ConsiGma™
Continuous Manufacturing
OSD

Road to Operational Excellence & Accelerated Drug Development

Harish Krishnan – APPLICATION MANAGER, CONTINUOUS MANUFACTURING
Why Innovation?

Pharmaceutical Manufacturing: The Path Ahead.

"Right now, manufacturing experts from the 1950s would easily recognize the pharmaceutical manufacturing processes of today. It is predicted that manufacturing will change in the next 25 years as current manufacturing practices are abandoned in favor of cleaner, flexible, more efficient continuous manufacturing."

Dr. Janet Woodcock, AAPS Annual meeting, October 2011

“The lack of agility, flexibility, and robustness in the pharmaceutical manufacturing sector poses a potential public health threat as failures within manufacturing facilities that result in poor product quality can lead to drug shortages. Drug shortages are a critical health care issue, affecting individual patients across the United States. Recognizing that shortages commonly begin with a supply disruption related to product quality, FDA is focusing on encouraging and sustaining advancements in pharmaceutical manufacturing.”
Quality by Test - QbT

- Traditionally used method of ensuring drug quality in the pharmaceutical Industry
- Uses an empirical based method for checking product quality which involves end product testing.
- Not a means to ensure that product is within quality but a check to see if they are within quality.
Quality by Design
Continuous Manufacturing

• A new approach to product quality as opposed to the existing Quality by Test
• QbD began with the recognition that increased testing does not necessarily improve product quality. Instead quality must be built/designed into the product.
• QbD is a scientific, risk-based approach that focusses on designing quality into a product from the earliest stages of planning to prevent quality failures from ever occurring and more readily address them if they do occur.
QbD - DoE – Design Space

• Continuous Manufacturing facilitates the QbD approach by enabling a large number of test samples to be taken, in minimum time & with minimum product, for carrying out a more comprehensive Design of Experiment (DoE) leading to the establishment of the operable design space.

This results in better characterization of process & product thereby mitigating risks in the drug formulation development stage & subsequent scale-ups.

• Process robustness is the ability of a process to deliver acceptable drug product quality and performance while tolerating variability in the process and material inputs.

So robustness needs to be built into the Design Space.
QbD – Control Strategy

- The knowledge gained through the establishment of CQAs, CMAs, CPPs and the Design Space culminates in the establishment of a Control Strategy which is defined as a planned set of controls, derived from current product & process understanding that ensures process performance and product quality.
- Use of PAT, soft sensors and predictive modelling is part of the control strategy.
QbD - Design Space

CPP
Critical Process Parameters

Pharmaceutical Process Operation within the Design Space established by a set of Design of Experiments

CMA
Critical Material Attributes

CQA
Critical Quality Attributes
Continuous Manufacturing

Dispensing
- Transfer

Granulation
- Transfer

Drying
- Transfer, QC, transfer

Blending
- Transfer, QC, transfer

Tableting
- Transfer, QC, transfer

Coating
- Transfer, QC, transfer

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Drug Discovery & Development Timeline

Drug Discovery and Development Timeline

Drug Discovery
- Pre-Discovrey
  - 3 - 6 YEARS
  - ~5,000 - 10,000 COMPOUNDS

Preclinical
- 250

Clinical Trials
- PHASE 1
  - NUMBER OF VOLUNTEERS: 20-100
  - 6 - 7 YEARS
- PHASE 2
  - NUMBER OF VOLUNTEERS: 100-500
  - 5
- PHASE 3
  - NUMBER OF VOLUNTEERS: 1,000-5,000
  - FDA Review
  - Scale-Up to Mfg.
  - Post-Marketing Surveillance

FDA Review
- ONE FDA-APPROVED DRUG
- 0.5 - 2 YEARS

Post-Marketing Surveillance
- INDEFINITE

November 25, 2019
Pfizer - Drug Development

• Daurismo – Leukaemia
• Lorbrena – Lung Cancer

• Both drugs developed at the “lab of the future’ facility at Groton, Connecticut & fast tracked using a GEA Consigma Direct Blending & Compression system

• Overall Development time shortened from around 10-12 years to around less than 5 years esp for the drug Lorbrena
Drivers for Continuous Manufacturing

**Clinical Development**
- Material Characterisation
- Process Understanding
- Accelerated product development
- Low API Consumption

**Transfer**
- Tech Transfer Risk Mitigation
- Nil / Minimised Scale Up

**Commercial Scale**
- Higher Yield
- Lower Variability
- Lean Manufacturing
- Facility Footprint
- Reduced Manpower
- Lower Operating Cost
- Agility
- Versatility
- Flexibility

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November 25, 2019
R&D and Manufacturing Platform

ConsiGma™ Product Portfolio

Continuous Granulation & Tableting Lines (ConsiGma™ 25, 50, 100)
- Tablet Coating
- Compression
- Dry Milling / Ext. Phase Blending
- FB Drying
- Wet Granulation
- Dry Blending
- Dispensing Feeding
- Roller Compaction
- Melt Granulation

Continuous Direct Compression (ConsiGma™-DC 50)
- Tablet Coating
- Compression
- 2nd step Ext. Phase Blending
- 1st step Dry Blending
- Dispensing Feeding
- 2nd step Ext. Phase Blending
- 1st step Dry Blending
- Dispensing Feeding

ConsiGma™ 1
- FB Drying
- Wet Granulation
- Dispensing Feeding

ConsiGma™ CDBU

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Continuous Wet Granulation
Consigma - 1
R&D Continuous Wet Granulation
ConsiGma™-1 GMP Granulator with Fluid Bed Dryer

- Loss-in-weight powder feeder
- Fluid bed dryer with blow back filter bags and HVAC system
- 21 CFR Part 11 compliant HMI & PLC control system incl. UPS
- Mass-flow controlled liquid dosing system
- Modular Twin Screw granulation system w/ split barrel and torque measurement
- End point determined by drying time or ΔT

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ConsiGma™: Efficient R&D: No scale-up
ConsiGma™ Continuous Wet Granulation
ConsiGma™ CTL-25
The Most Important New Drug Of 2012

Kalydeco, for cystic fibrosis, is a triumph of genetics and drug development. The first medicine to directly affect the genetic defect that causes the disease. It will only help 2% of the 70,000 people who suffer from declining lung function, damaged pancreases, and shortened lives due to CF worldwide, but in those few it has a dramatic effect. It makes medical history for three reasons:

- It's a genomics triumph: Francis Collins, later famous for heading the Human Genome Project and then the National Institute of Health, discovered the gene that, when mutated, causes cystic fibrosis 23 years ago. Kalydeco is the first drug to directly affect a genetic mutation, leading to improvements in patients’ lung function.

- A patient group powered its development: Khelcho shared royalty with Vertex and put a royalty on the drug. This success paved the way for other disease foundations including the Michael J. Fox Foundation, Multiple Myeloma Research Foundation.

- Its price: Kalydeco, given alone, will only help a few thousand patients the world over. Like other drugs for very rare disease, its price is very high: $540,000 per patient per year.

Vertex shares have fallen 37% from their high values this year because of doubts in investors that Vertex will succeed in its attempts to dramatically expand Kalydeco’s use by combining it with a second drug that will make it work in CF patients whose disease is caused by other, more common mutations. Initial results were very promising, but then Vertex had torestart these. Sales of its best-seller, Intevieb for hepatic C, are dropping. But whatever you think of Vertex shares, Kalydeco is already a success, with $1.5 billion in sales in the first nine months of 2012.

Kalydeco was not the only important drug this year, in which the FDA also approved the first flu vaccine made in cells, not chicken eggs (that’s a Novartis product) and several important cancer drugs including Oura’s Kyprolis, Medivation’s Xandi, and Ionova’s Parjeta. Nor is it the most commercially important — that honor goes to Gilead’s Truvada combination pill for HIV, which could help preserve that company’s HIV franchise through patent expirations. But it’s probably the most exciting as a harbinger of drugs to come.
Vertex Business Case: AAPS Mag, Aug 2013

Implementing Continuous Manufacturing to

Continuous processing enables streamlined development for breakthrough therapies

2013
-10kg scale

2014
~100kg scale

2015
~250kg scale
Commercial

2016

API Prod.

~1kg scale
Define pivotal formulation at small scale
Batch DP Dev.
Start Pivotal Studies
~5kg scale
~50kg scale
~500kg
Possible formulation modification
Final Formulation (BE if needed)
Commercial

Continuous DP Dev.
10-30kg/hr
Define final formulation on commercial scale
Start Pivotal Studies
10-30kg/hr
Establish QbD design space around target
Ready to Manuf. Commercial DP
10-30kg/hr - Commercial Production

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### Vertex Business Case: API Consumption

#### API Consumption: Batch vs Continuous

<table>
<thead>
<tr>
<th>Stage</th>
<th>Batch manufacturing</th>
<th>Continuous Manufacturing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>API used</td>
<td>API used</td>
</tr>
<tr>
<td>Formulation</td>
<td>90 kg</td>
<td>35 kg</td>
</tr>
<tr>
<td>Development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pilot Scale</td>
<td>120 kg</td>
<td>Together with Formulation development</td>
</tr>
<tr>
<td>Commercial</td>
<td>1650 kg</td>
<td>350 kg</td>
</tr>
<tr>
<td><strong>Total Amount</strong></td>
<td><strong>1860 kg</strong></td>
<td><strong>385 kg</strong></td>
</tr>
<tr>
<td><strong>of API used</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Difference in API consumption:** approx. 1475 kg (huge potential savings !)
Continuous Direct Compression
CDC 50 – Continuous Direct Compression & Coating
ConsiGma™ CDC
ConSiGma™ CDC-50 Overview

- Proven successful case studies over a range of conditions:
  - Throughput (kg/hr): 2.5 – 130
  - Drug loadings (%): (0.027*) 0.25 - 59.12
    * Pre dilution required to reach 0.027
- Long Run completed January 2018
  - Preliminary Results
    - 124h run
    - 10% APAP
    - 400 mg tablets
    - 6 tons of product = 15 million tablets
    - 99.5% yield
Tablet weight Control Over Run

Weight Control Over the Run
Process Capability > 2 when assessed against control limit of +/- 4%

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Case Study: Naproxen CR Formulation

Content uniformity of tablets

- UV method used to test tablets for content uniformity.
- High frequency samples taken during run 6 (every 10 seconds) over a 5 minute window from a 1 hour run.
- CU of tablets tested and aligned with on-line NIR model post trials.

RSD of CU measurement in line with RSD of BU measurement

Pharma Day
GEA Compact Feeder – Key Features

Adjustable top up valve with inflatable seals
Controlled and contained filling of feeder hopper

Flexible refill systems
Optimum match with feeding requirements (containment, volume, ...)

Compact, GMP design
Up to 6 feeders can feed into one collector in a contained way

Independent, wet-in-place pump area with flat-bottom hopper
Low operator exposure and easy offline cleaning

Twin screw feeder with optional exit-mesh
Self-cleaning action and delumping

Independent and contained base with drive and load cells
No cleaning requirement, fast and accurate load responsiveness

3 exchangeable gearboxes
Wide dosing range
Tablet press continuous operation as a “Servant”

- Blender outlet
- Level sensor
- HiHi to LoLo material volume
- Material column
- Tablet press feeder – volumetric feeding device
Effect of Extended Dwell Time on Tablet Hardness
Excellence in Process Control
Compression Technology

Applying a constant Force
Using a system with a moving compression roller
resulting in a displacement and an extended dwell-time
Continuous Manufacturing – The Way Forward

- Prezista (darunavir) is a Protease Inhibitor – Anti-viral Medication to target HIV cells from multiplying
- Solid dosage form biologic
- Prezista was the first legacy drug to be approved by the FDA which was switched over from Batch to CM
- Direct Compression process with an intermediate Dry Granulation step
- Manufacturing is at the Gurabo, Puerto Rico plant
- Obtained FDA approval for a surrogate model by Janssen to predict dissolution profile based on PAT data thereby enabling full Real Time Release protocol for Prezista.
- Janssen “is at the forefront of CM advancement, focusing on a more reliable process that will yield lower costs, waste reduction & time-to-market savings”
Financial & Operational Benefits

**Batch**
- Manufacturing Cycle Time: 13 days – 1 tonne
- Plant Footprint: 7 rooms
- In-Process tests & Release tests: 30 days
- Make-then-test approach to Quality Assessment

**Continuous**
- Manufacturing Cycle Time: 25 hrs – 1 tonne
- Plant Footprint: 2 rooms
- In-Line / At-Line Testing: 5 days
- Continuous monitoring of Quality

- 70% reduction in man hour
- Substantial reduction in floor plan
- 80% reduction in manufacturing & testing cycle time
- 33% increase in yield by reducing waste
ConsiGma® Coater
ConsiGma® Coater – Process Principles

A lone tablet

Tumbles through a cloud of coating

Passes into a current of warm air

Lands gently and is carried away
ConsiGma™ Coater Technology
Uniform coating thickness, even on the corners

Traditional

ConsiGma®

Data generated in collaboration with Colorcon Inc, coating material Acryl-EZE®
Regulatory Issues

- Current regulatory frameworks allow for implementation & commercialisation of products using CM.
- Regulatory authorities support the introduction of CM into the pharmaceutical industry
ICH Guidelines

- There is a lack of regulatory guidelines currently but ICH is working on guidelines to facilitate international harmonization leading to effective implementation of CM.

- ICH Q13 – Continuous Manufacturing for drug substances & drug products
  Endorsed in Nov 2018. Expected to be completed in three years
  - Key Definitions
  - Scientific Principles
  - Regulatory Expectation

- ICH Q14 – Analytical Procedure Development
  ICH Q2(R1) – validation of Analytical Procedures
  Endorsed in Nov 2018, Expected to be completed in three years
  - Enhanced approaches for analytical procedures
  - Demonstration of suitability for Real Time Release Testing
  - Validation principles applicable to multivariate methods – Spectroscopic PAT
FDA – Approach to CM

- FDA supports the adoption of innovative technology such as Continuous Manufacturing.
- FDA encourages the implementation of Continuous Manufacturing using a scientific & risk-based approach.
- FDA recommends pharmaceutical companies to have early & active discussions with the agency during CM implementation.
- CDER Emerging Technology Team (ETT) will help facilitate the development of innovative technologies.
- FDA/CDER/OPF (Office of Process & Facilities) is capable of reviewing Continuous Manufacturing applications & make appropriate recommendations on time.
- **NO** regulatory hurdles exist for implementing Continuous Manufacturing.
ConsiGma™ 50: Chinoin Aquascalientes - Mexico

Official approval: Chinoin's Antiflu-des®
Currently 3 Formulations approved,
4 more are waiting for approval
ConsiGma 100: J&J Latina – Italy
ConsiGma™ 25, ConsiGma™ 1 & Coater - Japan
ConsiGma™ CDC-50: MSD Cramlington, UK
ConsiGma™ 25: Vertex CR1– USA (at Hovione)
Thank You!