PHARMAprocess

Innovation Forum in Pharmaceutical Process

Portable, Continuous, Miniature & Modular (PCM&M) Development & Manufacturing Concept and Facility Implementation

27 Octobre 2015

www.pharmaprocessforum.com

Fira Barcelona

Presentation Topic's

- **Why Change the Current Development/Manufacturing Paradigm**
- **PCMM: The Concept**
- **PCMM for Oral Solid Dose: The Prototype**
  - **The CMT as key enabling technology**
- **Transformational Development, Manufacturing & Distribution**
- **What's Next?**
- **Concluding Remarks**

Why Change the Paradigm

Acceleration

- Breakthrough Therapies
- Market Exclusivity

Cost Pressures

- Inventory & Expiry
- Development Costs

Changing Markets

- More Lower Volume Products
- Access to Undeveloped Markets

- **Unprecedented pace of technology & informatics innovation**
- **Importance of uniformly high quality & supply reliability**

PCMM: Portable, Continuous, Miniature & Modular Development & Manufacturing *CORE Concepts*

Industry standard low cost technology platforms - equally applicable in development ***AND*** commercial operations

Continuous processing, or other ***small-footprint*** enabling technologies – allowing ***modularity***, environmental isolation, ***operations and location flexibility***

Design for ***multiple products***, ***rapid changeovers*** and ***production-on-demand***

Applicable to biologics, small molecules, API & Drug Product

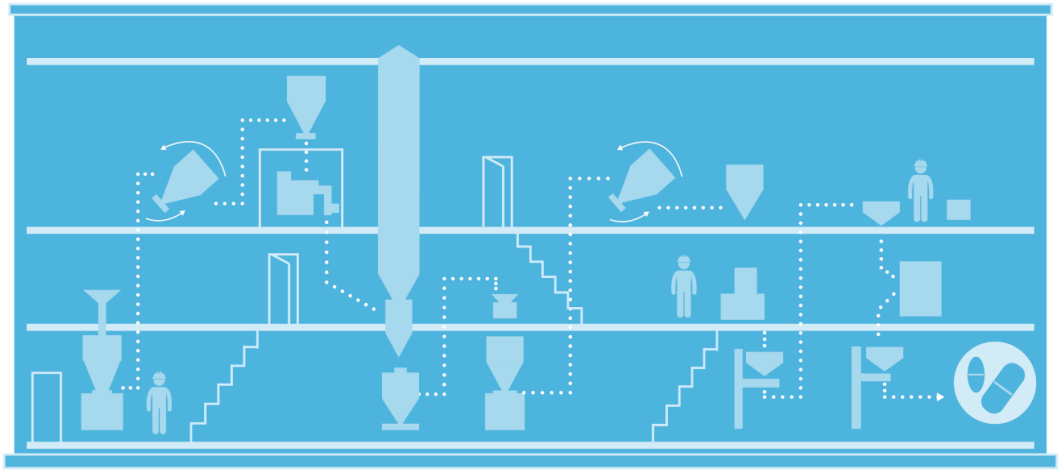
PCMM For Oral Solid Dose: From Costly & Complex to Simple & Economical

The Move to Portable, Continuous, Miniature and Modular Manufacturing

TODAY

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

Complex process with large, dedicated manufacturing facility



TOMORROW

Continuous operations make drugs from powder to tablet in minutes

Miniaturized equipment fits in portable, modular facility

GEA : G-CON MANUFACTURING Partners in the development of portable facilities, equipment and systems

Traditional Granulation Process

Continuous Direct Compaction

Continuous HS Wet Granulation

Future Vision of PCMM: Oral Solid Dose (OSD)

- Same equipment for development, clinical and commercial production
- Powders to uncoated IR tablets in minutes - - ultimately finished product / packaged goods

- Advanced Process Control (APC) for Continuous Quality Verification (CQV) and knowledge accrual from early development onwards
- Manufacture to demand rather than estimated forecast

- Rapid deployment (<12 mos) of *low cost* manufacturing units
- Maximum flexibility through ‘skid-mounted’ & POD technologies

- Autonomous factory modules in ‘warehouse-type’ infrastructure
- Redeployment & potential for shared multi-company facilities

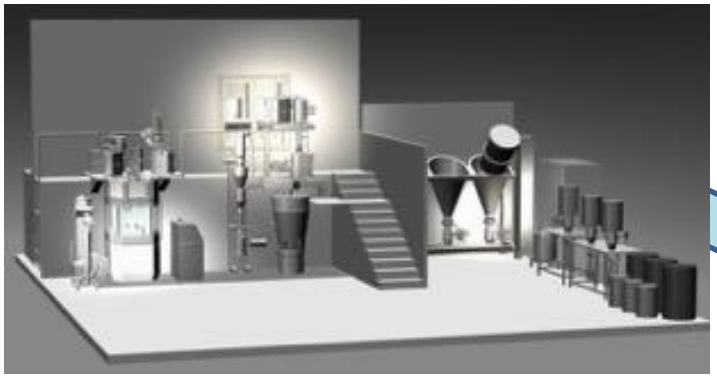
Examples: Continuous Manufacturing Oral Solid Drug Products

- **Vertex:** ORKAMBI (CF) received FDA approval July 2, 2015
  - Powders to coated tablets with PAT for IPC/RTRT control strategy
- **C-SOPS:** Rutgers, NJIT, Purdue, University of Puerto Rico at Mayaguez and a consortium of ~ 40 companies within the pharmaceutical sector
- **Janssen**: Recent $6M collaboration with Rutgers to help with implementation in Puerto Rico
- **Lilly:** Continuous Direct Compression with modelling
- **Novartis/MIT Center for Continuous Manufacturing:**
  - $65 million in 2007 for 10 year research program
  - End-to-end continuous synthesis and formulation
- **Aesica:** CMO with end-to-end continuous tablet processing

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

Continuous Processing Platform Technology skid for Solid Oral Dosage Forms HSWG and CDC

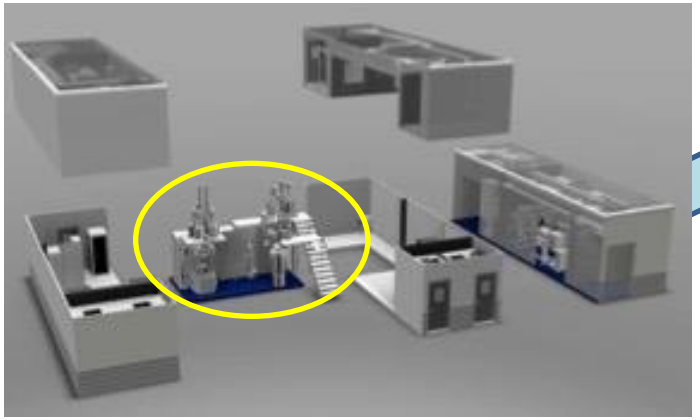
Pre-fabricated in Belgium



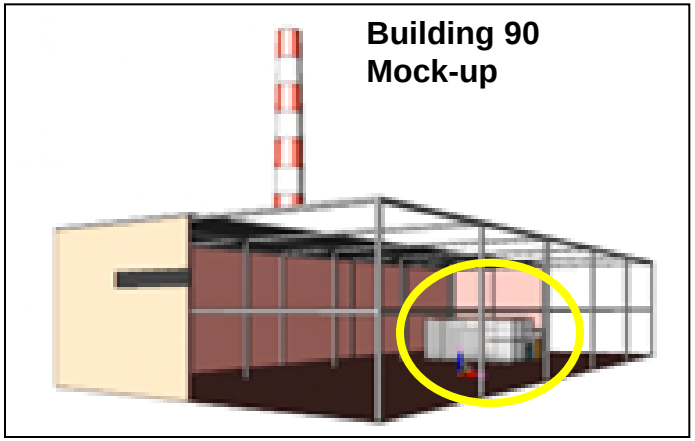
FAT in Belgium
Shipped to Groton

Integrated into a 'Portable' cGMP POD

5 Modules Pre-fabricated in College Station Texas



FAT in Texas
Shipped to Groton



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

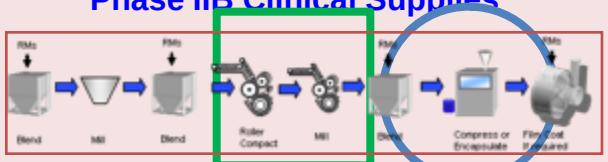
March 2015

Current State Batch Process: Transfer of Technology

Current State
(dry granulation / roller compaction)

Drug Product Quantities

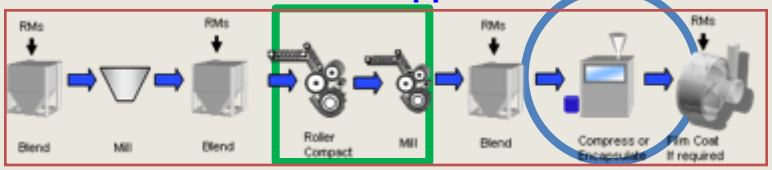
Phase IIB Clinical Supplies



<10 kg

Tech Transfer & Process Scale Up

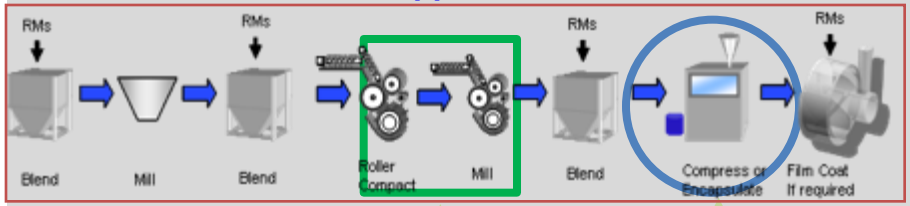
Phase III Clinical Supplies



<100 kg

Tech Transfer & Process Scale Up

Commercial Supplies



100 to 1000 kg

Transfer of Technology

Experiments

Engineering Models

Process Analytical Technology

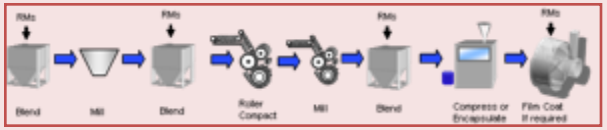
Advanced Process Control

Diluted Efforts

Future State PCM&M: Platform Technology

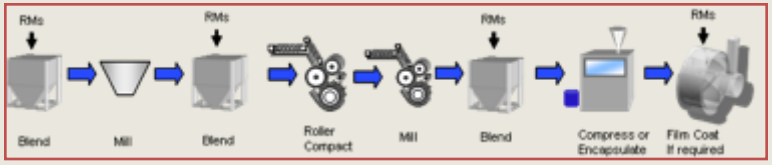
Current State
(dry granulation / roller compaction)

Phase IIB Clinical Supplies



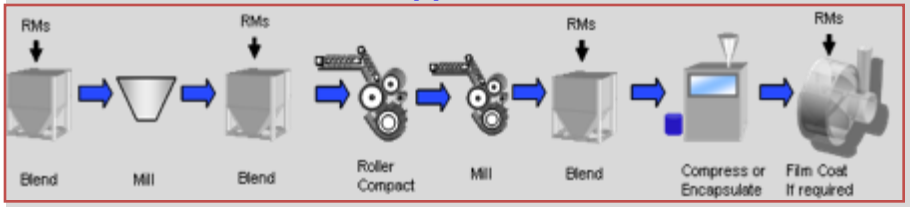
Tech Transfer & Process Scale Up

Phase III Clinical Supplies



Tech Transfer & Process Scale Up

Commercial Supplies

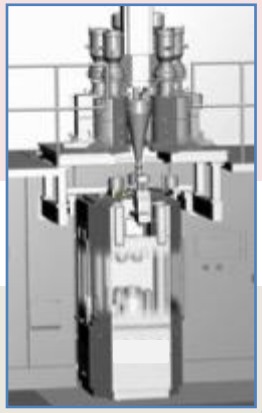


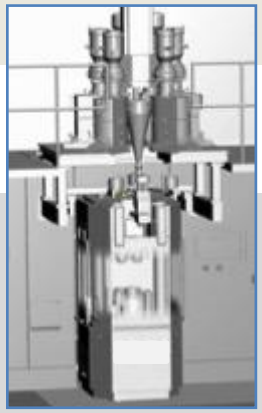
Drug Product Quantities

<10 kg

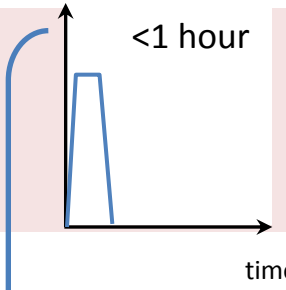
<100 kg

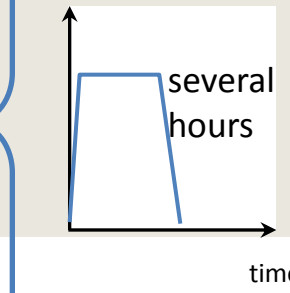
100 to 1000 kg

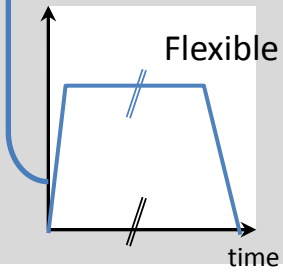




Future State
(dry blend / direct compaction)







Future State PCM&M: Platform Technology

Platform Technology

Experiments

Engineering Models

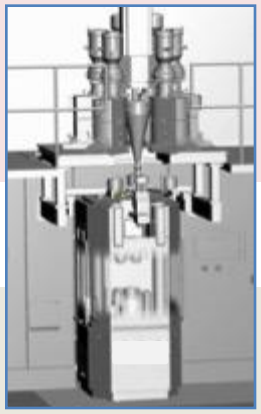
Process Analytical Technology

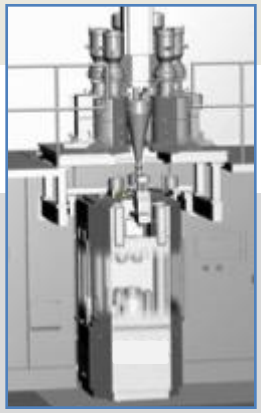
Advanced Process Control

Concentrated Efforts

Reduced Time, $, Resources

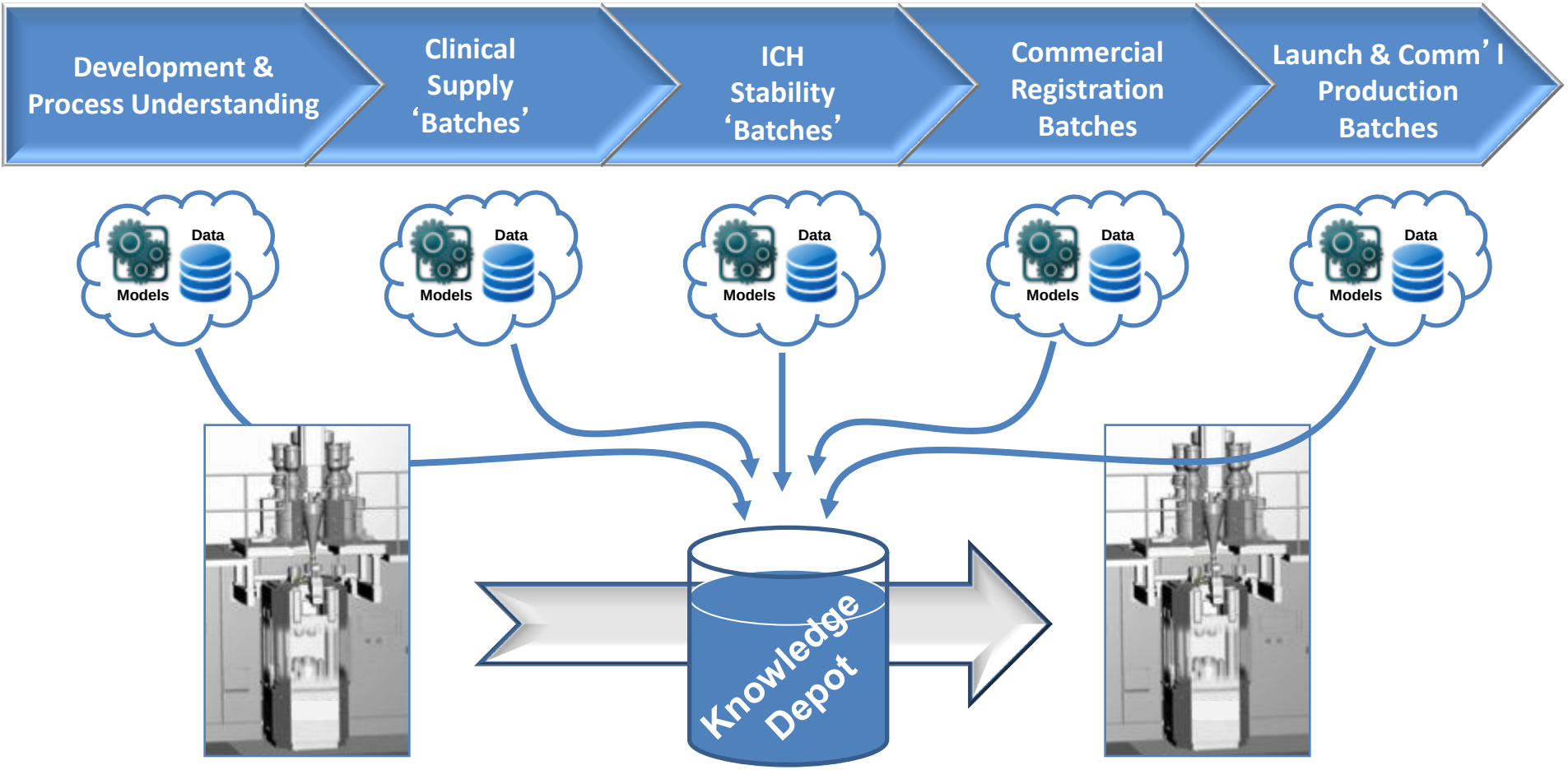
Drug Product Quantities	Future State (dry blend / direct compaction)
Phase IIB Clinical Supplies <10 kg	<1 hour; time
Phase III Clinical Supplies <100 kg	several hours; time
Commercial Supplies 100 to 1000 kg	Flexible; time





Continuous Knowledge Accrual Paradigm with PCMM

The same platform technology used at all scales…….

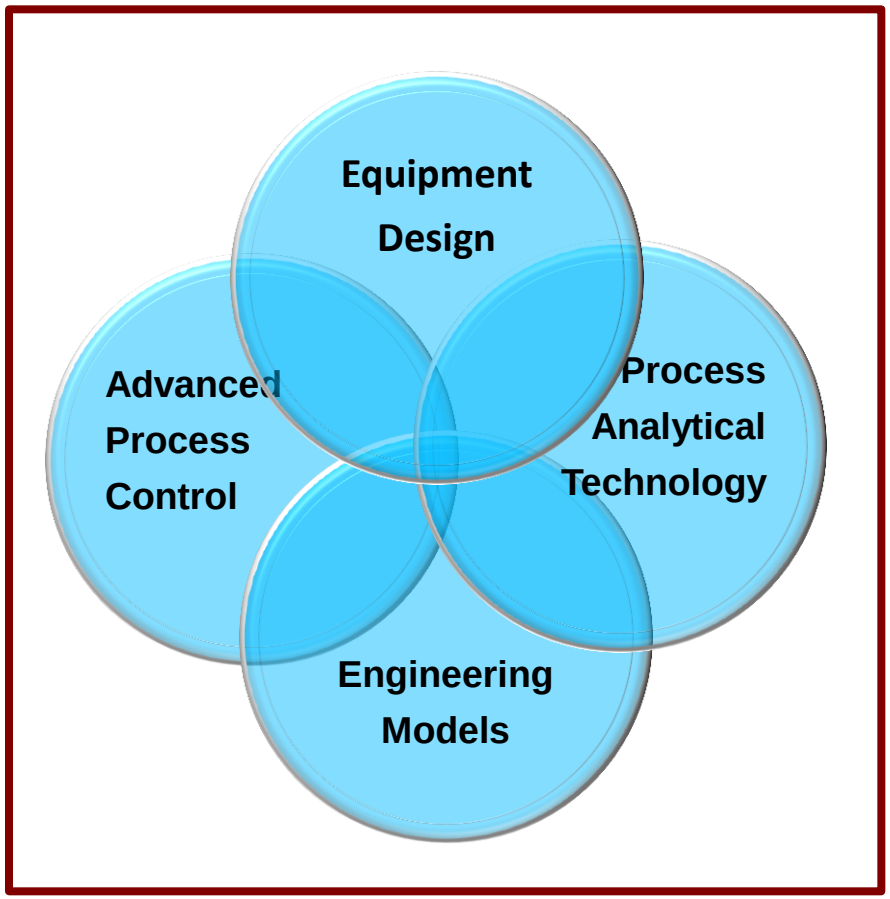


An Integrated Approach to a Platform Technology

World-class Materials Science & Formulation Development Practices

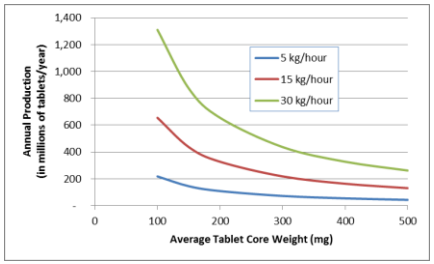
Particle Engineering for API and Excipients

Integrated System

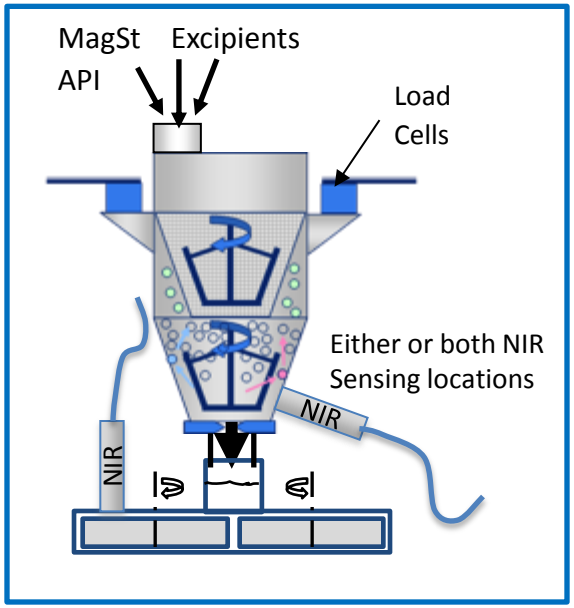


World-class Commercial Manufacturing & Engineering Partners

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

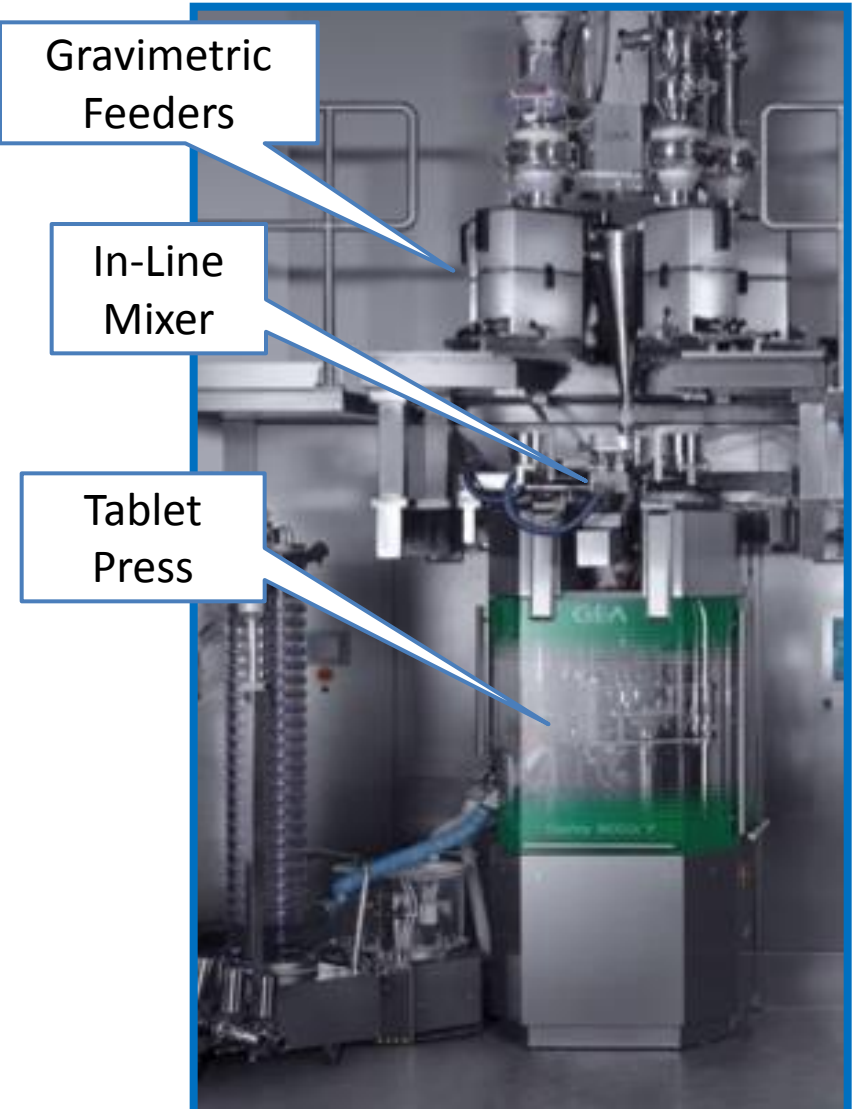


Initial CDC Prototype: *Vertical Continuous Mixing Element*



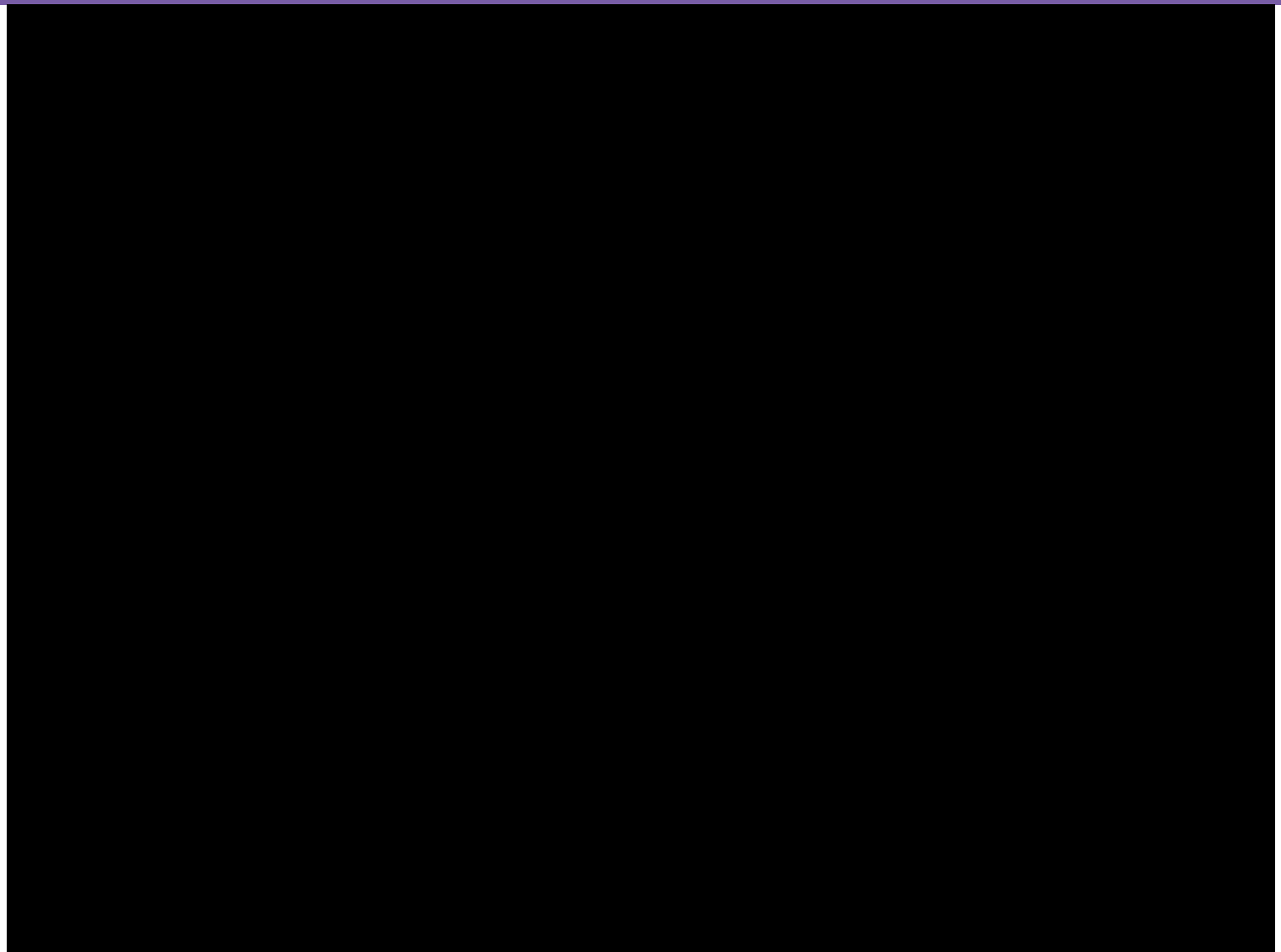
Making Continuous Direct Compaction More Prevalent

Vertical Continuous Mixing Element Objectives

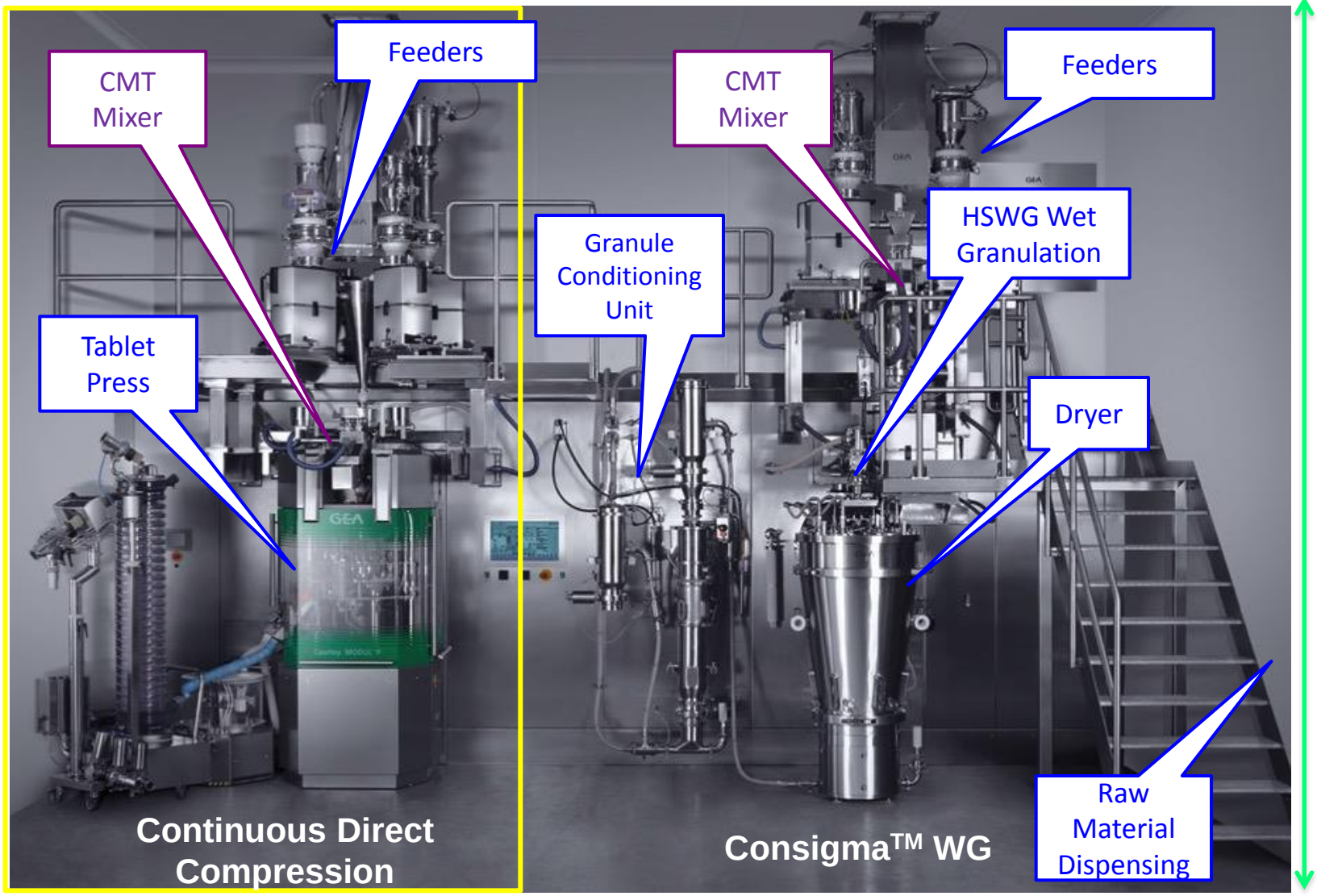


- Powder mixing as close to dosage form creation as possible
- Independent control of
  - Powder Hold Up Mass,
  - Mass Throughput, and
  - Impeller RPM
- Residence Time Distribution
  - Based on simple CSTR model
  - Consistent RTDs over a wide range of process conditions
- Integrated powder de-lumping capabilities
- Integrated PAT sensors
- ***Minimal/Zero Waste Start Up & Shutdown***

PCMM OSD: *Powder Flow*

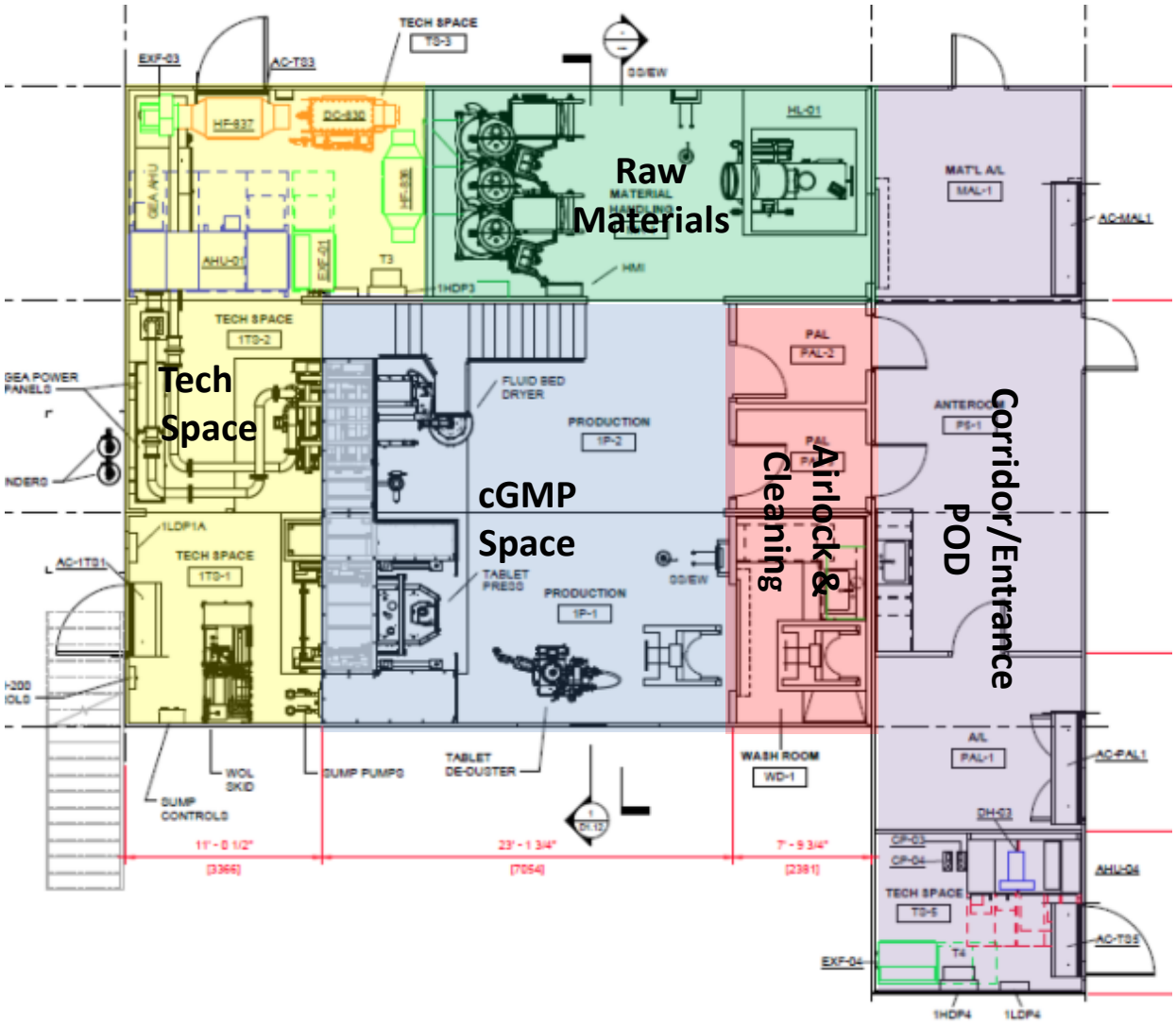


Continuous High Sheer WG + Direct Compaction in a '*POD*'



PCMM Assembled POD

PCM&M POD Layout

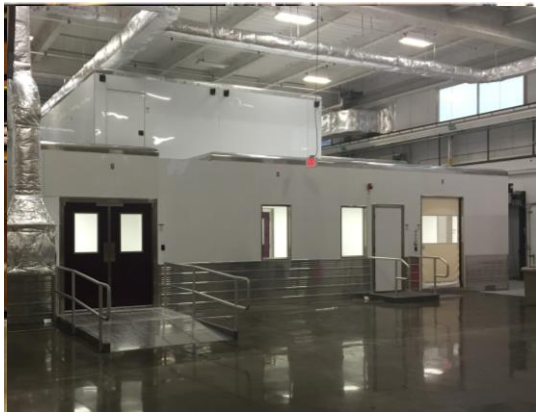


Preparations

2015

GEA Process Equipment in Belgium

G-Con PODS in Texas



Assembled in Groton Bldg 90

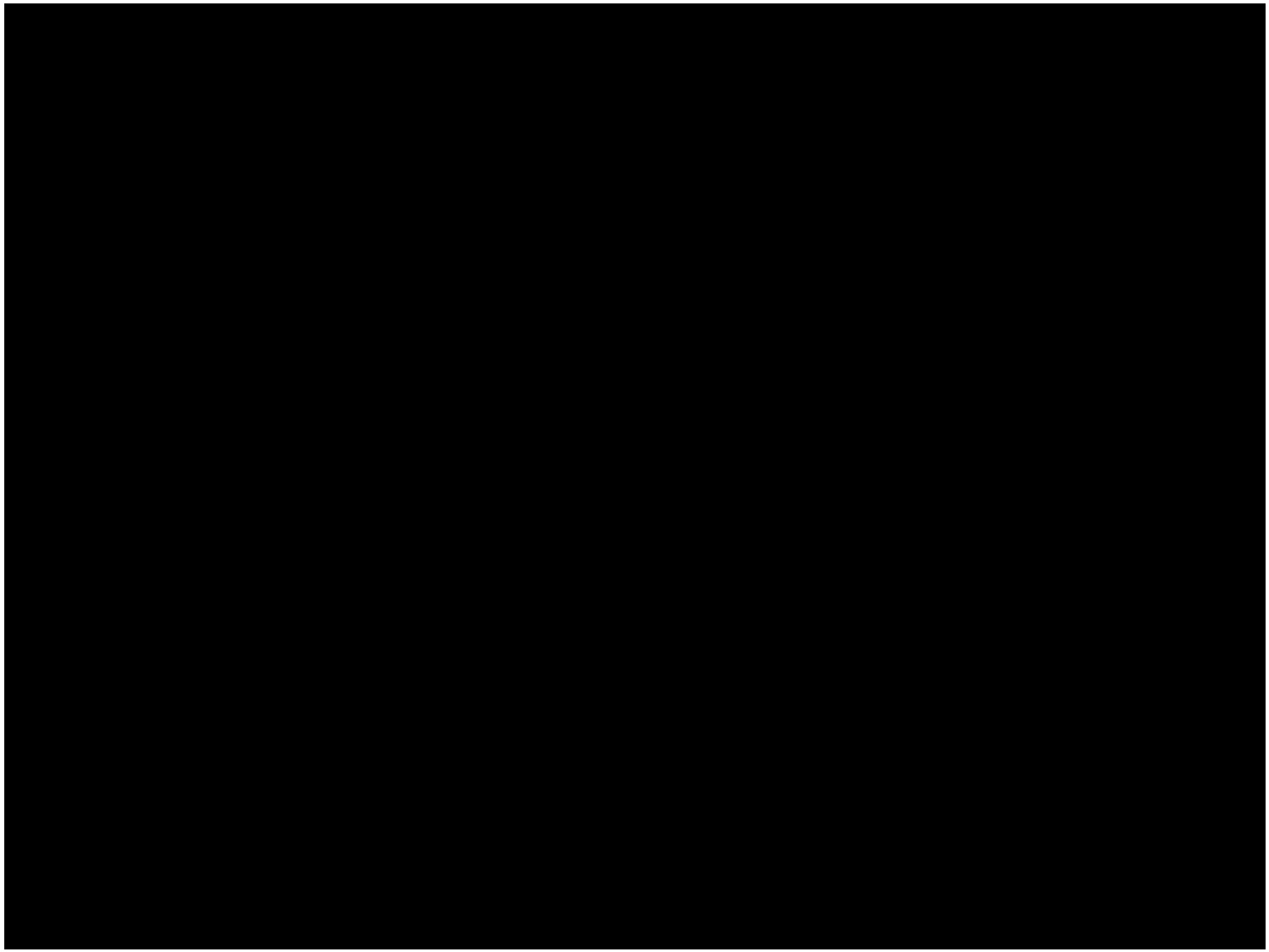
Collaborative Effort:

Commercial Global Supply
WRD Pharmaceutical Sciences
Global Operations
Also: Finance, Business Development, Legal, Procurement

Our collaboration partners: GEA & G-CON MANUFACTURING

Assembly in Groton Warehouse – March 2015

PCM&M Assembly in Groton, CT USA



Transforming the Traditional Development, Manufacturing & Distribution Model

Is There a Need to Change the Prevalent Development, Manufacturing & Distribution Model

- Pharmaceutical industry needs to increase the supply of medicines to patients in wider-ranging regions of the world - while under tremendous pressure to reduce costs

- Global divergence increases manufacturing costs, complicates the supply chain, hinders science & risk-based approaches, increases regulatory burden, reduces innovation & delays the delivery of medicines to patients

- ***Development, manufacturing & supply of medicines*** is a most critical component of the medicines to market process ***BUT*** also a very large corporate enterprise

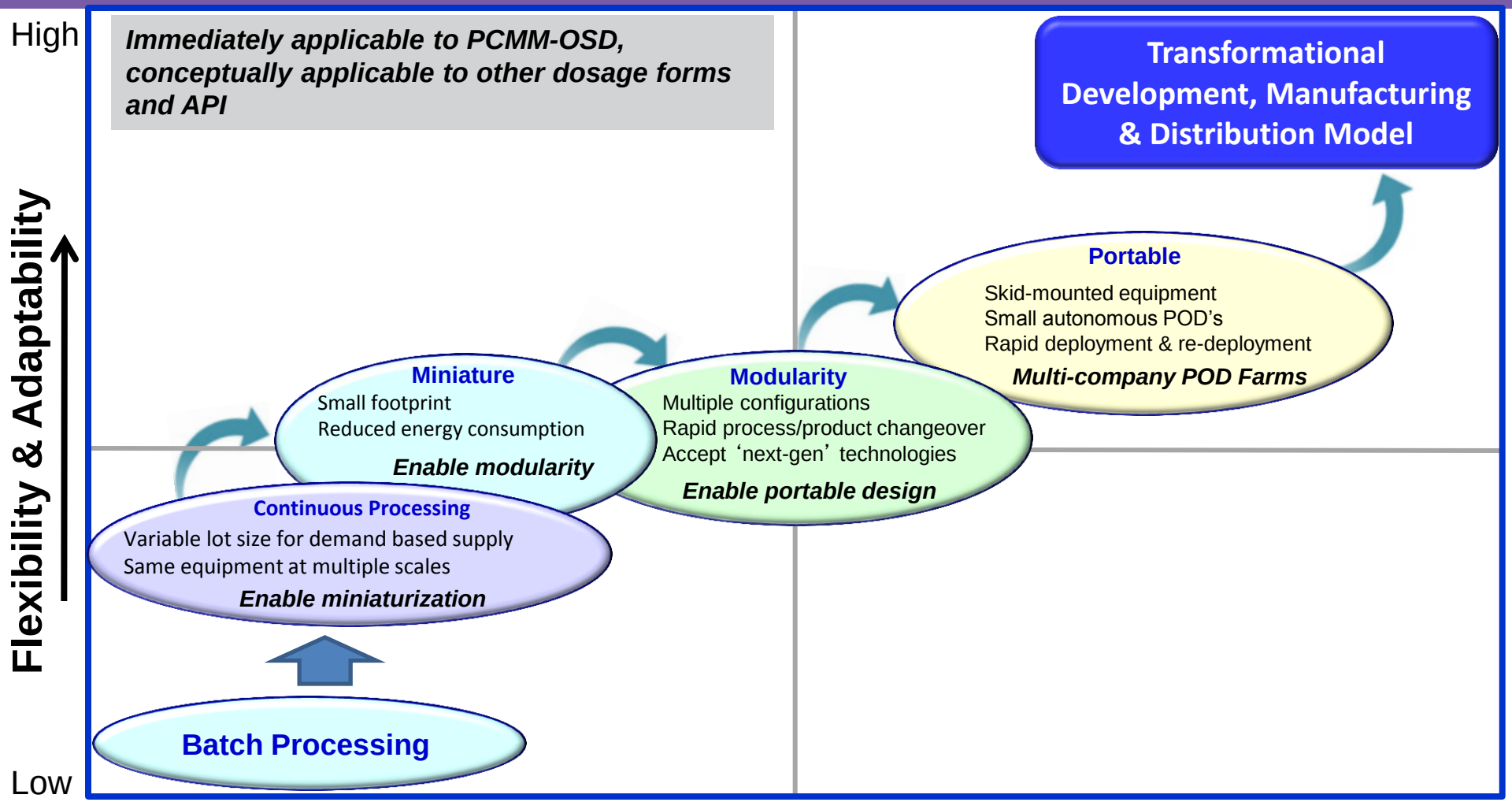
We can do it better

We can do it faster

We can do it cheaper

We can meet the needs of a highly diverse patient population

Transforming Development, Manufacturing & Distribution: PCMM as a Foundation



A Different Development, Manufacturing, & Distribution Model

Platform technologies to enable the same equipment for development, clinical and commercial production

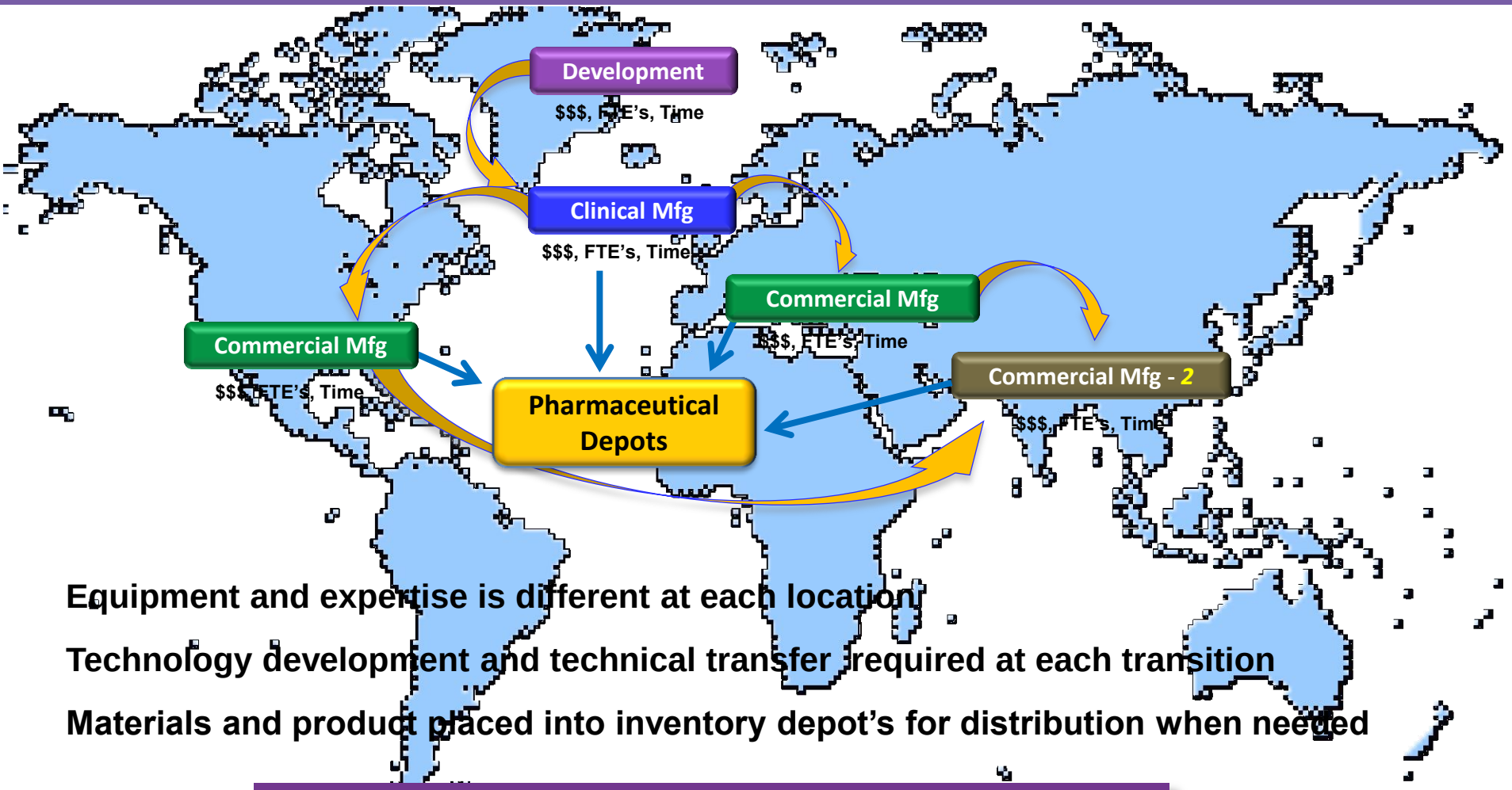
Deployment & Flexibility 1

- Rapid deployment (<12 mos) of *low cost* manufacturing units
- Maximum flexibility *via* small footprint 'skid-mounted' and autonomous POD technologies

Supply & Demand 2

- Manufacture medicines to demand rather than estimated market forecast
  - API-on-Demand to mitigate expiry issues & reduce inventory
- Distribution (Clinical & Commercial) from the point of manufacture in any region of the globe

Other Change Drivers: Today's Industry Development, Manufacturing & Distribution Model



Equipment and expertise is different at each location

Technology development and technical transfer required at each transition

Materials and product placed into inventory depot's for distribution when needed

$$$, FTE's, reliability, depot & expiration costs / issues

Future Development, Manufacturing & Distribution Model

Development 'laboratories' become manufacturing facilities

Manufacturing facilities will be warehouse space with autonomous mini-factories inside

Equipment and expertise is same/similar at each location

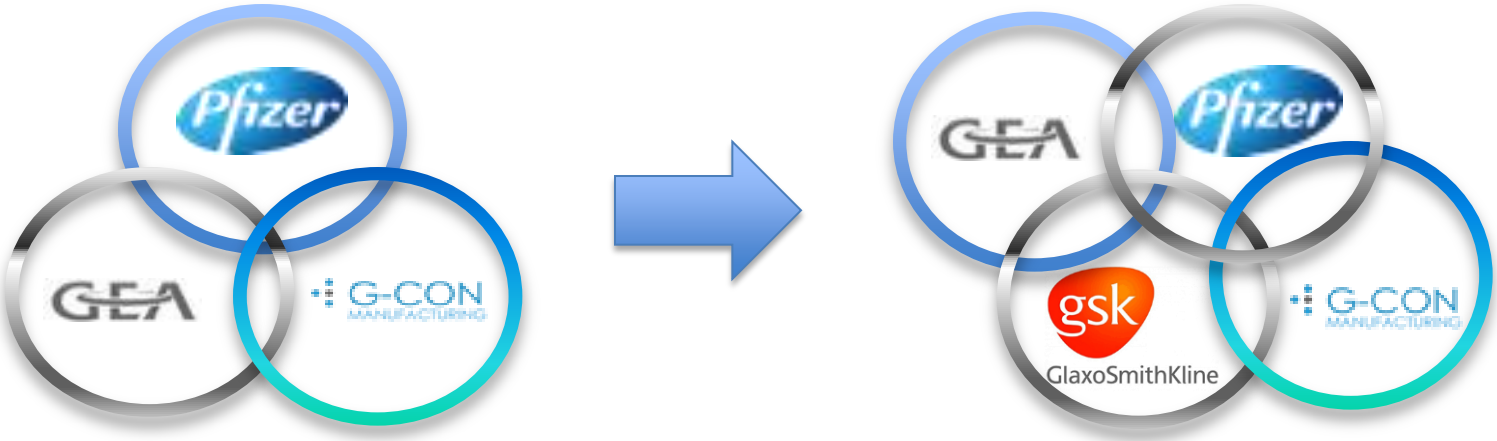
Process transfer to identical facilities or replicate facilities

Product can be distributed from point of manufacture in any global region

Future Development, Manufacturing & Distribution Model

What's Next?

PCMM 2nd Generation Collaboration to be Announced



***ca.* 20% Reduction in Height: 14' to 11' ('single-decker POD')**

Additional capabilities: *Continuous film coating & encapsulation*

Create more of an industry standard platform

Enhanced modularity

Consider additional like-minded partners

Potential Areas for Collaboration

most can be pre-competitive

- Enabling regulatory science
- Holistic solutions beyond the processing equipment
  - Sensors/PAT, informatics, APC, RtR, etc.
- Industry standards and common designs when possible
- Predictive computational models/tools
- Continued miniaturization
- Maximize use of continuous direct compression
- Shared facilities
- Other dosage forms and/or API

Concluding Remarks

The Pharmaceutical industry is under tremendous pressure to change

PCMM:

- **Same equipment for Development & Manufacturing**
  - **Minimize technical transfer costs and resources**
- **Continuous Direct Compression *via* novel mixing technology**
- **Rapid deployment - redeployment**
- **Factories in a POD**

What will Development, Manufacturing, & Distribution look like in the future

- **Distribution from point of manufacture**
- **Production & distribution on demand rather than forecast**
- **Get patients the medicines they need, when they need them – at lower cost**

Work closely together with global regulatory agencies

GSK & Pfizer to Announce PCMM 2nd Gen Collaboration with GEA & GCON

Concluding Remarks

- **WRD Pharmaceutical Sciences**: Michael O'Brien, Dan Blackwood, Jeff Moriarty, Phil Nixon, Cindy Oksanen, George Reid, Rob Noack, Neil Turnbull, Koji Muteki, Angela Liu, Brent Maranzano, John Groskoph
- **Pfizer Global Supple (PGS)**: Val 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
- **Procurement (PGS)**: Ian O'Callaghan, Dave McCarthy
- **WorldWide Business Development**: Mike Flakus, Bob Smith
- **Legal**: Mike Warner, Seth Jacobs, Rich Zanzalari
- **Emerging Markets**: Keith Dennie, Angelica Wong
- **Finance**: Liz Courtney, Paul Read, Dan Mendicino, Frank Orlowski
- **Early Research & Development Innovation**: Morten Sogaard, Uwe Schoenbeck
- **Colleagues at GEA and G-CON**

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