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IPA
Innovation, Quality and Global Reach

ConsiGma™ Continuous Manufacturing OSD

Road to Operational Excellence & Accelerated Drug Development

Harish Krishnan – APPLICATION MANAGER, CONTINUOUS MANUFACUTING

GEA engineering for a better world

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Why Innovation?

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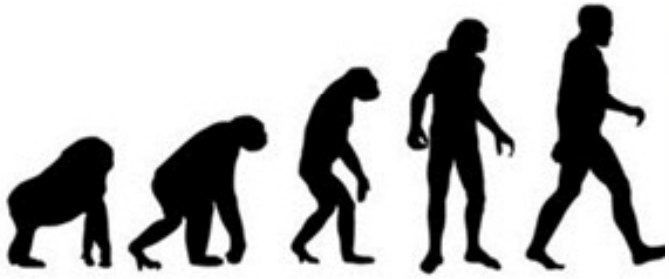
U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

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."

Batch Manufacturing

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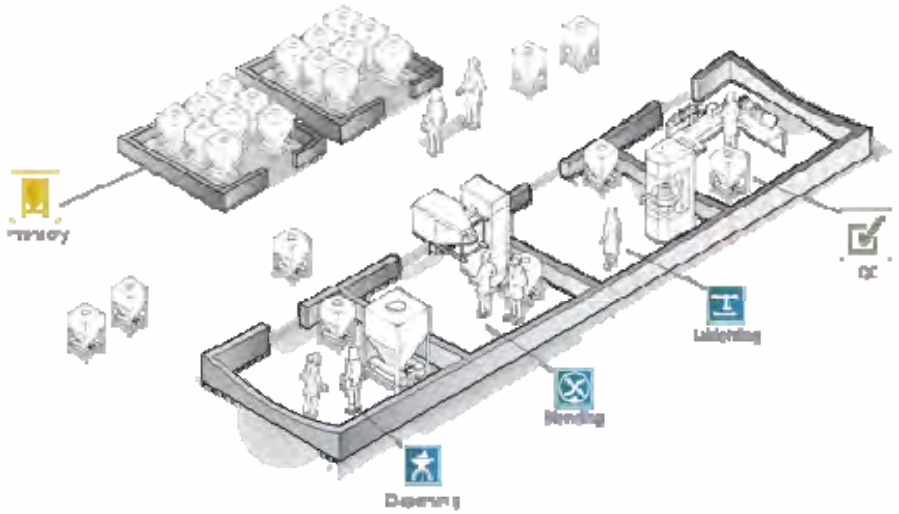

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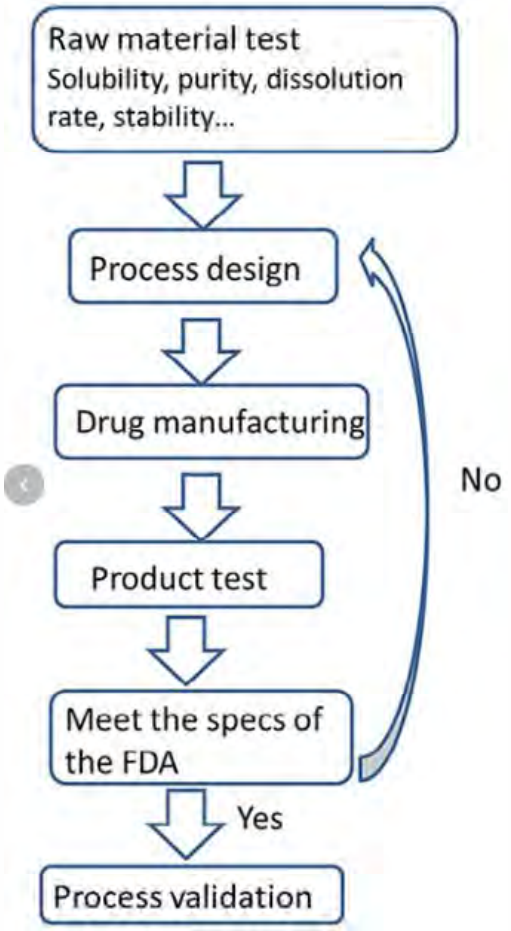
Quality by Test - QbT

- 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.



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Quality by Design
Continuous Manufacturing

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- 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.

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QbD - DoE – Design Space

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- 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.

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QbD – Control Strategy

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- 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.

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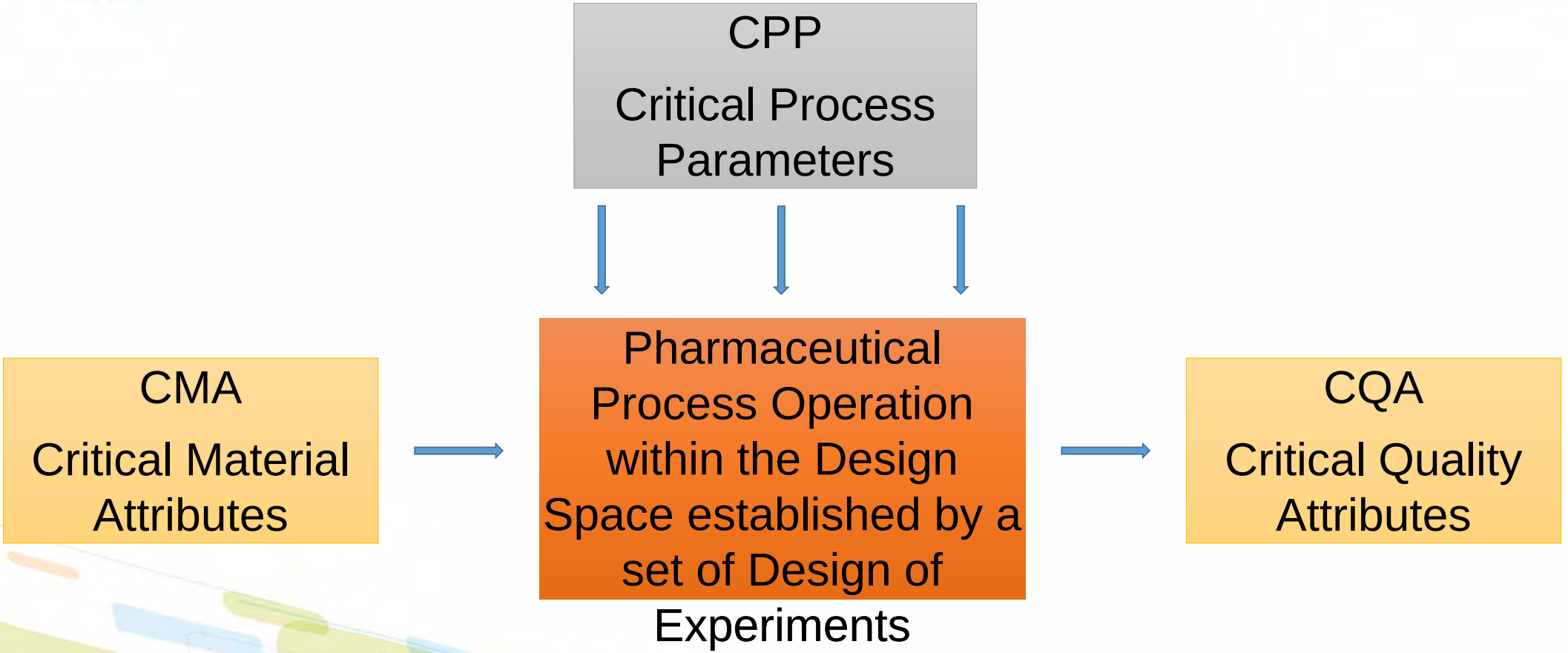
QbD - Design Space



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Drug Discovery & Development Timeline

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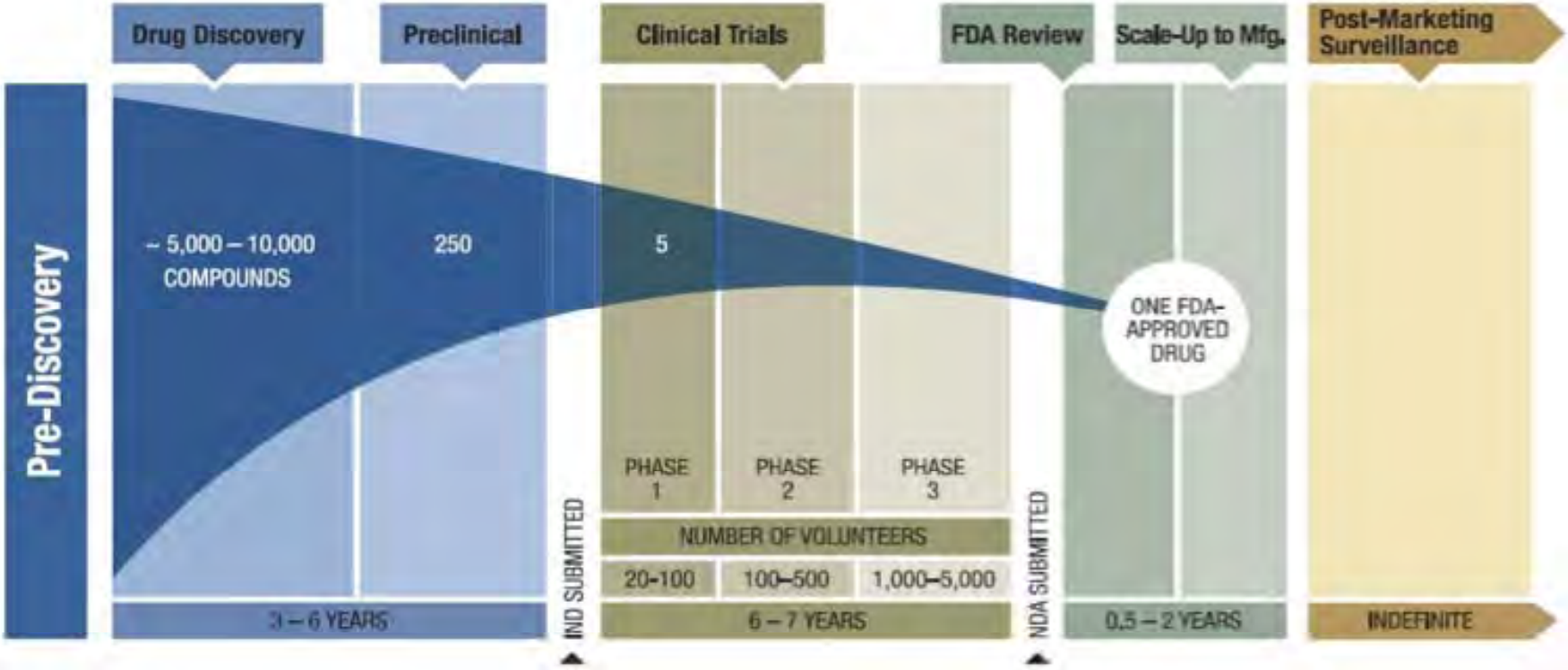
Drug Discovery and Development Timeline



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Pfizer - Drug Development

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- 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

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Drivers for Continuous Manufacturing

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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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GEA Consigma
Continuous Manufacturing

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R&D and Manufacturing Platfom

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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

ConsiGma™ 1

FB Drying | Wet Granulation | Dispensing Feeding

Continuous Direct Compression (ConsiGma™-DC 50)

Tablet Coating | Compression | 2nd step Ext. Phase Blending | 1st step Dry Blending | Dispensing Feeding

ConsiGma™ CDBU

2nd step Ext. Phase Blending | 1st step Dry Blending | Dispensing Feeding

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Continuous Wet Granulation

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Consigma - 1

R&D Continuous Wet Granulation

ConsiGma™-1 GMP Granulator with Fluid Bed Dryer

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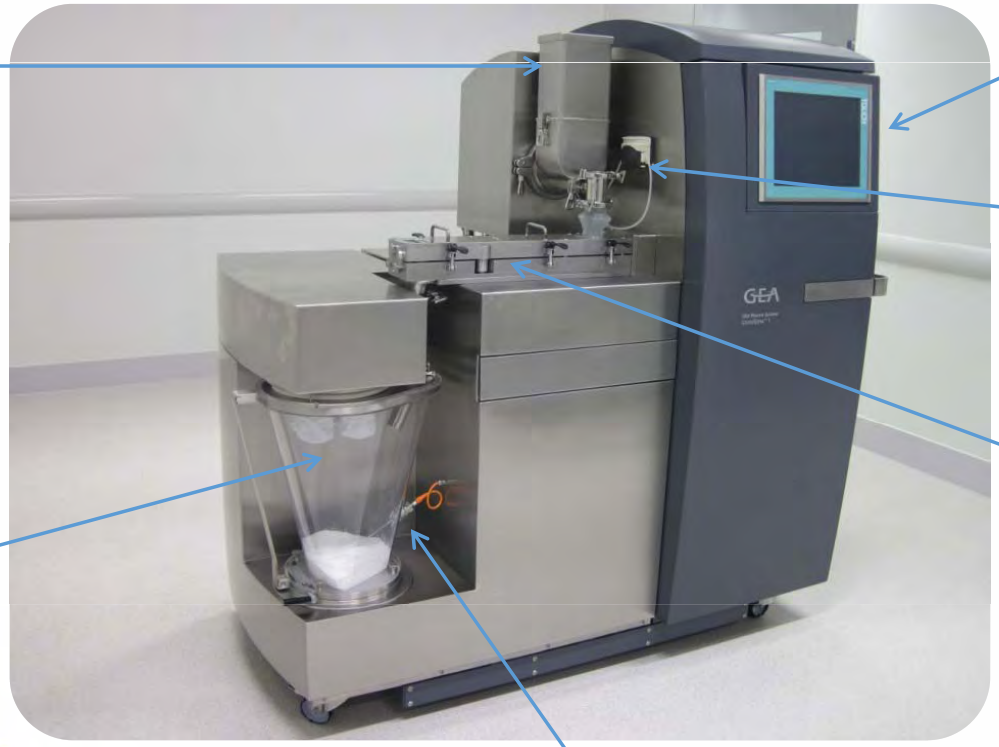

Loss-in-weight powder feeder

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

Fluid bed dryer with blow back filter bags and HVAC system

End point determined by drying time or ΔT

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ConsiGma™: Efficient R&D : No scale-up

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ConsiGma™ Continuous Wet Granulation

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ConsiGma™ CTL-25

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ConsiGma 25™; Vertex Boston (US)

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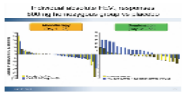
The Most Important New Drug Of 2012

11 comments, 6 called-out + Comment Now + Follow Comments

The Food and Drug Administration looks set for a great 2012; with a few days left to go, it has approved 40 new drugs and vaccines, one of the most impressive totals ever, according to data from Pharmaceutical Approvals Monthly and FDA press releases. In this haul, one medicine stands out for its scientific and medical importance.

Ten Lessons On Fighting Disease From Michael J. Fox

Matthew Herper
Forbes Staff



The Best Argument That Vertex's CF Drug Combination Works

Matthew Herper
Forbes Staff

Battleground Vertex

Matthew Herper
Forbes Staff

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 4% 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 Institutes of Health, discovered the gene that, when mutated, causes cystic fibrosis 23 years ago. Kalydeco is the first drug to directly affect the defects caused by these mutations, leading to improvements in patients' lung function.
- **A patient group powered its development:** Kalydeco would probably not exist were it not for the Cystic Fibrosis Foundation, which funded its early development at Vertex and gets a royalty on the drug. This success paved the way for other disease foundations including the Michael J. Fox Foundation, Myelin Repair, and the 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 diseases, its price is very high: $294,000 per patient per year.

Vertex shares have fallen 37% from their high earlier this year because of doubts by 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 to restate them. Sales of its best-seller, Incivek for hepatitis C, are dropping. But whatever you think of Vertex shares, Kalydeco is already a success, with $113 million 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 Onyx's Kyprolis, Medivation's Xtandi, and Roche's Perjeta. Nor is it the most commercially important — that honor goes to Gilead's Stribild 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.

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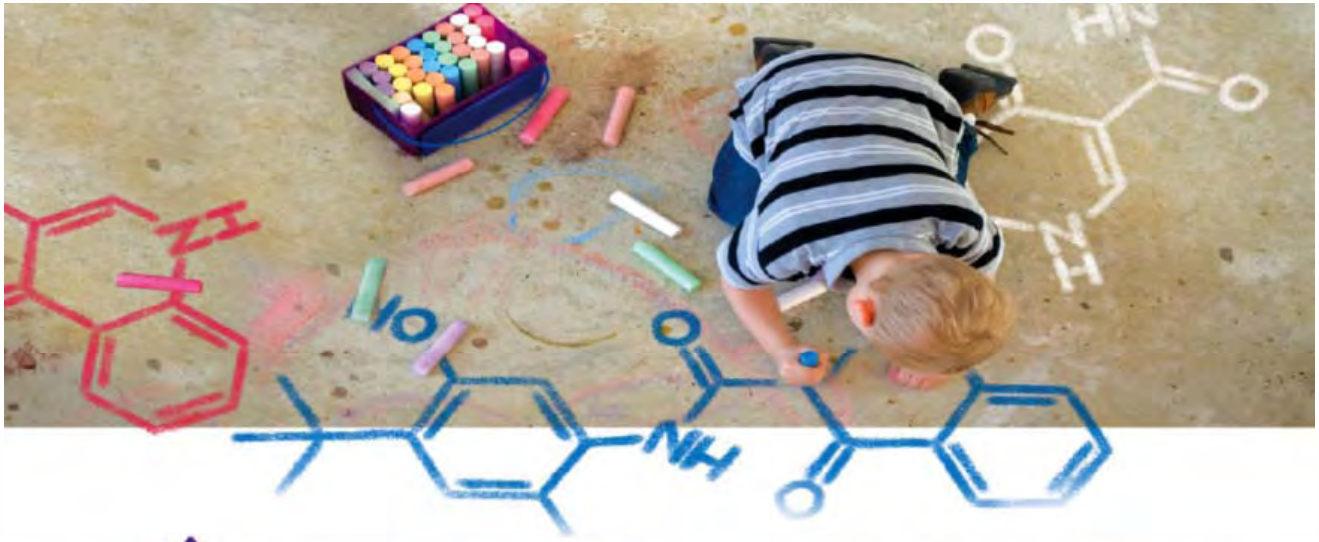
VERTEX



VERTEX
THE SCIENCE of POSSIBILITY

Continuous Processing – GMP Manufacturing Principles and DP Development Strategy

Vertex Business Case: AAPS Mag, Aug 2013

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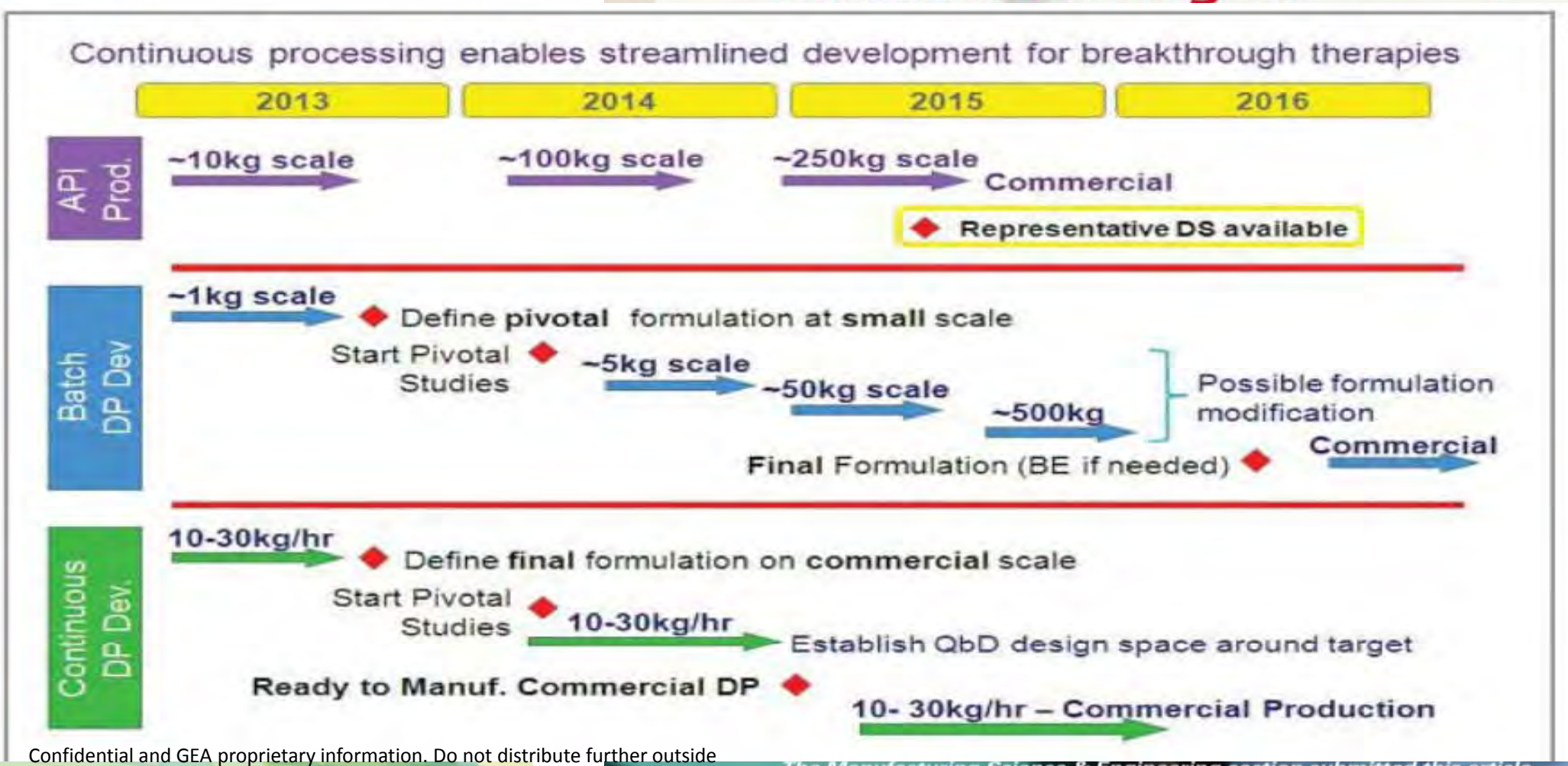
Implementing Continuous Manufacturing to



The Manufacturing Science & Engineering section submitted this article.

Vertex Business Case: API Consumption

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API Consumption: Batch vs Continuous

Stage	Batch manufacturing	Continuous Manufacturing
	API used	API used
Formulation Development	90 kg	35 kg
Pilot Scale	120 kg	Together with Formulation development
Commercial	1650 kg	350 kg
Total Amount of API used	**1860 kg**	**385 kg**

Difference in API consumption: approx. 1475 kg (huge potential savings !)

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ConsiGma 25TM – Vertex Boston (USA)

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VERTEX

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Continuous
Direct Compression

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CDC 50 – Continuous Direct Compression & Coating

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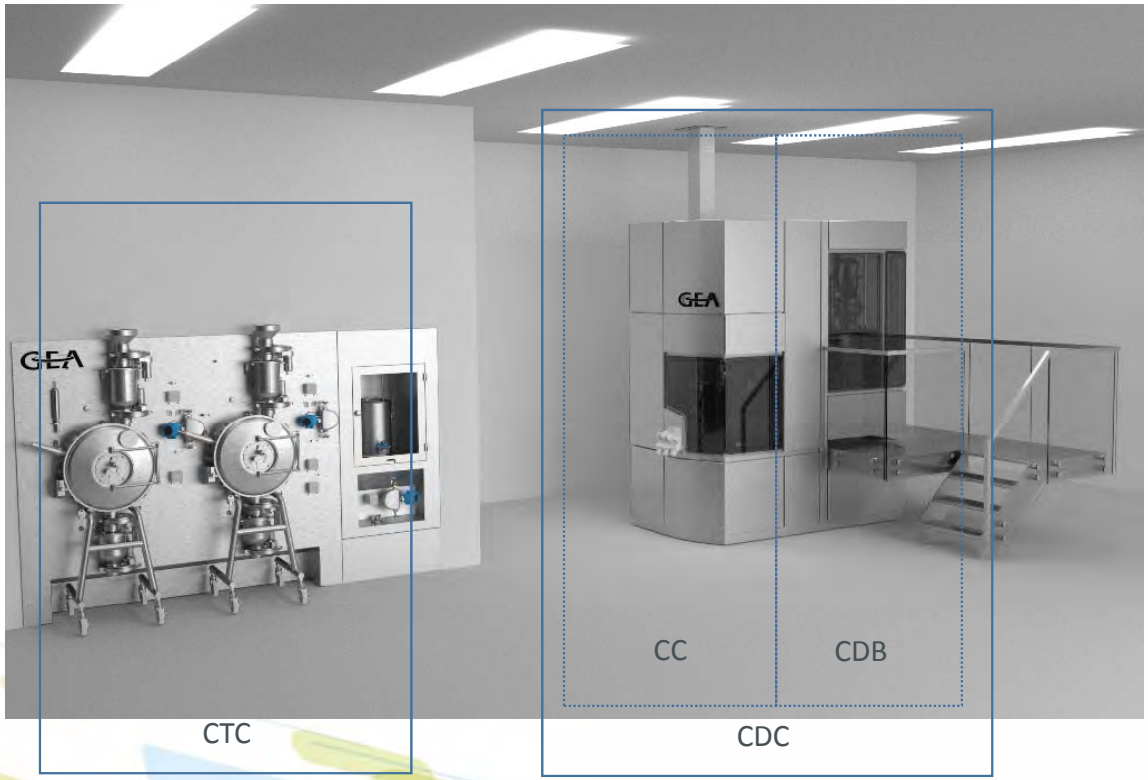

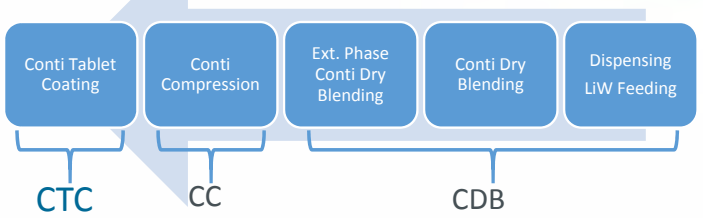

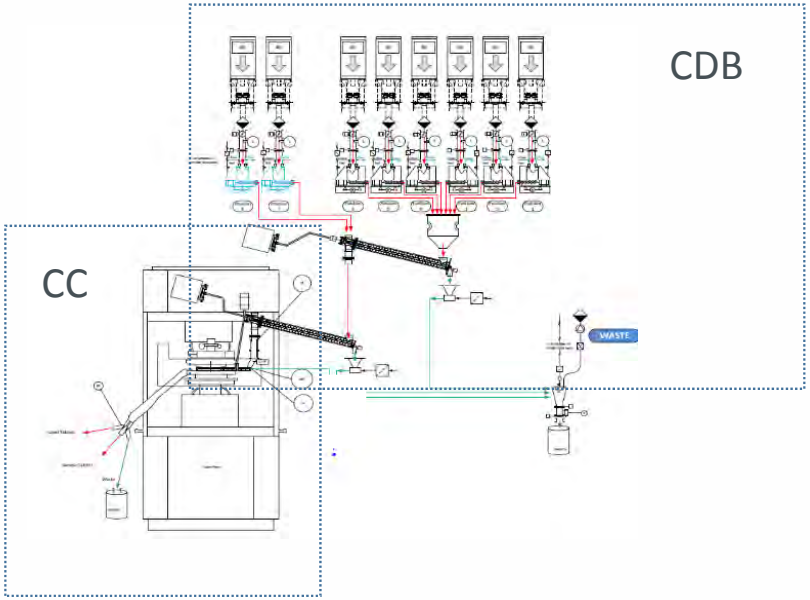

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ConsiGma™ CDC

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ConsiGma™ CDC-50 Overview

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- 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

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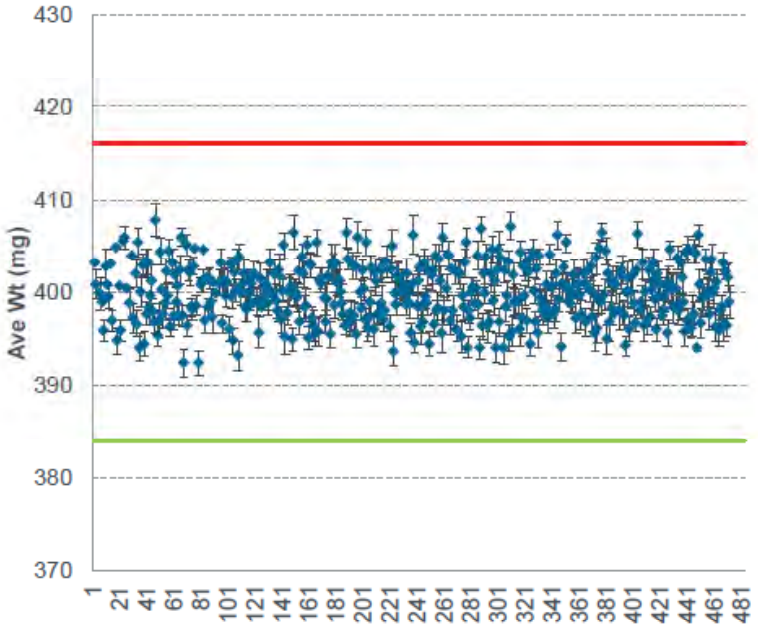
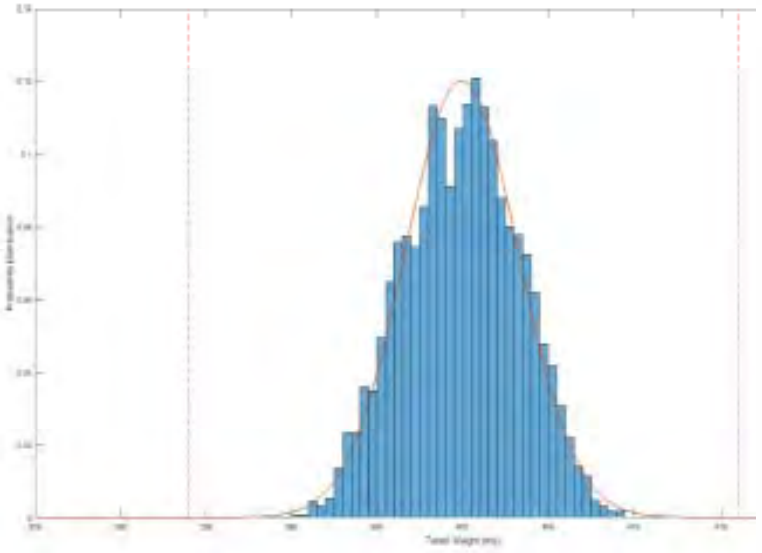
Tablet weight Control Over Run



Weight Control Over the Run



Overall Distribution Plot

Process Capability > 2 when assessed against control limit of +/- 4%

Case Study: Naproxen CR Formulation

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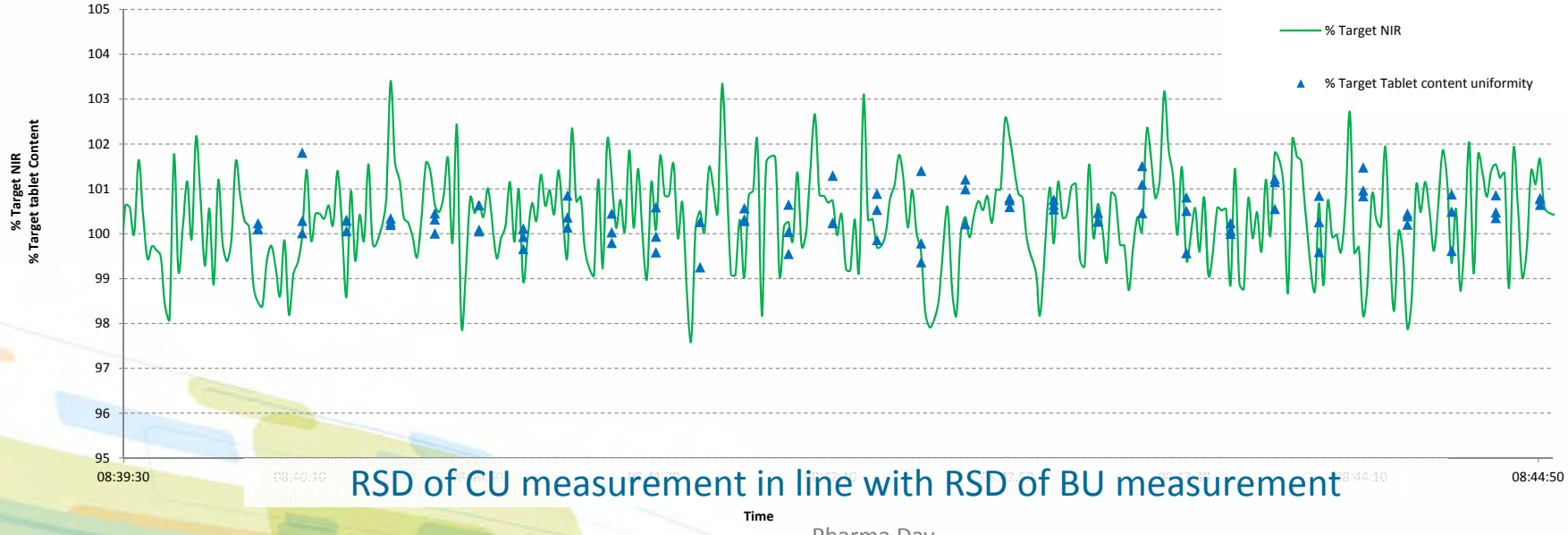
Content uniformity of tablets

- 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

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GEA Compact Feeder – Key Features

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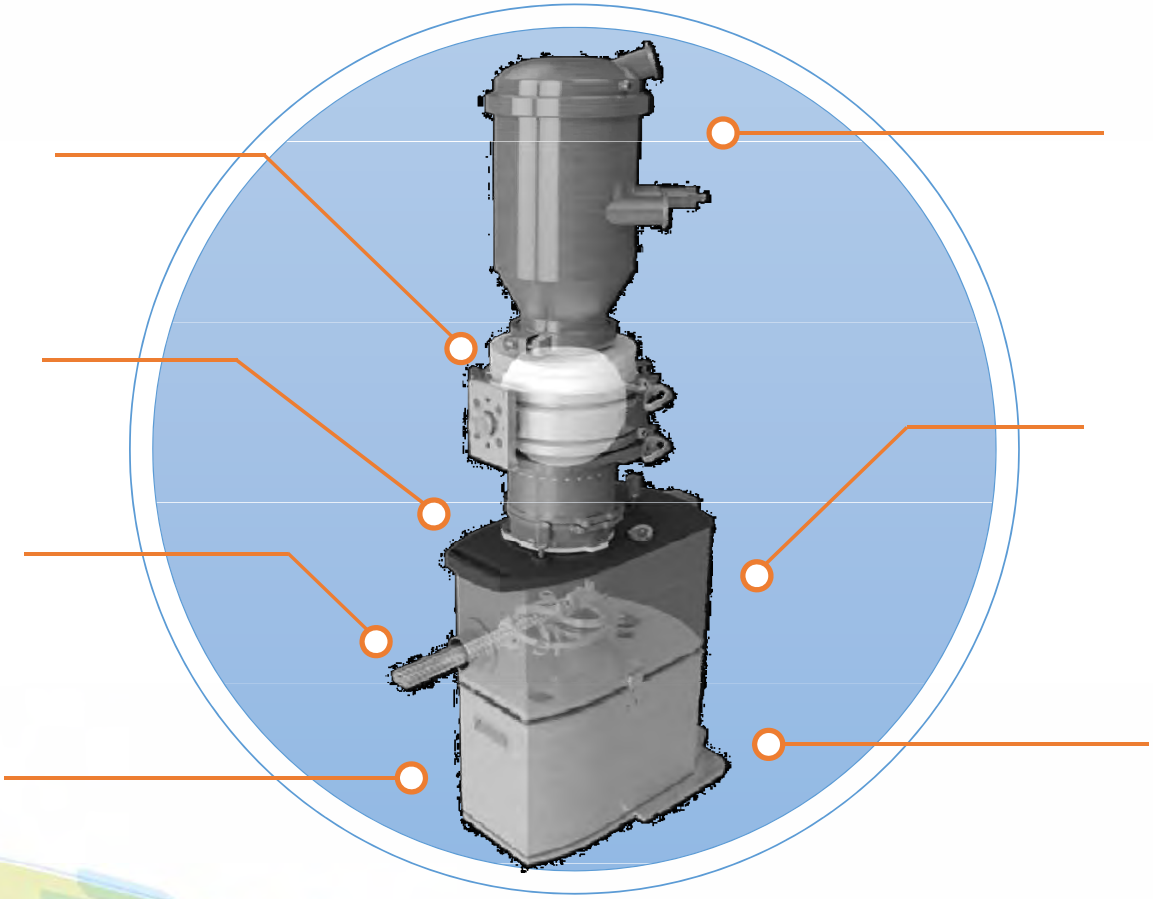
Adjustable top up valve with inflatable seals
Controlled and contained filling of feeder hopper

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

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

3 exchangeable gearboxes
Wide dosing range



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

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

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

Tablet press continuous operation as a“Servant”

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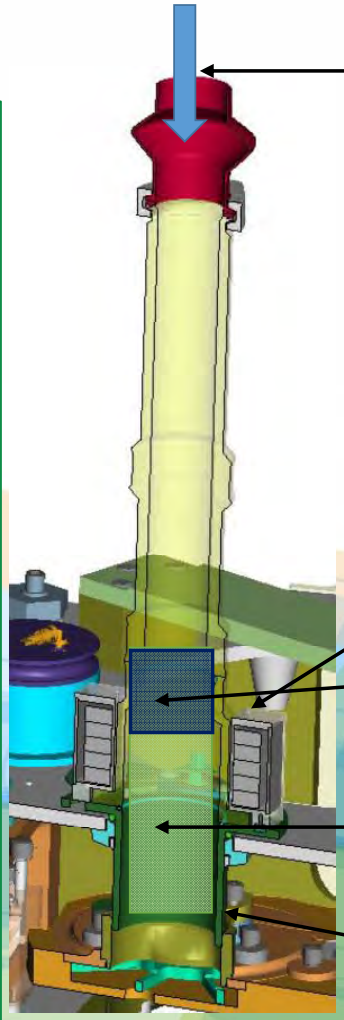
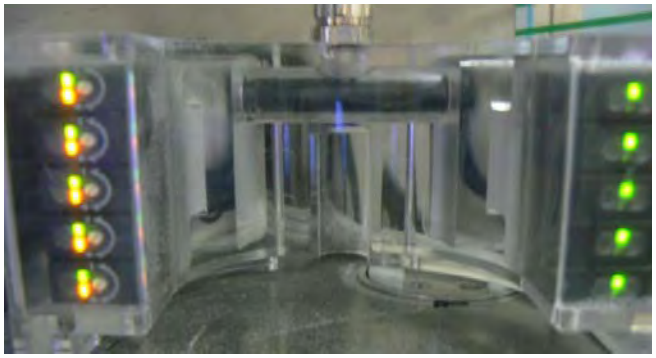


Blender outlet

Level sensor



HiHi to LoLo material volume

Material column

Tablet press feeder – volumetric feeding device

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Effect of Extended Dwell Time on Tablet Hardness

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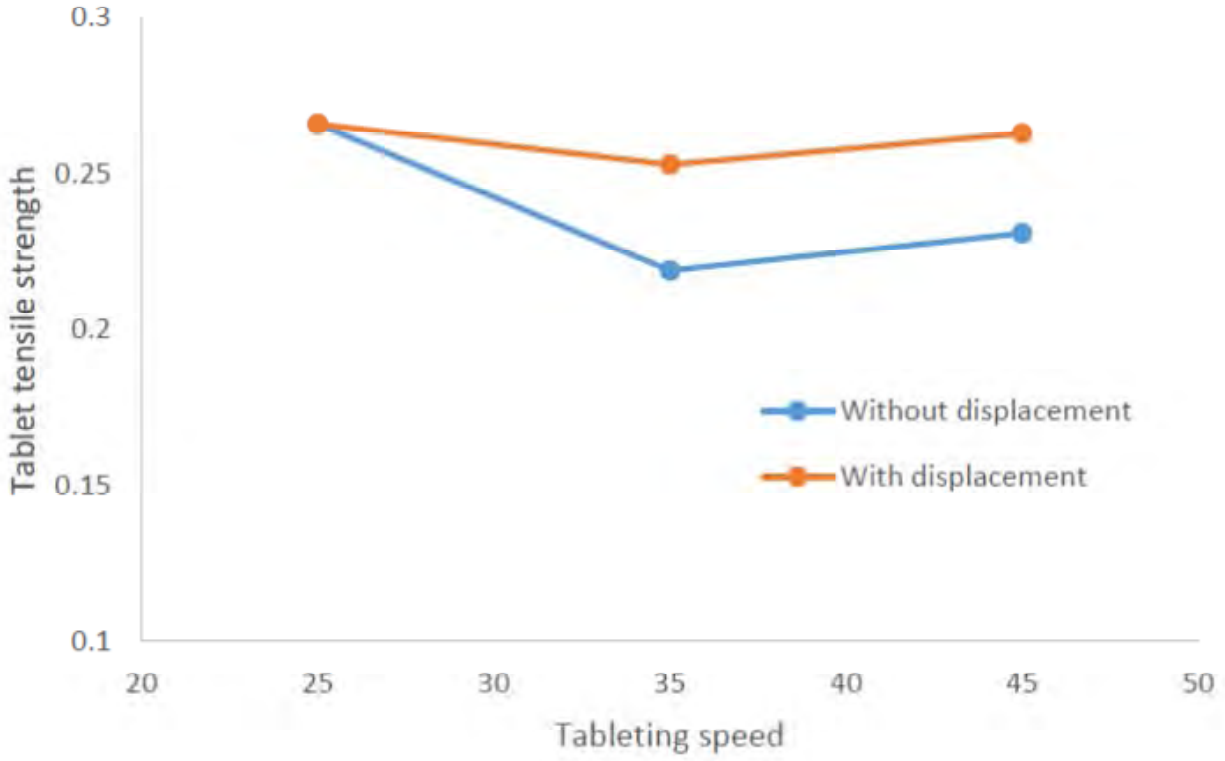

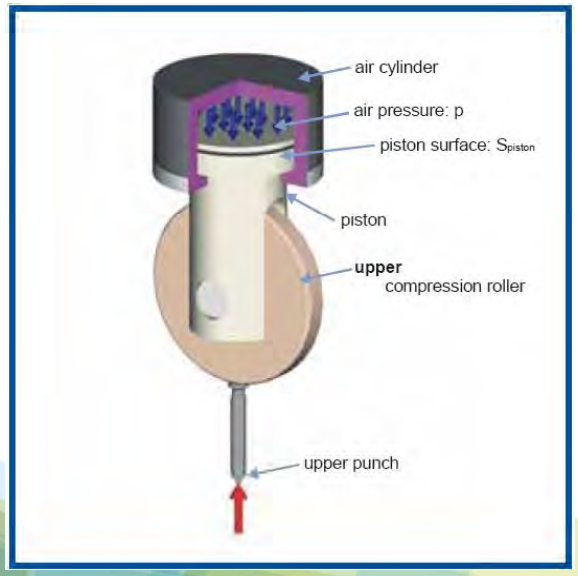

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Excellence in Process Control Compression Technology

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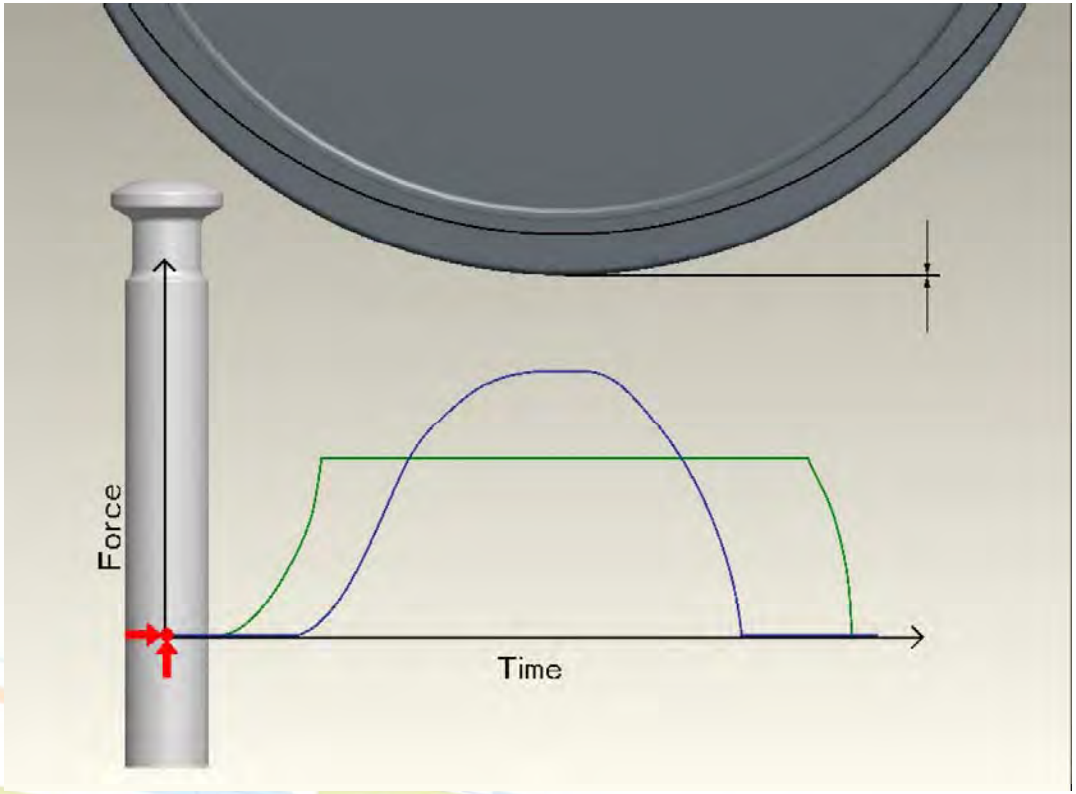

Applying a constant Force

Using a system with a moving compression roller

resulting in a displacement and an extended dwell-time

Continuous Manufacturing – The Way Forward

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janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

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- 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

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Janssen Pharmaceutical Companies of Johnson & Johnson

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Batch		Continuous	
13 days – 1 tonne	Manufacturing Cycle Time 	25 hrs – 1 tonne	70% reduction in man hour
7 rooms	Plant Footprint 	2 rooms	Substantial reduction in floor plan
In-Process tests & Release tests 30 days	Testing 	In-Line / At-Line 5 days	80% reduction in manufacturing & testing cycle time
Make-then-test approach to Quality Assessment	Quality Control 	Continuous monitoring of Quality	33% increase in yield by reducing waste

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ConsiGma® Coater

ConsiGma® Coater – Process Principles

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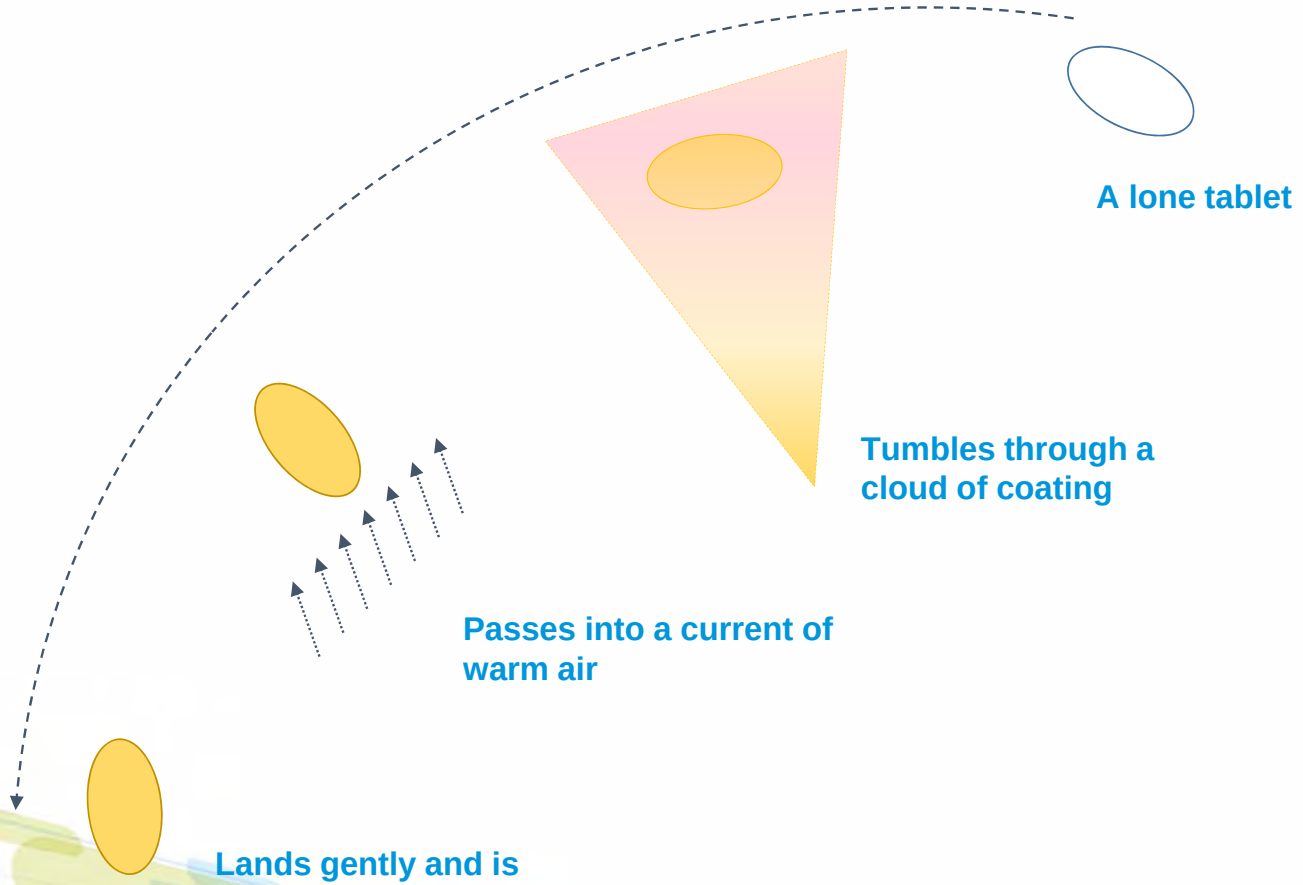

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ConsiGma™ Coater Technology

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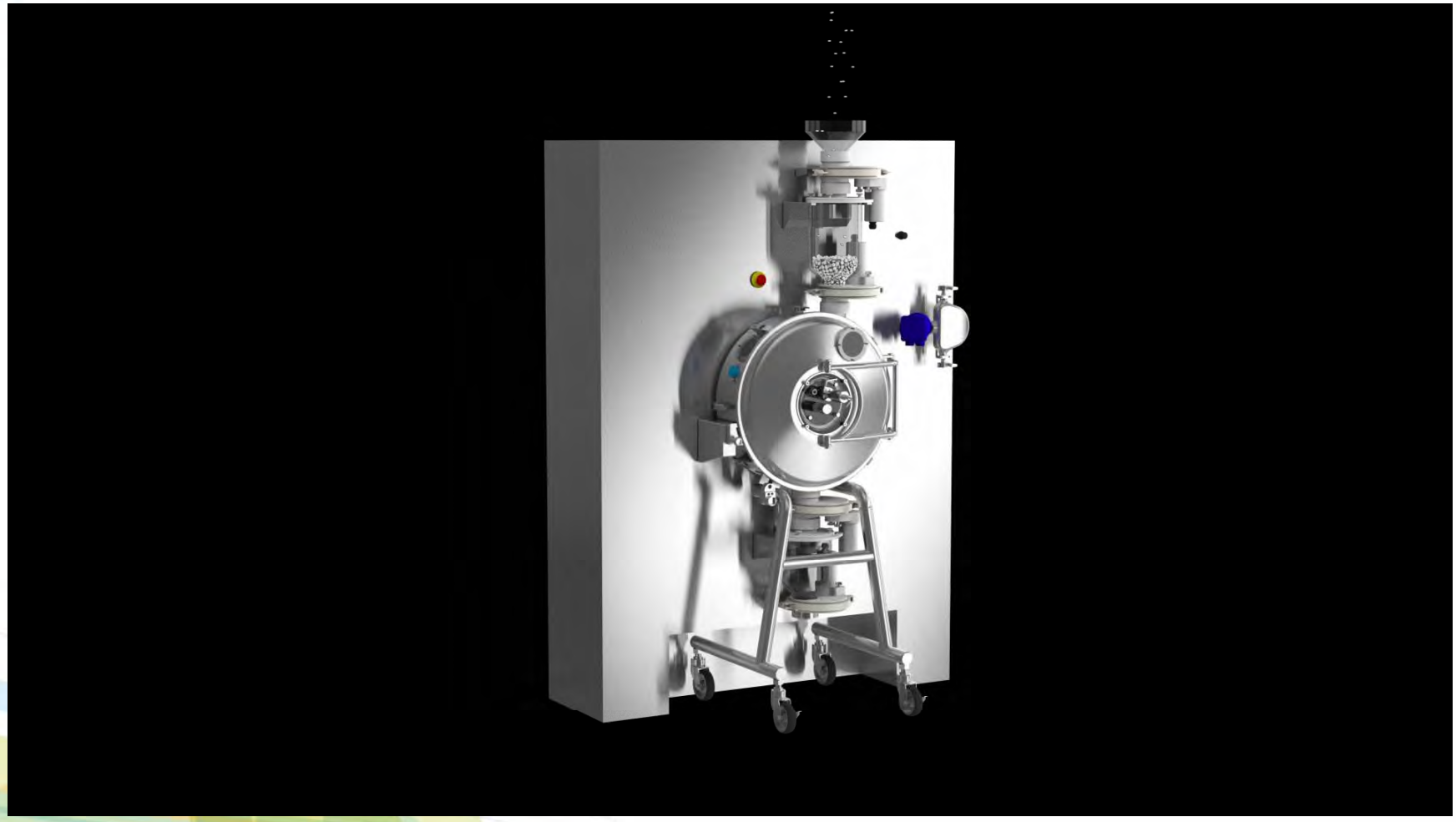

Uniform coating thickness, even on the corners

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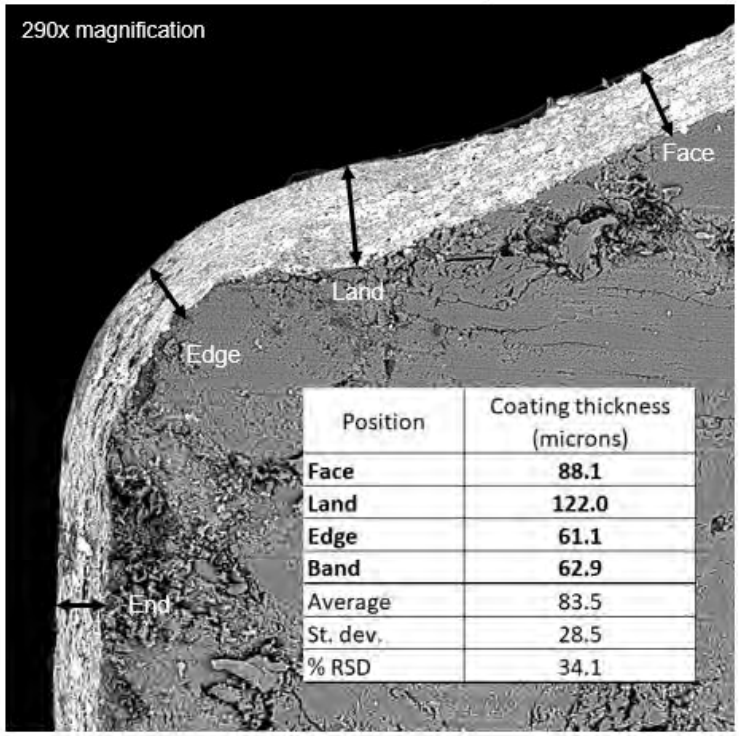
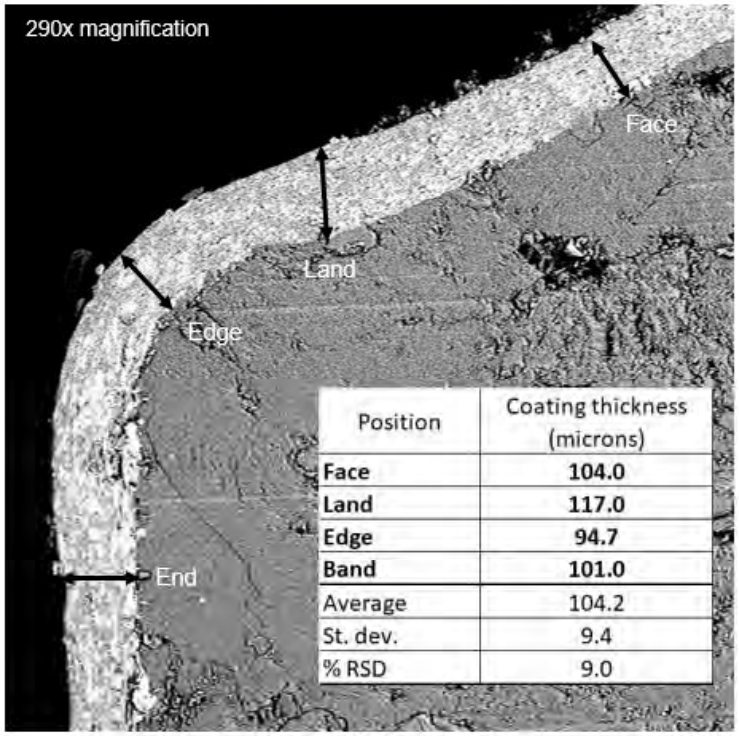
Traditional



Position	Coating thickness (microns)
Face	**88.1**
Land	**122.0**
Edge	**61.1**
Band	**62.9**
Average	83.5
St. dev.	28.5
% RSD	34.1

ConsiGma®



Position	Coating thickness (microns)
Face	**104.0**
Land	**117.0**
Edge	**94.7**
Band	**101.0**
Average	104.2
St. dev.	9.4
% RSD	9.0

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

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Regulatory Issues

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

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ICH Guidelines

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- 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

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FDA – Approach to CM

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- 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.

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ConsiGma™ 50: Chinoin Aquascalientes - Mexico

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Official approval: Chinoin's Antiflu-des®
Currently 3 Formulations approved,
4 more are waiting for approval

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ConsiGma 100: J&J Latina – Italy

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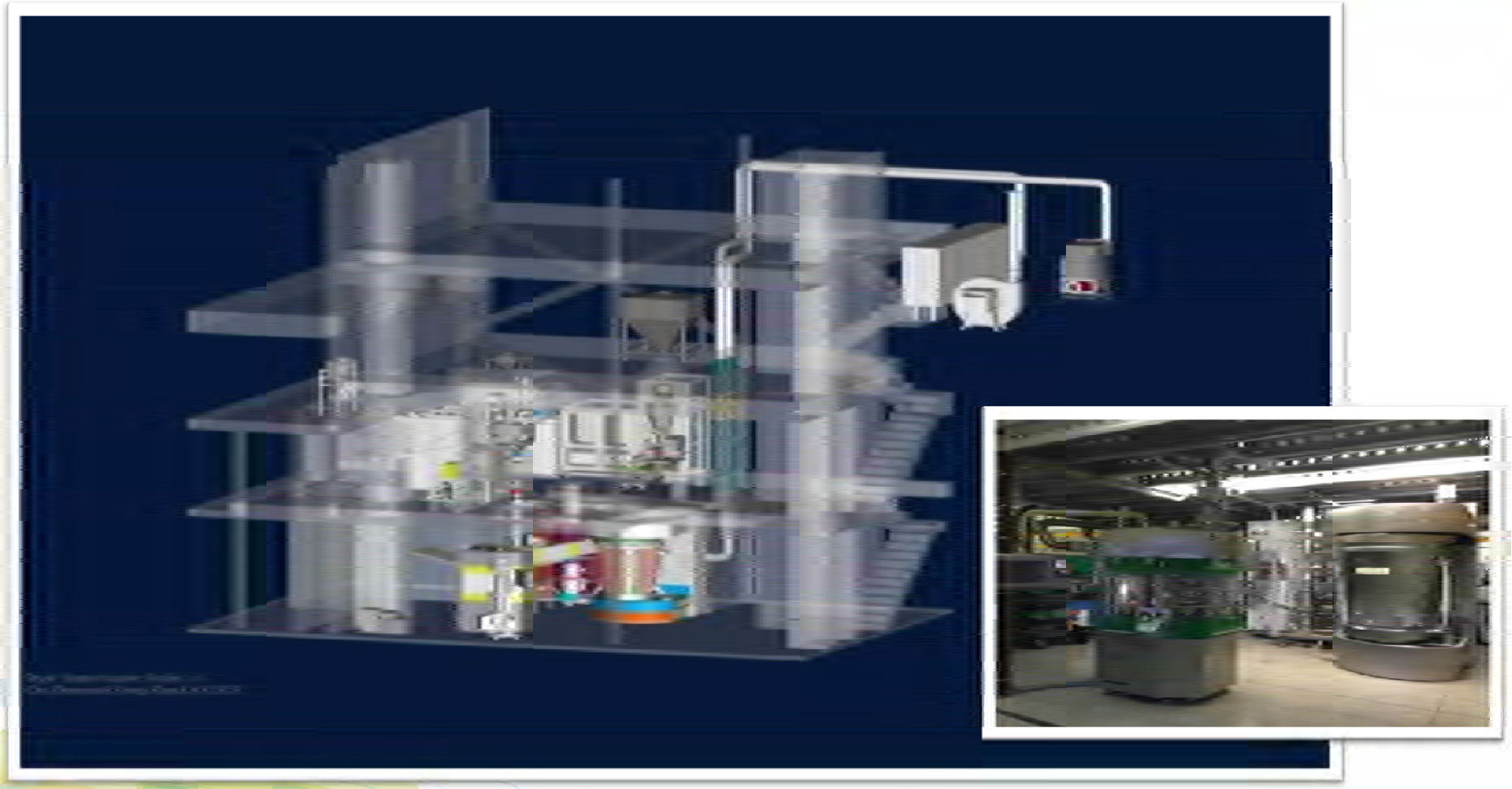

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ConsiGma™ 25, ConsiGma™ 1 & Coater - Japan

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ConsiGma™ CDC-50: MSD Cramlington, UK

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ConsiGma™ 25: Vertex CR1– USA (at Hovione)

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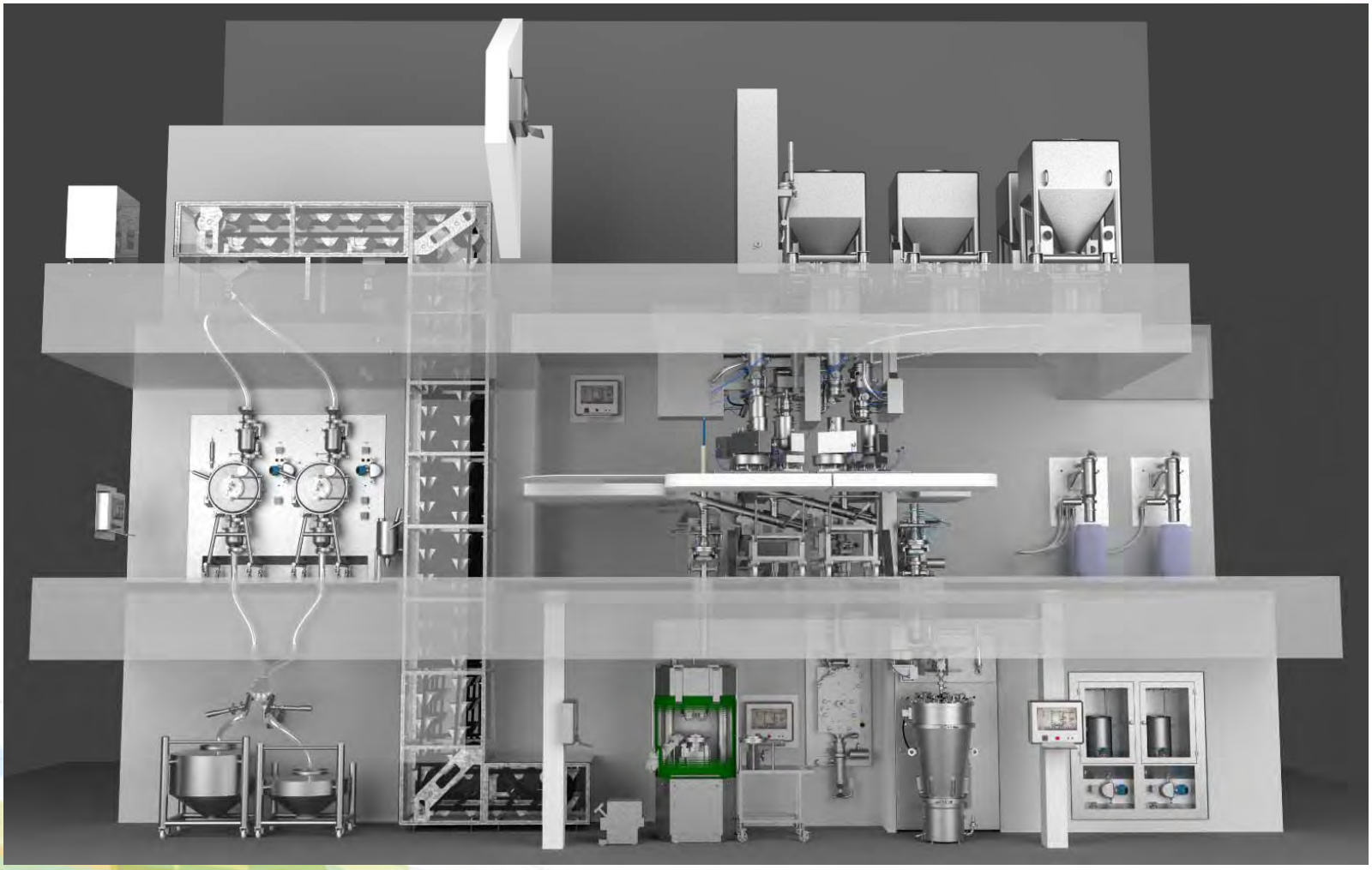

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Thank You!

GEA engineering for a better world