

Potential Regulatory Challenges for Worldwide Approval of Continuous Manufacturing

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MSD

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Agenda

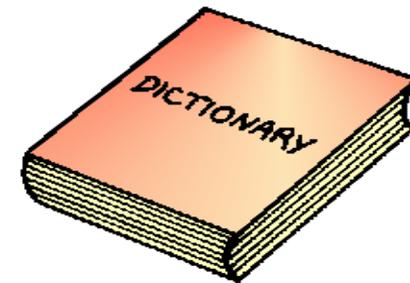
- Background on continuous manufacturing
- MSD's approach for continuous manufacturing for solid oral dosage forms
- Anticipated regulatory challenges
- Future opportunities
- Conclusions

What is Continuous Pharmaceutical Manufacturing?

A manufacturing scheme where the material(s) and product are continuously charged into and discharged from the system, respectively, throughout the duration of the process



Continuous Processes vs. Unit Operations



Many common drug product single unit operations run in a continuous mode, for example:

- Tableting
- Roller compaction
- Spray drying
- Hot melt extrusion

In current terminology, “continuous manufacturing” is commonly used to describe:

- 
- For drug product: connected manufacturing, most commonly for solid oral dosage form, even if run for a discreet period of time
 - For API: single flow chemistry reaction or crystallization steps
 - For biotechnology product: single or connected unit operations, for upstream or downstream processing

Continuous Manufacturing: Agility, Predictability & Quality

Agility advantages:

- Flexible batch sizes to respond to patient demand
- Decreased cycle times and fast turnarounds

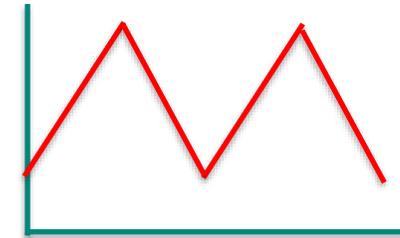
Predictability advantages:

- Improved overall reliability and robustness
- Decreased potential for quality related drug shortages

Quality assurance advantages:

- Integrated measurement and control in real time
- Potential for decreased variability
- Inherently better mixing and segregation control

CURRENT:



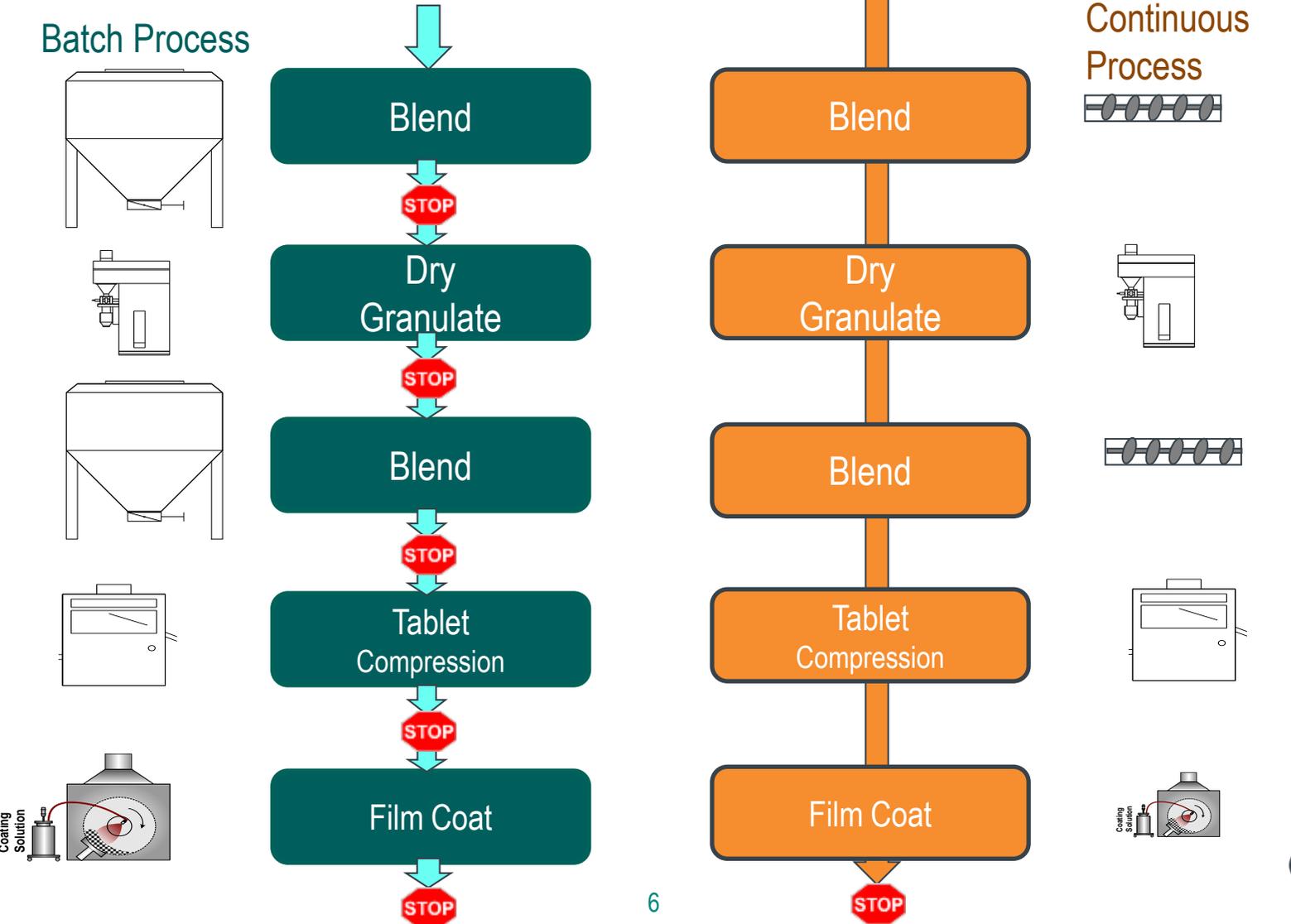
- Large, centralized facilities
- Few campaigns of large batches

FUTURE:



- Smaller volume products
- Small and agile local plants
- Many campaigns, quick turnaround

Comparison of Continuous and Batch Equipment for Tablet Manufacture



Main differences:

- Type of blenders
- Equipment size
- Flow of material

GEA CDC-50 Process Flow

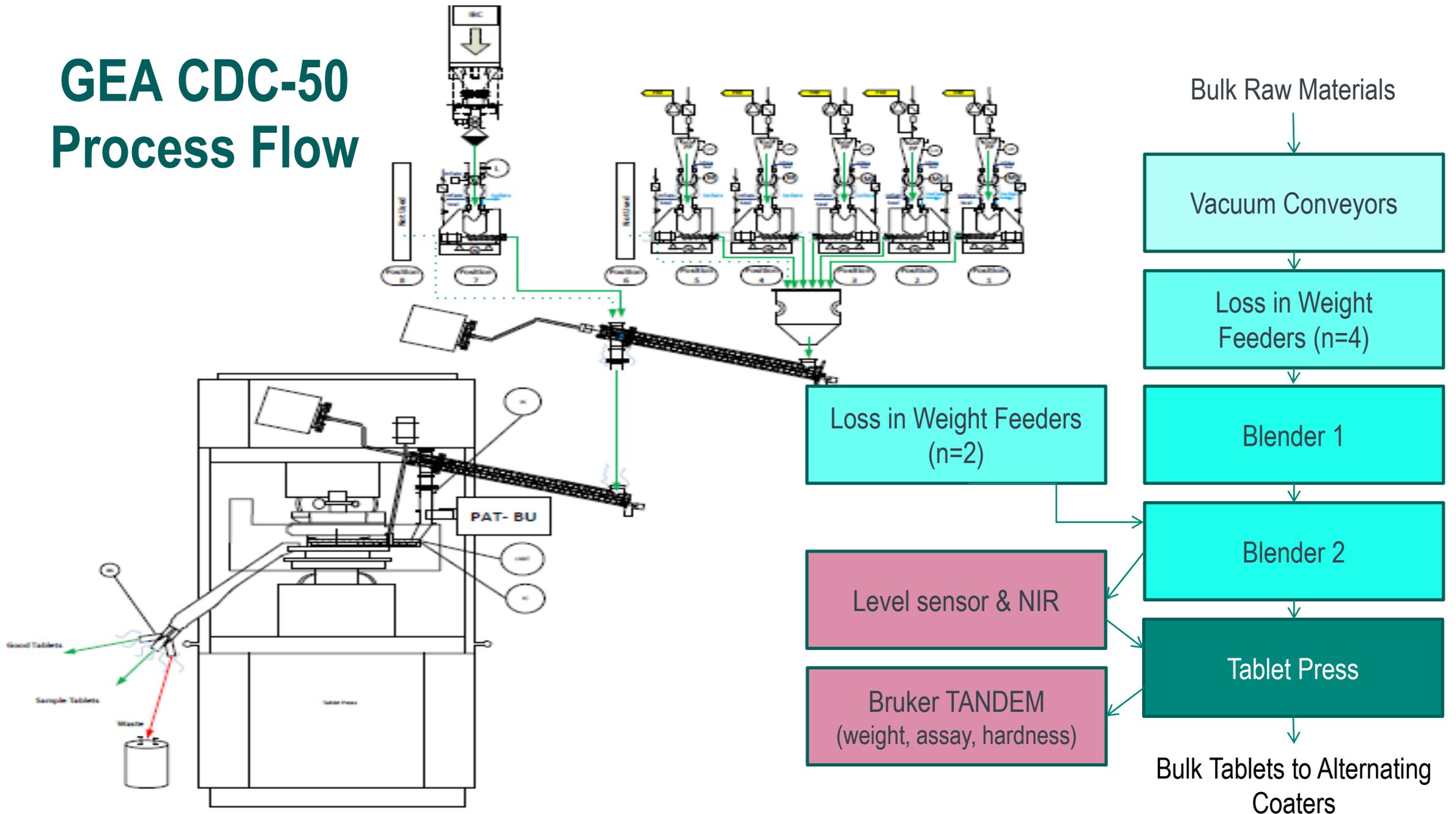


Image courtesy of GEA

Continuous Manufacturing Unit Operations are Logical!

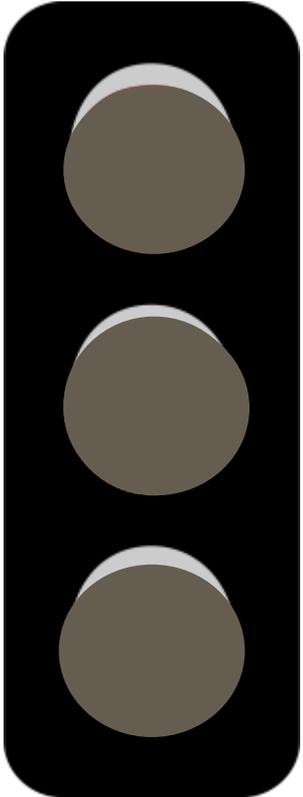


Current Regulatory Landscape

- At least 2 products made by continuous manufacturing have been approved by health authorities:
 - Vertex's Orkambi – New drug approved in US, EU, Canada, Australia & Switzerland
 - Janssen's Prezista – Batch to continuous conversion approved in US
- Many large innovator companies have ongoing programs in continuous manufacturing of SODs
 - Several investigational drugs are being produced by continuous manufacturing
- US, Europe and Japan regulatory agencies all have specialized groups to help facilitate new manufacturing technology:
 - EU PAT Team
 - FDA Emerging Technology Team
 - PMDA Innovative Manufacturing Work Group
- Little or no experience with other health authority expectations for continuous manufacturing

<http://blogs.fda.gov/fdavoices/index.php/2016/04/continuous-manufacturing-has-a-strong-impact-on-drug-quality/>
<http://investors.vrtx.com/releases.cfm?view=all>

Regulatory Risks for Batch to Continuous Conversions (or applications with both batch and continuous processes)



High risk aspects:

- Compositional changes between batch and continuous formulations
- Non alignment of control strategies

Moderate risk aspects (emerging regulatory regions):

- Multiple manufacturing methods/control strategies in a single dossier
- Segregation of potentially non-conforming material

Low risk aspects:

- Definition of batch
- Acceptance of RTRT approaches

Other business risks:

- Difference in approval timelines
- Differences in stability and/or bridging expectations
- Differences in process validation approaches

Definition of “Batch”



Batch (or Lot) – ICH Q7 Definition

- A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits.
- In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Strong alignment between regulators and industry that:

- Batch can be based upon a **pre-determined** amount of material entering or exiting the system or by time.
- Flexibility of batch size should be attainable within validated ranges (fixed per run)
- Raw material traceability is important if needed to segregate “non-homogeneous” material

Acceptance of RTRT Approaches



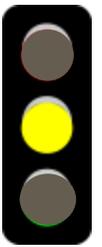
- Process Analytical Technologies (PAT) and Real Time Release Testing (RTRT) have been a part of QbD for nearly a decade
- MSD has experience in getting advanced control strategies, including RTRT approved worldwide
 - First candidate product for continuous manufacturing has RTRT approved worldwide in over 120 markets, include at-line NIR and disintegration in lieu of dissolution
- However, regulatory divergence can occur:
 - Differences in expectation for model validation
 - Expectations for reporting of model updates and changes
 - Concerns of emerging regulatory regions having divergent expectations, as expertise grows

Both Batch and Continuous Processes in Dossier

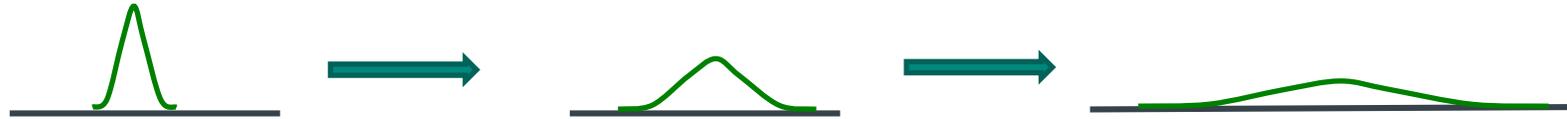


- Supported by ICH Q8/9/10 Points to Consider
 - Different control strategies could be applied at different sites or when using different technologies for the same product at different sites
 - Differences might be due to equipment, facilities, systems, business requirements, etc.
- Unclear how this approach will be accepted by non-ICH regulatory authorities

Segregation of Potentially Non-Conforming Material



- Disturbances introduced in the system propagate down the line



- Sections of the batch impacted by the disturbance can be segregated as “potentially non-conforming material”
 - This material does not conform to expected process conditions can be detected by in-line measurements or through process models
 - Segregated material can be removed from the system at a point that minimized downstream disturbances
 - Material might still be of acceptable quality; it is either discarded or investigated for potential acceptance
- Concern of partial batch rejection may be challenging for some inspectors and assessors
 - Because of the high level of understanding and control, partial lot rejection does not implicate the quality of the whole batch
 - Typically, a minimum yield would be expected to be met to demonstrate a “state of control”

Formulation Compositional Changes



- When switching from batch to continuous it may be necessary to adjust the composition, for example:
 - Different grades of excipients
 - Slight changes composition (e.g., lubricant amount or non-functional film coating thickness)
- Can also support flexible feedback control by changing excipient ratios
- These small changes can enhance consistency and operability of the continuous manufacturing operation
- Concerns occur based upon the ability to have two registered compositions in the dossier
 - Product performance and appearance need to be identical for product made from different processes
- Expectations to only have one composition (or manufacturing process) could unnecessarily decrease the agility gained from continuous manufacturing
 - May discourage future growth in continuous manufacturing through retrofitting older processes

Non-alignment of Control Strategies



- Continuous manufacturing processes for SODs are anticipated to use sophisticated software to control and monitor the system
- As such it would be difficult if not impossible have different control models for different regulatory regions
- Areas of concern include consistency of:
 - PAT and RTRT models
 - Sampling frequency and location
 - Level of redundancy in control strategy

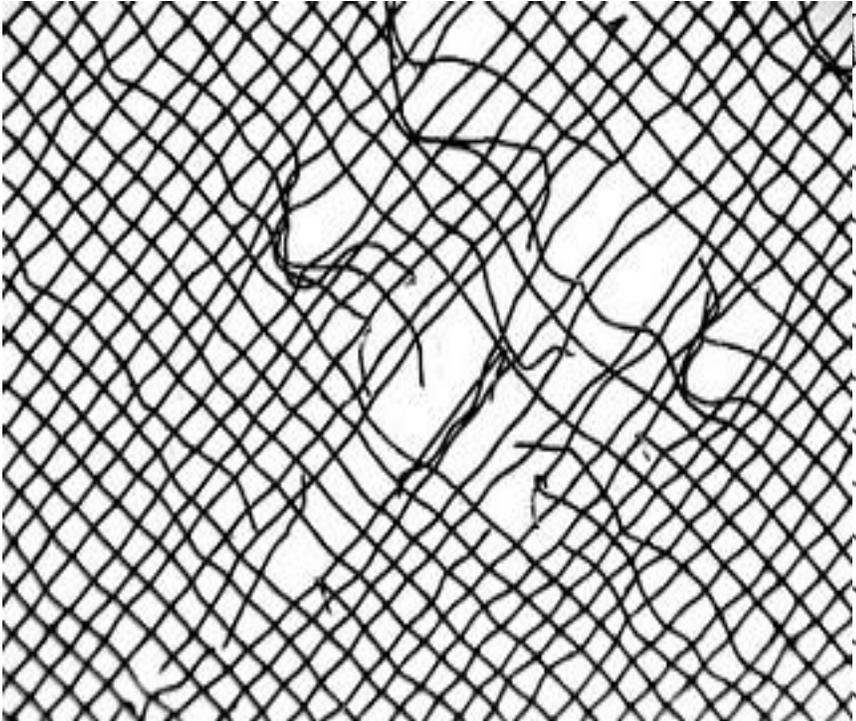
One size does not fit all for control strategies!

- Quality for continuous processing can be assured through:
 - Direct measurement of in-process material attributes
 - Parametric measurements of the system
 - Process models
 - A combination of the above
- Continuous manufacturing can **inherently** have more consistent operation and higher detectability than traditional batch operations
- Control strategies for continuous processing should be **appropriate** for the product and process risks



Connectivity in Pharmaceutical Manufacturing

Success in continuous manufacturing is dependent upon mutual understanding and aligned expectations



- Supply chains are strongly interconnected, globally
- Disruptions in one site or supplier ripple throughout the chain
- Similarly, differences in approved applications can strain or break the whole supply chain
- High degree of product or process variants can lead to public health issues:
 - Increased likelihood of stock outs and shortages
 - Compliance and conformance challenges due to increased complexity
 - Delay of introduction of process improvements or new technology

Looking forward: ICH Harmonization



- Several ICH Guidelines are in progress or under consideration that could have potential impact on continuous manufacturing
- ICH Q12: Technical and Regulatory Considerations for Post-Approval Changes
 - Established Conditions (ECs)
 - Post Approval Change Management Protocols (PACMPs)
- Potential future ICH Quality topics:
 - Continuous Manufacturing – as stand alone topic or Q&A to ICH Q8/9/10/11
 - Process Validation

Potential Benefits of ICH Q12 for Continuous Manufacturing

“Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management”

- Established Conditions (ECs):
 - Are defined as legally binding information considered necessary to assure product quality and that if changed requires a submission to the health authority
 - Provide clarity on what aspects of the process and analytical methods need to be reported, if changed
 - Support inclusion of supportive development and QMS data (e.g., validation information, batch records) for information purposes without fear of it being a commitment
 - Can be described through performance based approaches, which aligns well with PAT and advanced controls
- Post Approval Change Management Protocols (PACMPs)
 - Can provide pre-agreement on how future changes will be evaluated and filed
 - Currently only available in US & EU but Japan and Canada have pledged to adopt



Where Is Industry Now?

Cautiously Optimistic



Industry Perspective

- Will all regulators approve of our new processes? Plants? Filings?
- Will we get too many questions with this new process? Will approvals be delayed?
- Can we justify converting old products?
- Can we financially justify a new plant when we have idle capacity?
- **Is it worth all the extra work and risk?**

Regulatory Perspective

- What will processes, plants and filings look like in the future?
- How can I learn without asking questions? How can I review complex filings without more time?
- How long will old batch processes stick around?
- Why isn't industry moving faster, when the incentives are clear?
- **Is it worth all the extra work and risk?**

*The transition to the continuous manufacturing platform takes time.
Our timeline can be burdened with non-aligned regulations.*

Path Forward: Continued Conversation & Collaboration



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Thank you!

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