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

27 Octobre 2015
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

- 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
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

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

Integrated into a ‘Portable’ cGMP POD 5 Modules Pre-fabricated in College Station Texas

FAT in Belgium
Shipped to Groton

Building 90
Mock-up

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**
- Tech Transfer & Process Scale Up
  - <10 kg

**Phase III Clinical Supplies**
- Tech Transfer & Process Scale Up
  - <100 kg

**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 IIIB Clinical Supplies
  - Tech Transfer & Process Scale Up

- Phase III Clinical Supplies
  - Tech Transfer & Process Scale Up

- Commercial Supplies

**Drug Product Quantities**

- Phase IIIB Clinical Supplies: <10 kg
- Phase III Clinical Supplies: <100 kg
- Commercial Supplies: 100 to 1000 kg

**Future State**
(dry blend / direct compaction)

- <1 hour
- Several hours
- Flexible
Future State PCM&M: Platform Technology

Platform Technology

Experiments

Engineering Models

Process Analytical Technology

Advanced Process Control

Drug Product Quantities

Future State (dry blend / direct compaction)

Phase IIB Clinical Supplies
<10 kg

<1 hour

time

Phase III Clinical Supplies
<100 kg

do several hours

time

Commercial Supplies
100 to 1000 kg

Flexible
time

Reduced Time, $, Resources

Concentrated Efforts
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

Integrated System

Equipment Design

Advanced Process Control

Process Analytical Technology

Engineering Models

World-class Commercial Manufacturing & Engineering Partners

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

Particle Engineering for API and Excipients
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’

- Continuous Direct Compression
- CMT Mixer
- Tablet Press
- Feeders

- Consigma™ WG
- CMT Mixer
- Granule Conditioning Unit
- Raw Material Dispensing
- HSWG Wet Granulation
- Dryer
- Feeders

Total Elevation ~14.5 ft
PCMM Assembled POD

- Technical Space
- Processing POD
- Raw Materials POD
- Corridor/Entrance POD
PCM&M POD Layout

- Raw Materials
- cGMP Space
- Tech Space
- Airlock & Cleaning
- Corridor/Entrance
- POD
Collaborative Effort:
Commercial Global Supply
WRD Pharmaceutical Sciences
Global Operations
Also: Finance, Business Development, Legal, Procurement

Our collaboration partners: GEA & G-Con

Assembly in Groton Warehouse – March 2015
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

- **High**
  - Immediately applicable to PCMM-OSD, conceptually applicable to other dosage forms and API

- **Low**
  - Batch Processing

**Technology & Strategies**

- **Continuous Processing**
  - Variable lot size for demand based supply
  - Same equipment at multiple scales
  - Enable miniaturization

- **Modularity**
  - Multiple configurations
  - Rapid process/product changeover
  - Accept ‘next-gen’ technologies
  - Enable portable design

- **Miniature**
  - Small footprint
  - Reduced energy consumption
  - Enable modularity

- **Portable**
  - Skid-mounted equipment
  - Small autonomous POD’s
  - Rapid deployment & re-deployment
  - Multi-company POD Farms

**Immediate Applicability**

- Immediately applicable to PCMM-OSD, conceptually applicable to other dosage forms and API

**Transformative Development, Manufacturing & Distribution Model**

- PCMM as a Foundation

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**Established** ➔ **Current State-of-the-Art** ➔ **Future/Emerging**
A Different Development, Manufacturing, & Distribution Model

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

1. Deployment & Flexibility
   - Rapid deployment (<12 mos) of low cost manufacturing units
   - Maximum flexibility via small footprint ‘skid-mounted’ and autonomous POD technologies

2. Supply & Demand
   - 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

More $$ for Drug Innovation

Supply to demand vs. forecast

Reduce year over year inventory

Increase assurance of quality (e.g. 6 Sigma)

Never required to redesign a process (aspirational)

Transform co-development & technical transfer paradigm

Right-size industry workforces (with complementary ‘upskilling’) 

Provide patients, around the world, the medicines they need when they need them
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
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- **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
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