



PCMM Manufacturing

2016 ISPE Facility of Year: Equipment Innovation Winner

- *Why*
- *Uniqueness*
- *Impact*

February 23, 2017
ISPE- New Jersey Chapter
Sanofi - Bridgewater, NJ



OUR SPEAKERS

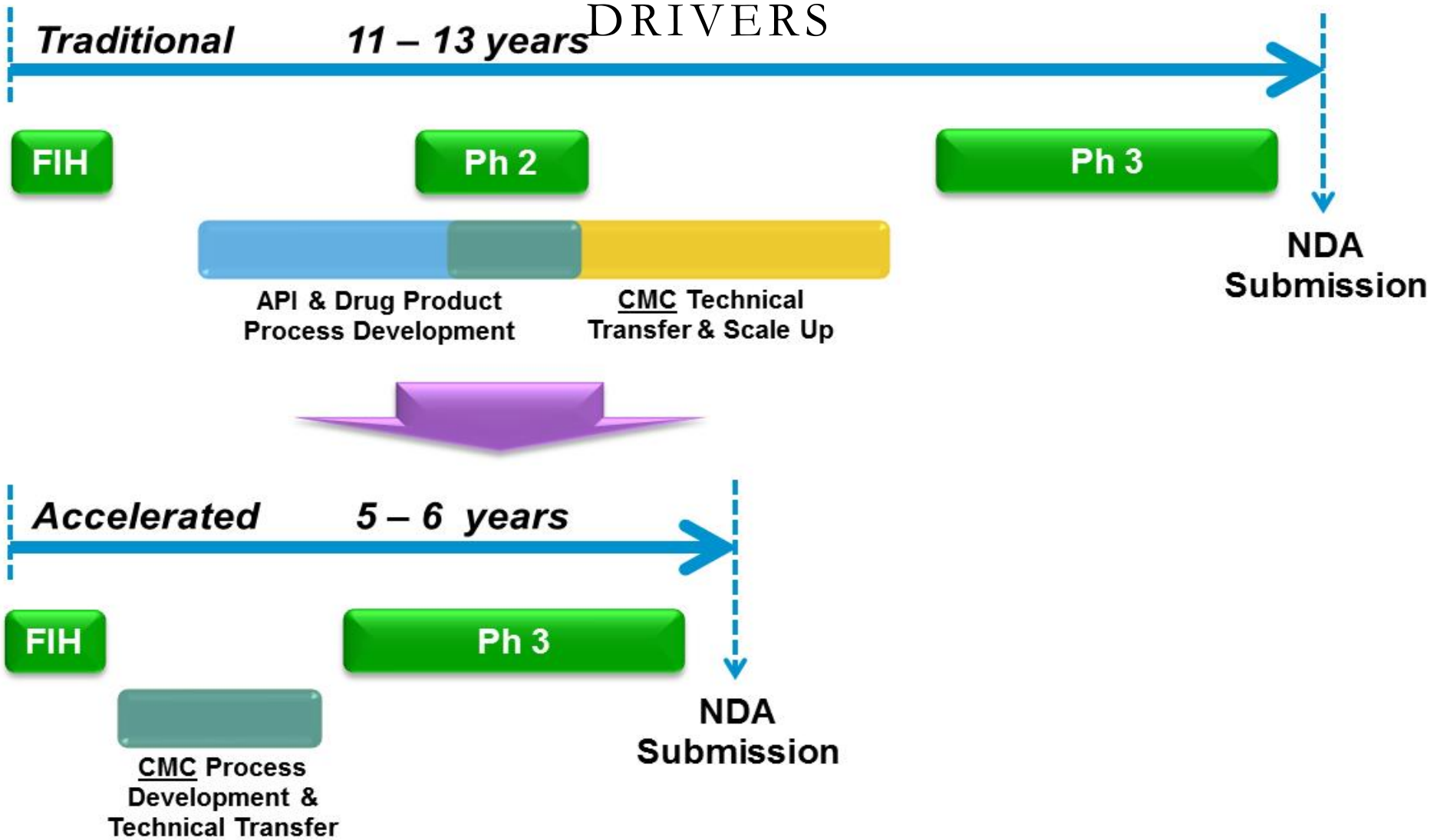


OVERALL AGENDA

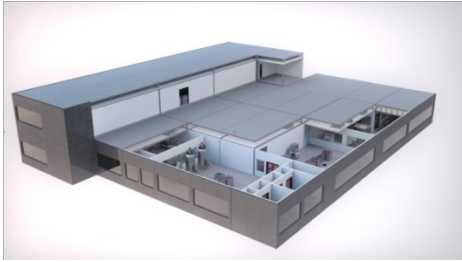
1. The Drivers & “Germ” of a concept – Jeff / Valentin
2. Project Execution Approach & Team Structure – Fred
3. PCMM OSD: “Factory in a POD” – Valentin
4. Impact Integrated Approach – Jeff
5. Conclusion – Fred

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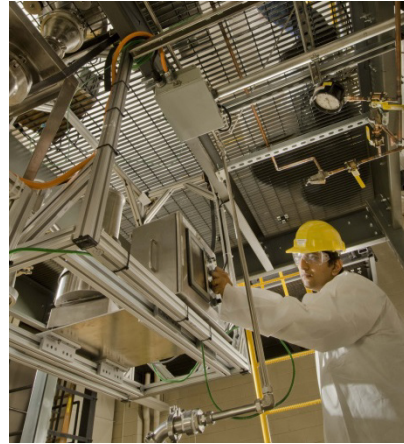
ADVANCED DEVELOPMENT AND MANUFACTURING PLATFORMS: THE DRIVERS



Examples of Industry Approaches



GE Healthcare KUBIO



Rutgers C-SOPS



Novartis/MIT



Vertex
ISPE®



Pfizer – GEA – GCON
(PCMM)

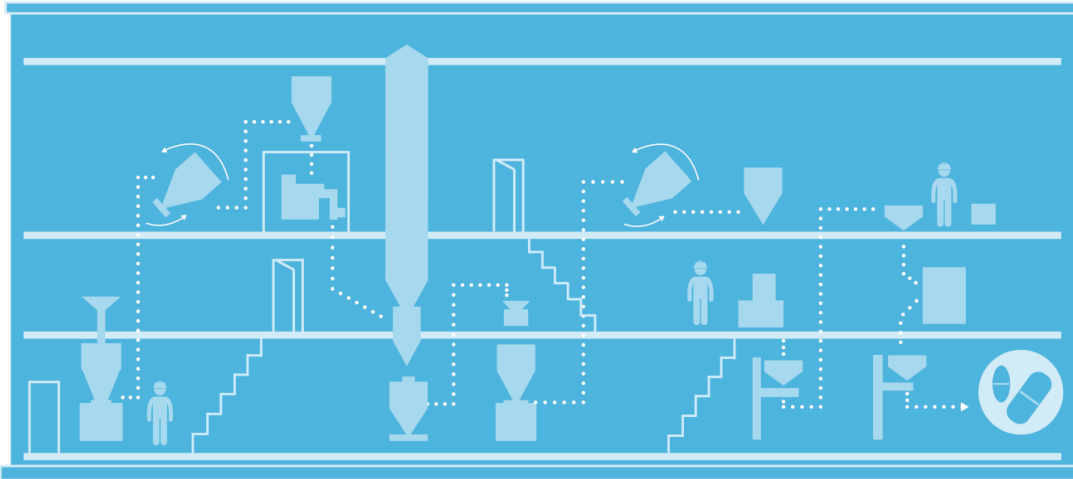


The Move to Portable, Continuous, Miniature and Modular Manufacturing

HISTORICALLY

Batch operations make drugs from powder to tablet in weeks or months

Complex process with large, dedicated manufacturing facility



Traditional Granulation Process

CURRENT STATE BATCH PROCESSES -

TRANSFER OF TECHNOLOGY

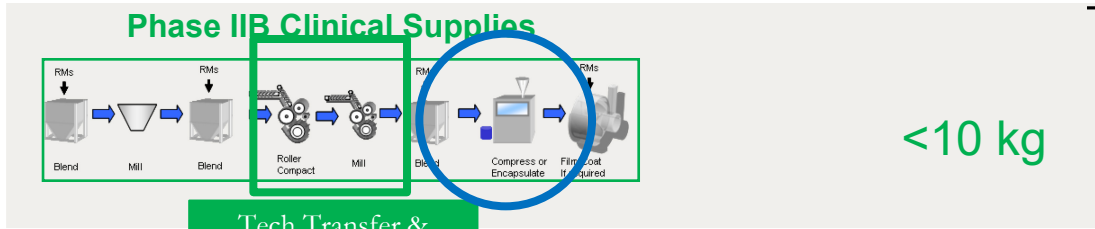
Current State

(dry granulation / roller compaction)

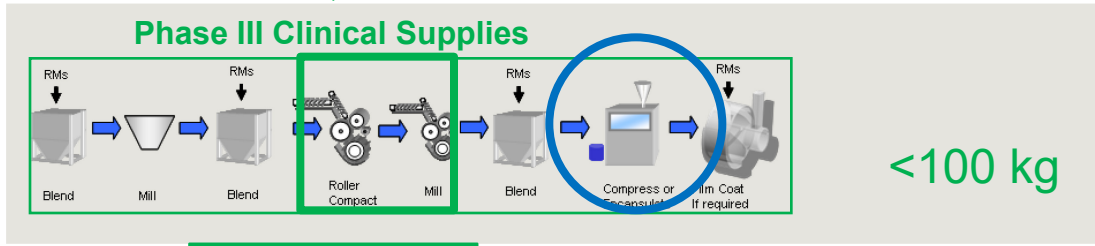
Drug Product

Quantities

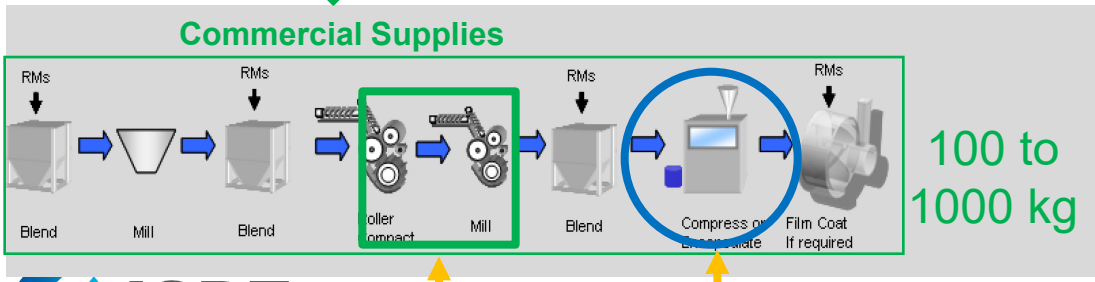
Transfer of Technology



Tech Transfer & Process Scale Up



Tech Transfer & Process Scale Up



Experiments

Engineering Models

Process Analytical Technology

Advanced Process Control

Time, \$, Resource Impact

Diluted Efforts



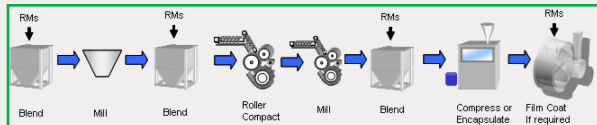
FUTURE STATE PCM&M PLATFORM TECHNOLOGY

Current State
(dry granulation / roller compaction)

**Drug Product
Quantities**

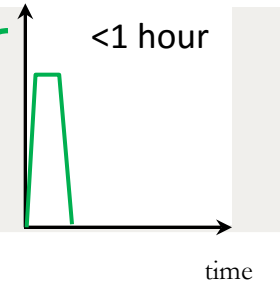
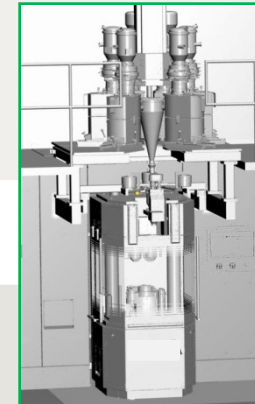
Future State
(dry blend / direct compaction)

Phase IIB Clinical Supplies

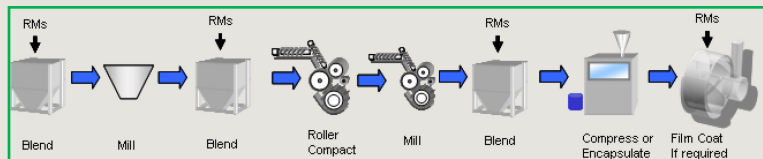


Tech Transfer &
Process Scale Up

<10 kg

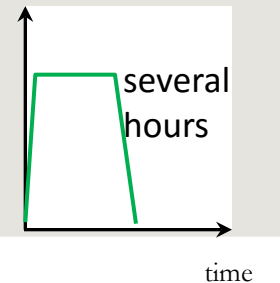
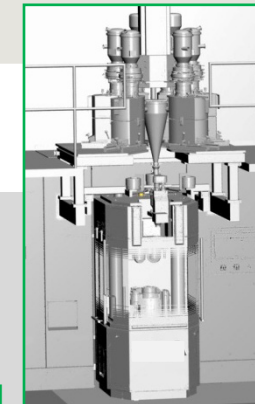


Phase III Clinical Supplies

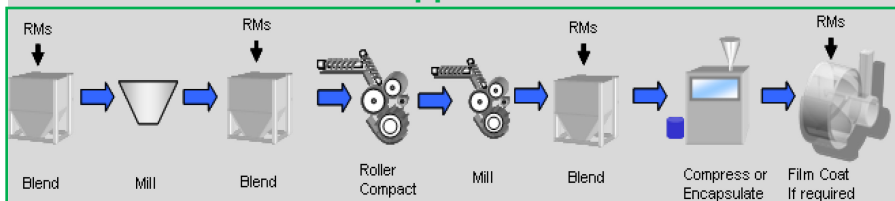


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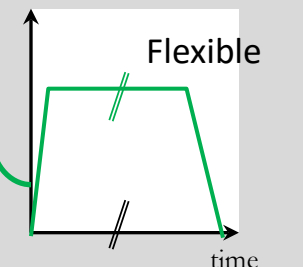
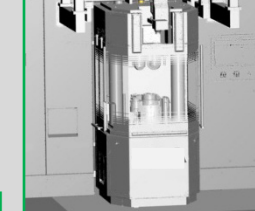
<100 kg



Commercial Supplies



100 to
1000 kg



FUTURE STATE PCM&M

PLATFORM TECHNOLOGY

Platform Technology

Experiments
 Engineering Models
 Process Analytical Technology
 Advanced Process Control

Concentrated Efforts

Reduced Time, \$, Resources

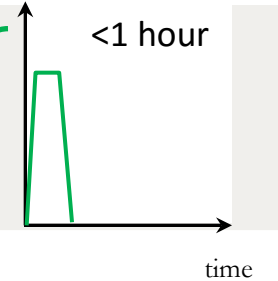
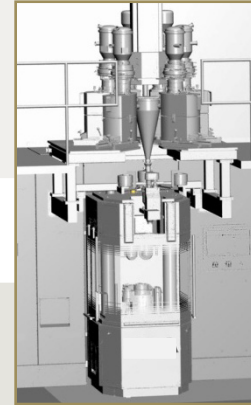


Drug Product Quantities

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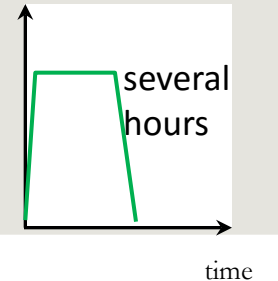
Phase IIB Clinical Supplies

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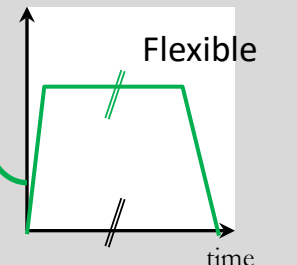
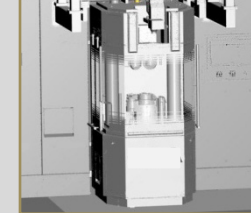
Phase III Clinical Supplies

<100 kg



Commercial Supplies

100 to 1000 kg

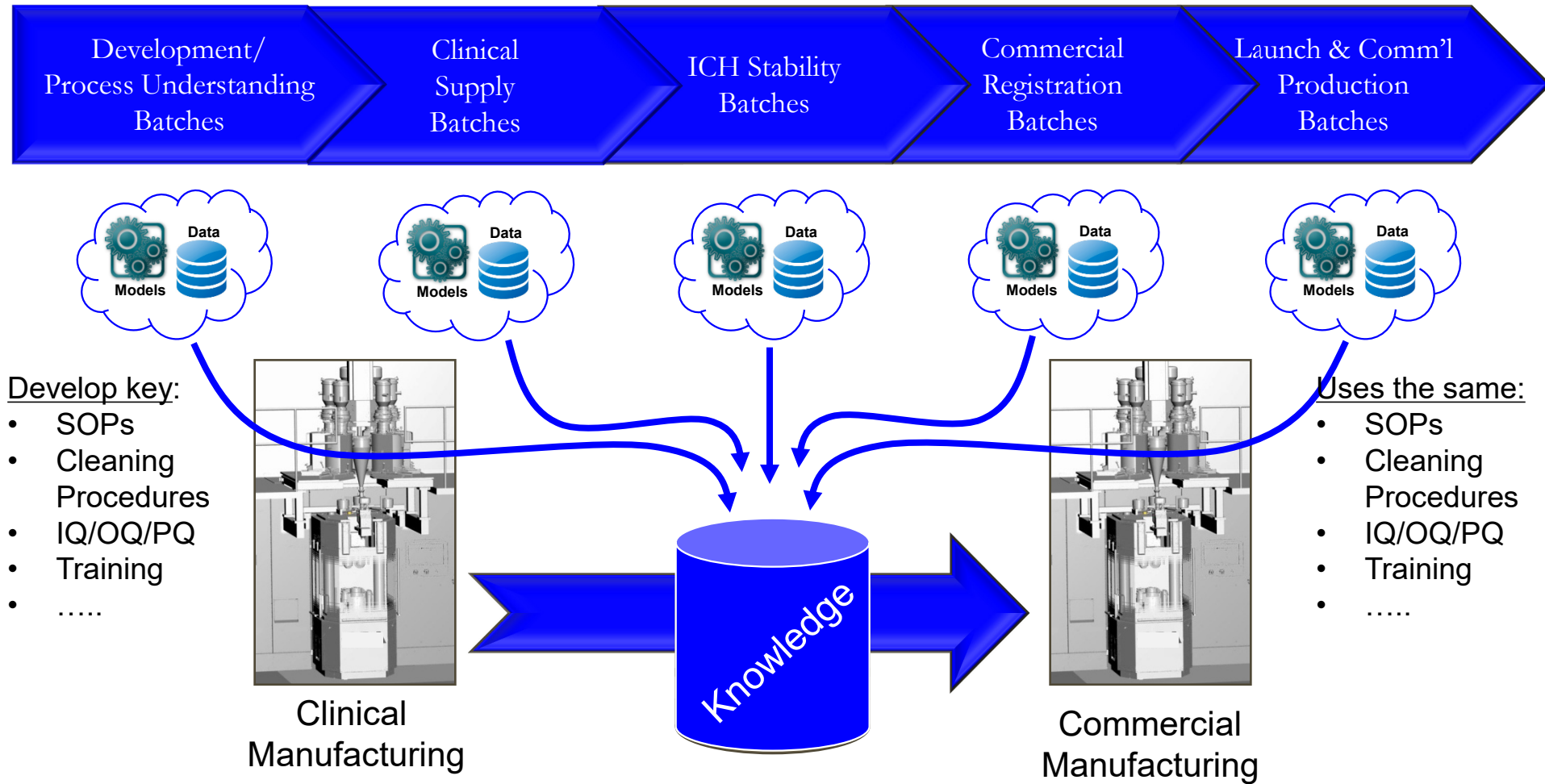




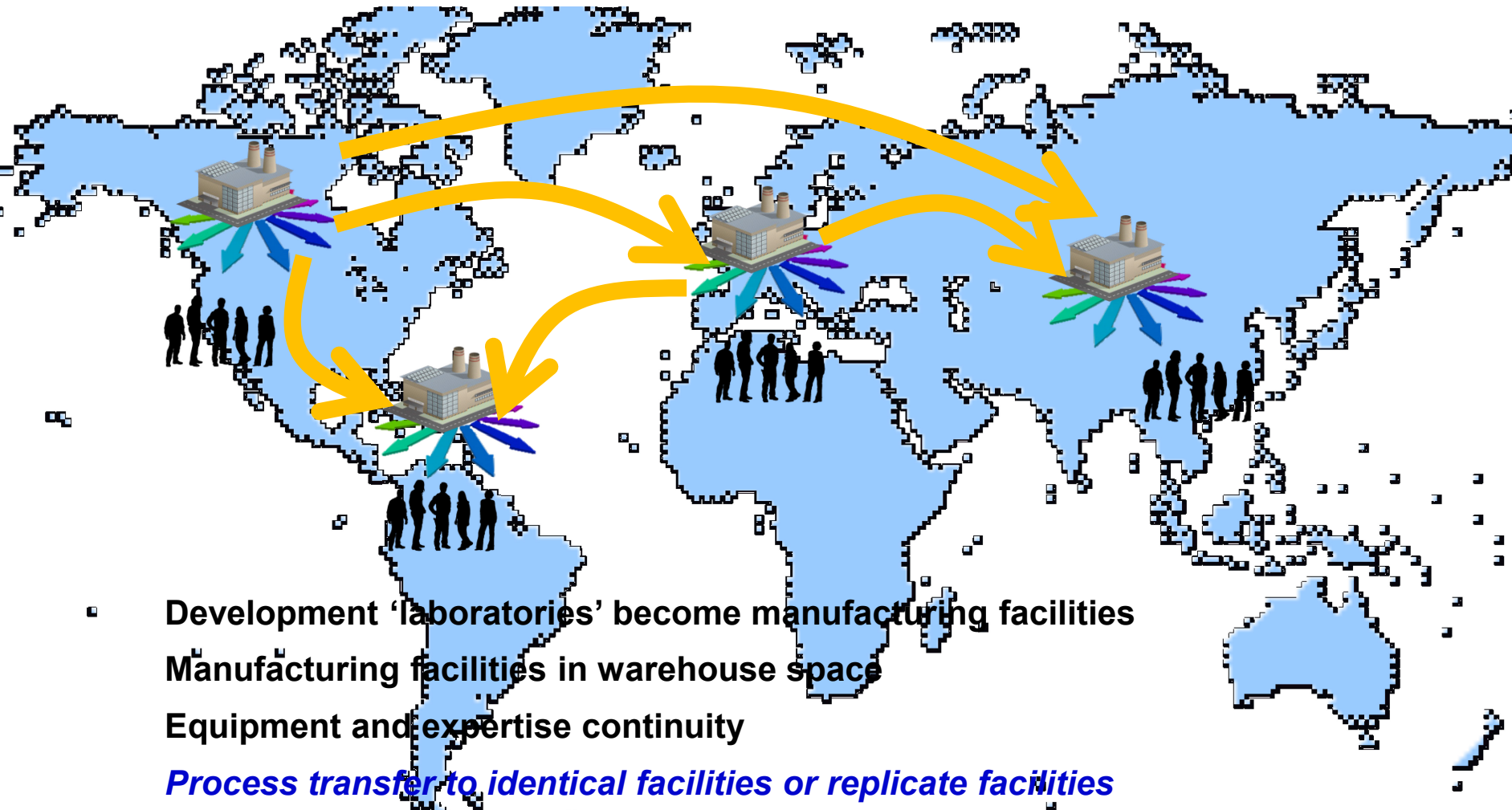
What if....

WHAT IF....

... THE SAME PLATFORM TECHNOLOGY WAS USED TO
MAKE KEY...

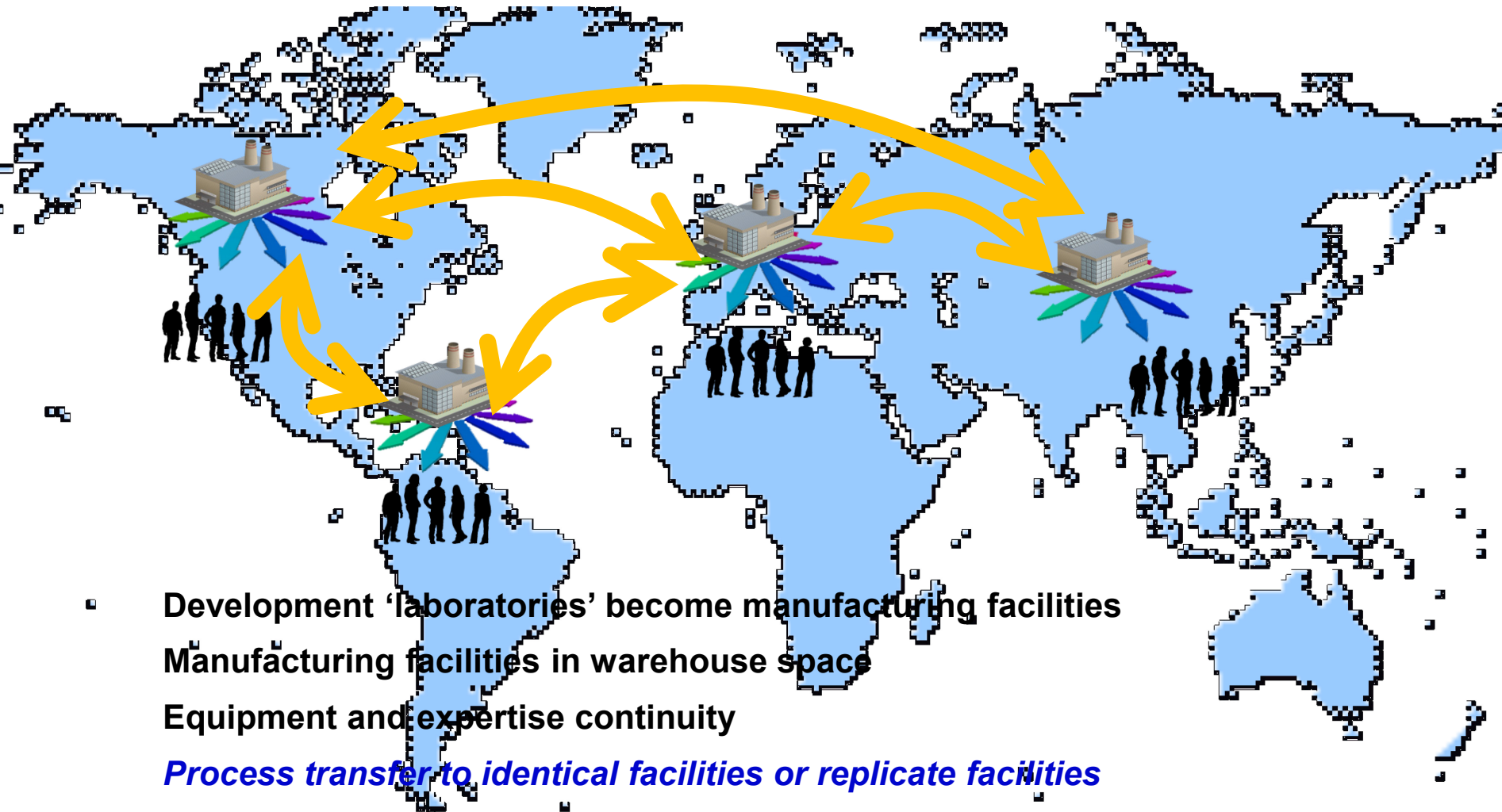


Evolving towards a Central Hub Plus Regional **Development, Manufacturing & Distribution Model (1)**



- Development ‘laboratories’ become manufacturing facilities
- Manufacturing facilities in warehouse space
- Equipment and expertise continuity
- *Process transfer to identical facilities or replicate facilities*
- *Product distributed from point of manufacture*

Evolving towards a Central Hub Plus Regional **Development, Manufacturing & Distribution Model (2)**



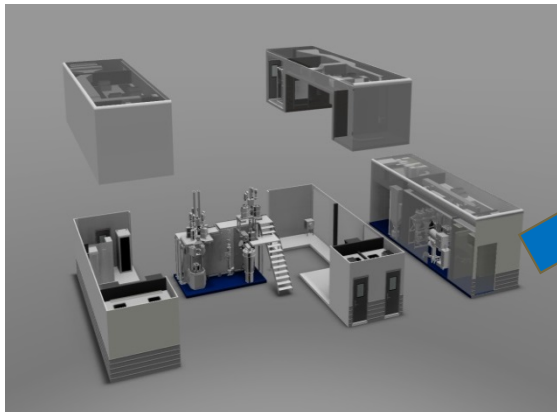
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PCMM OSD: *A Factory in a POD Through a Unique Collaboration*

Drug Product Continuous Processing Platform Skids



Integrated into a
'transportable' POD



... re-assembled into a grey space warehouse in
Groton, CT



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Project Execution Approach and Team Structure



*Compromise to Quality, Compliance or Safety
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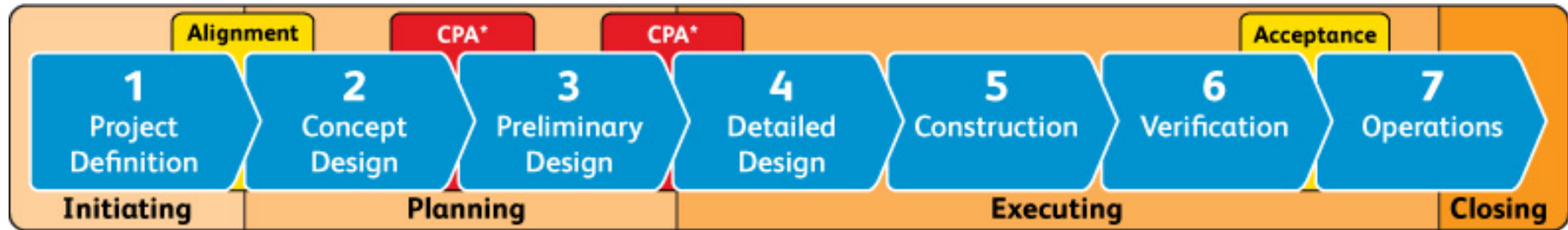
Project Management Approach

A very unique project to manage but the same fundamentals:

- Scope
- Schedule
- Budget

Project Management Triangle





Progressive Phases

- Create appropriate discipline through specific reviews/approvals required to advance a project
- Process and content are important
- Deliverables are integral to project success

- **Process Equipment**
 - Two continuous processing trains (0-25 kg/hour capacity)
 - Wet Granulation and Direct Compression processes
 - Unit operations: dispensing to compression
 - OEB 4 containment levels
- **Process Automation**
 - PLC based process control
 - Process Analytical Technologies (PAT)
 - Advanced Process Control (APC)
- **“POD” Facility**
 - Portability
 - Footprint of ~2,000 SF
 - Grade D Design (not classified)
 - Utilities single points of connection
- **Receiving Site Enabling**
 - “Grey Space” conditions
 - Site Utilities (Chilled Water, Potable Water, Compressed Air, Electric)

Project Schedule Overview

Key Milestones

Milestone Activity	Date
Landscaping to Identify Partners	2Q-4Q / 2012
Concept Design Effort	1Q-2Q / 2013
Project Full Funding	3Q2013
Major Equipment Orders	4Q2013
Detailed Design and Groton Enabling	1Q-3Q2014
POD & Equipment Delivery	1Q2015
Mechanical Completion	2Q2015
SAT and Qualification Activities	3Q2015
Begin Demonstration Lots (with API)	4Q2015
Manufacturing of 1 st Clinical Lots for NCE	2Q2016

- **Funding Approach**

- Research: ~30 %
- Manufacturing: ~70 %

- **Actual Cost (% TIC)**

- Equipment: 60 %
- POD Facility: 20 %
- Automation: 8 %
- Groton Enabling: 9 %
- Indirects: 3 %

- **Key Elements of Integrated Project Delivery (IPD)**
 - Partnership (consortium) with Key Suppliers
 - Leverage Expertise of Partners
 - Common Vision of Success
 - Shared Risks (“skin in the game”)
 - Non-standard Pfizer Contractual Approach
 - 3 Party Engineering Services Agreement
 - Negotiated Limits of Liability / Indemnification Language for Partnership

Collaborative Partnership

	Expertise Brought to Consortium	Business Interest
GEA	Industry leading expertise in continuous processing technology , including the best in class “Consigma” solids processing system.	Opportunity to market transformational solids processing technology to the pharmaceutical industry.
G-Con	Industry leading expertise in portable GMP facility “pods” focused on the biologics industry.	Opportunity to develop an offering in small molecule pharmaceuticals, thereby increasing market share.
Pfizer	Leading expertise in materials science, computational modeling, PAT technology, Advanced Process Control (APC) . Considerable experience in continuous solids processing technologies, along with specific intellectual property related to internally designed Continuous Mixing Technology (CMT) .	Access to transformational solids processing technology. Consortium offers the opportunity to share portable equipment development costs with consortium partners and future consortium members.

Windows of Wisdom Exercise

Alignment on a Common Vision

Flexible, modular unit operations enable **easy reconfiguration**, ability to integrate emerging process technologies for other dosage forms and very **rapid changeover**

Context:		Constraints:		
G-CON	<ul style="list-style-type: none"> •New Product, Small Company •Open Architecture for " Smart Environment" •New Field of Expertise •Large Pharma Interaction •Leader in Process Eng 		<ul style="list-style-type: none"> •CAN DO 	<ul style="list-style-type: none"> •CAN NOT DO:
GEA	<ul style="list-style-type: none"> •Our Future •No 1 	G-CON	<ul style="list-style-type: none"> •Leverage experience with partners •Work Rapidly without Corp overhead •Prototype Quickly 	<ul style="list-style-type: none"> •Small Company/Big Ideas •Working Capital •Make Large Investments
PFIZER	<ul style="list-style-type: none"> •Quality high, Reliability supply vs. Batch •Reduce cost to develop products •Reduced capital cost / facilitates/ sites •Reduced carrying costs of inventory •Local Mfg capabilities / access to markets •Speed to market •Increased flexibilities •Lower tech transfer risk •Opportunity for Intelligence based Mfg 	GEA	<ul style="list-style-type: none"> •Plug and Play •Rapid Change Over 	<ul style="list-style-type: none"> •1 Process fits all
		PFIZER	<ul style="list-style-type: none"> •Look for support of key vendors •Other sources of funding •Leverage prior experience •Practice humility: Pfizer does not know everything 	<ul style="list-style-type: none"> •Focus on Bios, API, packaging, •Other DP forms •Capital is needs to be < \$10 MM
Success:		Politics:		
G-CON	<ul style="list-style-type: none"> •Mega Pod Functional/Delivered •Real Data Generated •Presented to Pharma Community •Multiple Installations 		<ul style="list-style-type: none"> •HELP 	<ul style="list-style-type: none"> •HINDER
GEA	<ul style="list-style-type: none"> •Increase Continuous Mfg business •Win-Win-Win 	G-CON	<ul style="list-style-type: none"> •Partnerships with top tier groups and collaborative partners/technologies 	<ul style="list-style-type: none"> •Slow project development not resulting in sales/product •Acceptance of new paradigm in Portable/Flexible
PFIZER	<ul style="list-style-type: none"> •This is the way it is done by 2016 for NCEs at Pfizer and others •The technology platform of choice at Pfizer used to make SOD 	GEA	<ul style="list-style-type: none"> •Senior Management commitment from Pfizer •Regulatory cooperation support from Pfizer •LESS = MORE 	<ul style="list-style-type: none"> •Changes midway in project •Phase gate delays •Complexity-Follow KISS principle
		PFIZER	<ul style="list-style-type: none"> •Loss of product volume •Regulators •Densification of Mfg •Go to external supplier 	<ul style="list-style-type: none"> •Loss of product volume •Regulators •Sites that could close •Flexibility vs. Complexity "meets no ones needs" •Internal complexity in Pfizer



Partner Costs & Contributions

Engineering & Development Consortium

Company/Division	Fees to be Received for Services	“Skin in the Game”
GEA	Process equipment and startup costs	<ul style="list-style-type: none"> • CMT Development and licensing contribution • Margin reduction
G-Con	POD facility and install costs	<ul style="list-style-type: none"> • No profit, mark ups, etc.
WRD	Payer	<ul style="list-style-type: none"> • 30 % capital project costs • Pre-engineering costs • SMEs assigned to support project
PGS	Payer	<ul style="list-style-type: none"> • 70 % capital project costs • Pre-engineering costs • SMEs assigned to support project

- **Joint Steering Committee**
 - Pfizer/GEA/GCON Senior Leadership
 - Quarterly Face to Face Meetings
- **Pfizer Internal Steering Committee**
 - Pfizer Manufacturing/Research Sponsors
 - Monthly Review Meetings
- **Project Technical Sub-Teams**
 - Pfizer/GEA/GCON SMEs
 - Weekly Progress Review Meetings
 - Workstreams:
 - Process Equipment/POD Facility/Automation/Operational Readiness

Purpose/Mission

- Provide leadership and governance for the business, engineering and scientific components of the PCMM OSD collaboration to ensure all obligations under the Statement of Work (SOW) are fulfilled
- Ensure the necessary alignment, integration, and communication exists across the participating companies to deliver the PCMM OSD prototype unit
- Develop and manage the external communication strategy
- Pursue extension of the collaboration beyond the prototype unit
- Consider opportunities for expansion of the collaboration beyond the prototype unit

Scope

In Scope:

- The primary focus (80% of JSC effort) is successful delivery of the prototype unit per the SOW. A secondary focus is pursuing PCMM OSD-related opportunities beyond the prototype unit.

Out of Scope:

- Advanced Process Control (APC) and Process Analytical Technologies (PAT) beyond ensuring the ability to seamlessly integrate Pfizer's APC and PAT technologies onto the prototype unit
- Amendments or modification of any terms of the Engineering Services Agreement or Purchase Orders or to waive any Party's rights or obligations under the Engineering Services Agreement

Team Membership

Pfizer: Mike O'Brien (co-chair), Phil Nixon, Holly Bonsignore, Matt Roberge, Cindy Oksanen, Mike Flakus

GEA: Jan Vugts (co-chair), Steve Lancos, McCoy Knight, Richard Steiner

G-CON: Maik Jornitz, Barry Holtz, Sid Backstrom

Responsibilities

- Monitor progress against major project plan milestones and budget, including risk analysis
- Approve 1) material changes to the project plan, scope and/or budget and 2) amendments to the SOW
- Resolve issues/problems arising with respect to the performance of the SOW that cannot be addressed by the technical team and alliance managers
- Encourage and facilitate ongoing cooperation and information exchange between companies
- Prepare and approve overview/promotional materials to facilitate discussions with other parties interested in the PCMM OSD collaboration
- Approve PCMM OSD presentations, publications, promotional materials, etc. for public disclosure

Key Principles

- Decisions by consensus
- Open, honest, transparent discussions
- Consistently demonstrate a collaborative relationship that drives outcomes bringing value to all companies

JSC Logistics & Communication

- Face-to-face meetings once per quarter, coordinated with other business as possible to manage cost and time
- Ad hoc participation by pertinent technical team members at the invitation of a JSC member
- Hosting party is responsible for issuing formal minutes
- Ad hoc telecons/meetings as needed
- E-mail for quick turnaround of items not requiring oral discussion (eg, public disclosure approvals)

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**Pfizer Project Sponsors/
Pfizer Internal Steering
Committee**

**Project Management
Function**
Project Lead (R&D)
Project Manager: (Mfg)

R&D Technical Lead

Mfg Technical Lead

**External-facing
First Points of Contact**

Automation/
APC Subteam

Process Equip.
Subteam

POD/Landing
Site Subteam

... evolves as
needed....

Connection to Long-term
Implementation Team

Verification
Subteam

Operations/GMP
Subteam

PAT
Subteam



Additional Pfizer Subject Matter Experts

- Regulatory & Compliance
- Development/ Technical Transfer
- Maintenance/Reliability
- Environmental Permitting
- Automation/APC
- Process Validation
- EHS
- Operations
- Verification
- Finance
- Materials & Logistics
- Technical Learning
- Business Technology
- PAT
- Quality
- Consigma Wet Granulation SME
- Tablet Press SME
- Other

**Internally-oriented
Technology and Facility/User
Work Groups**
(SME's interact directly with
partner companies as required)

- Maintaining Innovative Approach within a Fixed Budget
- “Must Haves”- Prototype versus Commercial Unit
- Trade offs- “Include Today” versus “Defer to Tomorrow”
- Freezing Final Design / Team Spirit of Continuous Improvement
- Defining PAT / APC Scope Requirements for Prototype
- Education and Acceptance by Local Building Department Officials
- Early Acceptance of Procurement Approach
 - Limited competitive bidding
 - Non-standard contracts
- Funding Mechanism- Managing 2 Pfizer Budgets
- Truly Virtual Team- Limited F2F Meetings

GEA	GCON	PFE- Manufacturing	PFE- Research
Wommelgem, BE	College Station, TX	Peapack, NJ	Groton, CT
		New York, NY	Sandwich, UK
		Collegeville, PA	Pearl River, NY
		Andover, MA	Peapack, NJ
		Pearl River, NY	
		Freiburg, Germany	

F2F Meetings

- Concept Study Review (Pfizer- Pearl River)- February 2013
- Project kickoff meeting (GEA- Belgium)- September 2013
- 60 % design review (Pfizer- NYO)- January 2014
- Interphex (Pfizer- NYO)- April 2014
- Install / startup planning session (Pfizer- Groton)- November 2014

- Identifying the correct collaboration partners
- Proper confidentiality and contractual agreements
- Full support from senior leadership
- Strong collaboration between manufacturing and research
- Small core team of “A Team” players from all organizations
- “Can do” approach / Dare to Try / OWNIT / Innovation
- Separate forums for commercial versus technical discussions
- Fully integrated project schedule- use of IAP sessions
- Verification (ASTM 2500) approach to qualification
- Early proactive engagement with FDA

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PCMM OSD: “Factory in a POD”



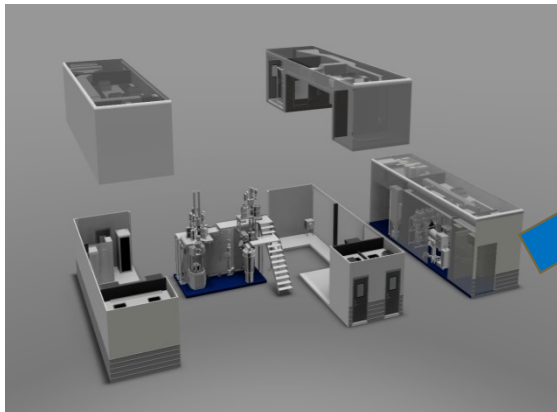
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PCMM OSD: *A Factory in a POD Through a Unique Collaboration*

Drug Product Continuous Processing Platform Skids



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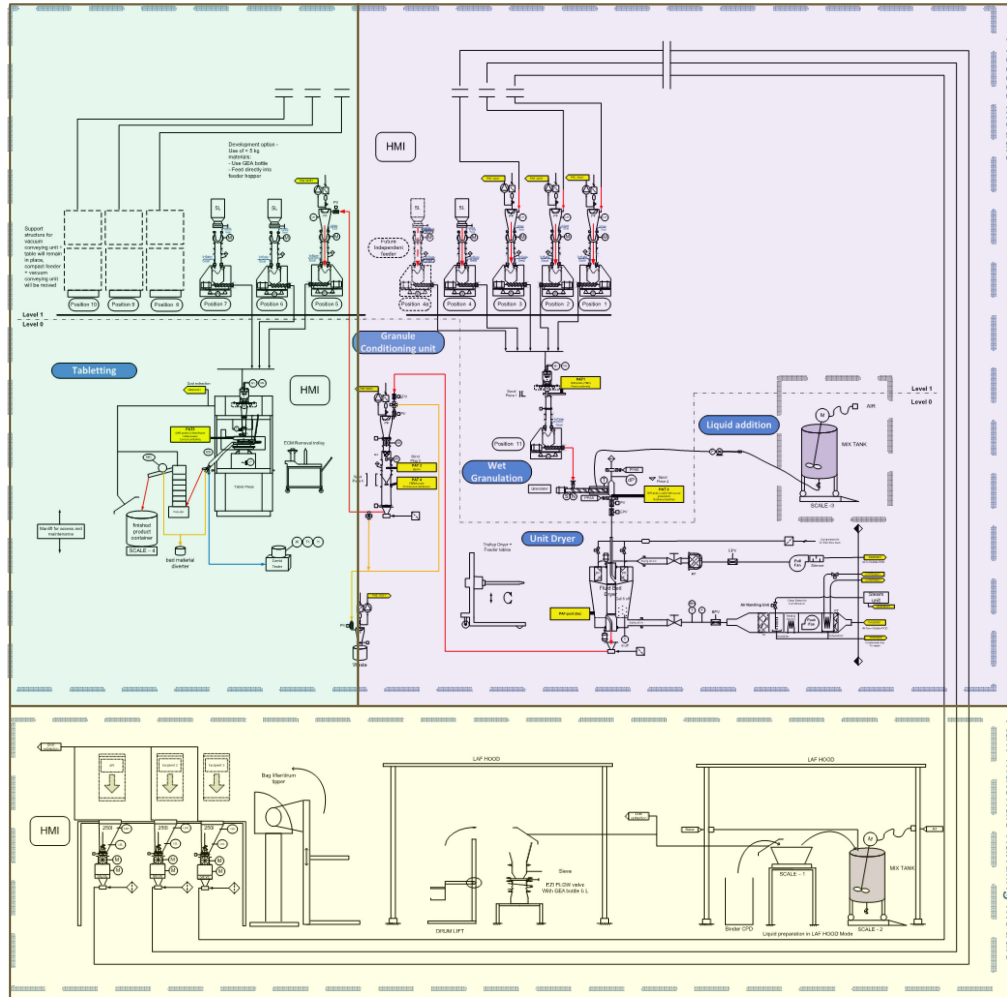


❖ Process:

- Flow diagram
- Material Handling-EHS and EZI DOCK
- GEA process equipment:
 - Compact Feeders
 - CMT
 - Tablet Press-WOL
 - Wet Granulation



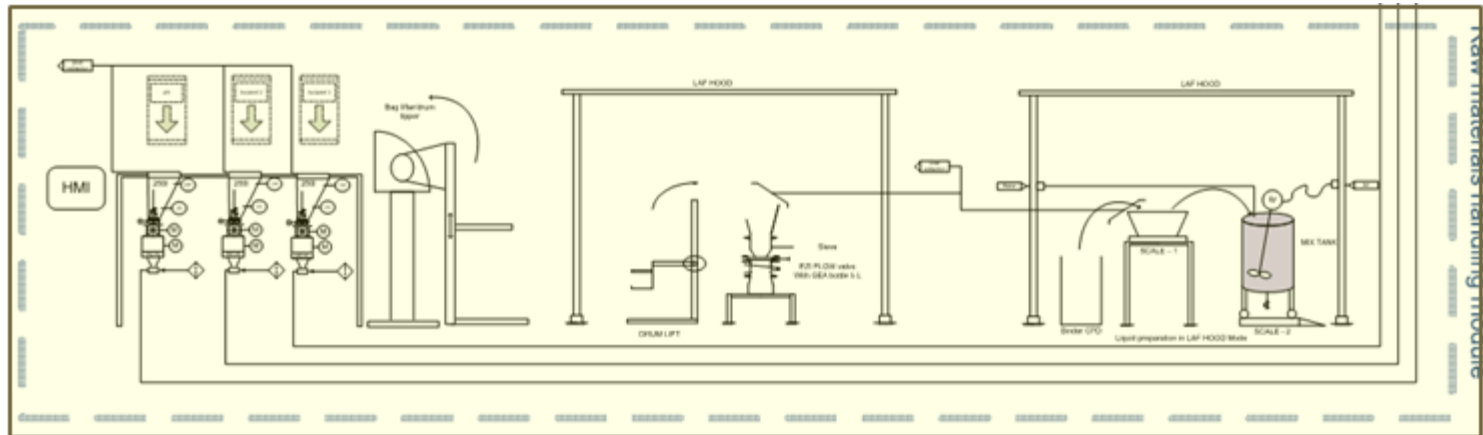
FLOW DIAGRAM



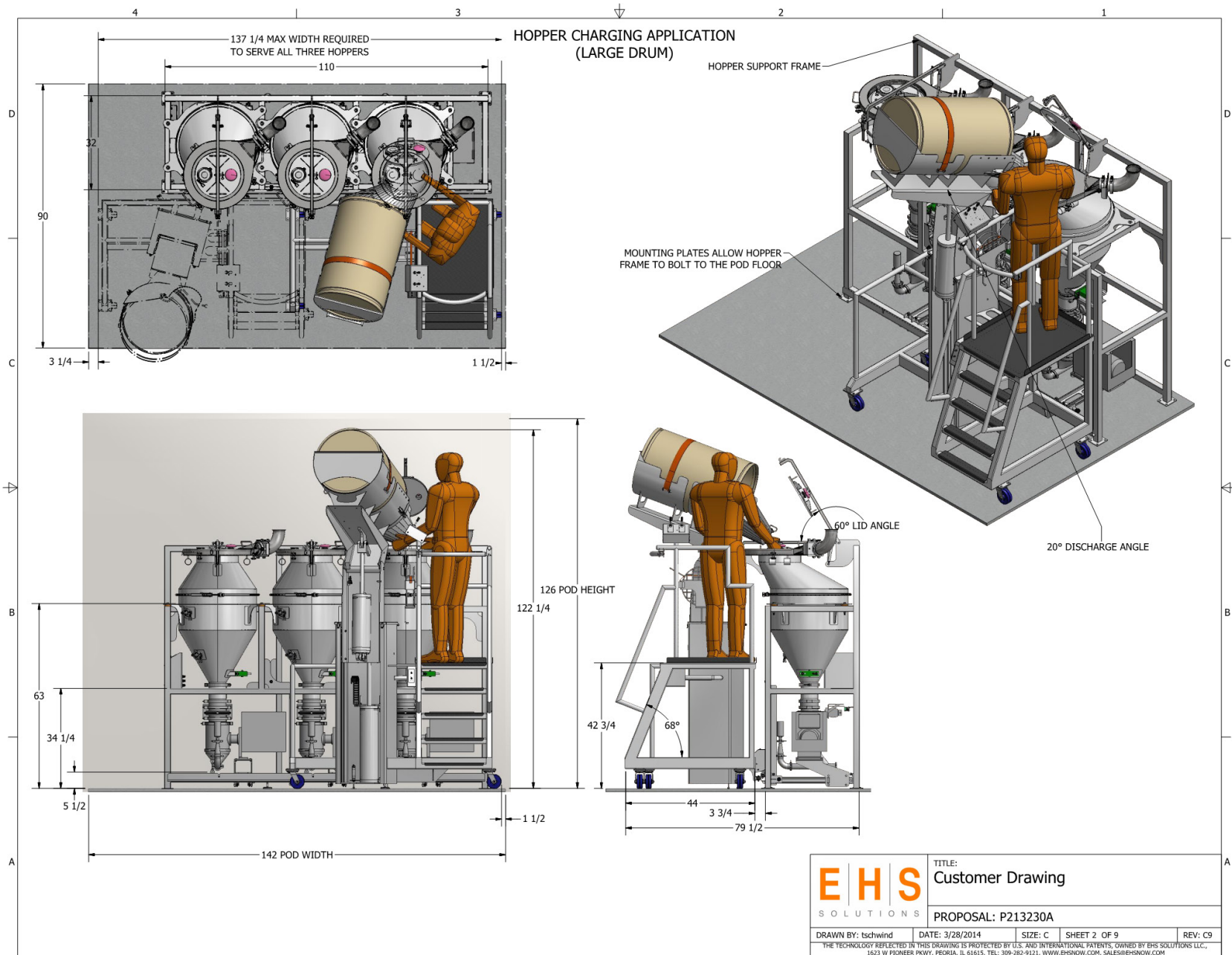
MATERIAL HANDLING CONCEPTS

❖ Operation:

- 3 hoppers w/ tipper and extraction hoods
- LAF hood w/ drum charging work station & ezi dock connection
- Disposable isolator & Ezidock connection

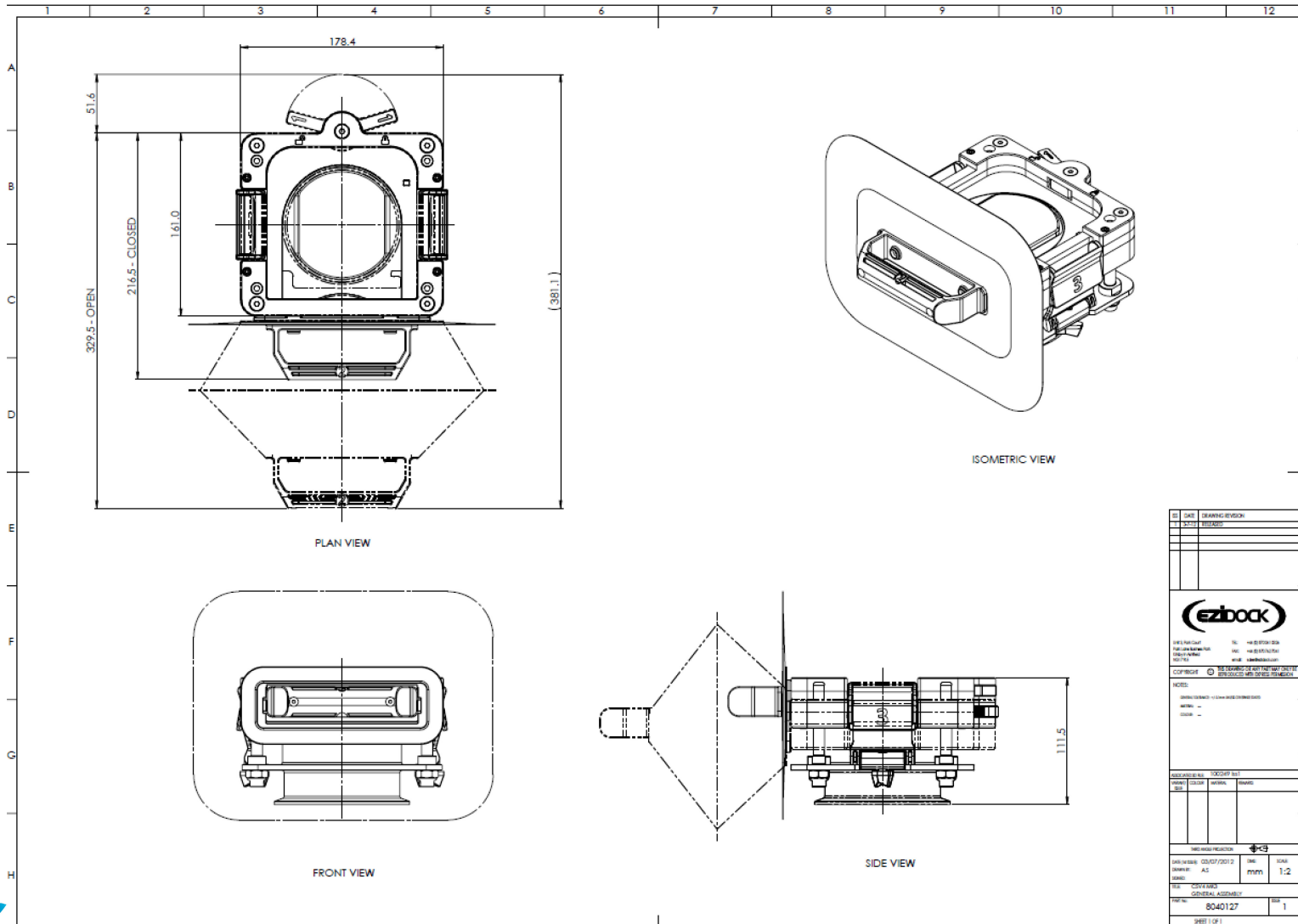


DRUM MATERIAL HANDLING APPROACH





SMALL SCALE: USE POLY BAGS/ BOTTLES W/ DISPOSABLE SB VALVES



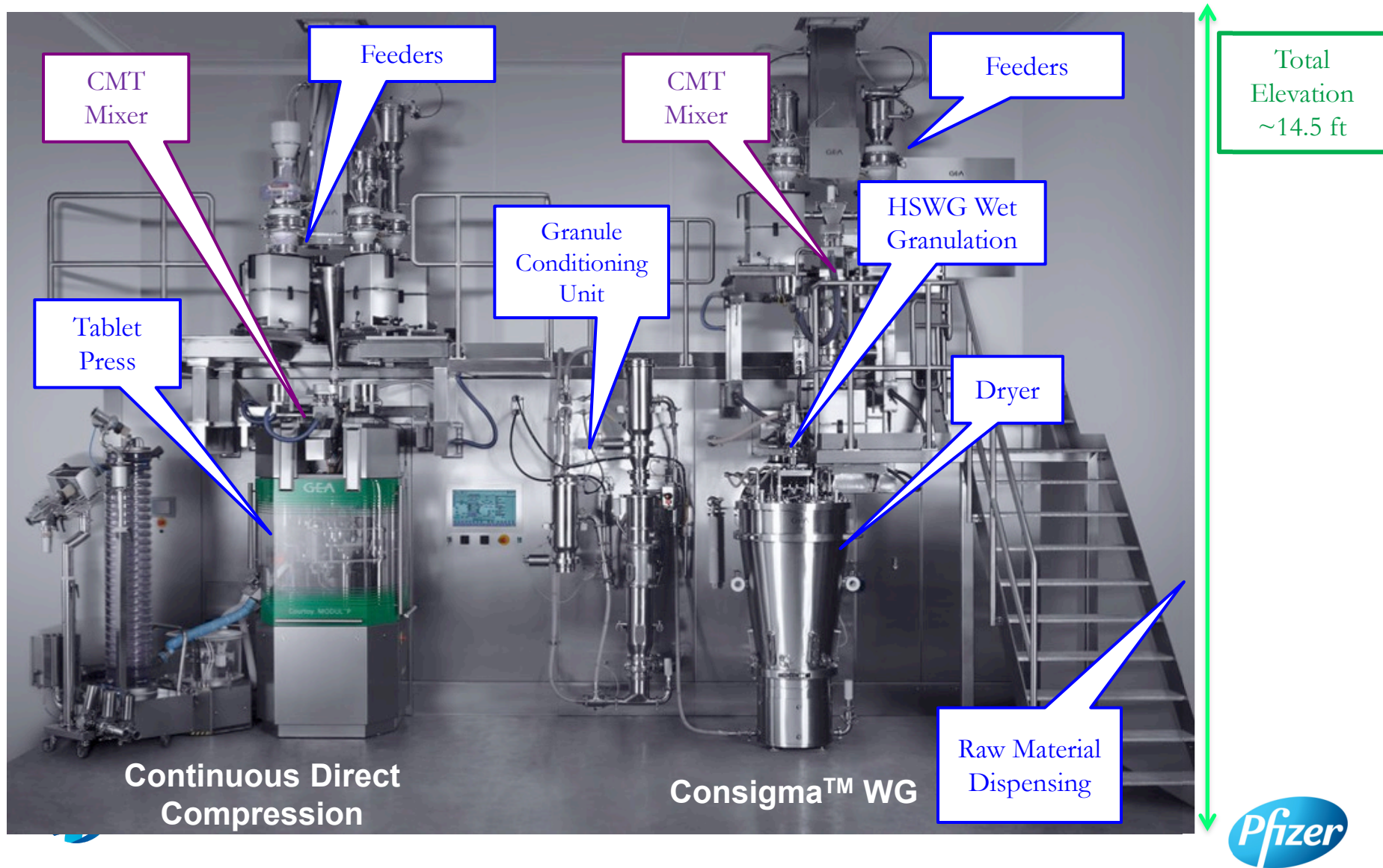
EZI DOCK :poly bags



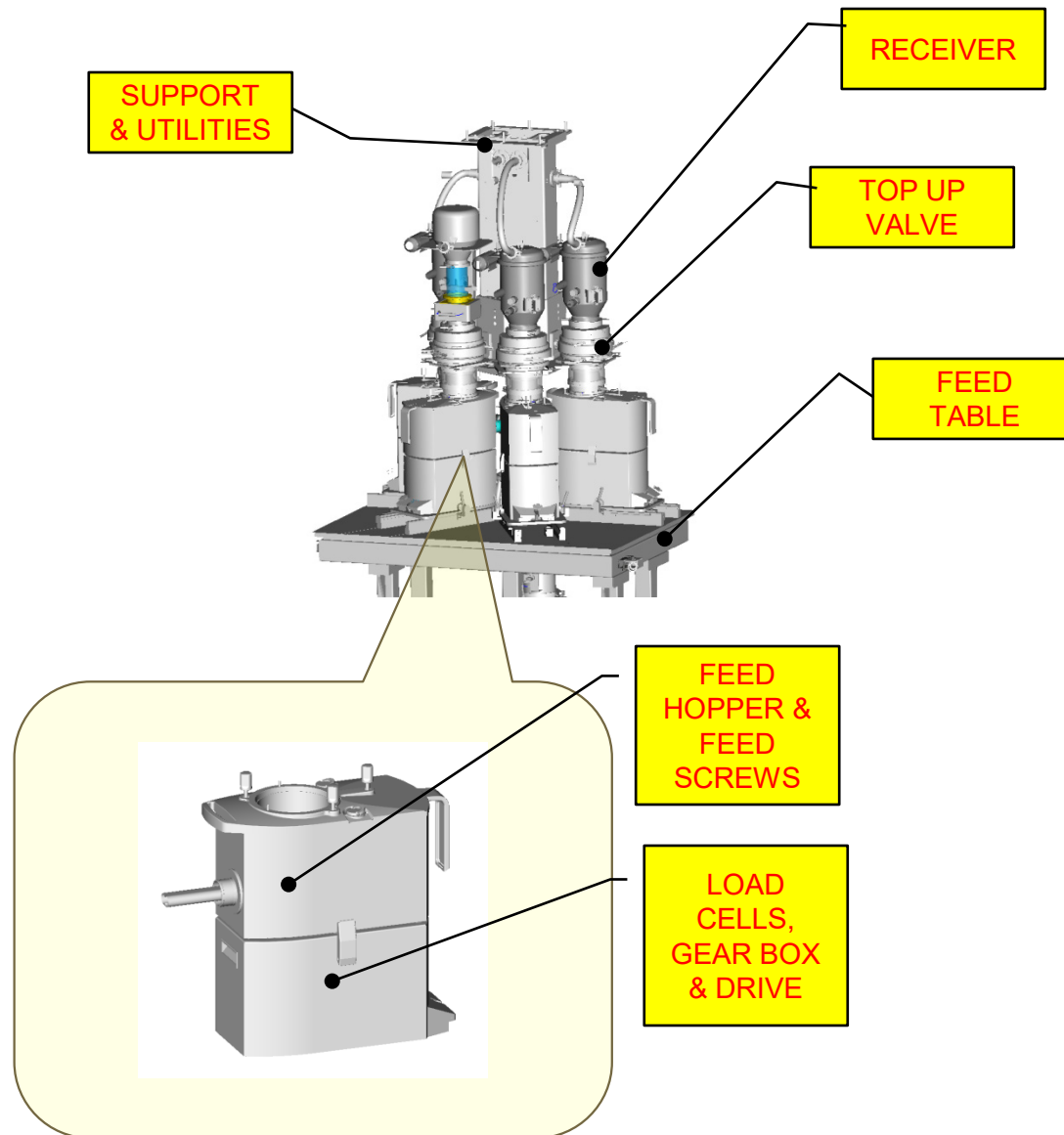
EZI DOCK :poly drums view is 15 l

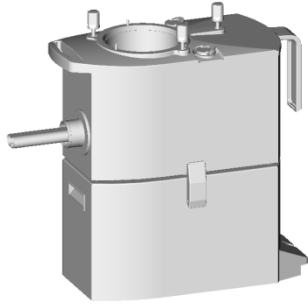
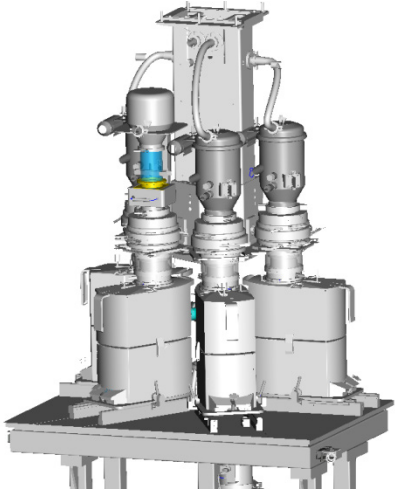


Continuous High Shear WG + Direct Compaction in a 'POD'

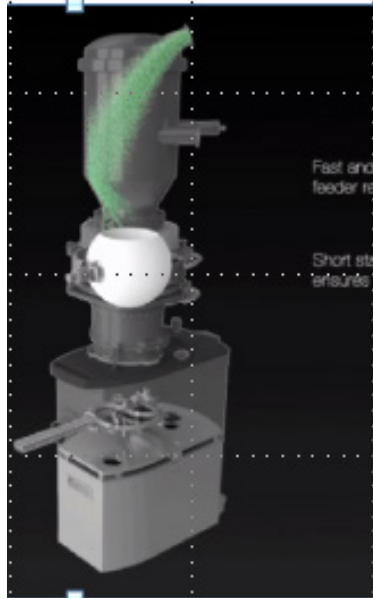


COMPACT FEEDER DESIGN

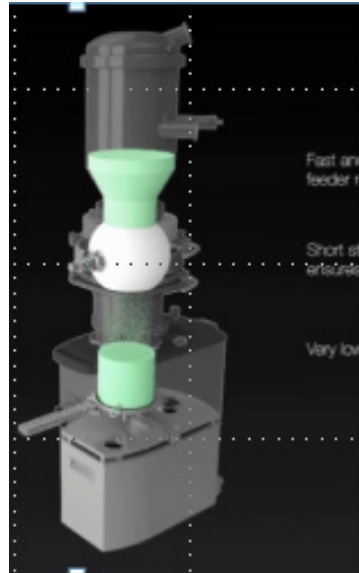




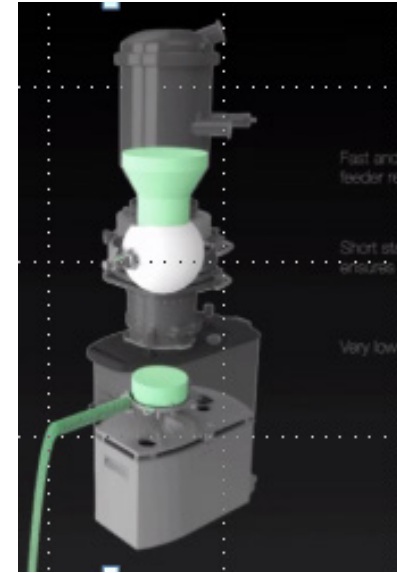
1) Load receiver



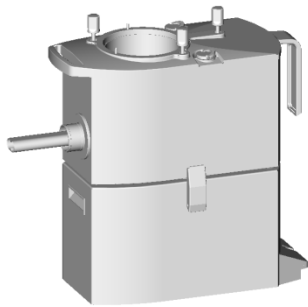
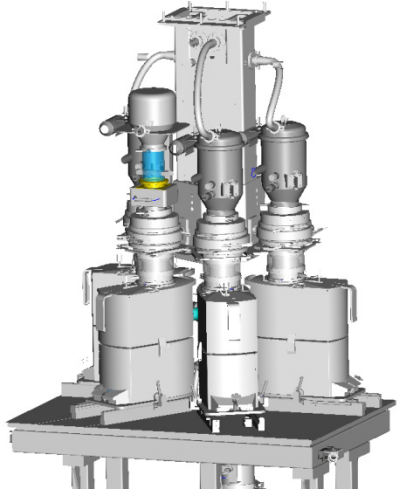
2) Top off valve



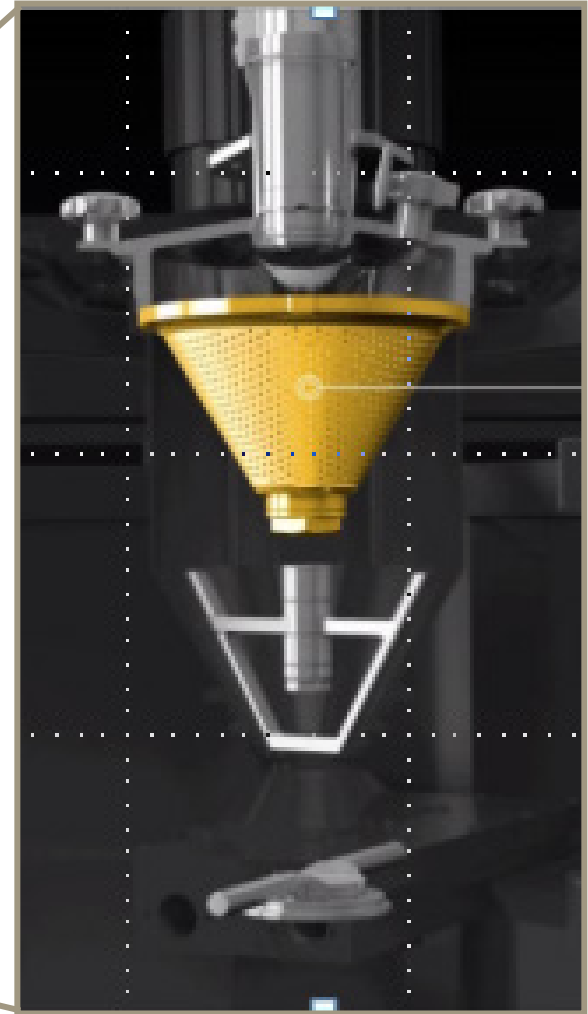
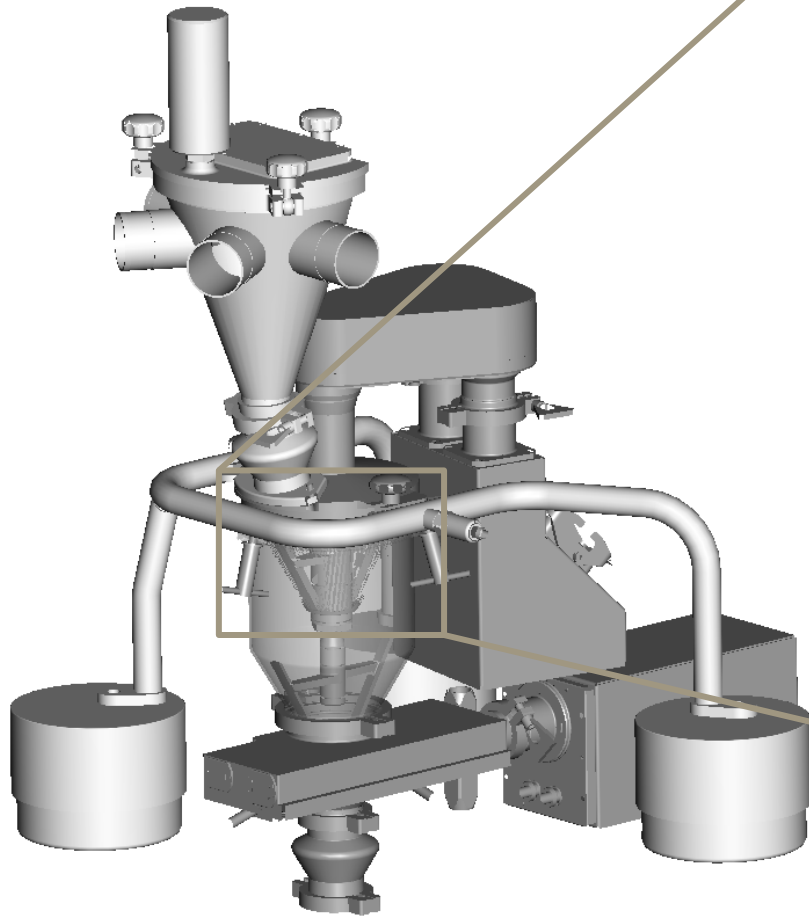
3) Discharge and refill



COMPACT FEEDERS

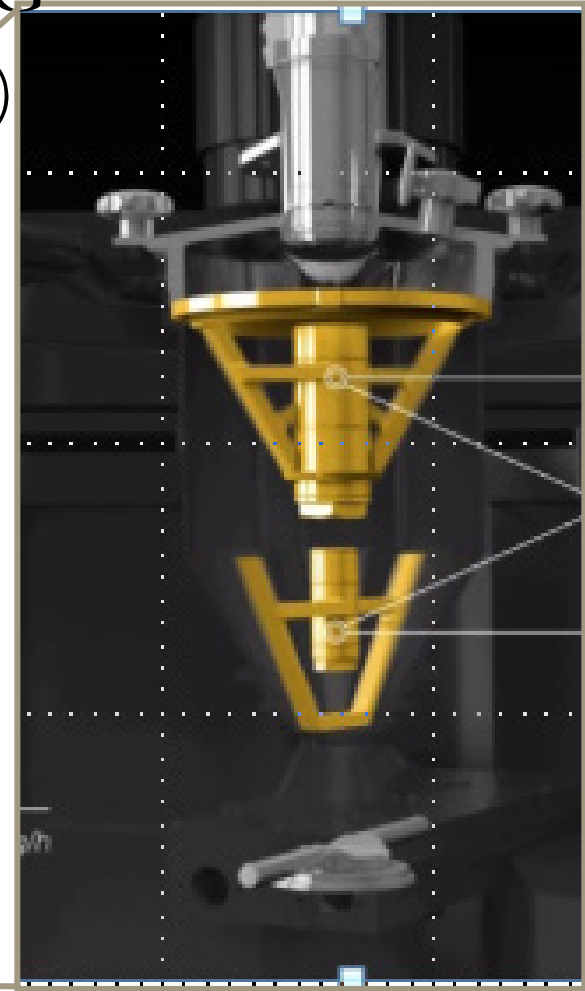
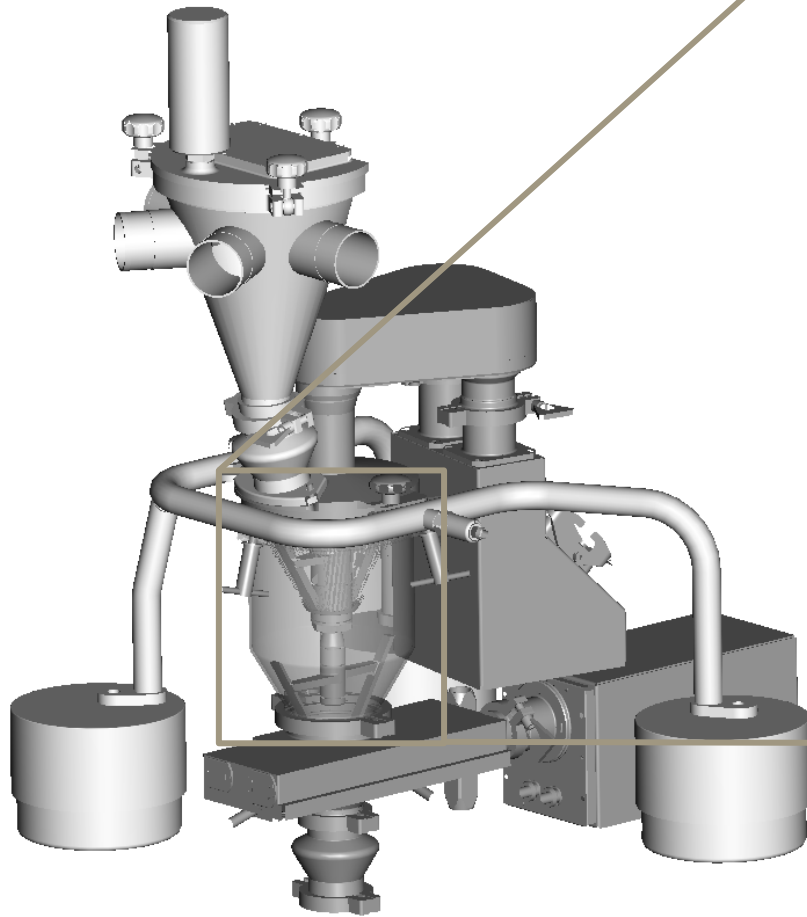


CMT MIXER



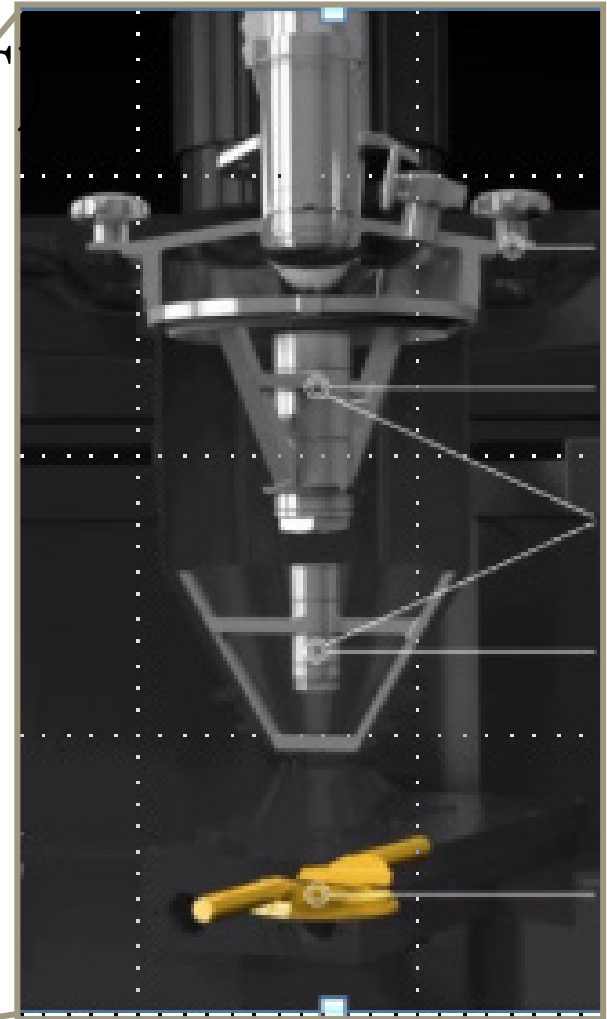
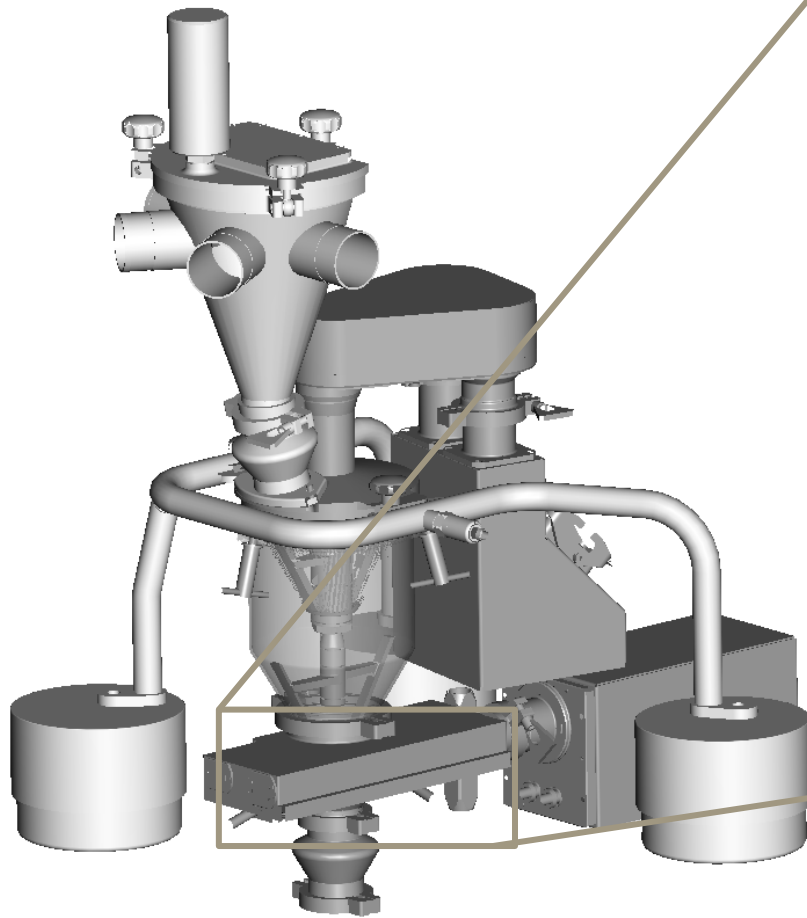
Upper Delumping Screen

CONTINUOUS MIXING TECHNOLOGY (CMT)



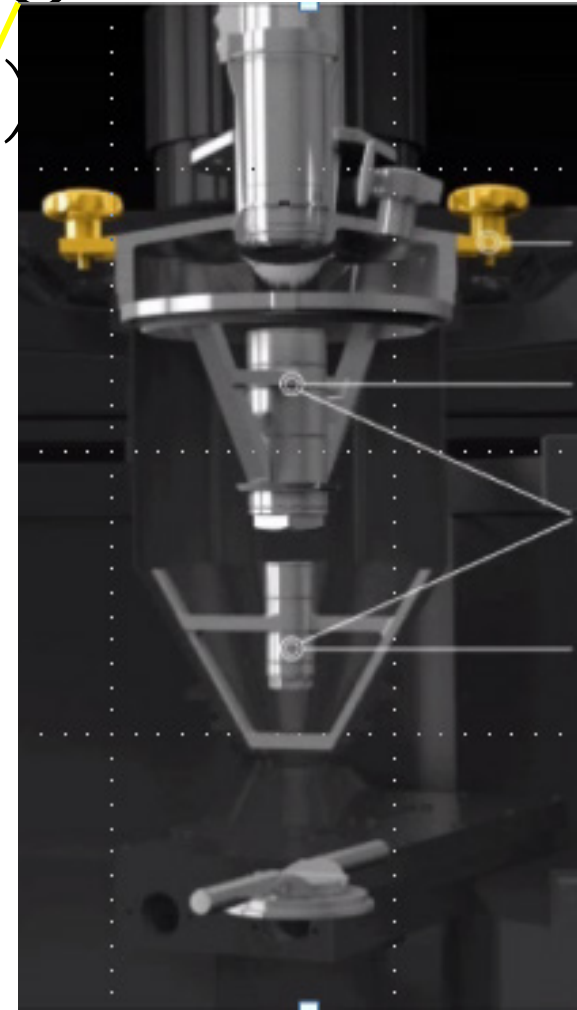
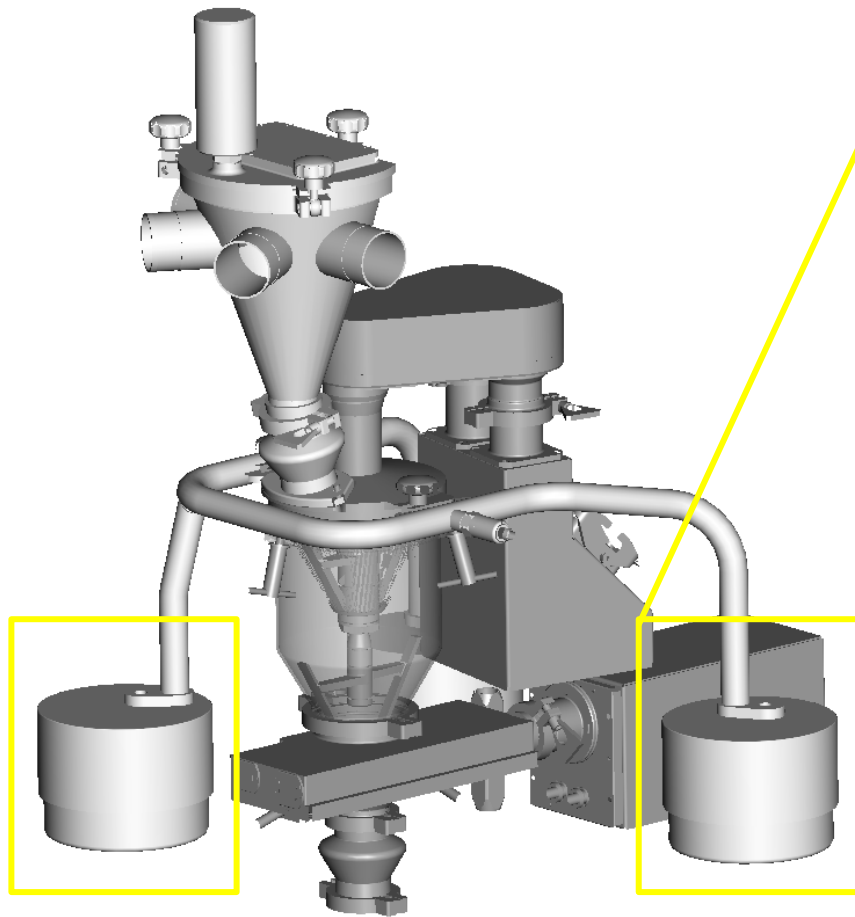
Upper & Lower Mixing Impeller

CONTINUOUS MIXING TECHNOLOGY (CMT)



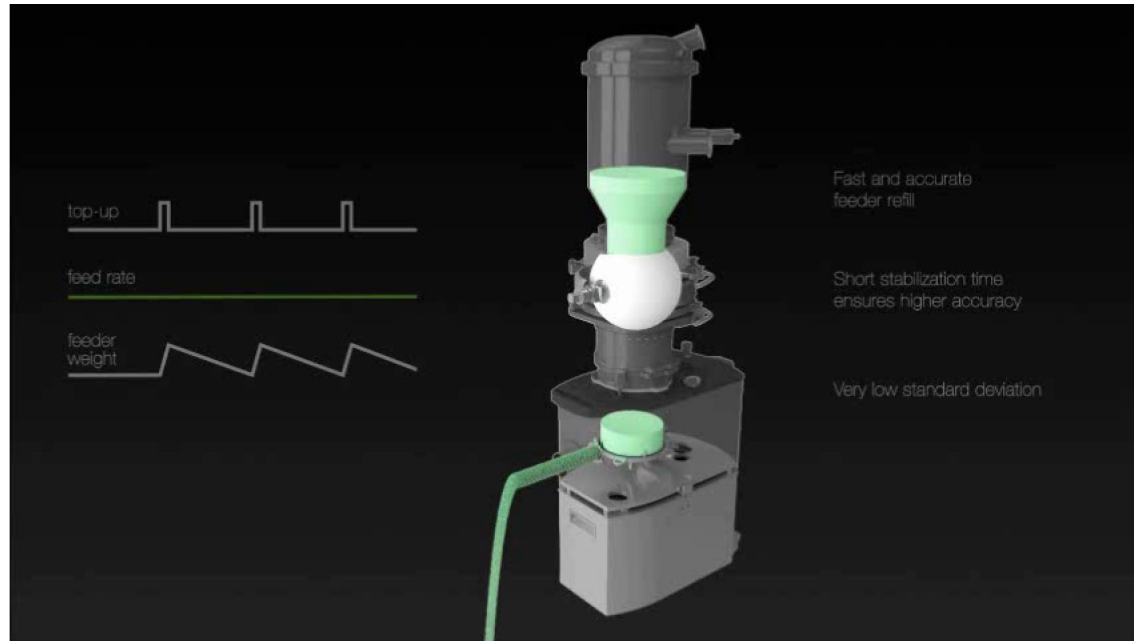
Exit Valve

CONTINUOUS MIXING TECHNOLOGY (CMT)

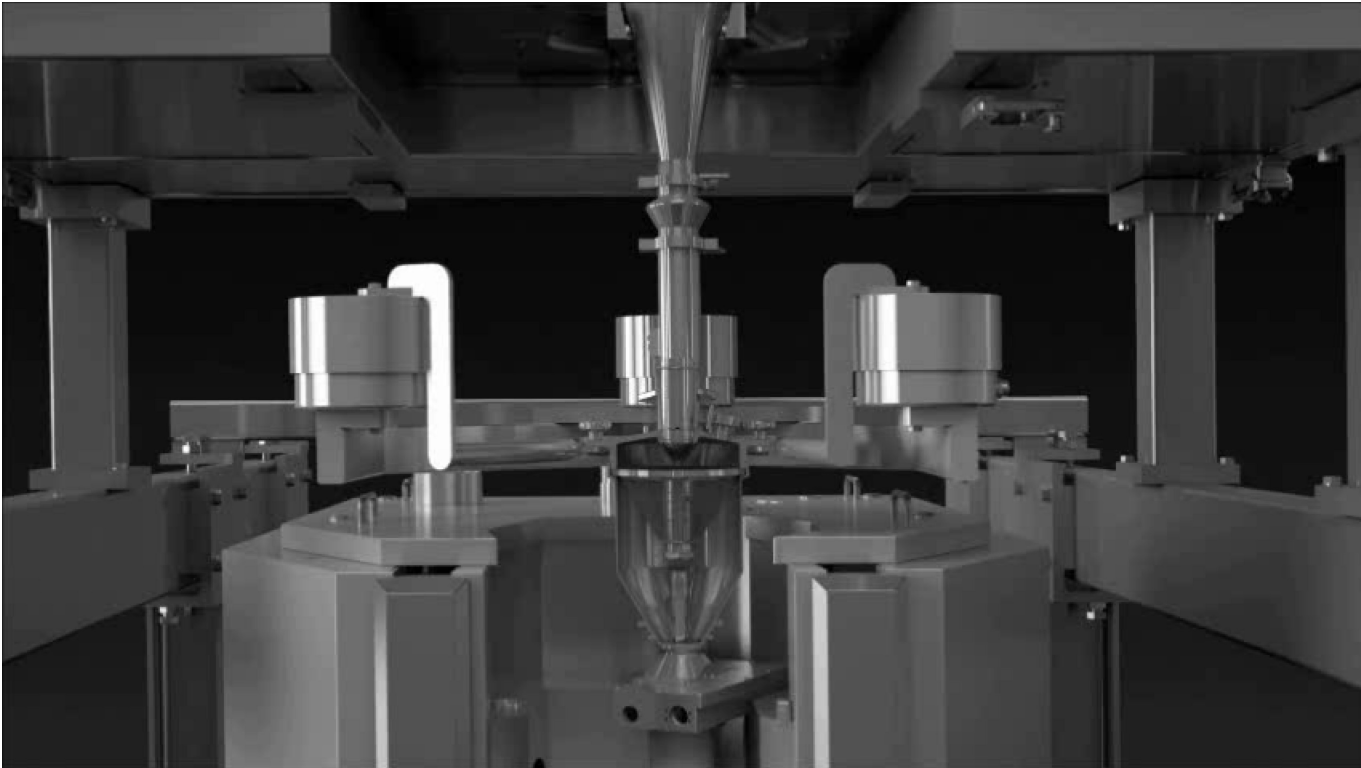


Load Cells

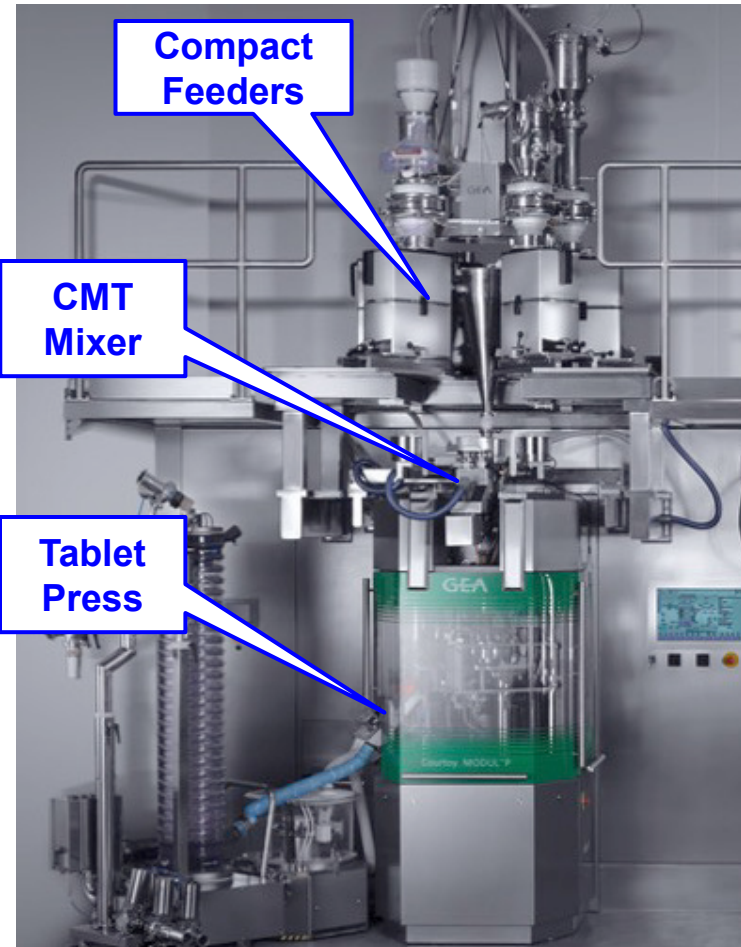
CONTINUOUS MIXING TECHNOLOGY (CMT)



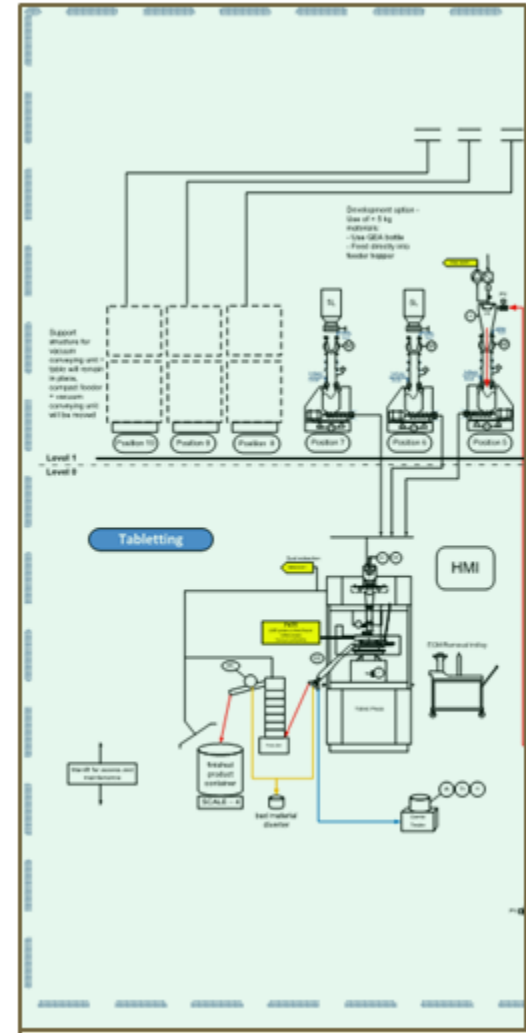
CONTINUOUS MIXING TECHNOLOGY (CMT)
PROCESS START UP AND TRANSITION TO
STEADY STATE CONTINUOUS OPERATION



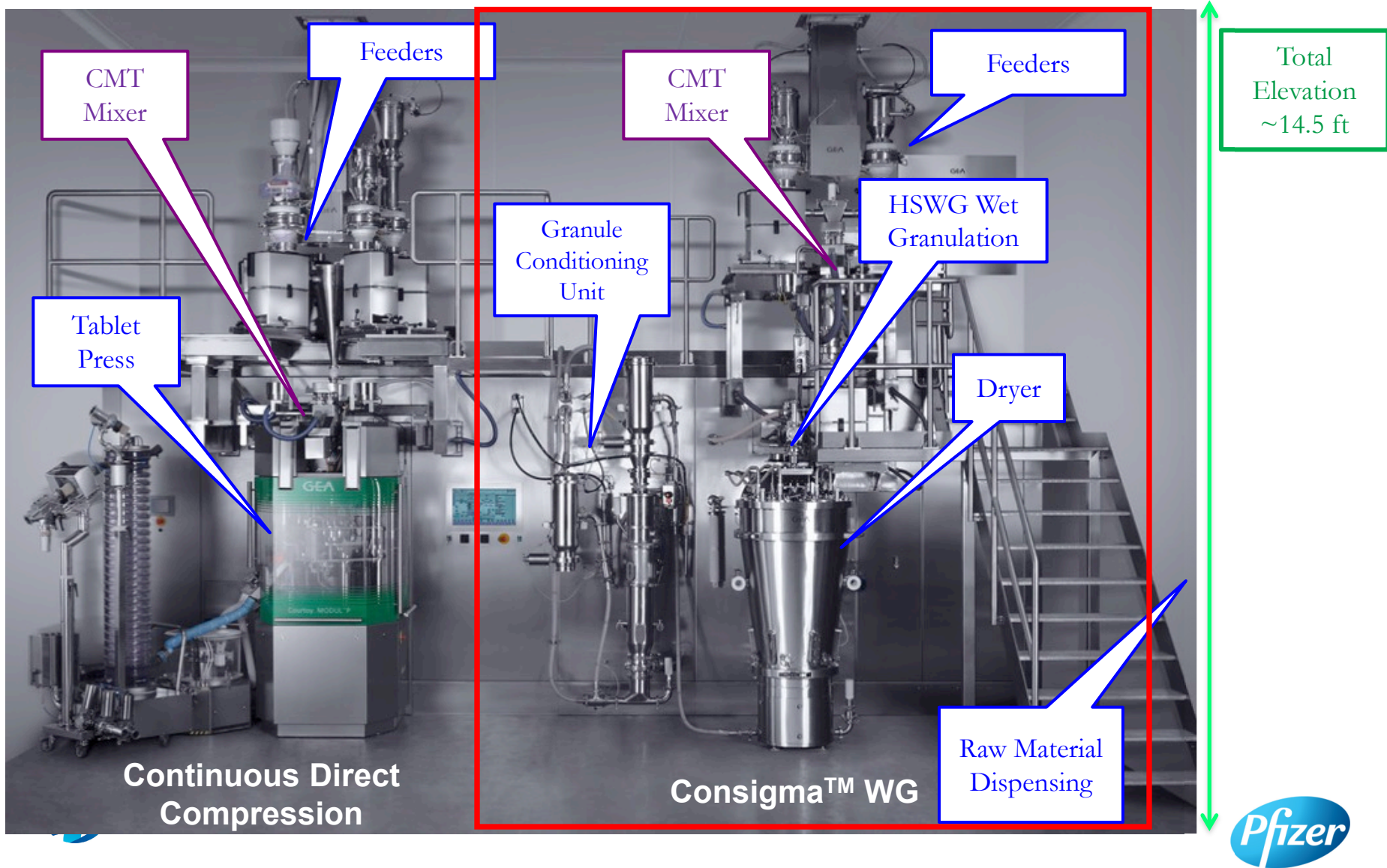
PCMM DIRECT COMPRESSION LINE



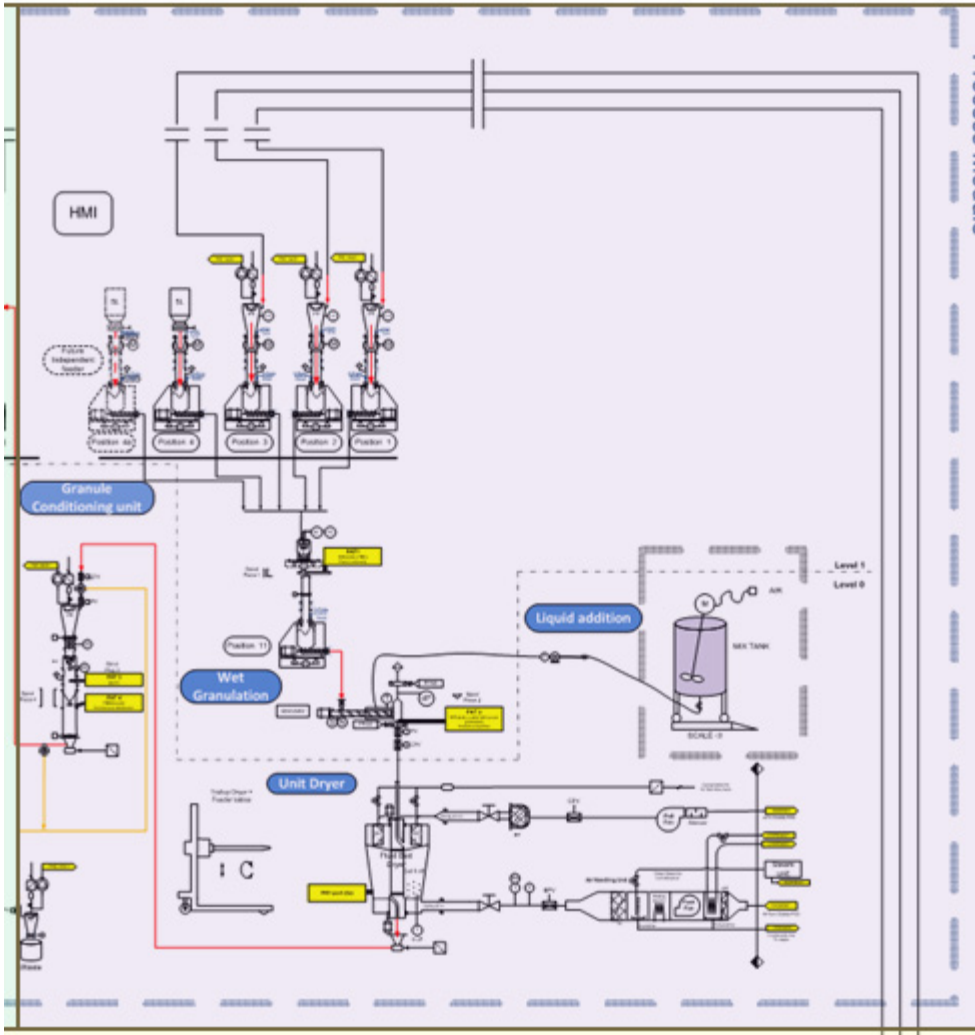
- ❖ Tablet Press
- ❖ ECM
- ❖ WOL SKID
- ❖ Metal Checker
- ❖ Deduster
- ❖ PAT 5 Feed frame



Continuous High Shear WG in a 'POD'



WET GRANULATION



❖ Operation:

- All equipment ATEX rated , CE, grounded and bonded
- No solvents in binder solution, IPA wiping only
- GEA Consigma is a closed system using closed pneumatic transfer systems- transfer 1.5kg slugs operation
- GEA Consigma dryer is 10 bar PSR w/ isolation valves
- CMT <10mj use nitrogen inerting
- Two locations for diversion possible

PCMM OSD PAT AND PRODUCT DIVERSION

Diversion 1
Post Fluid Bed
Drying

PAT 1 (NIR)
Post CMT
Potency & Blend Uniformity

PAT 2 (NIR)
Post TSWG
Granule Formation

PAT 3 (NIR)
Post Granule Sizing
Potency & Granule
Uniformity, Moisture

PAT 4 (FBRM)
Post Granule Sizing
PSD

PAT 5 (NIR)
Feed Frame
Potency & Blend/Granule
Uniformity

Diversion 3
Tablet Eject Chute

Diversion 2
Post Granule Sizing

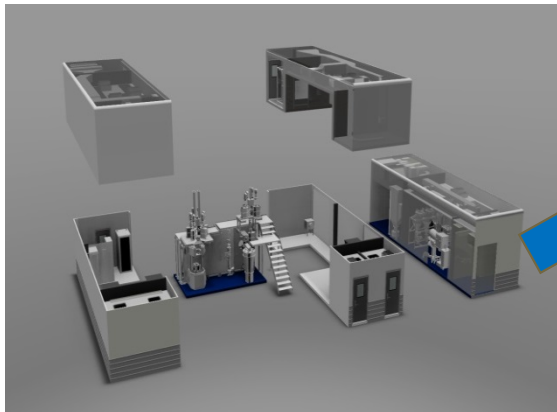
PCMM OSD: *A Factory in a POD Through a Unique Collaboration*



❖ POD design:

- Cleanable GMP interiors
- Technical, process and Air locks
- HVAC w/ inlet & outlet HEPA
- Pressurization zones
- Process dust collection system part of extraction system and air balance
- Integrated GEA process equipment
- Connect to gray space

Integrated into a
'transportable' POD

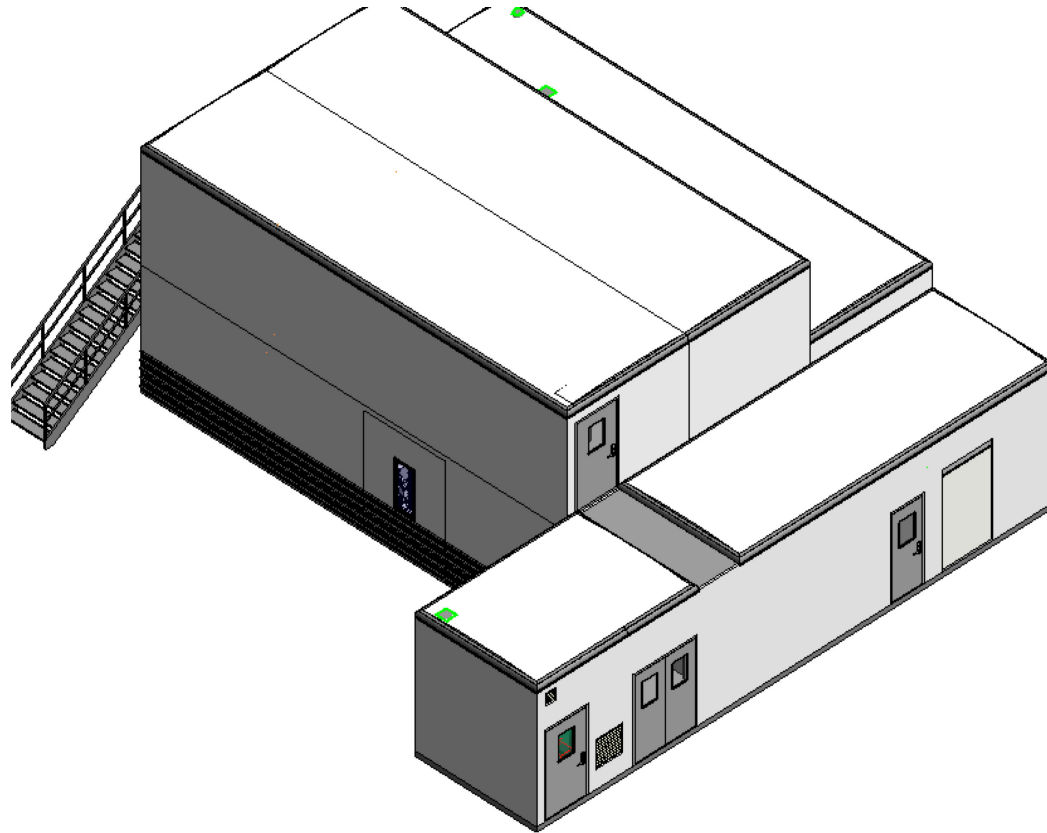


PCMM OSD POD

G-CON Manufacturing, Inc.

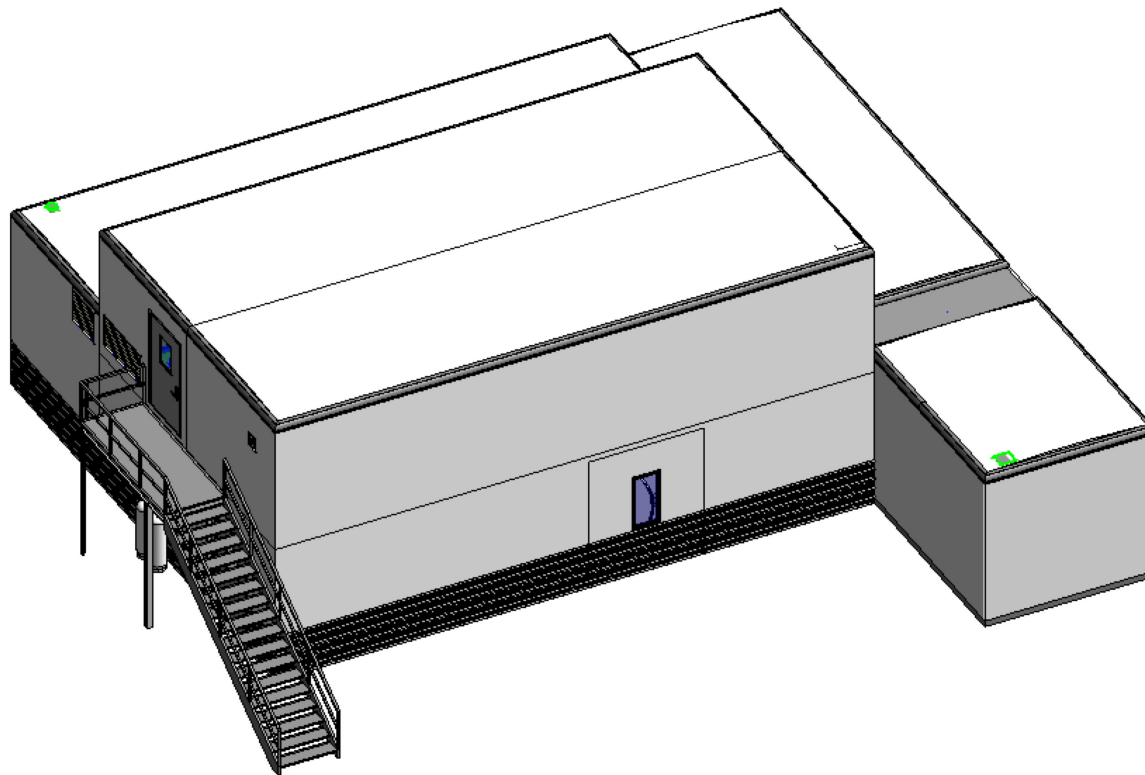
Leading Autonomous Cleanroom Designs

3D Model Rendering



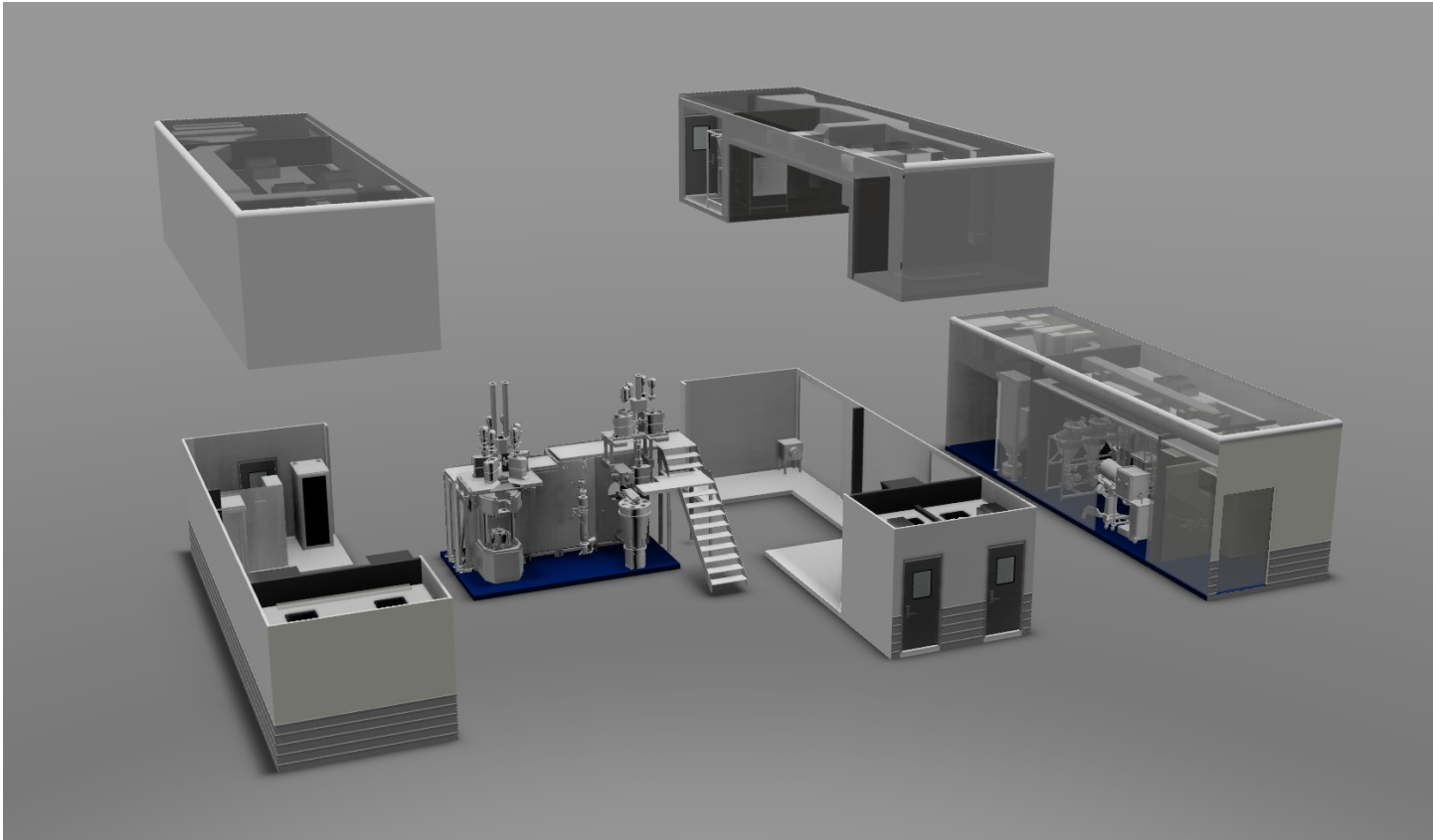
PCMM modular system exterior view showing the Corridor POD, Process POD, and Materials Handling POD (Front View)

3D Model Rendering

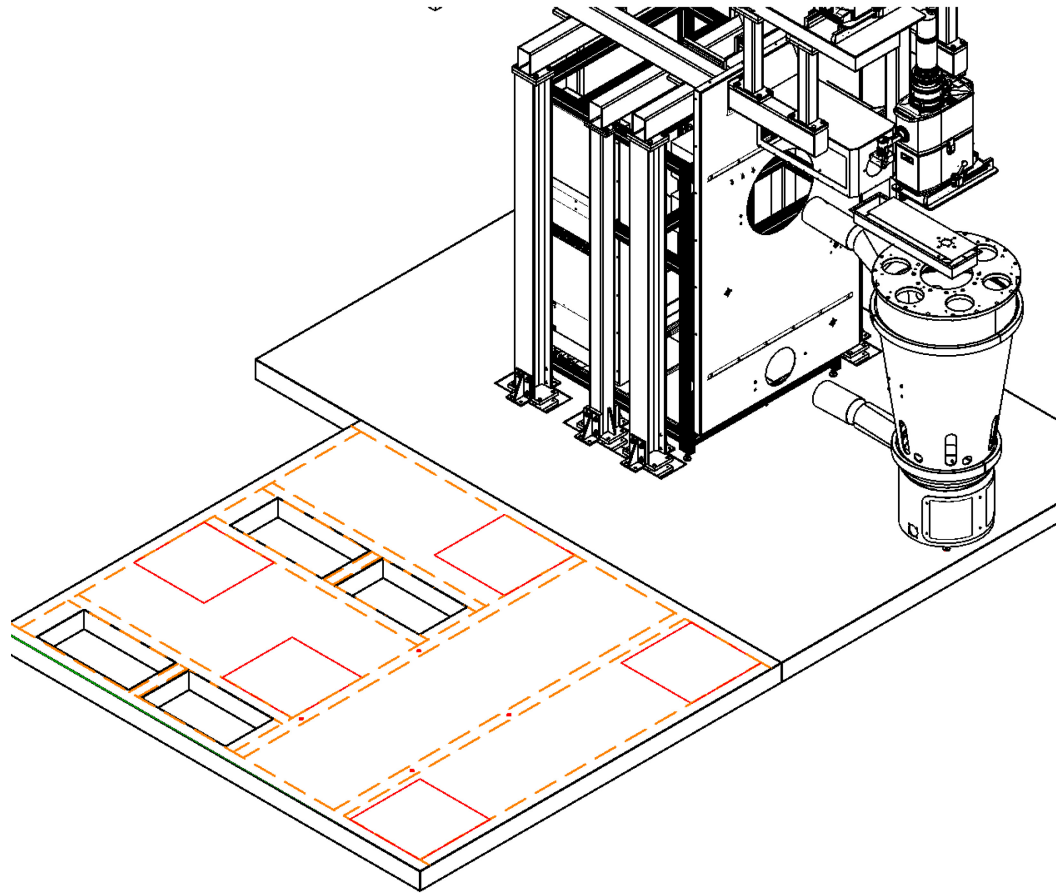


PCMM modular system exterior view showing the Corridor POD, Process POD, and Materials Handling POD (Back View)

Exploded View

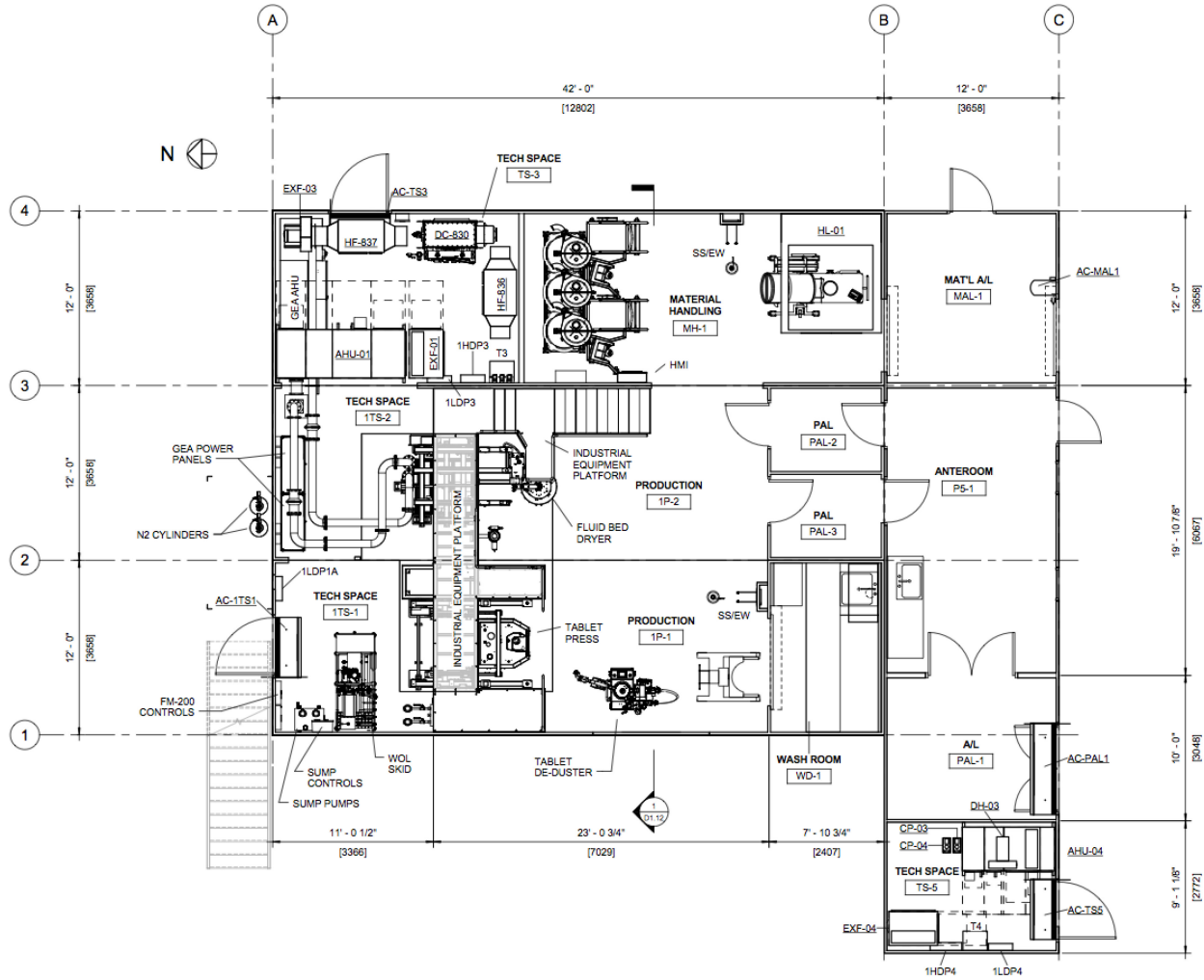


Equipment Floor Plates

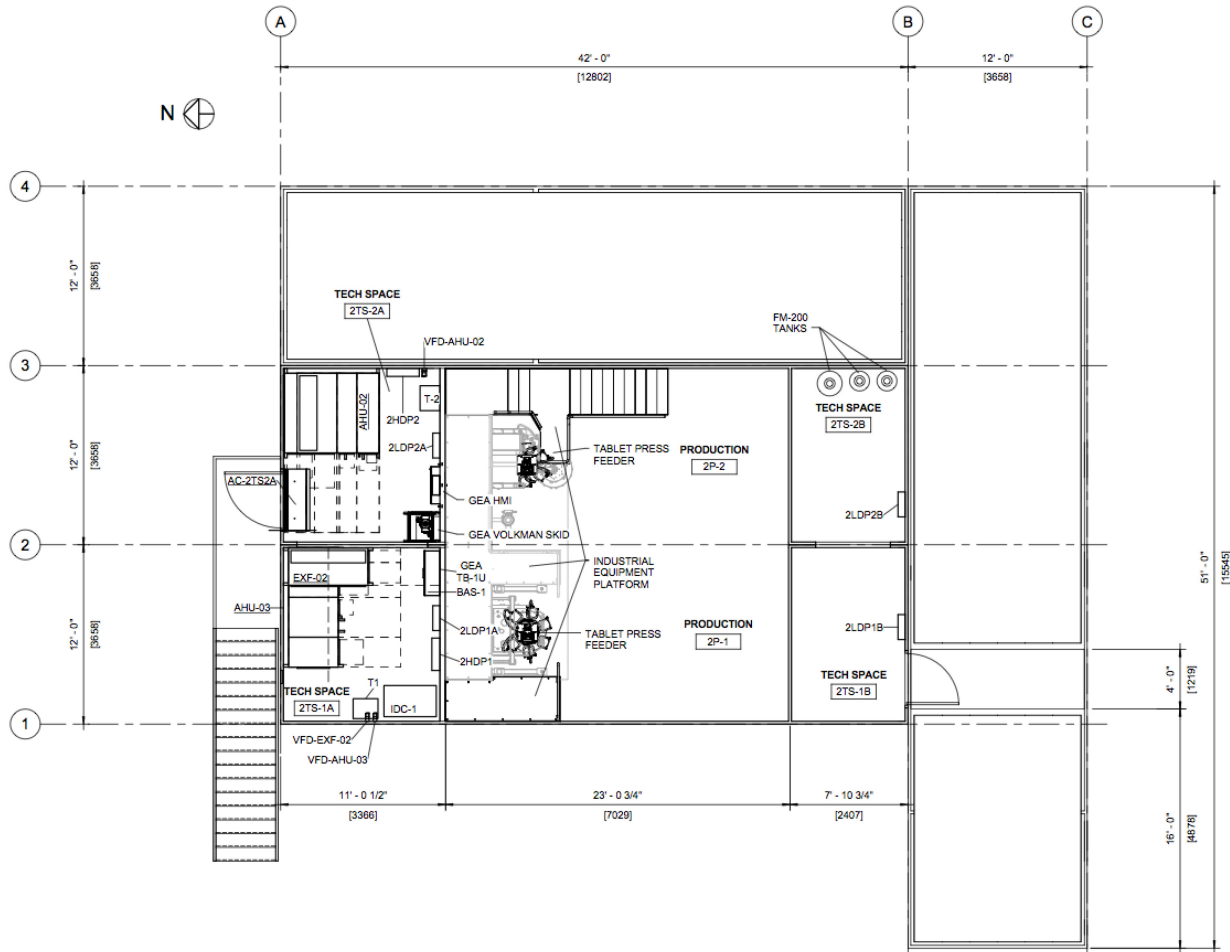


Floor Sections designed for GEA Equipment

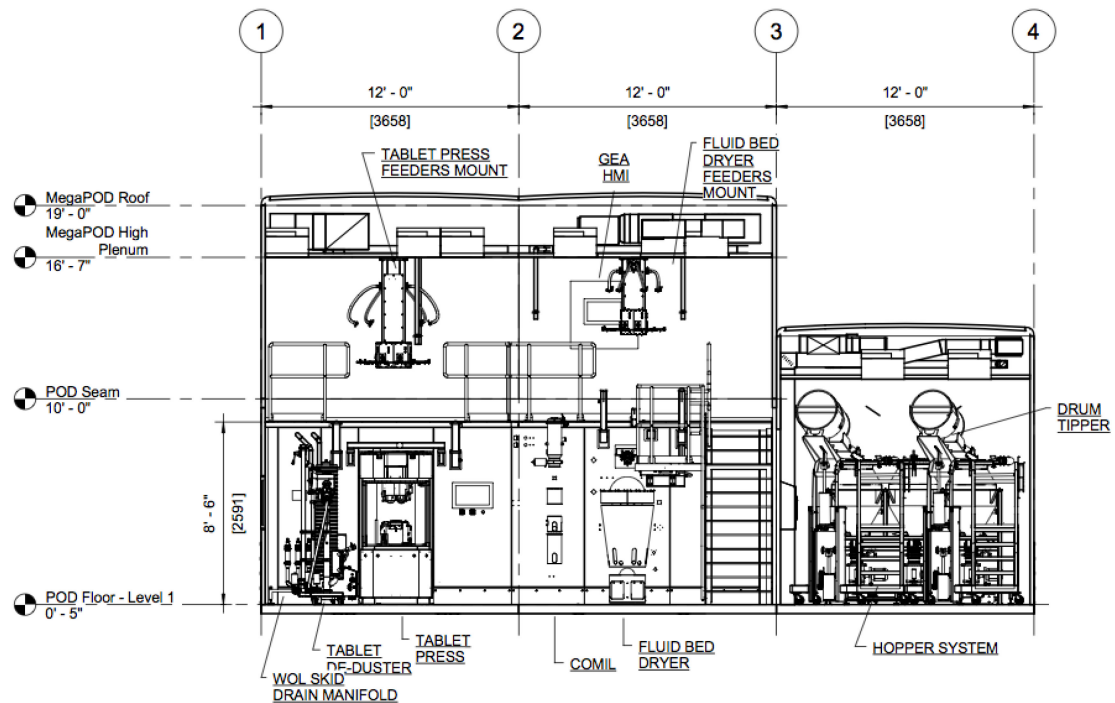
Plan View – 1st Level



Plan View – 2nd Level



Elevation View



① SECTION - PRODUCTION AREA NORTH
1/4" = 1'-0"

Interior



Assembled



Assembled



Assembled



Shipment Prep



Transport



PFIZER SITE TEAM EFFORTS:

- ❖ Cleaned up existing warehouse space
- ❖ Conducted a face to face preliminary meeting with City of Groton officials highlighting the scope of project
- ❖ Selected Engineering Firm
- ❖ Completed the B90 design “The glove” and obtained permits.
- ❖ Selected a mechanical contractor
- ❖ Completed major B90 readiness elements- **without any safety and business disruption:**
 - *New substation hook up and B90 panel upgrades*
 - *New chilled water supply, steam, hot/ cold water and compressed air*
 - *New POD HVAC system*
 - *Integration to all existing B90 systems: fire , security*
 - *Final painting and preparations for PODS*
 - *Project office space*



Bldg 90 1/24/14

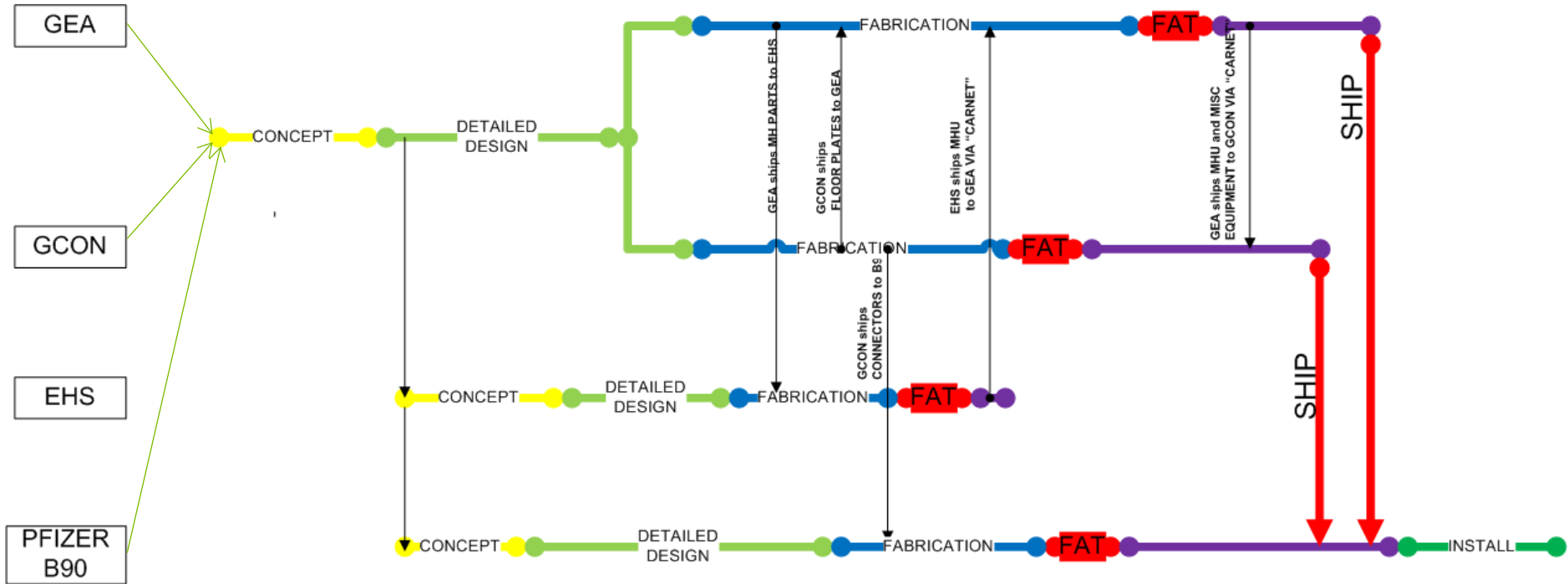


Feb 2014





Logistics Planning





Delivering Innovation PCMM Collaboration

Pfizer, Inc. / G-CON Manufacturing, Inc. / GEA

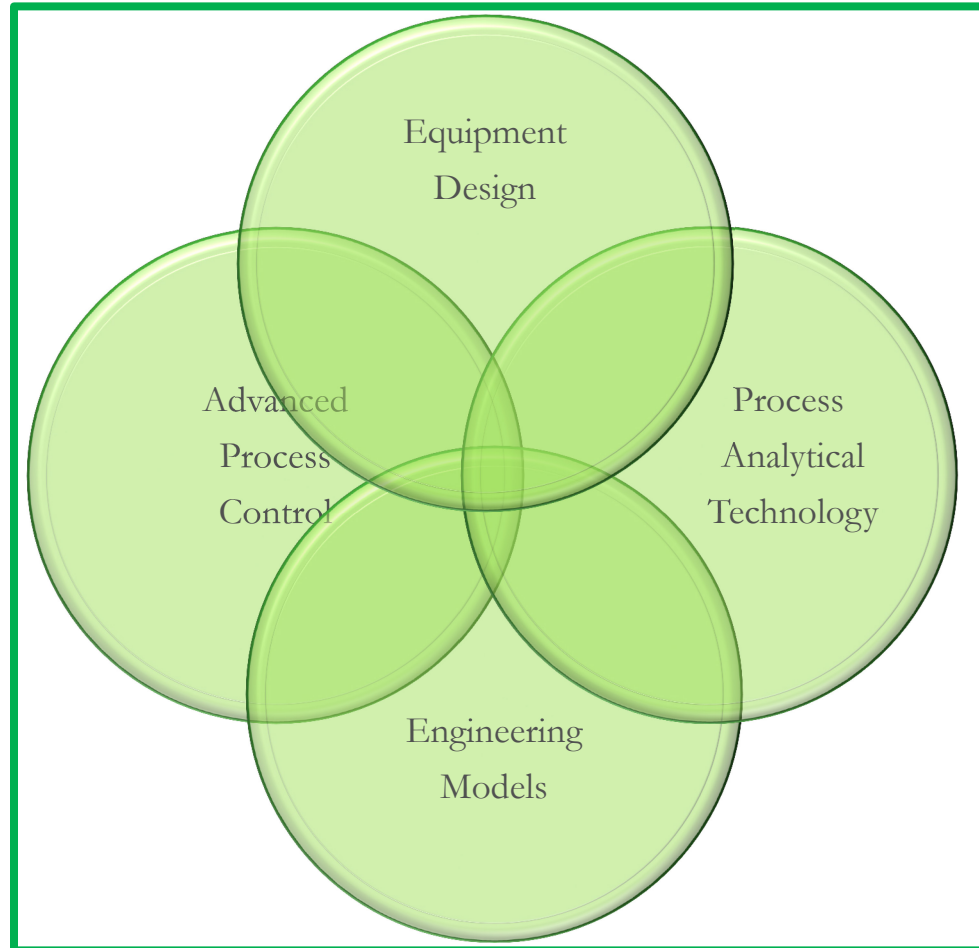
Mega-POD Deployment and Delivery

1. The Drivers & “Germ” of a concept – Jeff / Valentin
2. Project Execution Approach & Team Structure – Fred
3. PCMM OSD: “Factory in a POD” – Valentin
4. **Impact Integrated Approach** – Jeff
5. Conclusion – Fred

AN INTEGRATED APPROACH TO A PLATFORM TECHNOLOGY

AN OPPORTUNITY TO TRANSFORM THE DEVELOPMENT TO MANUFACTURE PARADIGM

Integrated System



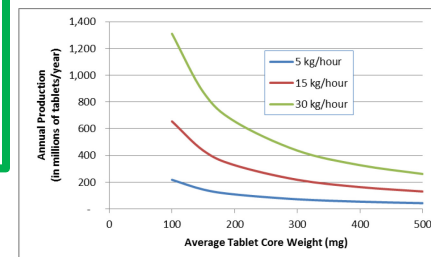
World-class
Material Science,
Formulation &
Development
Practices



World-class
Commercial
Manufacturing

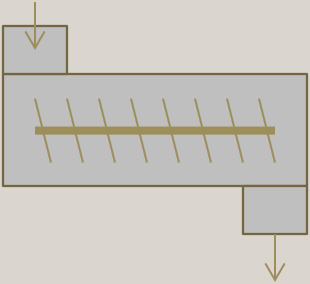


~500 MM tab/year
24/5 operation,
30% downtime



CONTINUOUS POWDER MIXING CURRENT STATE

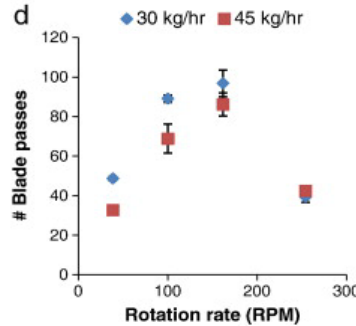
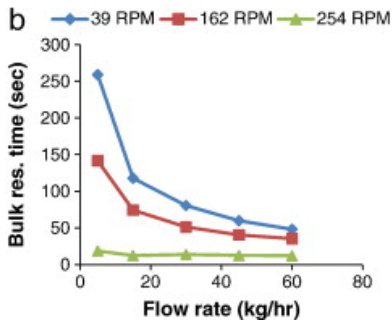
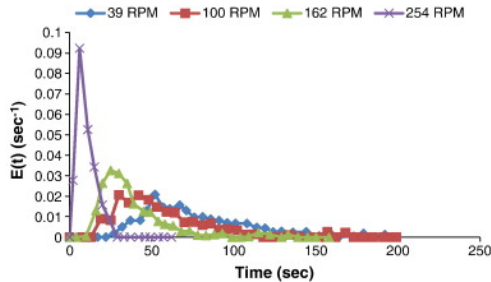
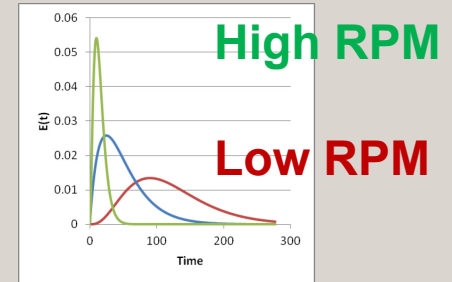
In-Line Powder Mixer



Conduct Experiments/ Computational Models

Mixer Blade RPM
Mixer Blade Geometry
.....
Mixer Geometry

RTD Characterization

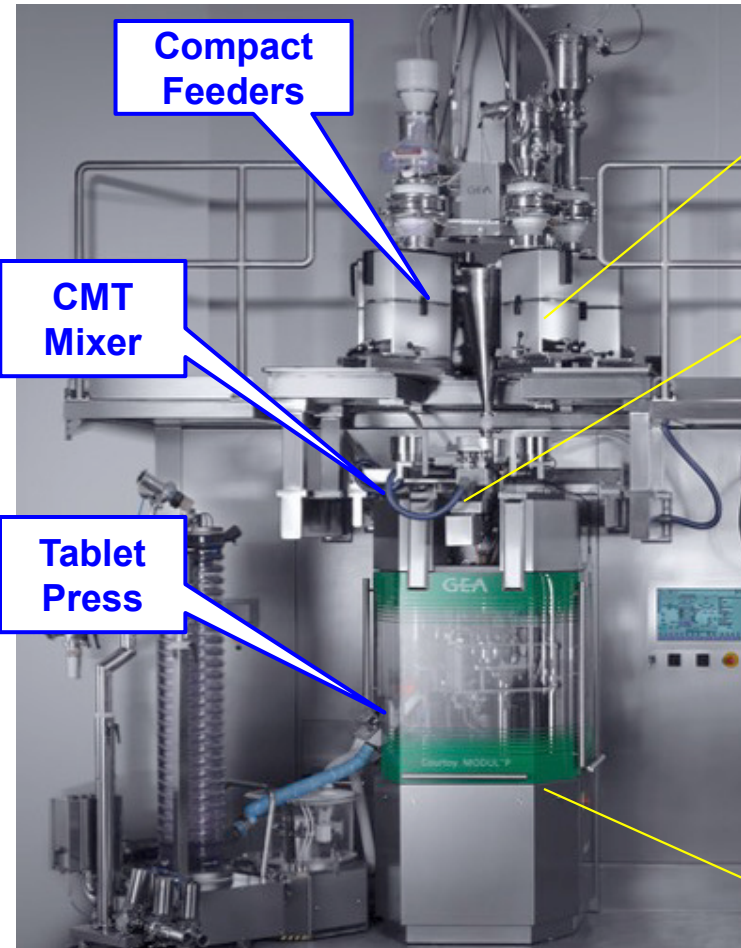


Challenges

- RTDs vary with mixer speed
- Higher mixer speed comes at the expense of shorter residence time
- Maximum # of blade passes through resident powder bed occurs at moderate speeds

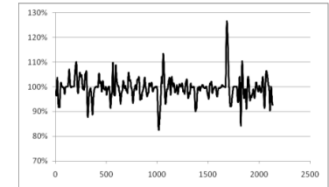
DEVELOPING A PRODUCT ON PCMM

PCMM DIRECT COMPRESSION LINE



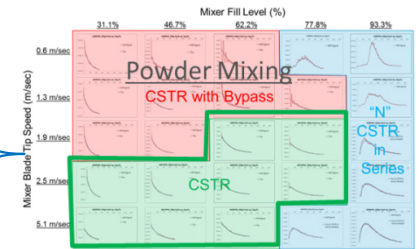
Compact Feeders

- 1 Achieve Minimal Feed variability at target flowrate



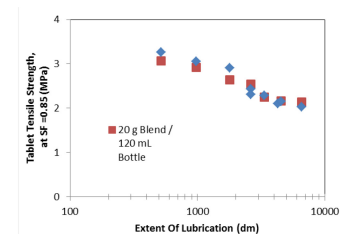
CMT Mixer

- 2 Achieve Ideal Mixing Conditions
- 3 Achieve desired Mean Residence Time
- 4 Achieve Mass Throughput (Mass in = Mass Out)
- 5 Achieve target Extent of Lubrication



Tablet Press

- 6 Achieve target Tablet Physical Properties



PCMM DIRECT COMPRESSION LINE

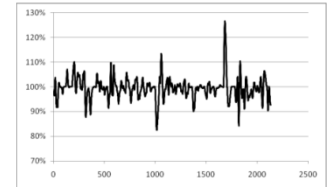
Compact Feeders

CMT Mixer

Tablet Press

Compact Feeders

1 Achieve Minimal Feed variability at target flowrate



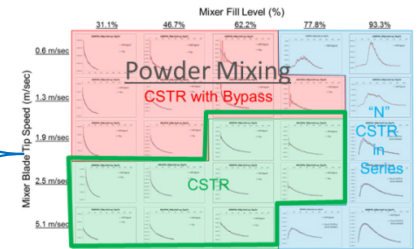
CMT Mixer

2 Achieve Ideal Mixing Conditions

3 Achieve desired Mean Residence Time

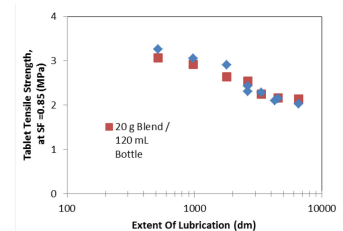
4 Achieve Mass Throughput (Mass in = Mass Out)

5 Achieve target Extent of Lubrication



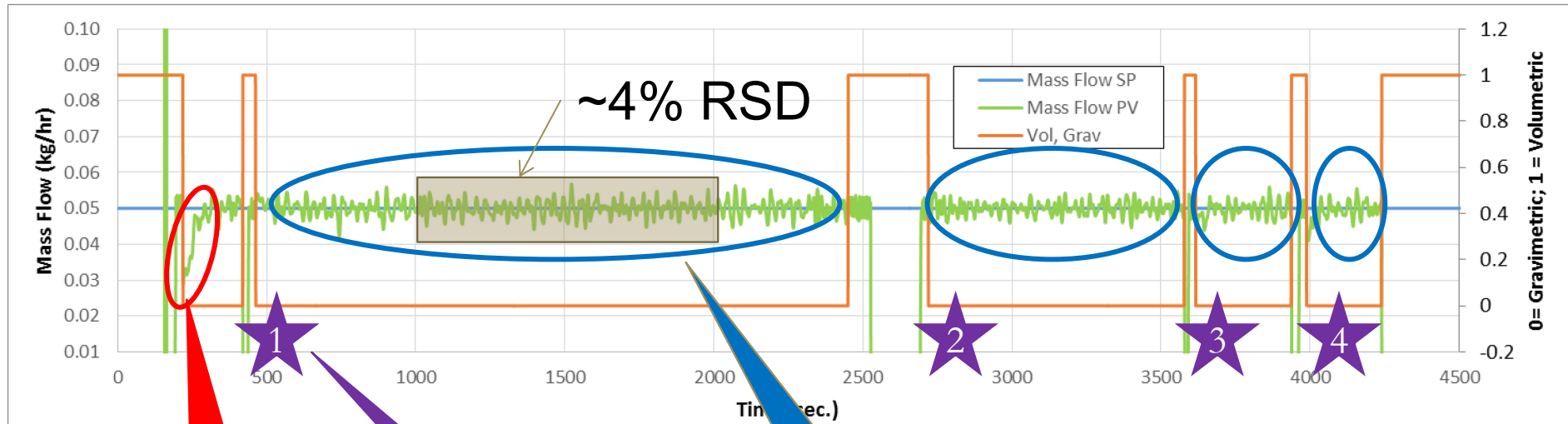
Tablet Press

6 Achieve target Tablet Physical Properties



EXAMPLES OF GRAVIMETRIC FEEDING - MAG STEARATE

50 grams/ hour



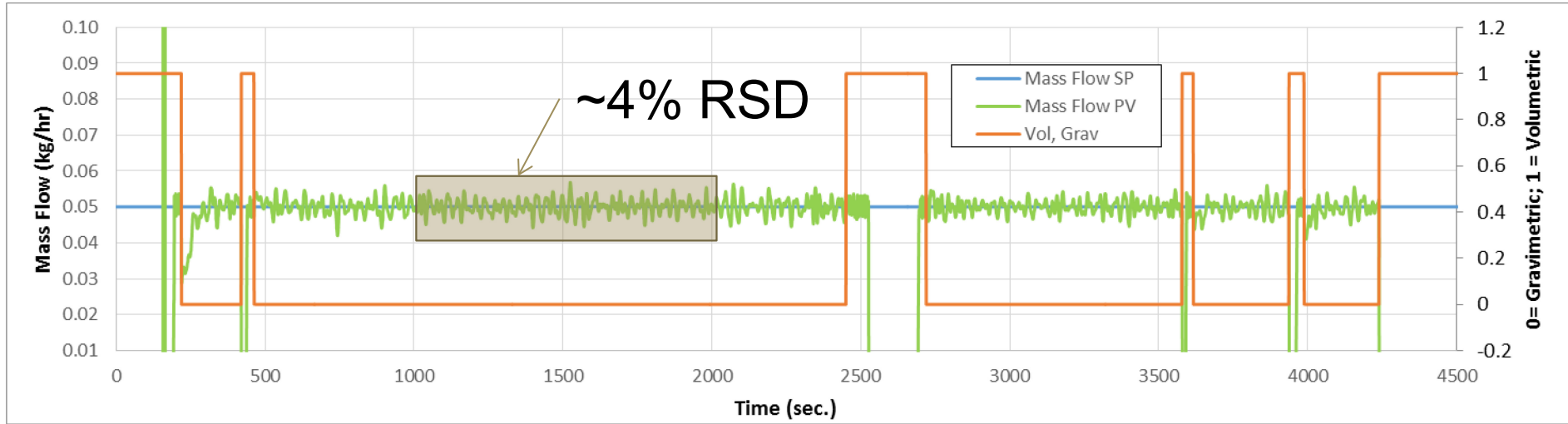
Upon start, controller rapidly guides feeder to set point: 50 g/hour

Feeder turned OFF
Then turned ON
Four times.

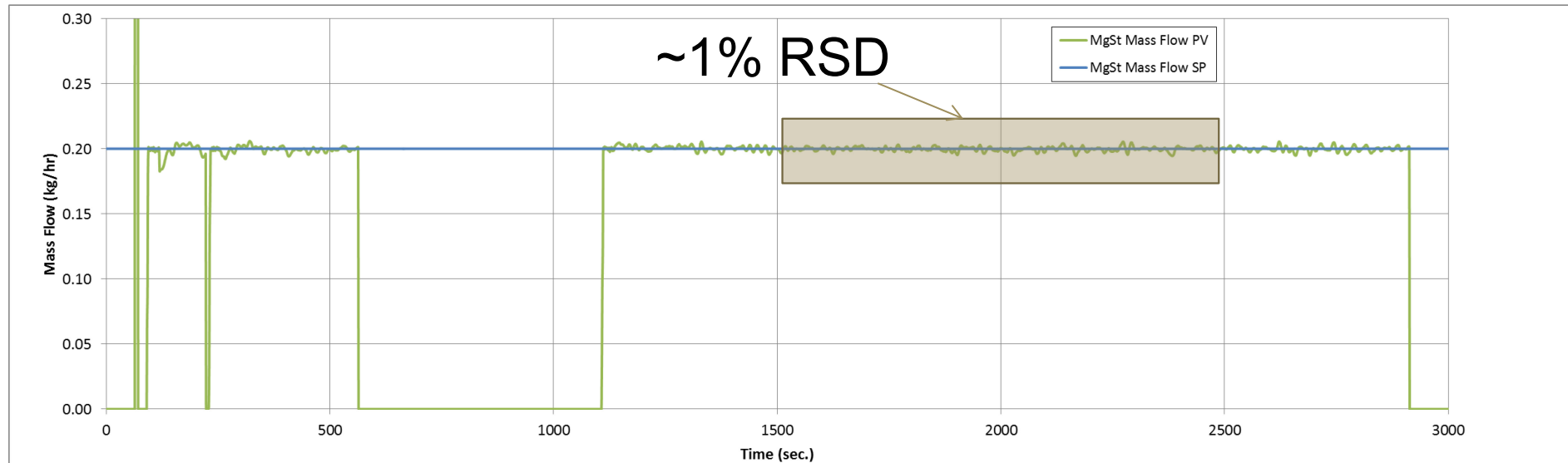
Upon restart, controller returns to set point and maintains feeder at target

EXAMPLES OF GRAVIMETRIC FEEDING - MAGNESIUM STEARATE

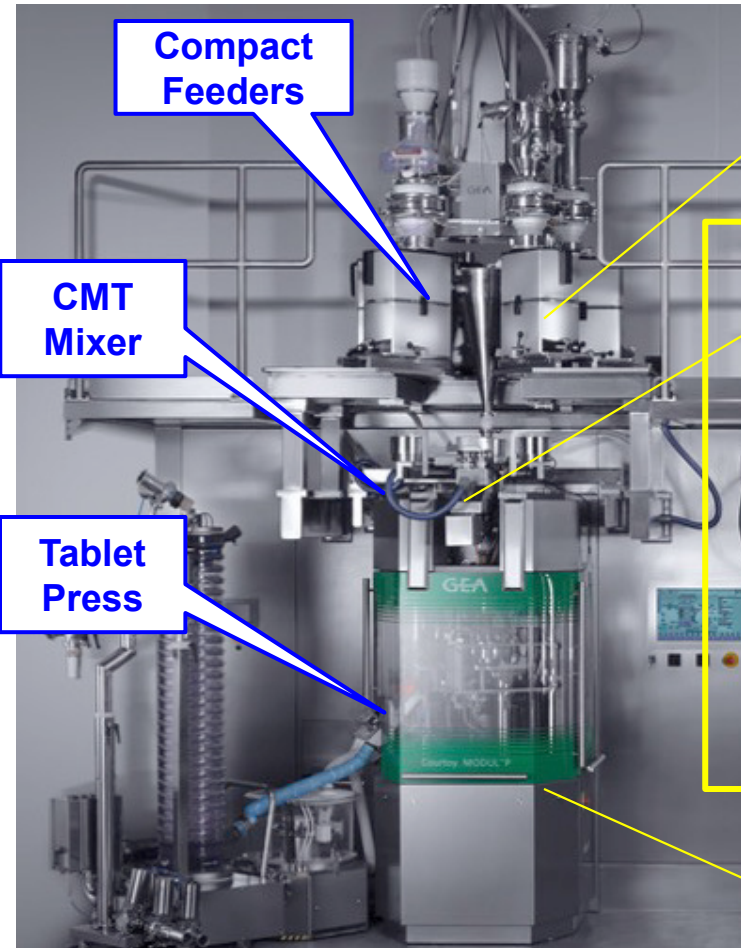
50 grams/ hour



200 grams/ hour

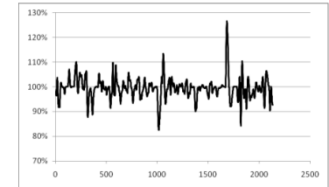


PCMM DIRECT COMPRESSION LINE



Compact Feeders

1 Achieve Minimal Feed variability at target flowrate



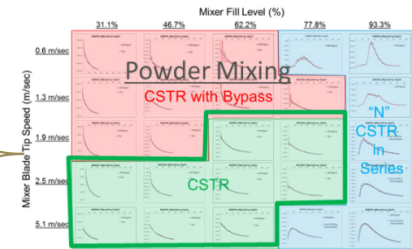
CMT Mixer

2 Achieve Ideal Mixing Conditions

3 Achieve desired Mean Residence Time

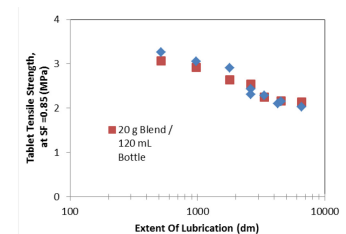
4 Achieve Mass Throughput (Mass in = Mass Out)

5 Achieve target Extent of Lubrication



Tablet Press

6 Achieve target Tablet Physical Properties

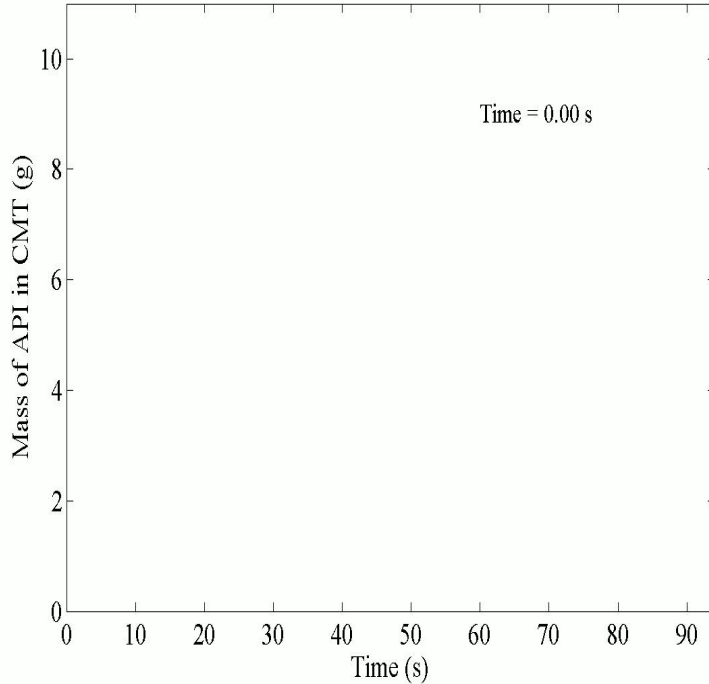


Engineering Models: DEM Modelling of CMT Mixer

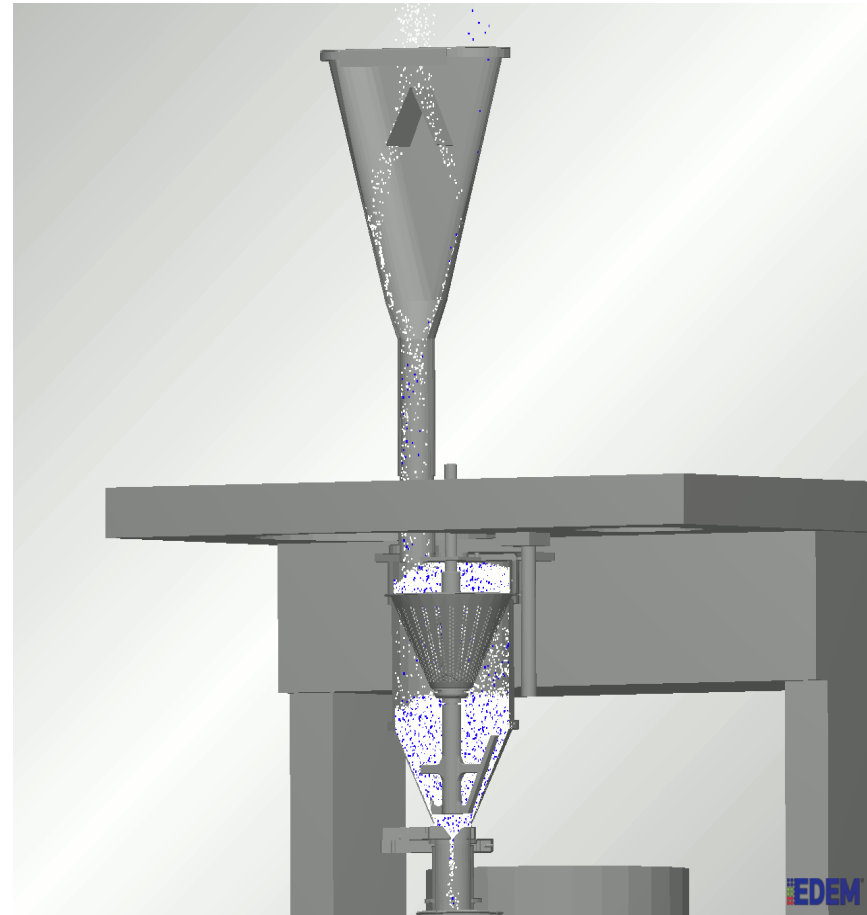
Excipients

API

Mag St



API spike (10 g)
added at t=0 s



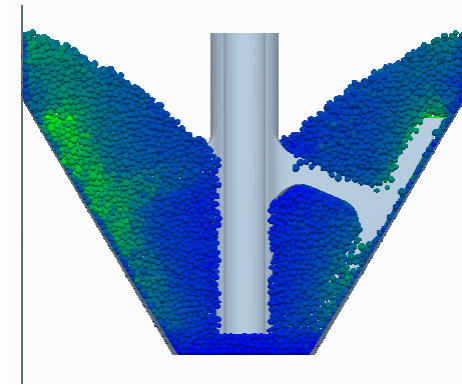
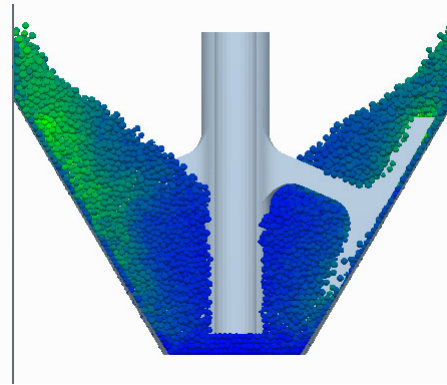
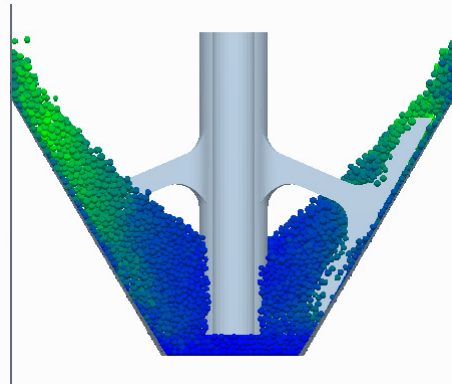
DEM –
investigate flow
pattern

31.1% fill
66.8 g

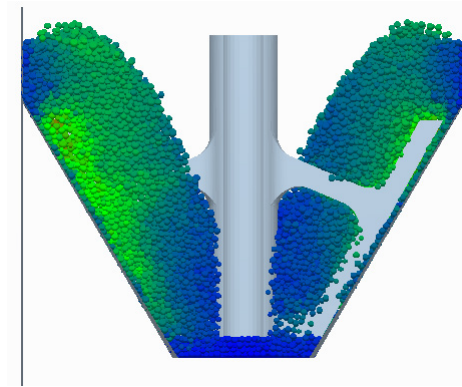
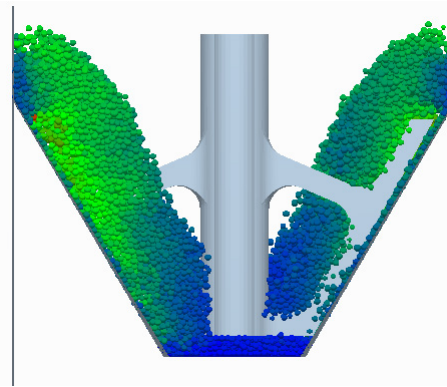
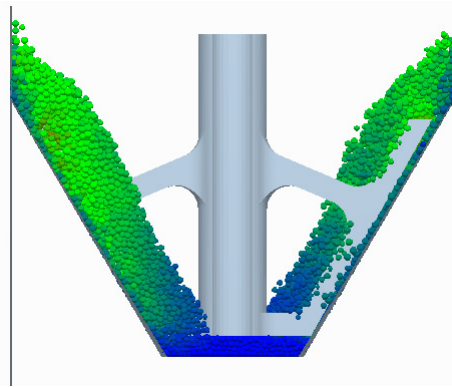
62.2% fill
133.6 g

93.3% fill
200.4 g

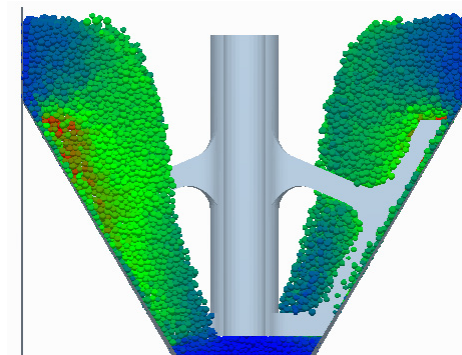
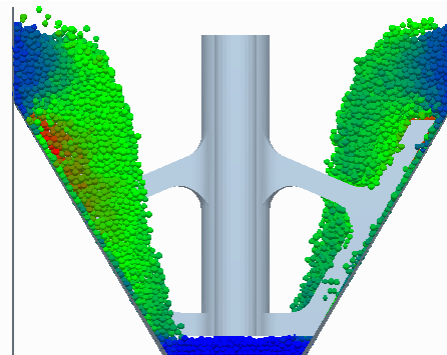
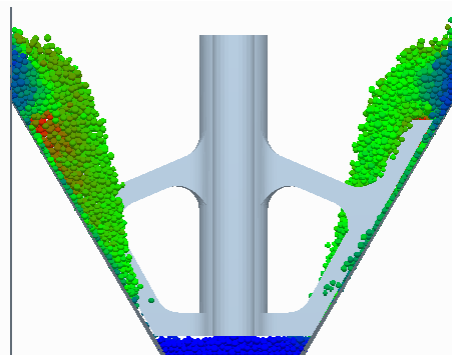
200 RPM
1.3 m/s



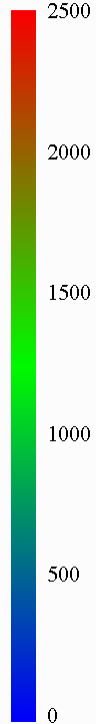
300 RPM
1.9 m/s



400 RPM
2.5 m/s



Velocity (mm/s)



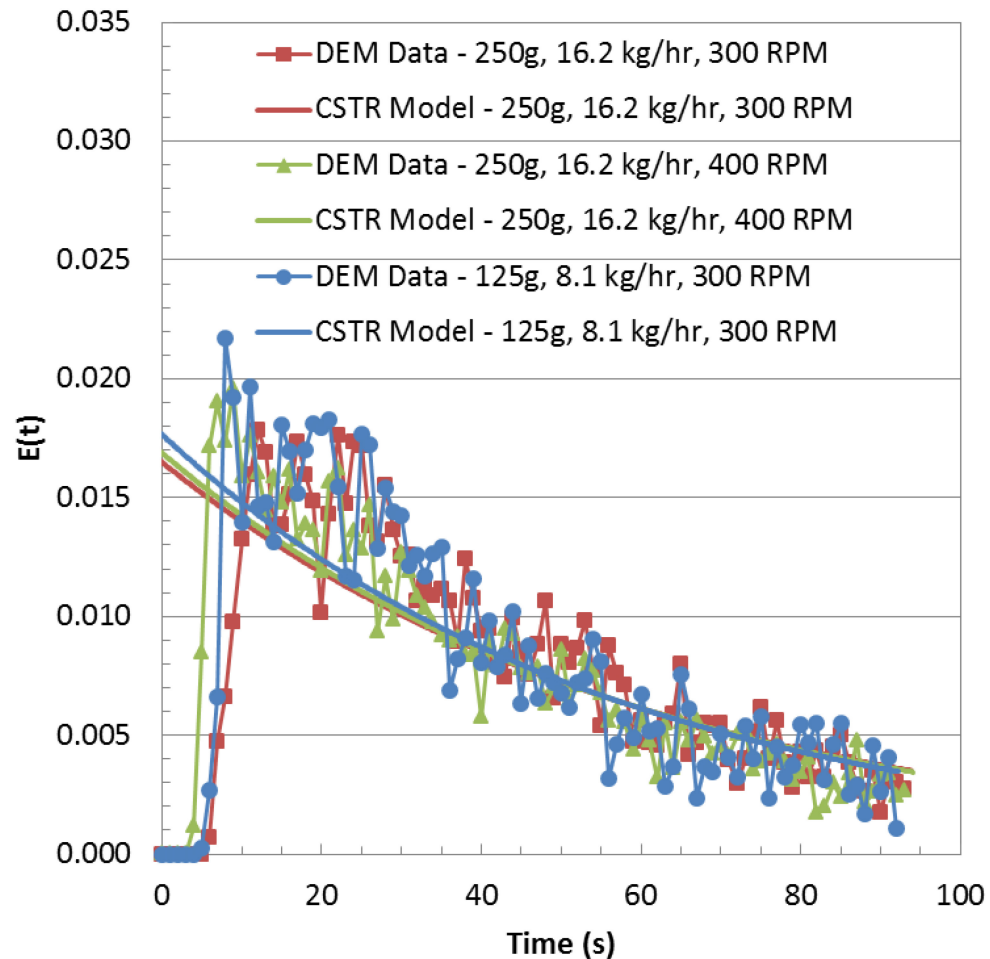
DEM Simulations – Residence Time Distributions

❖ Process conditions

- Speed = 300 RPM, 400 RPM
- Mass hold-up = $\sim 125\text{g}$, $\sim 250\text{ g}$
- Mass throughput = 8.1 , 16.2 kg/hr
- Theoretical mean residence time = $\sim 56\text{ s}$

❖ A fixed, CSTR-like RTD observed for multiple hold-up/throughput conditions

- Ability to maintain a fixed RTD for varying hold-up/throughput



PCMM DIRECT COMPRESSION LINE

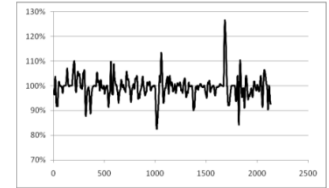
Compact Feeders

CMT Mixer

Tablet Press

Compact Feeders

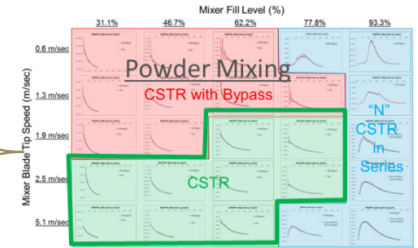
1 Achieve Minimal Feed variability at target flowrate



CMT Mixer

2 Achieve Ideal Mixing Conditions

3 Achieve desired Mean Residence Time

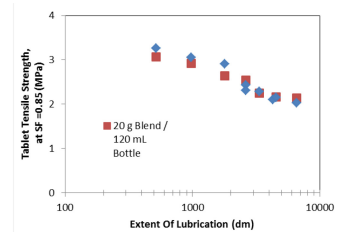


4 Achieve Mass Throughput (Mass in = Mass Out)

5 Achieve target Extent of Lubrication






Tablet Press

6 Achieve target Tablet Physical Properties

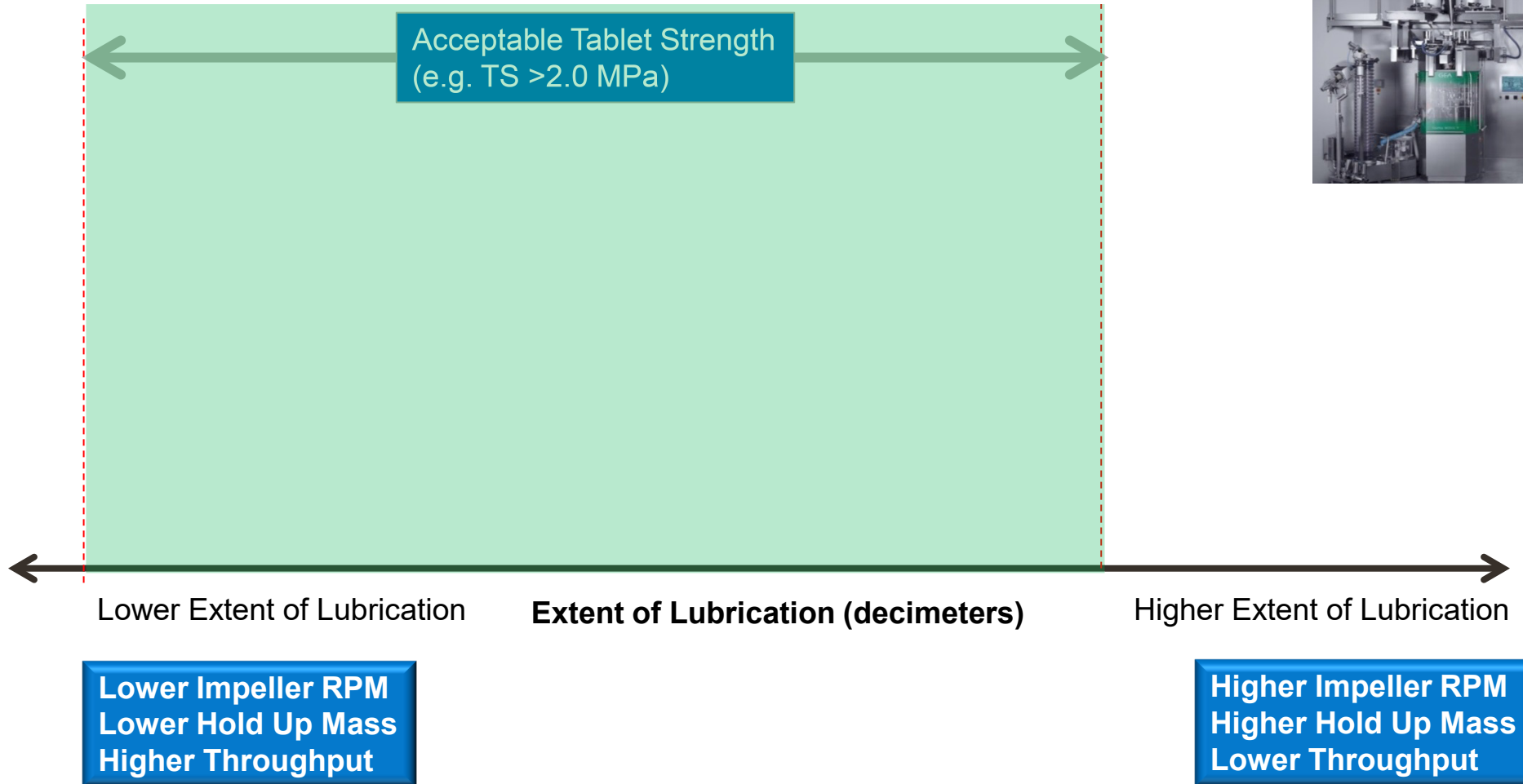


MOTIVATION

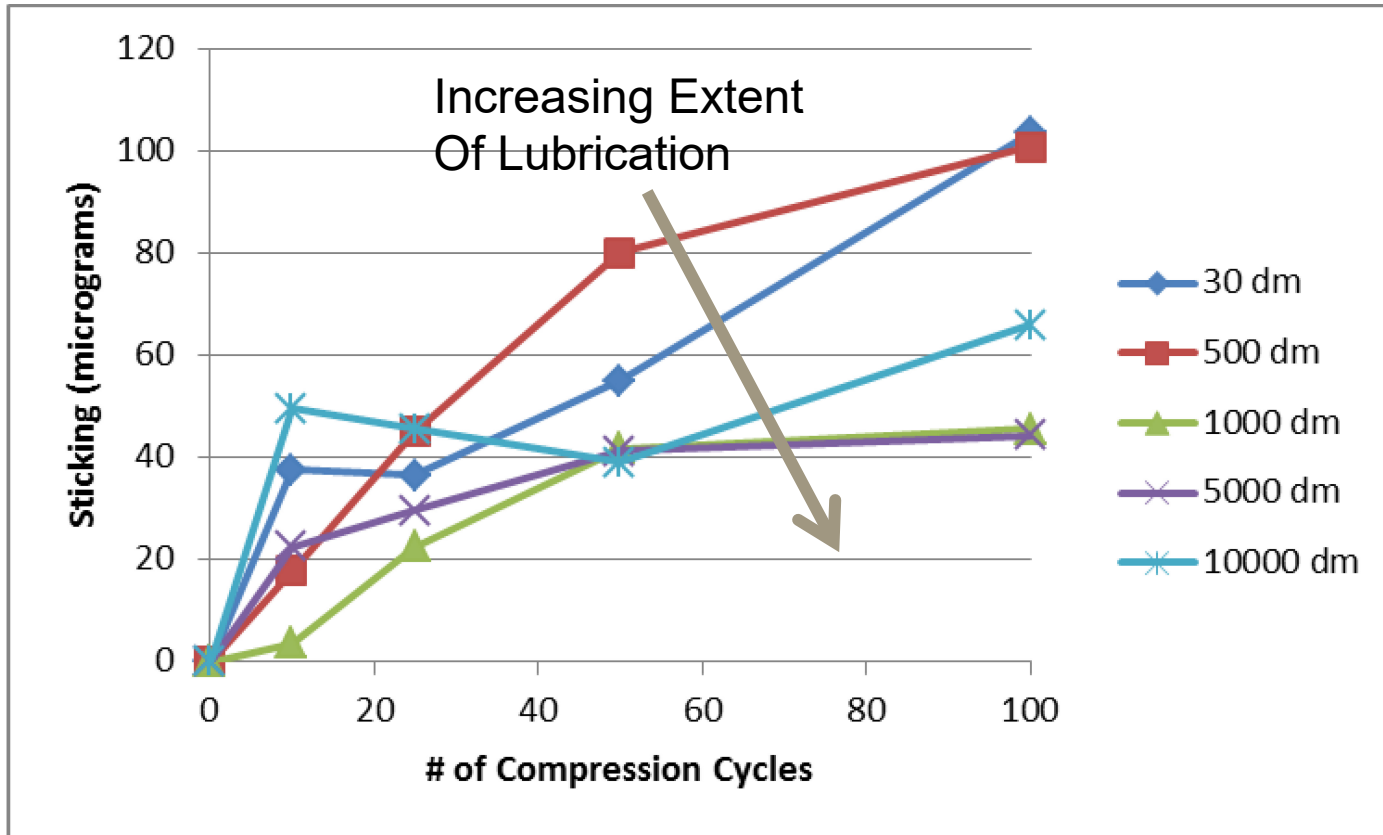
- ❖ Powder Lubrication facilitates dosage form creation
 - Tablet ejection force, punch face sticking, etc.
- ❖ Extent of Powder Lubrication influences

Blend Attributes	Tablet Quality Attributes	Increasing Extent of Lubrication, typically	
Compaction Strength	Tablet Hardness at Target Solid Fraction	↓ Decreases strength	
Powder Flow	Tablet Weight Tablet Weight Variability	↑ Increases Flow	
Powder Density	Tablet Weight Tablet Weight Variability	↑ Increases Density	
Powder Wettability	Tablet Dissolution Tablet Disintegration	↓ Decreases Wettability	
Powder Sticking (to compression tooling)	Tablet Appearance	↓ Powder sticking	

PROCESS DEVELOPMENT FOR CONTINUOUS MIXING EXTENT OF LUBRICATION



ASSESSMENT OF POWDER STICKING TO COMPRESSION TOOLING

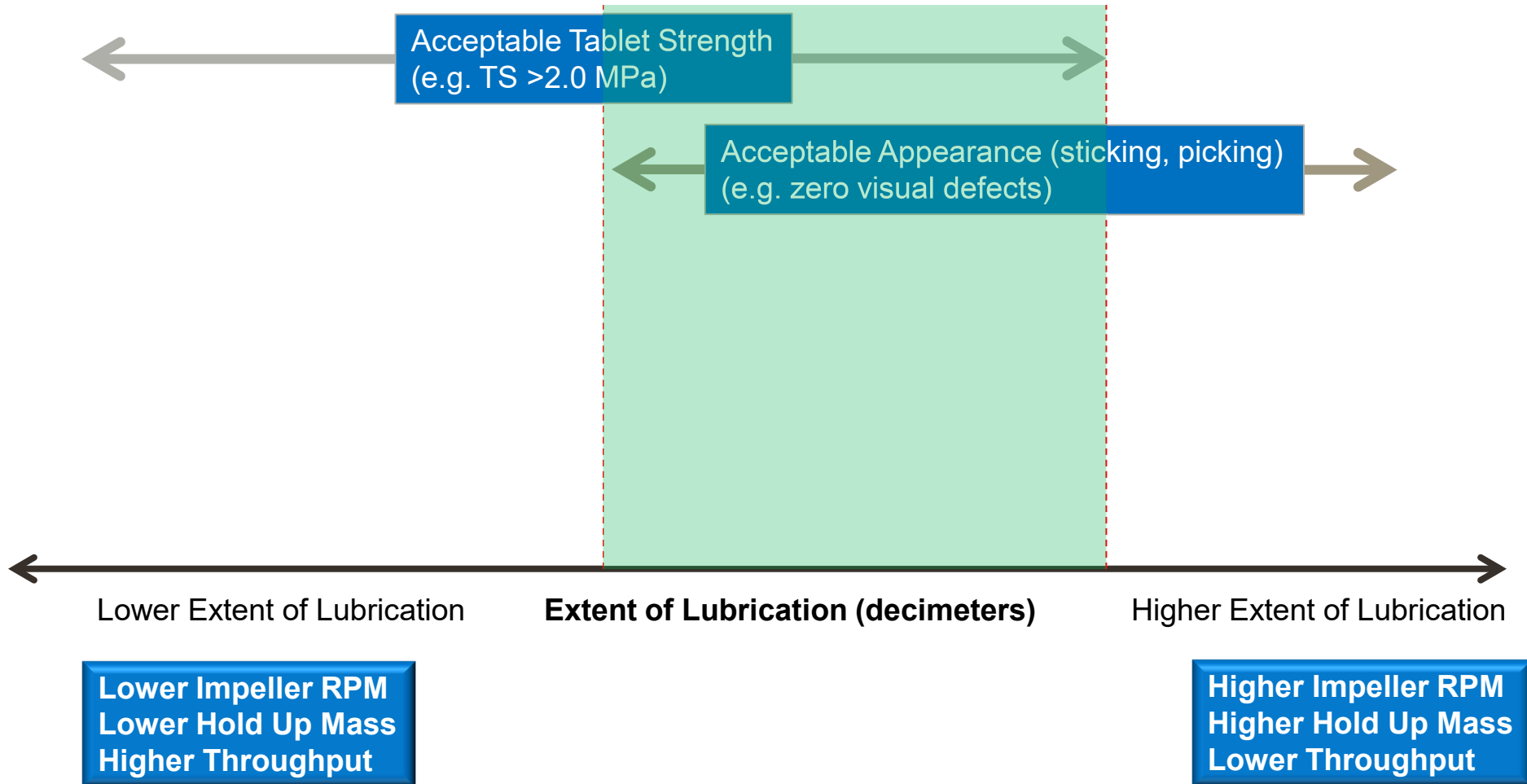


Removable Punch Tip¹

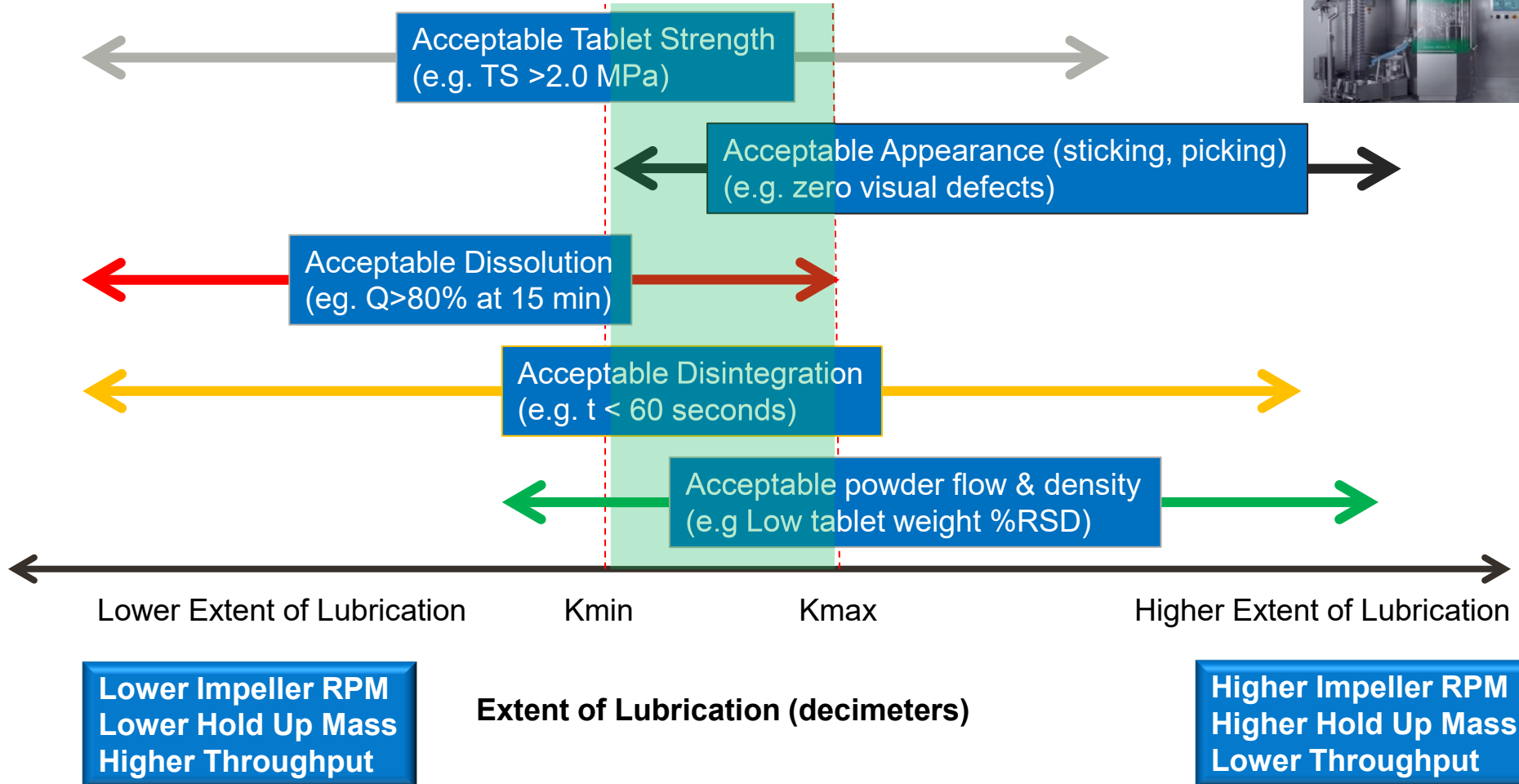


Courtesy
Patrick Daugherty

PROCESS DEVELOPMENT FOR CONTINUOUS MIXING EXTENT OF LUBRICATION



PROCESS DEVELOPMENT FOR CONTINUOUS MIXING EXTENT OF LUBRICATION



PROCESS DEVELOPMENT FOR CONTINUOUS MIXING OPTIMIZATION OF POTENCY/UNIFORMITY AND EXTENT OF LUBRICATION

Gravimetric Feeder

Potency & CU

To achieve CSTR RTD and dampen feeder fluctuations

Continuous Mixing

Select

- Impeller RPM
- Hold Up Mass
- Throughput

Tablet Chemical & Physical Properties

Acceptable

- Tablet Potency
- Content Uniformity

Minimize Feeder Variability at target Flow rates

Acceptable

- Tablets Dissolution
- Tablet Weight
- Tablet Weight %RSD
- Tablet Hardness
- Tablet Disintegration
- Tablet Appearance

Extent of Lubrication
To achieve Min and Max Extent of Lubrication

CASE STUDY: DEVELOPMENT DOE ON PCMM

❖ To develop process understanding for a product manufacturing on PCMM, a risk assessment (following ICH Q9 guidelines) can be undertaken.

- Goal: Identify experiments and analyses that will provide process understanding and lead to a robust control strategy

Process Parameters

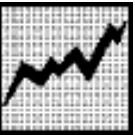
INPUTS (x)



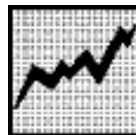
People



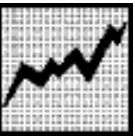
Process



Equipment



Materials

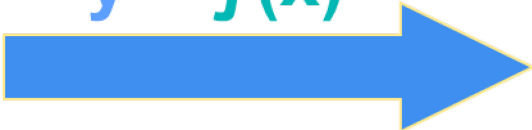


Measurement



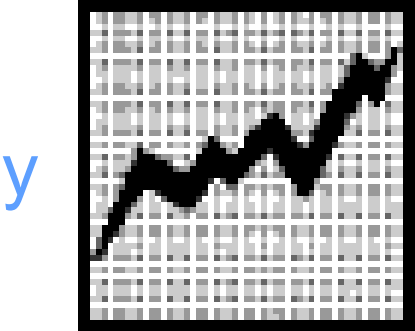
Environment

$$y = f(x)$$



Quality Attributes

INPUTS (x) to the process control variability of the Output (y)

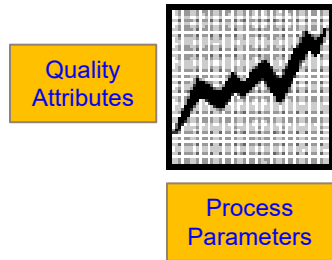


y

x

PCMM DOE DESIGN

1. Build Cause & Effect Matrices for manufacture process.



2. Parameter Prioritization & Range Definition

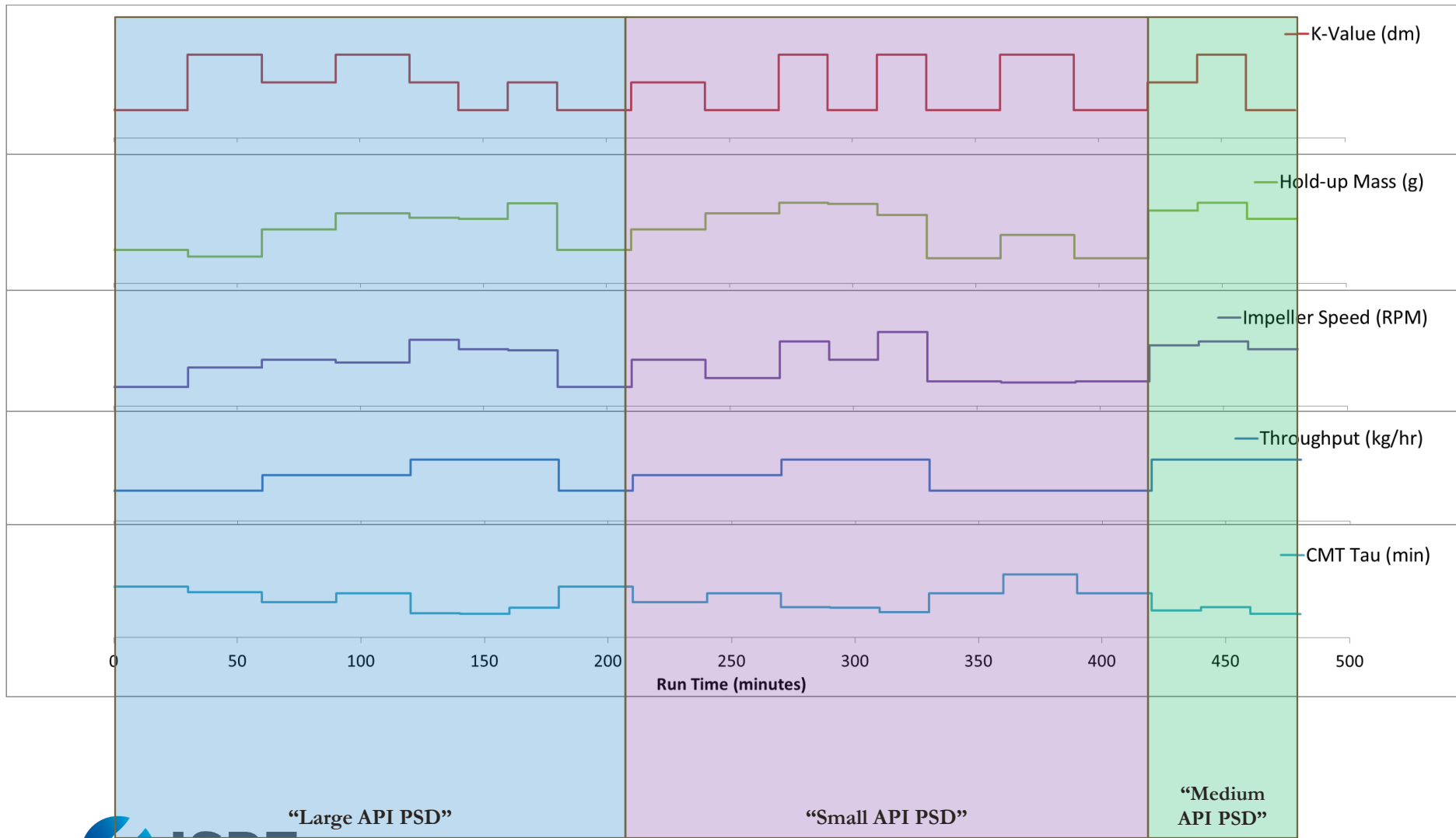
Parameter	Low	Mid	High
Mass Throughput (kg/hr)	Low	Middle	High
CMT K-value (dm)	Low	Middle	High
API PSD	Small	Middle	Large
Hold-up Mass (g)	Low	Middle	High
Impeller Speed (RPM)	Low	Middle	High

3. Multivariate DOE Design

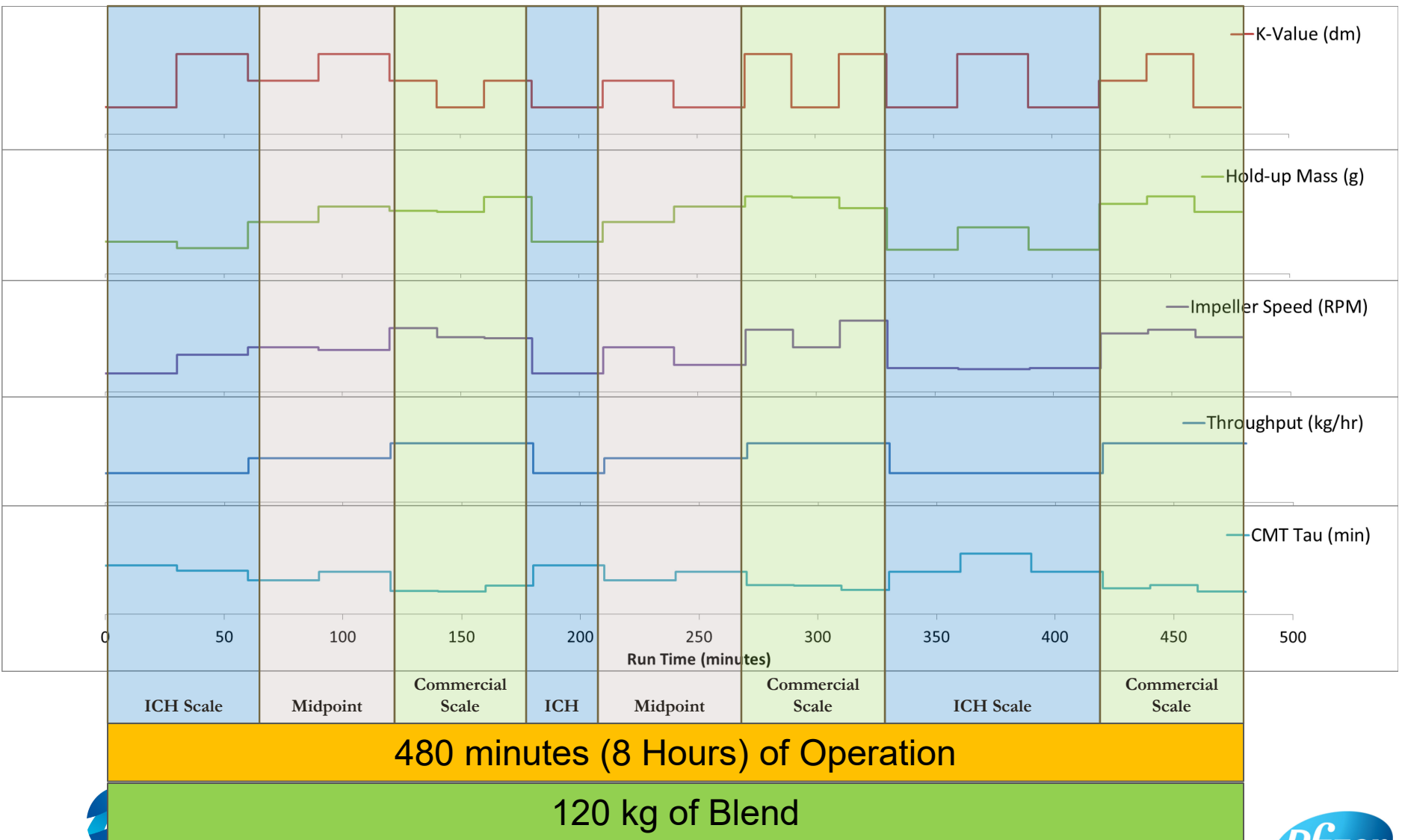
Run Order	Throughput (kph)	K-value (dm)	Hold-up Mass (g)	API Lot	Impeller Speed (RPM)
1	Low	Low	High	Large PSD	Low
2	Low	High	Low	Large PSD	Middle
3	Middle	Middle	Low	Large PSD	High
4	Middle	High	High	Large PSD	Middle
5	High	Middle	Low	Large PSD	High
6	High	Low	Low	Large PSD	High
7	High	Middle	High	Large PSD	High
8	Low	Low	High	Large PSD	Low
9	Middle	Middle	Low	Small PSD	Middle
10	Middle	Low	High	Small PSD	Low
11	High	High	High	Small PSD	High
12	High	Low	High	Small PSD	High
13	High	High	Low	Small PSD	High
14	Low	Low	Low	Small PSD	Low
15	Low	High	High	Small PSD	Low
16	Low	Low	Low	Small PSD	Low
17	High	Middle	Mid	Medium PSD	Middle
18	High	High	High	Medium PSD	High
19	High	Low	Low	Medium PSD	Low



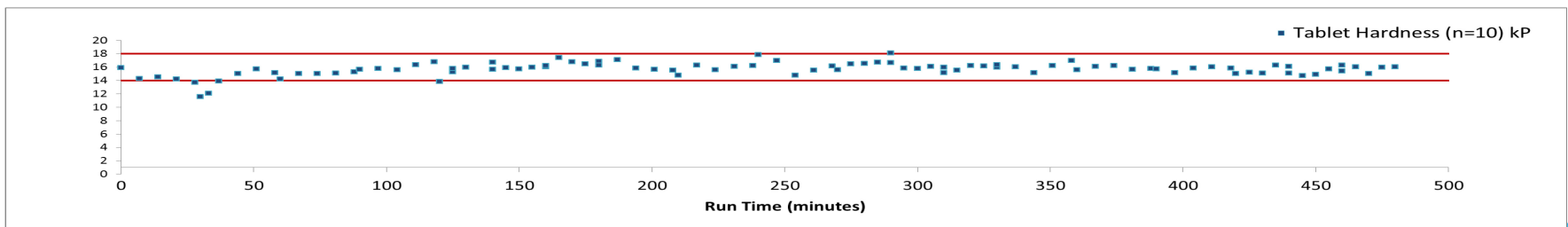
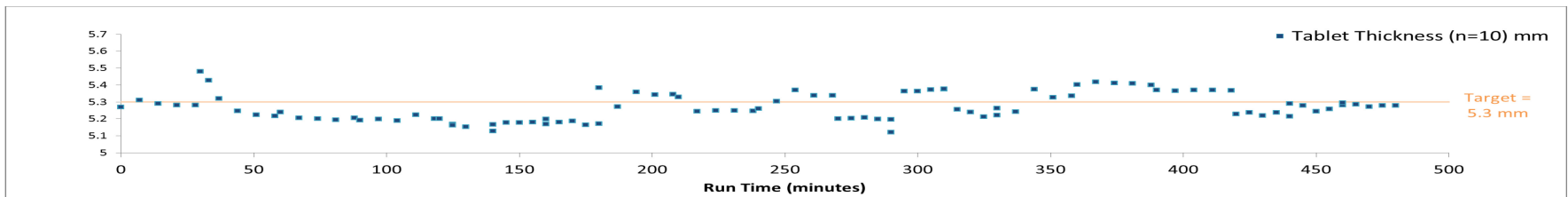
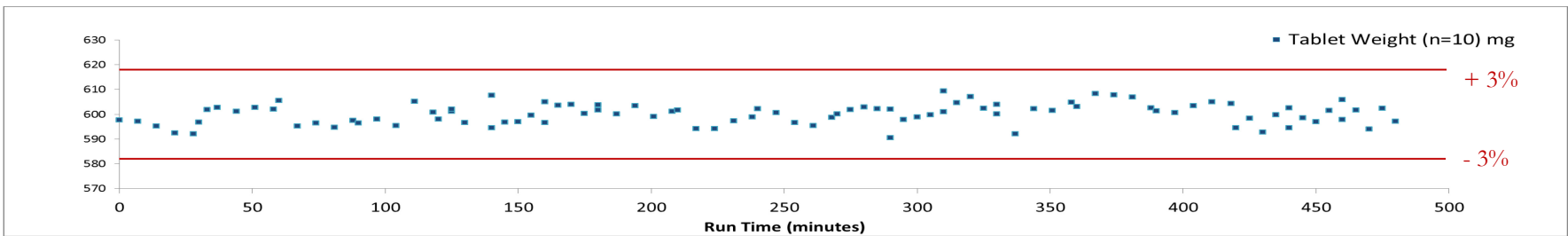
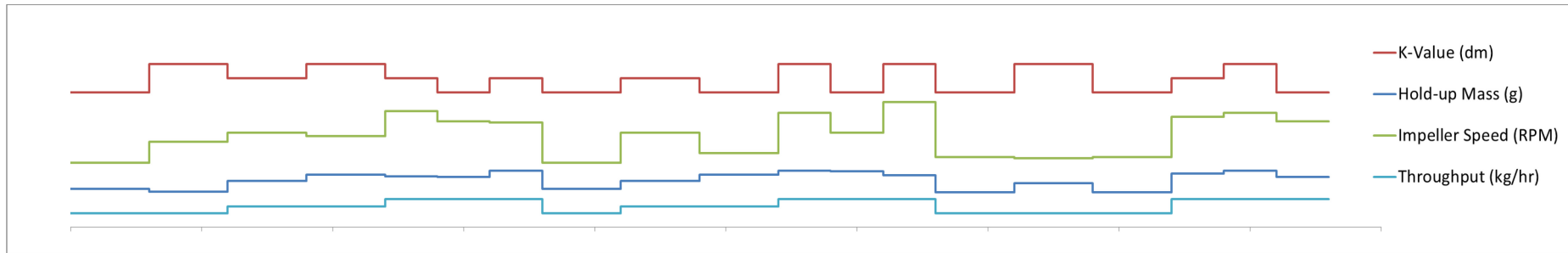
PCMM DOE VISUALIZATION



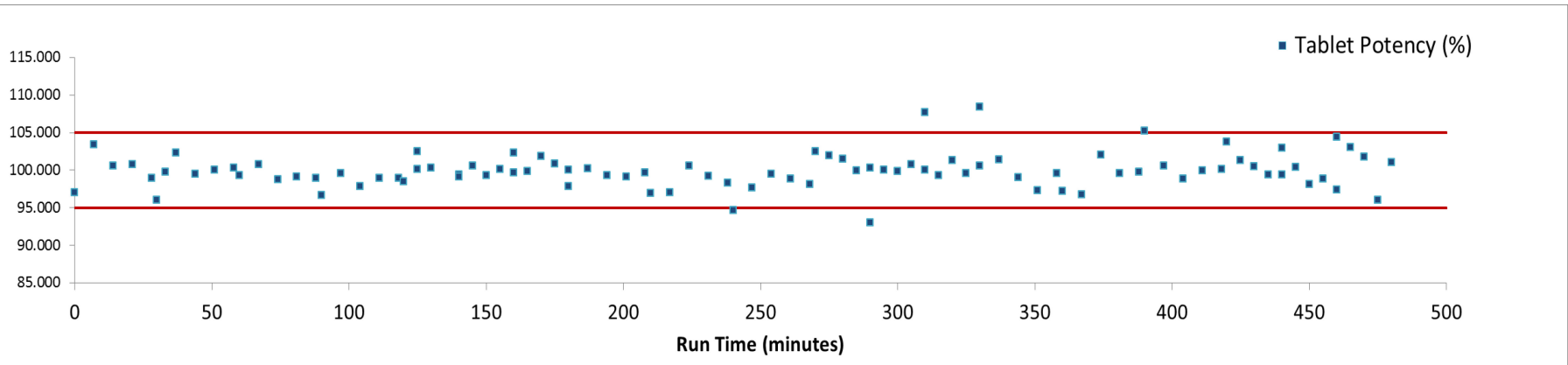
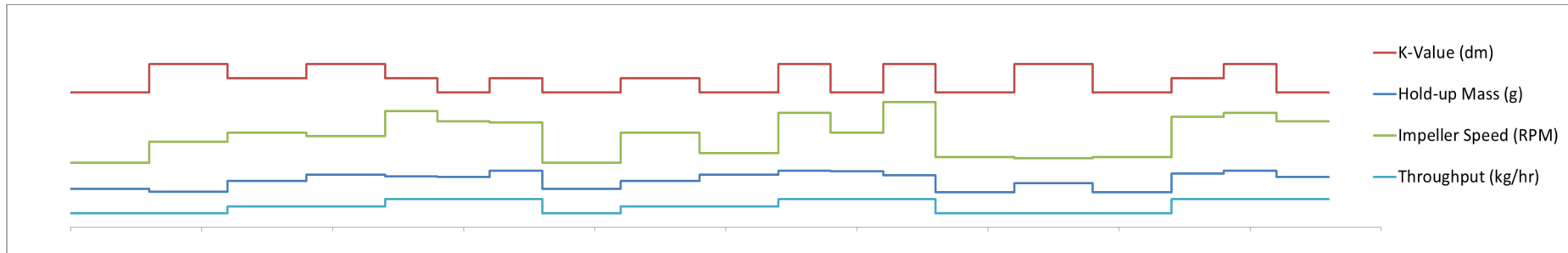
PCMM DOE VISUALIZATION



PCMM DOE VISUALIZATION – TABLET RESULTS



PCMM DOE VISUALIZATION – ANALYTICAL RESULTS



210 Total Tablets
Average Potency = 99.91 %
Standard deviation = 2.29
% RSD = 2.29%

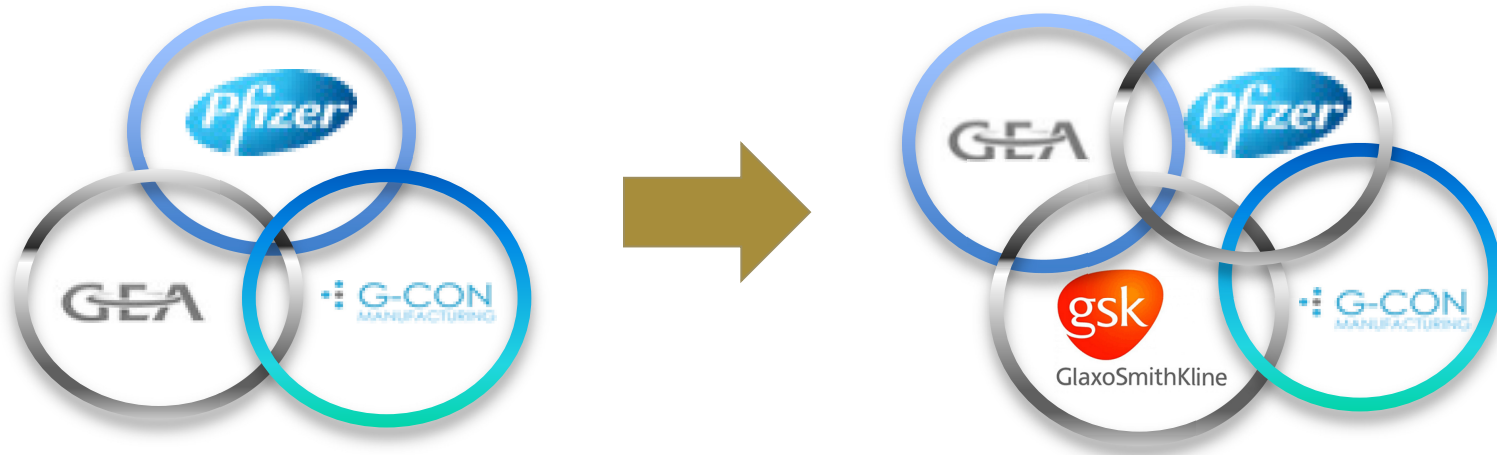
1. The Drivers & “Germ” of a concept – Jeff / Valentin
2. Project Execution Approach & Team Structure – Fred
3. PCMM OSD: “Factory in a POD” – Valentin
4. Impact Integrated Approach – Jeff
5. Conclusion – Fred



- ❖ The PCMM installation represents a collaboration between three companies (Pfizer, GEA, and G-Con Manufacturing) that:
 - Conceptualized, designed, fabricated, installed, and commercialized a novel facility to continuously manufacture pharmaceutical solid oral dosage forms using a POD based installation and exploiting portability, miniaturization and modularity concepts
 - The three organizations invested company resources, talents, and capital to create a OSD platform technology.
 - Created a new paradigm to develop and commercially manufacture solid oral dosage forms that does not use traditional batch pharmaceutical processing.
 - Developed and intergated novel in-line vertical continuous powder mixing technology, customized PAT interfaces, and advanced process control systems into this facility.
 - Lastly, with the help and support of many diverse scientist and engineers, Pfizer today has a working OSD cGMP continuous tableting operation at rates of 5 to 30 kg per hour inside a former warehouse space.

- ❖ Together, these features will transform the pharmaceutical industries and bring medicines to patients quicker.

PCMM 2nd Generation Collaboration



Continued efforts towards creation of an industry 'standard' platform

Pfizer Announces Collaboration With GSK On Next-Generation Design Of Portable, Continuous, Miniature And Modular (PCMM) Oral Solid Dose Development And Manufacturing Units

Further Enhances Pfizer's Collaborative Effort to Help Establish PCMM as Industry Standard in Continuous Processing

Thursday, October 29, 2015 - 8:00am EDT

Pfizer Inc. (NYSE:PFE) announced today a multi-year collaboration with GSK on the development of a next-generation equipment design, building upon Pfizer's existing portable, continuous, miniature and modular (PCMM) prototype for oral solid dose (OSD) pharmaceutical development and manufacturing.

Pfizer's current PCMM prototype is an autonomous and transportable pod that may be quickly shipped from location to location and readily brought online to create a fully functional module that is compliant with industry-standard good manufacturing practice (GMP) guidelines.

Together with GSK, which has notable technical and regulatory experience in continuous processing, Pfizer will conduct coordinated experiments to create the next-generation design of Pfizer's current PCMM prototype. This collaboration expands upon Pfizer's existing collaboration with GEA and G-CON

"This strategic collaboration allows Pfizer and GSK to align on a vision for PCMM-OSD equipment designs and enables us to deploy flexible, agile and reliable manufacturing solutions to benefit patients."



Acknowledgements



- **GEA:** Richard Steiner, Jan Vugts, McCoy Knight, Joel Aerts, Stefaan Lefever, et al
- **GCON:** Maik Jornitz, Dennis Powers, Barry Holtz, Sidney Backstrom, et al
- **Pfizer:** Michael O'Brien, Dan Blackwood, Jeffrey Moriarty, Patrick Daugherty, Phil Nixon, Cindy Oksanen, Rob Noack, Neil Turnbull, Koji Muteki, Angela Liu, Brent Maranzano, John Groskoph, Julia Wood, Valentin Tarasenko, Fred Furman, George Sienkiewicz, Murugan Govindasamy, Jim Labonty, Ke Hong, Mike West, Mike Gershman, Rick Mitzner, Alex Chueh, Steve Hammond, Holly Bonsignore, Will Waterfield, Matt Roberge, Ian O'Callaghan, Dave McCarthy, Mike Flakus, Bob Smith, Mike Warner, Seth Jacobs, Rich Zanzalari, Keith Dennie, Angelica Wong, Liz Courtney, Paul Read, Dan Mendicino, Frank Orlowski, Morten Sogaard, Uwe Schoenbeck, Michael Lallier, Paul J Wiseman, Mike Whittaker, et al
- **Misc. Support:** EHS Solutions Team, Foster Wheeler Team, Whitman Team, Jacobswyper Team, TLBA Team, Hallam ICS Team, City of Groton Officials, Harry Grodsky Team, et al





Thank you!

