A Spotlight on a Major Corporate Implementation Strategy for Continuous Manufacturing

Janssen Pharmaceuticals

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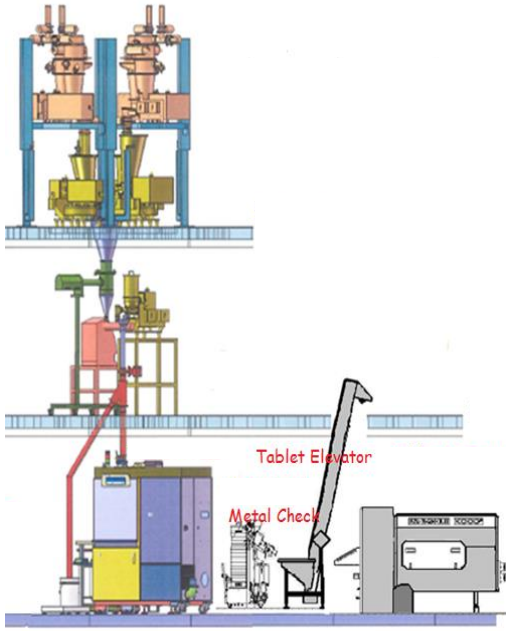
CM deployment at Janssen: Different capabilities



Inspire Line

Only DC
K-tron feeders, Glatt Blender, Korsch press,

Semi continuous Bohle coater
In line BU with multihead NIR
At line CU

~ 40 kg/hr throughput

Latina Line

Bin to bin feeding
GEA Consiga type WG
Space available for Coaters
In line BU and humidty with LHP
At line CU with Bruker Tandem

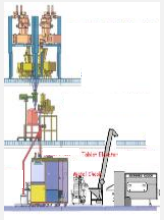
~ 100 kg/hr throughput

R&D Line

GEA Consiga type DC, WG & RC
Mix of GEA and K-Tron feeders
Courtoy press, Gerteis RC
Space available for Coaters
In line BU and humidty with LHP
At line CU with Bruker Tandem

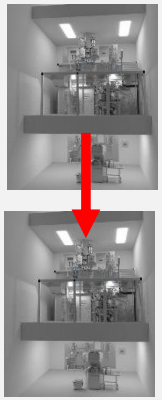
~25 kg/hr throughput

Janssen Deployment Strategy



Inspire

Latina



Mirror

CM will deliver on the needs of the business related to **agility, reliability, cost, and quality**. Our strategy for next 5 years is :

Optimizing CM performance by focusing on:

- Yield improvement
- Reduction of cleaning and change over time
- Real Time Release
- Batch Record review by exception

} Using PAT and Modeling

Increasing utilization of current manufacturing lines

- Optimization of loading according to volume projections and new products coming in.

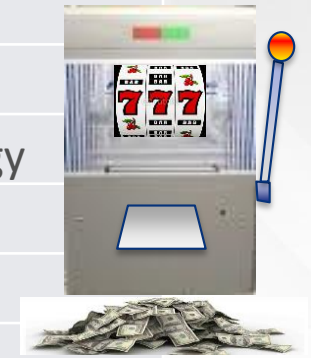
Launching New Products

- Initially on existing lines if possible
- Prepare to build an additional line by when it is needed

Investing in people and knowledge, collaborating with others to help **aligning the industry** and **to Prepare the future.**

Can we make the business case – Challenges for Janssen and others

Benefits	Challenge
ROI	Facility cost, volume variation, free batch capacity
Flexible batch size	Initially limited by validation run time
Speed to market	Combination with first installation of new technology
Platform deployment	Convince product teams to move to CM
QA/QC	FTE's need to be reduced in budget
Yield improvements	Start and stop losses during unforeseen stops
TT effort	Keeping eqt identical with Technology fast evolving
Inventory	Safety stocks not reduced because of larger batch size
Less development effort	Initially: additional effort for PAT & RTR
TT effort	Pipeline volatility – need for flexible supply chain
All integrated equipment	Integration software – communication - qualification



Can we make the business case? Current Status

Benefits	Current status
Cycle time	Significant reduction achieved
Operators	Yes : only 2-3 operators needed for DC process
QA, BR handling	Reduction achieved, no full FTE due to low volume
QC	Reduction achieved, no full FTE due to low volume Full RTR in progress
Investigations	Quantification needed
Yield - fixed/variable yield, rejects, exceeded WIP holding time	Yield improvements not as easy as initially thought, seems feasible, but will need time and work
Less water for cleaning	More CIP might eliminate this benefit
Supply chain flexibility	Achieved – change over time is key
Better process understanding	Achieved – QbD & PAT driven
Lower inventory	Only WIP

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Can we make the business case - Conclusion

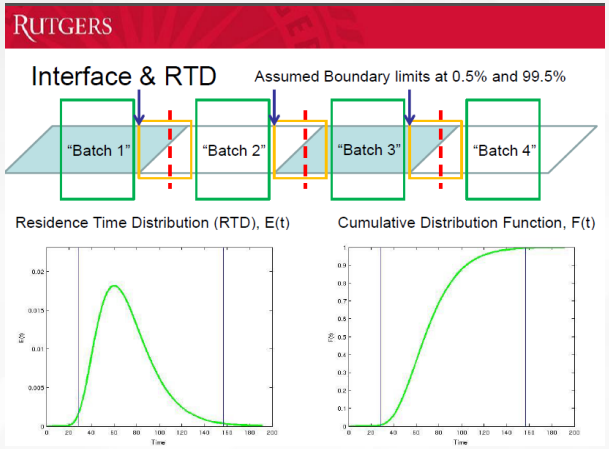
Conclusion: YES WE CAN – but improvement needed:
→ TRUST
→ Installation Cost & Risk
→ Efficiency & Change over time

Knowledge needed:
→ Process understanding
→ Predictive models
→ Regulatory alignment

→ More capacity internal and external

Control Strategy Considerations

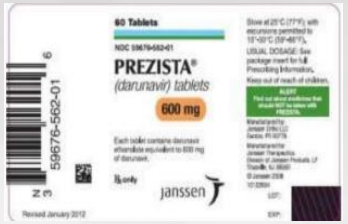
- Perturbations
- Understanding sources of variaton
  - Particle properties – Material behavior – Blend behavior
  - Material variation
  - Disturbances
  - Drift, system dynamics
  - Start-up & Shut down, state of control
- Determine blender backmixing
- Impact of throughput
- Define your tracer
- RTD or PAT
- Feeder studies
- Sampling considerations, Measuring frequency



Development steps of Janssen first CM product

CM Line Feeder Studies

- Catch Scale Test Procedure
- Re-Fill Studies
- Control Tuning Optimization
- Control of sources of perturbation
- Material transfer vs accuracy
- Noise filtration analysis
- Tolerance and Control Limits

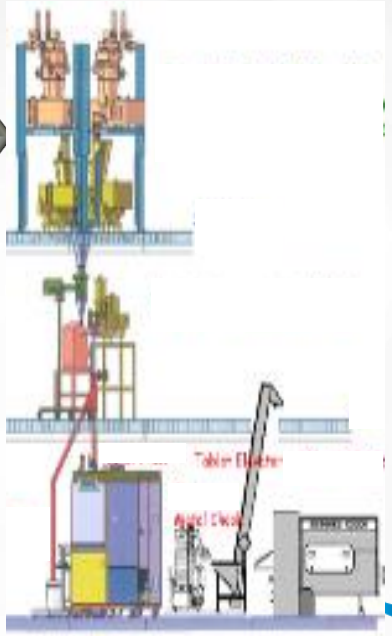


Engineering Studies

- Placebo Based Mill, Blend and Sensing Interface Study
- Placebo Based Tablet Press Study
- API blend and Blend and Sensing Interface Study

CM RTD Studies

- API Tablet Press RTD Study
- Tablet Transfer RTD study



CM Design Space Studies

- Phase A: Placebo Based Factor Effect Screening Design
- Phase B: Drug Product Factorial Design Space Study
- Phase C: Film Coating Process DoE

PAT Development

- Feasibility at UPRM
- Blend PLS Models
- Blend PCA Models
- Tablet PLS Models
- Tablet PCA Models
- Dissolution Model

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Different approaches: Equipment design

Line design	• Throughput 25-200kg; lean & simple <-> flexible • One technology WG or DC <-> DC, WG, RC, DE
Techn. Options	• Vertical vs horizontal set-up; one floor vs several floors • Pre-blend or in-line feeding ; Coating or not
Feeding	• Throughput, Solutions for difficult flow • Change over speed, equipment size
Blending	• Ribbon, horizontal, inclided, vertical • Adjustable hold-up – adjustable peddles
Granulation	• Roller compaction, Twin Screw, FBG, ring granulator • Dryer: 6 or 10 segments - separate pots - Screw
Coating	• Semi batch coating – small or large – Full continuous • Spray location; Tablet Relaxation system;
PAT	• BU: LHP,

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Different approaches: Control Strategies

PAT	• Use PAT for maximum understanding and monitoring • Minimize use of PAT – only for development
Process Control	• No feedback – feed forward • Automated Process control of throughput/holdup vs RTD
BU measurement	• Last BU measurement in feed frame of tablet press • Last BU measurement between blender & hopper tablet press
Rejection	• Only at exit tablet press • Automatic/manual rejection points before tablet press
Traceability	• Assume all impacted for low volume products • PAT <-> RTD
Supporting Data	• Leverage existing data and experience • Only new data from CM process and unit operations
RTR	• Full RTR from the beginning <-> file in phases <-> no RTR • Use of RTR depending on the business case

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Different approaches: Business strategies

Business Cases	• Quality • Cost: Development – TT – Commercial • Supply chain flexibility & agility
Deployment	• Product focus – New product or conversion <-> Platform • Identical lines <-> different lines development & commercial
Development	• At vendor <-> At CMO <-> In house • Integrated with DS <-> clear reqts. for API <-> ad hoc API improvement
Technology	• One technology WG or DC <-> DC, WG, RC, DE • Pre-blend or in line feeding; Coating or not
Modeling	• Impact of : transfer – material variation – cumulative variations • Up scaling <-> downscaling

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Implementation difficulties of New vs. Marketed products

	New Product Introduction	Batch to CM Conversion
Volumes	unknown or inaccurate	better known, but still subject to change
Launching time	critical, but volatile – speed is key	benefit driven
Baseline for business case	averages from the past	well known - current batch numbers
API characteristics	can still change - next gen	stable
modeling	need for downscaling solutions, DOE predictions	need for transfer models
Technology	highly flexible line needed	lean manufacturing unit, cost is deciding
PAT	many tools for data collection	only need coming out of risk analysis
capacity	leave space on the line for launch	leave space on the line for development – think about back-up
people	transform how developers think	strong supporting organisation

Future evolutions needed to support deployment in the Industry

Alignment between Regulatory reviewers/inspectors/countries:

→ Mechanismes for early interaction

→ Same and clear reqts. for BE studies, CPV, data before PPQ

→ Parallel alternate Control Strategies

Find more ways to minimize API consumption in development

Improve efficiency of commercial lines

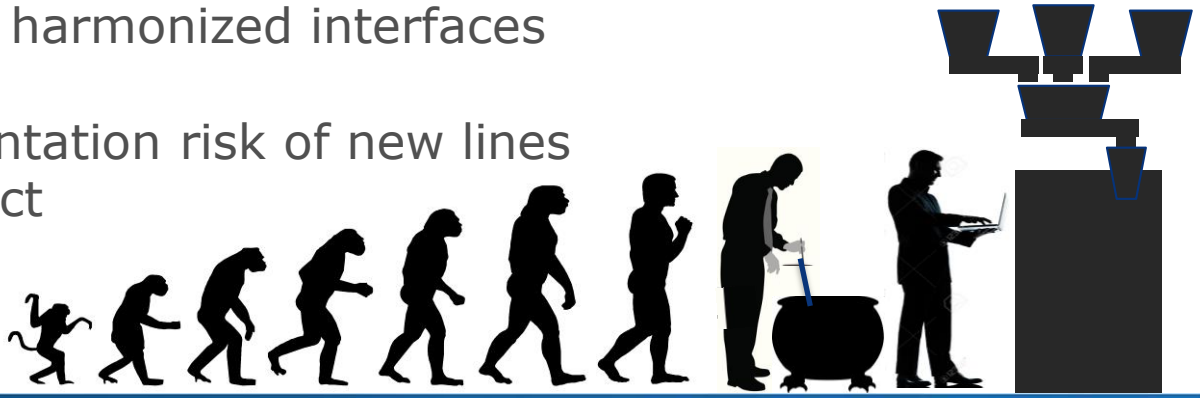
→ Shorter CO and cleaning time, less yield losses

Flexibiliy towards future designs

→ Modular approach, harmonized interfaces

Reduce cost and implementation risk of new lines

→ Less facilities impact



How collaboration can help

How can Pharma companies help each other?

→ Share understanding of differences between brands, types and sizes of unit ops.
→ Share understanding of risks and impact of variation in material, process, environment
→ create trust based on data and real case studies
→ Create a network of TPM capacity that is flexible and compatible with different types of lines
→ Align on concepts for equipment harmonization

How can Vendors help?

→ Deep understanding of the difference between different brands, types and sizes of unit ops.
→ Translate expertise into CM knowledge in useful format for Pharma
→ Build strong knowledge on yield losses, share data
→ Minimize yield losses, Change Over and Cleaning time
→ Maximize throughput
→ Design new ways to feed difficult API
→ Offer strong support package: process, validation, chemometric models, model maintenance packages,...
→ Modular equipment design, interchangeability of unit operations

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