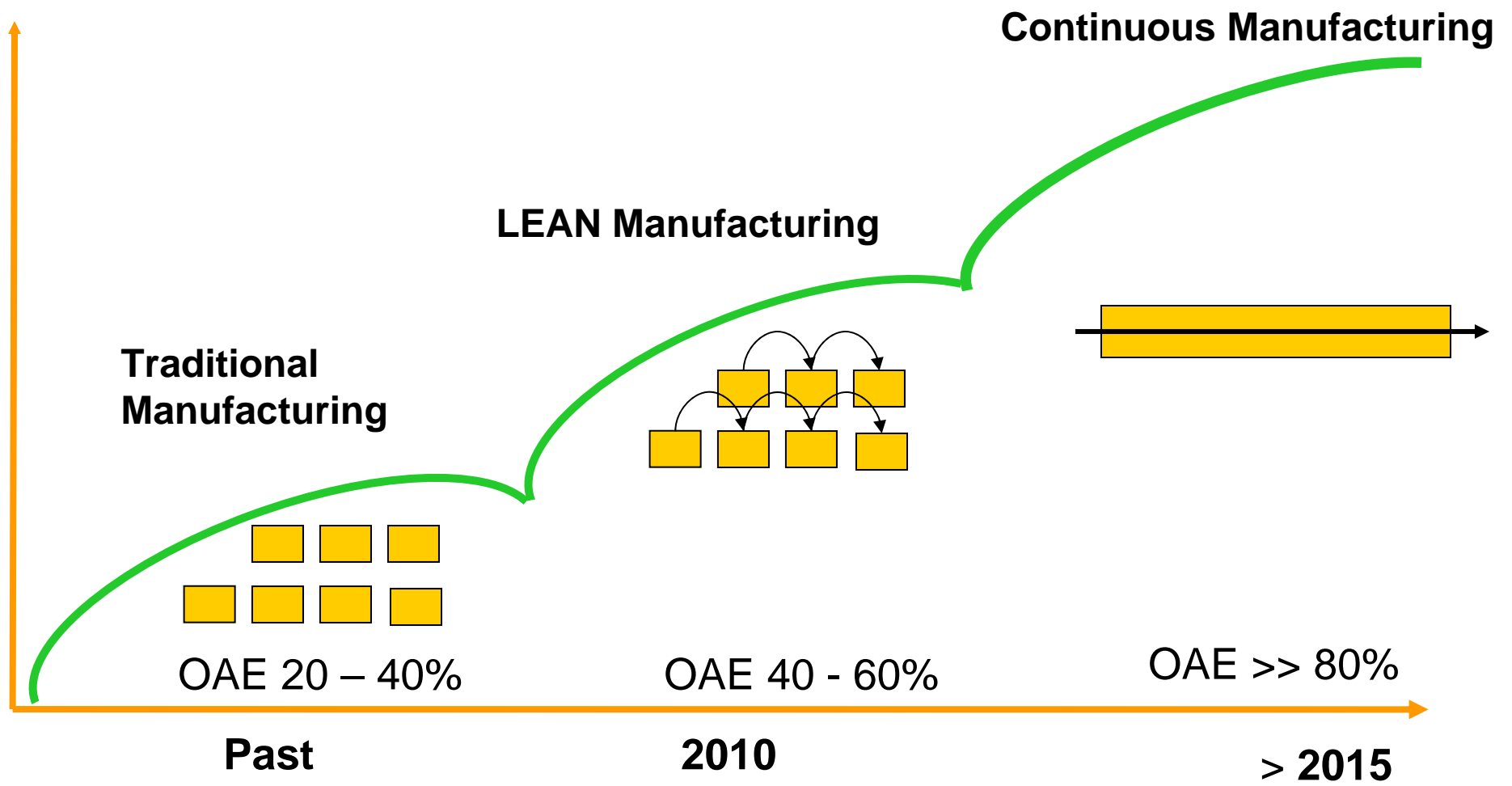
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- Past and Future of Process Improvements
- Batch Manufacturing
- Transforming Pharmaceutical Manufacturing (Video)
- Blue Sky Vision Continuous Manufacturing
- Expected Benefits
- Economic Evaluation



# From Past to Future

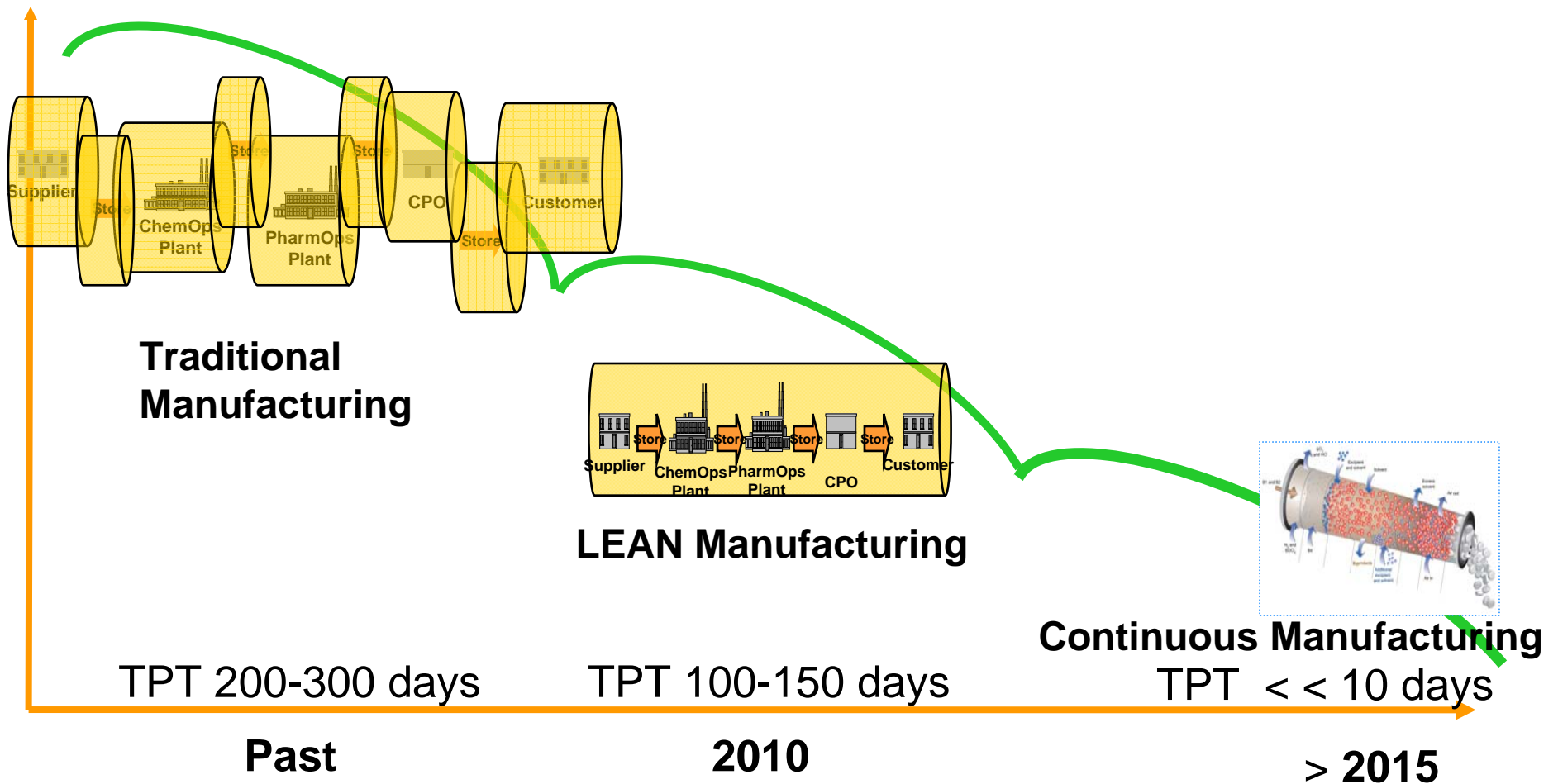
*LEAN: increasing throughput rates*



OAE: Operational Asset Effectiveness

# From Past to Future

## *LEAN: decreasing throughput times*

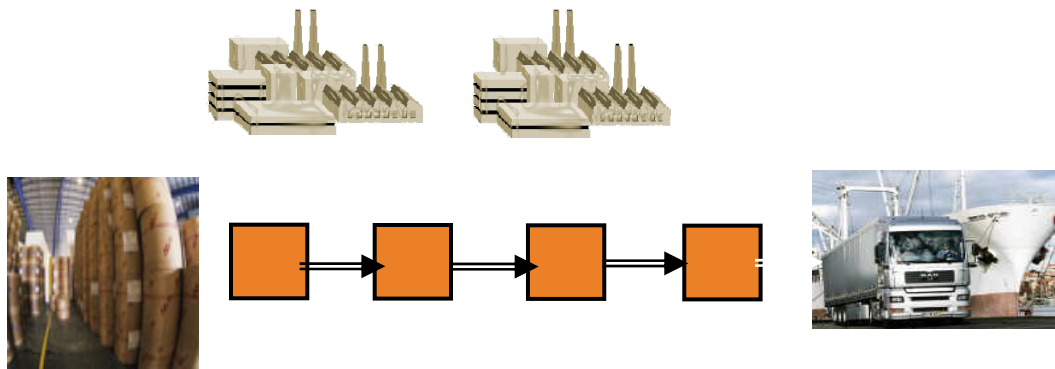


TPT Throughput Time Pharmaceutical Manufacturing

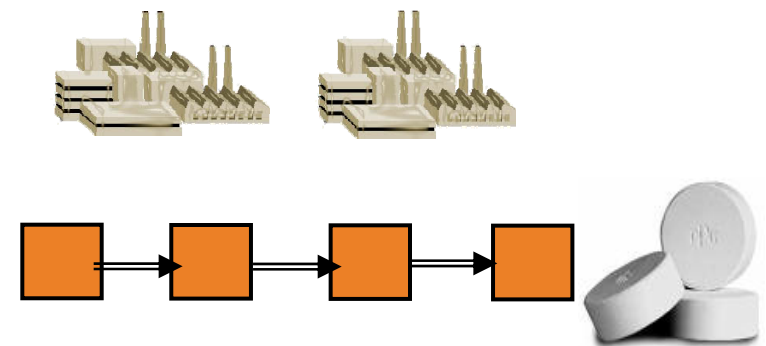
# Batch Processes

*Additional quantum leap improvements are unlikely to happen with traditional manufacturing concepts*

## Drug substance



## Drug product

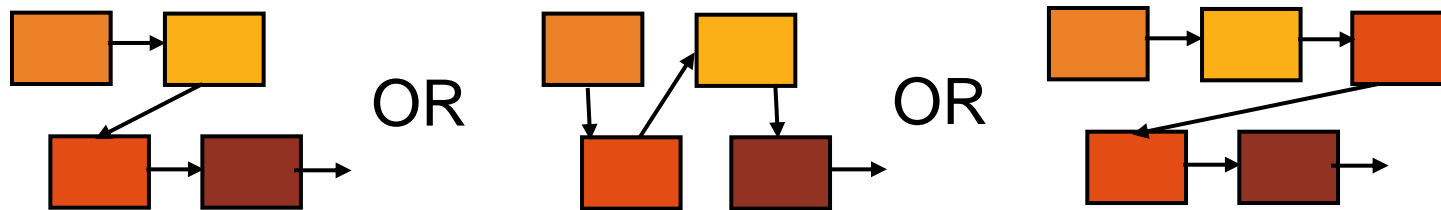


- **Operations:** Major efficiency gains have been implemented. Additional quantum leap efficiency gains are unlikely
- **Compliance:** Many manual checks, deviations/investigations, difficult root/cause analysis
- **Quality:** Reliance on in process and end product testing

# Batch Processes - Advantages

*Flexible – can use equipment for multiple drugs, can rearrange in whatever order necessary*

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**Equipment in place**

**Unit Operations understood**

**Productivity optimized**



# Batch Processes - Disadvantages

*Disconnected, long throughput times, end product testing*

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- Defined batch size (output quantity driven by batch size)
- Multiple, sequential process steps, end to end
- Many interruptions between/during process steps
- Long waiting times between single process steps
- Numerous transport steps between process steps
- Lengthy throughput times from start to finish
- High levels of raw material and intermediate inventories required
- Extensive validation and scale-up activities needed
- Physical and organizational separation in operations and development
- Quality measured by in process sampling/control and end product testing

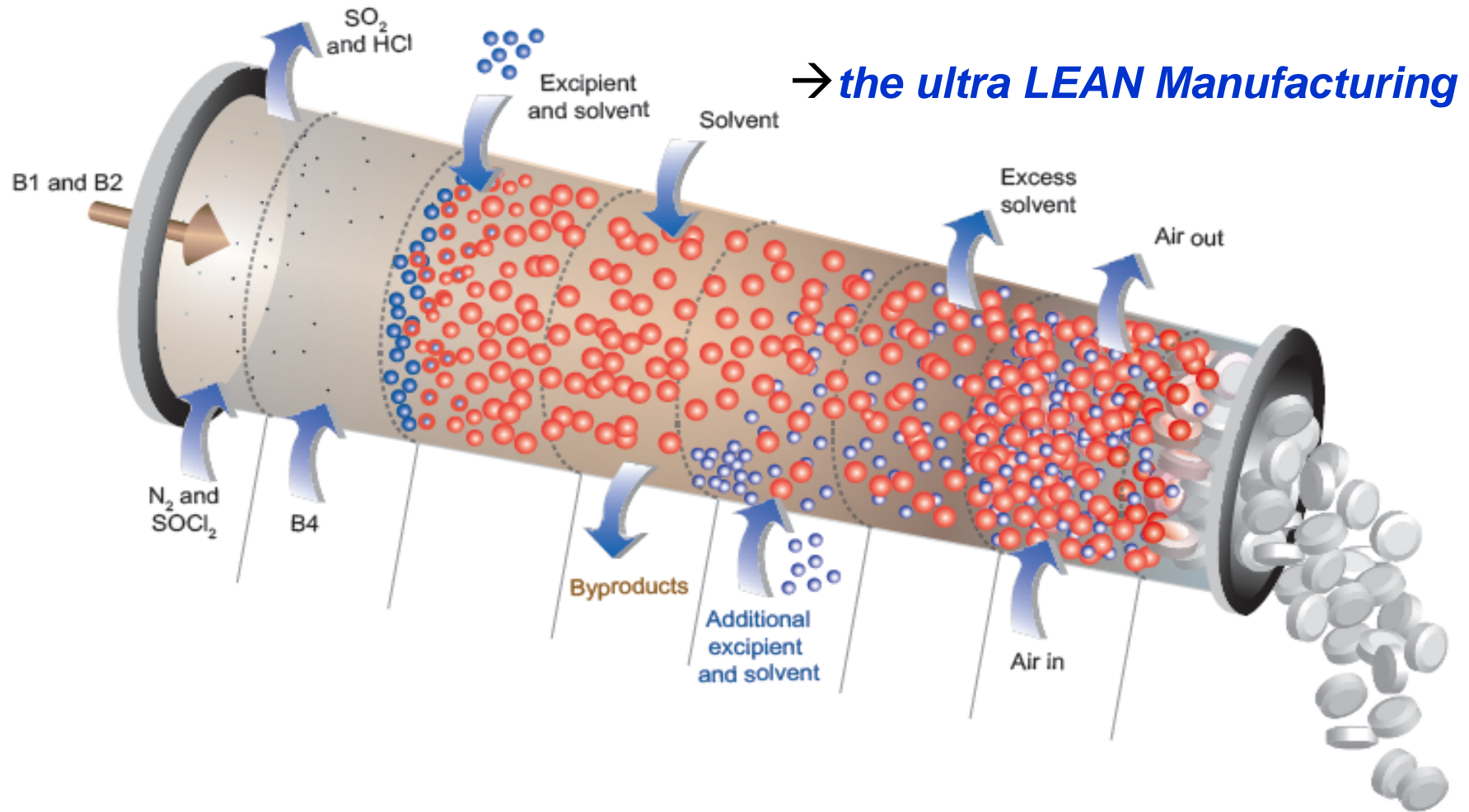
## Video

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- Novartis-MIT Center for Continuous Manufacturing  
“Transforming Pharmaceutical Manufacturing”

# Novartis-MIT Blue Sky Vision

## Continuous Manufacturing: *A radical transformation*



**From start of chemical synthesis through final pharmaceutical dosage form**

# Novartis-MIT Blue Sky Vision

## Continuous Manufacturing: *A radical transformation*

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- Integration of full Quality by Design concepts
- Implementation of a new product development process (integrated chemistry and pharmaceuticals)
- Utilization of new methodologies, technologies and equipment
- Development of a new streamlined facility lay-out
- Major change in technical skills and mindset
- Major change in organizational structures for cohesive development, quality and technical operations

# Expected Benefits

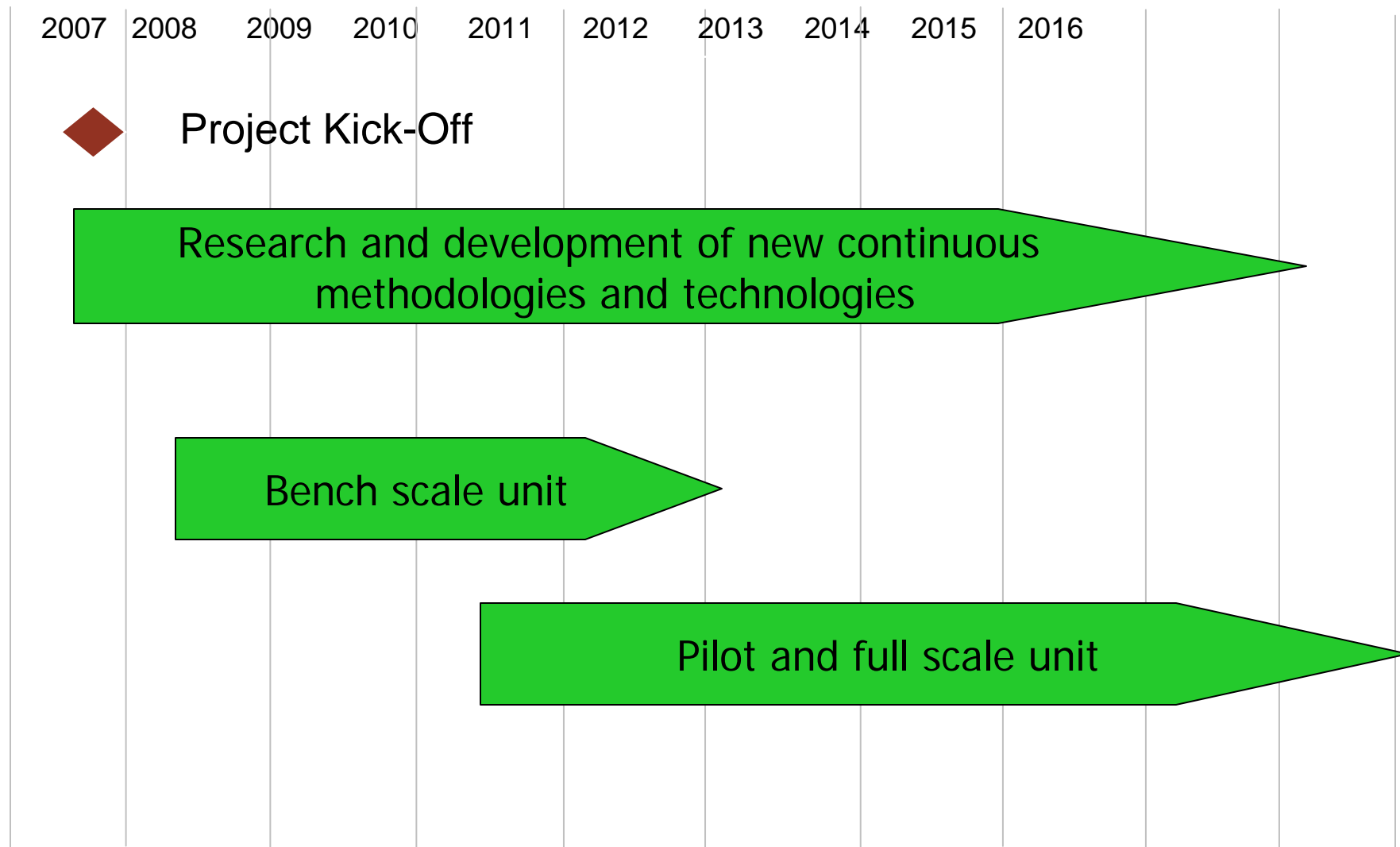
## *Continuous Manufacturing: A radical transformation*

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- Integration of Compliance/Quality within the process
- Reduction of asset footprint (40-90%)
- Reduction in capital expenditure (25-60%)
- Reduction of operational costs (25-60%)
- Reduction of raw material and intermediate inventories
- Flexibility in supply size
- Reduction of overall drug substance and drug product development times, improving time to market and assuring the availability of high quality, safe and efficacious drugs to patients

# Project Timelines

*Novartis - MIT Center for Continuous Manufacturing*



# Economic Evaluation

Assumptions (batch= real; conti.= BSV)

- Basic Assumptions

- Production

26,000 kg API / yr  
104 million 250 mg tablets / yr

- Dedicated plants

Hours of operation

Labor

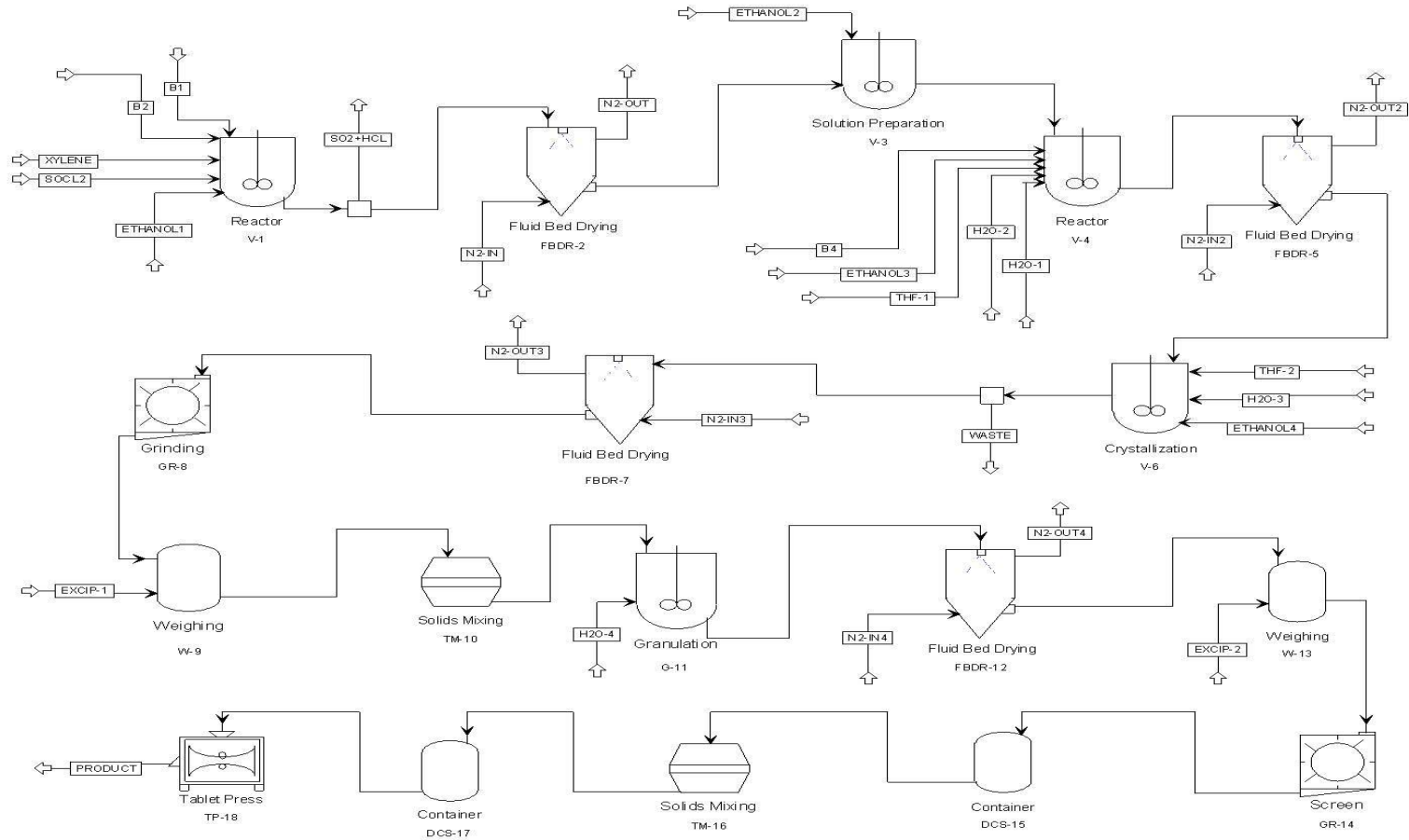
- Process Yield

Step 1 & 2 Conversions

	Batch	Continuous
	370 kg/batch DP	12 kg/hr DP
	2 x 8 hour shifts 5 days / week 52 wks/yr	24 hrs/day 7 days/wk 50 wks/yr
	2 FTE / 9 hr formulation 2 FTE / 6.5 hr tableting	2 FTE on day shift 1 FTE on other shifts
	1	0.99

# Batch Process "as is"

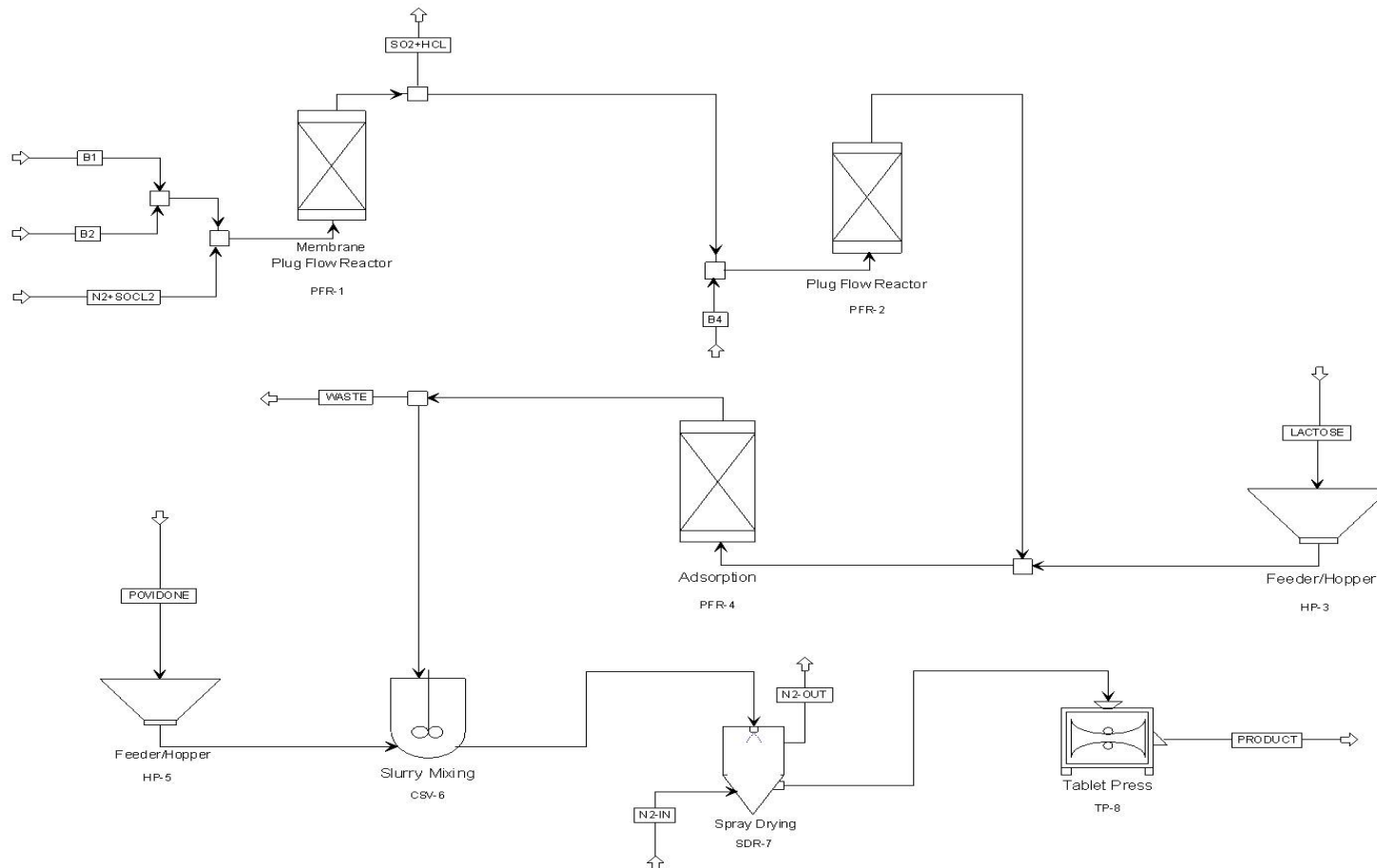
## Flow sheets chemical and pharmaceutical Processes



# Continuous Process “Blue Sky”

*Flow Sheets end to end process*

## ■ Continuous Flow Sheet



# Business Case Model

## *Results SuperPro Simulation*

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### Total Capital Costs

**BATCH**

24,602,000 CHF

**CONTINUOUS**

7,009,000 CHF

### Operating Cost

**BATCH**

8,636,00 CHF/yr

**CONTINUOUS**

6,411,00 CHF/yr

### Economics: NPV

**BATCH**

-5,3 million CHF

**CONTINUOUS**

18,6 million CHF

# Summary of Challenges

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- Mindset/Organizational
- Regulatory
- Technological

# Acknowledgements

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## MIT- Professors

- Paul Barton: Chem E
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- Allan Myerson: Chem E
- Greg Rutledge: Chem E
- Bernhardt Trout: Chem E

## Novartis

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*Head Global Techn. Operations*
- Juan Andreas  
*Head Group Quality*
- Steffen Lang  
*Head Global Techn. R&D*
- Berthold Schenkel  
*Chemical Development*
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*Pharmaceutical Development*