Development of continuous manufacturing process (Q13)

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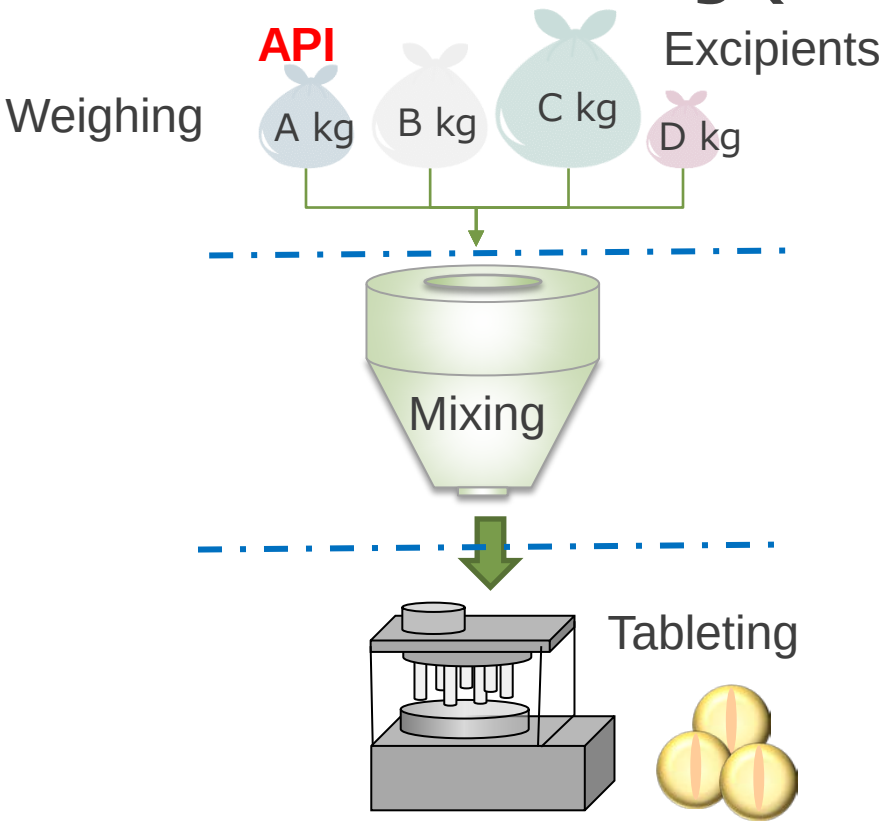
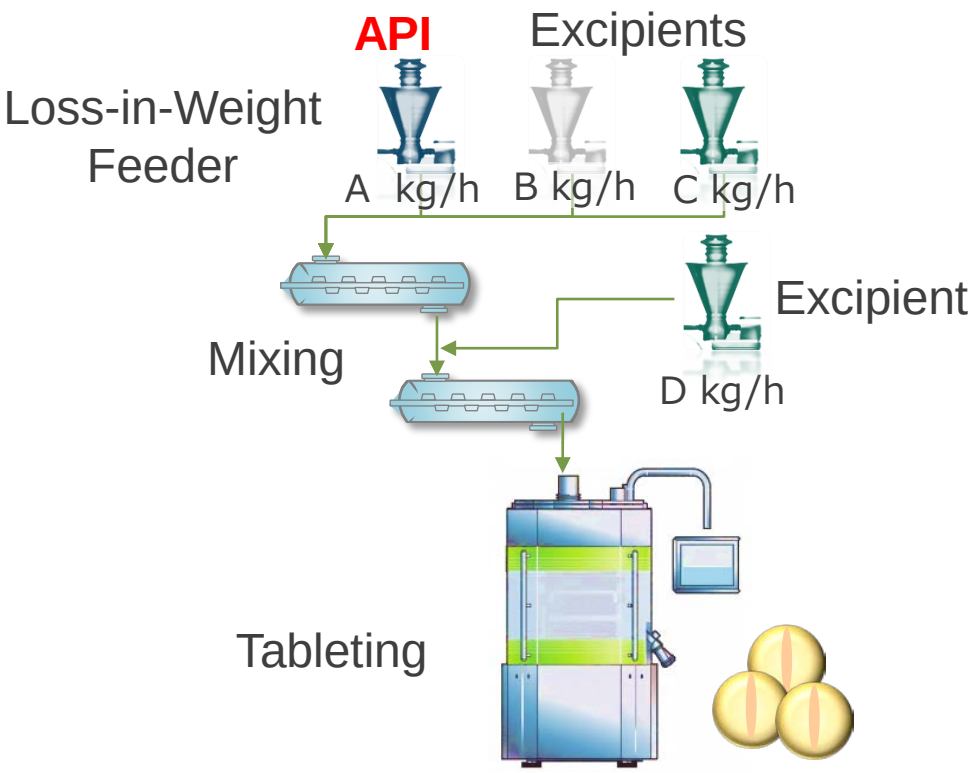
What is continuous manufacturing (CM) ?

Batch Manufacturing (BM)



CM



Why is Continuous Manufacturing (CM) drawing attention?

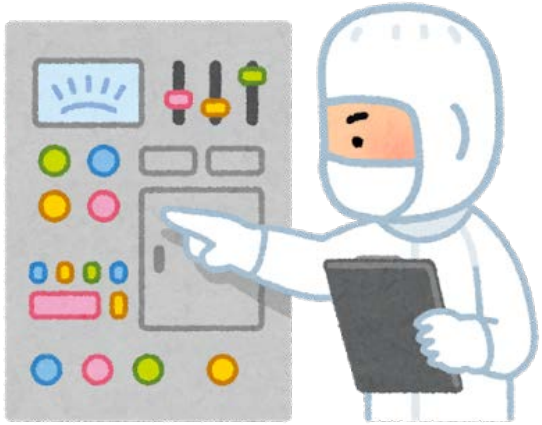
- Are there any problems with conventional Batch Manufacturing (BM)?

- There is nothing wrong with BM, which should remain one of the manufacturing methods to be used in the future.
- However, CM may offer us what is challenging to achieve with BM.

Expectations for CM

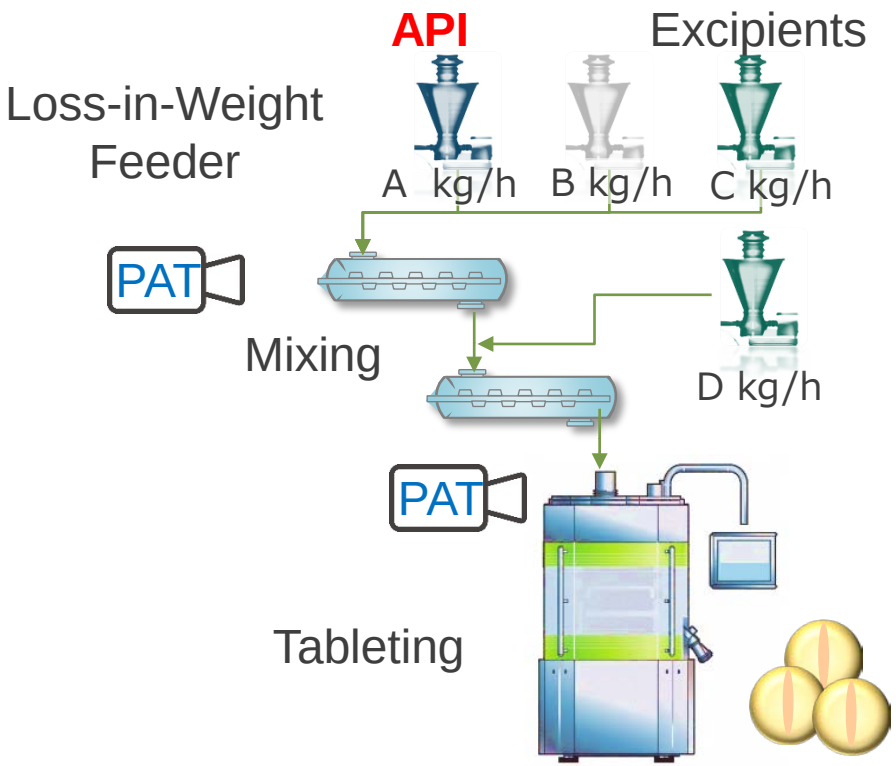
- Flexible manufacturing
  - Production in response to demand
- Detectability of poor-quality products
  - Prevention of drug shortage problems
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

and so on



CM offers us a wider choice of manufacturing methods

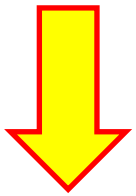
What is the difference in control strategy between BM and CM?



- In CM, fluctuations in the upstream process directly affect the downstream process, so more integrated system management is required compared to conventional BM.

How do we control CM specific matters?

- CM specific matters
  - Equipment design and system integration
  - Material traceability
  - Process dynamics, etc.



We need a new guideline for CM

Road to ICH Q13

- In 2014, CM was selected as a topic which would be developed into a guideline.

- CM was chosen as a nominee of future ICH quality topics.

  （As of the ICH Minneapolis meeting, 2014）

- In June, 2018, CM was endorsed as a new topic at the ICH Kobe meeting.（ICH Q13）

ICH Q13
Continuous Manufacturing of Drug Substances and Drug Products

- Rapporteur: Dr. Sau (Larry) Lee (FDA, US)
- Regulatory Chair: Dr. Yoshihiro Matsuda (MHLW/PMDA)

- ANVISA, Brazil
- BIO
- EC, Europe
- EFPIA
- FDA, US
- Health Canada, Canada
- HSA, Singapore
- IGBA
- JPMA
- MFDS, Republic of Korea
- MHLW/PMDA, Japan
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- APIC
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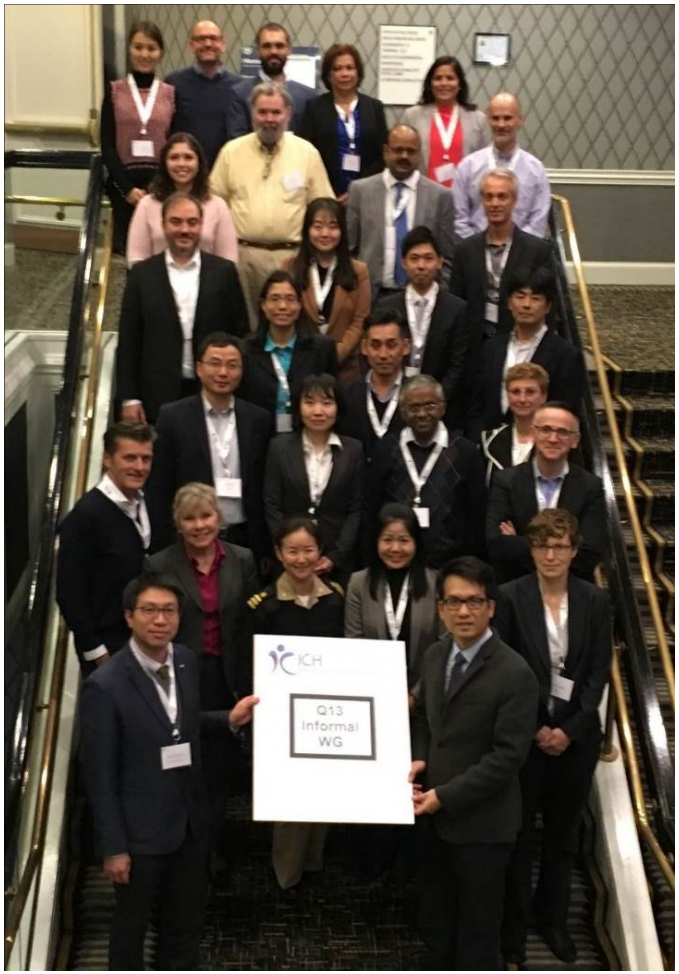
- National Center, Kazakhstan
- USP
- PIC/S
- EDQM



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  - II. Continuous manufacturing of drug products (chemical entities)
  - III. Continuous manufacturing of drug substances (therapeutic proteins)
  - IV. Integrated drug substance and drug product continuous manufacturing
  - V. Perspectives on managing disturbances

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Objectives

- Describe scientific and regulatory considerations for the development, implementation, operation, and lifecycle management of CM.
- Provide clarification on CM concepts.

Scope

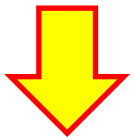
- Applies to the CM of drug substances and drug products for chemical entities and therapeutic proteins.
- Applicable to CM for new products (e.g., new drugs, generic drugs, biosimilars) and the conversion of batch manufacturing to CM for existing products.
- The principles described in this guideline may also apply to other biological/biotechnological entities.
- Focuses on the integrated aspects of a CM system in which two or more unit operations are directly connected.

Batch definition

- The ICH Q7 definition of a batch is applicable to all modes of CM, for both drug substances and drug products. Based on this definition, the size of a batch produced by CM can be defined in terms of one of the following:
  - Quantity of output material
  - Quantity of input material
  - Run time at a defined mass flow rate
- Other approaches to define batch size can also be proposed, if scientifically justified based on the characteristics of the CM process and Good Manufacturing Practice (GMP).

Control Strategy

- The development of a successful control strategy for CM is enabled by a holistic approach, considering aspects specific to CM and the principles described in ICH Q7–Q11.



- State of Control
- Process Dynamics
- Equipment Design and System Integration
- Material Traceability and Diversion

etc.

State of Control

- A state of control (ICH Q10) is a condition that provides assurance of continued process performance and product quality.

(1) Stable period → (2) Unstable period → (3) Re-stabilization

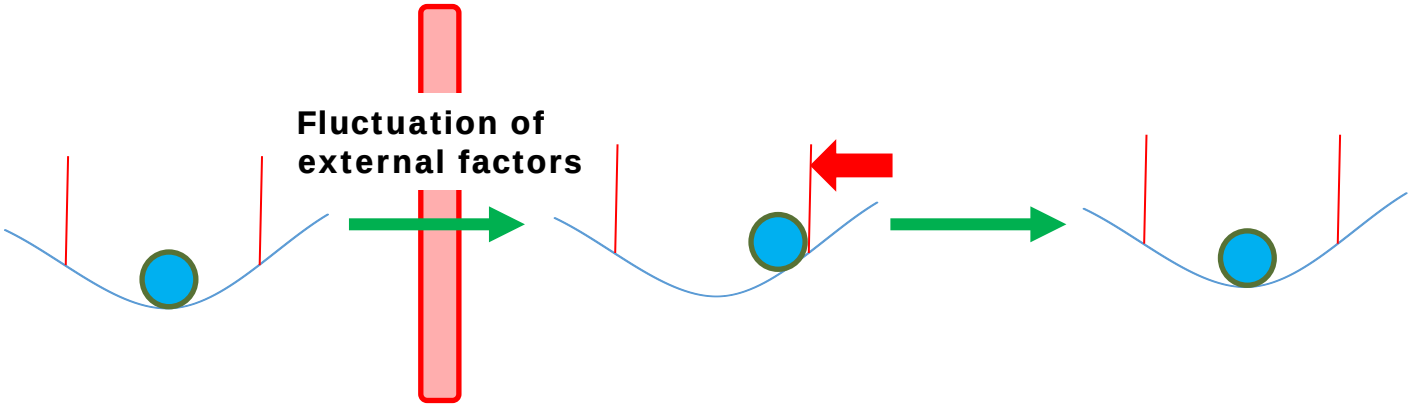


Figure : Conceptual diagram depicting the State of Control
(Note: The red belt indicates the control range and the red arrow indicates the designed control.)

Reference: http://www.nihs.go.jp/drug/section3/AMED_CM_CONTROLST.pdf

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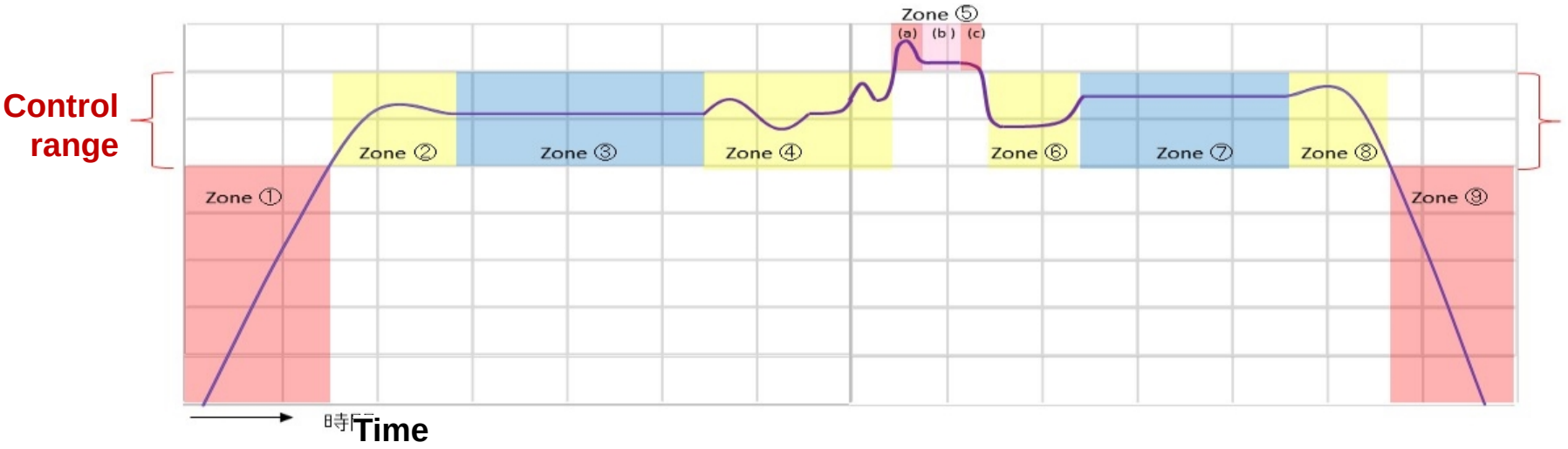
Concept of the Relation between “Steady State” and “State of Control”



Zone	(1)	(2)	(3)	(4)	(5)			(6)	(7)	(8)	(9)
Description of state	Start-up (yet to reach control range)	Start-up (within control range but non-steady state)	Steady state	Disturbance has occurred but within control range	(a) Deviation from control range (b) Entered steady state but outside control range (c) Entered non-steady state and still outside control range			Returned within control range but non-steady state	Steady state with values different from those in Zone3	Shut-down procedure has started but still within control range	Shut-down (Deviated from control range)
					(a)	(b)	(c)				
Steady state	N	N	Y	N	N	Y	N	N	Y	N	N
State of control	N	Y	Y	Y	N	N	N	Y	Y	Y	N
Discharge outside the system	Y	Y/N	N	Y/N	Y	Y	Y	Y/N	N	Y/N	Y

(Y: Yes, N: No, Y/N: Yes or No)

Reference: http://www.nihs.go.jp/drug/section3/AMED_CM_CONTROLST.pdf

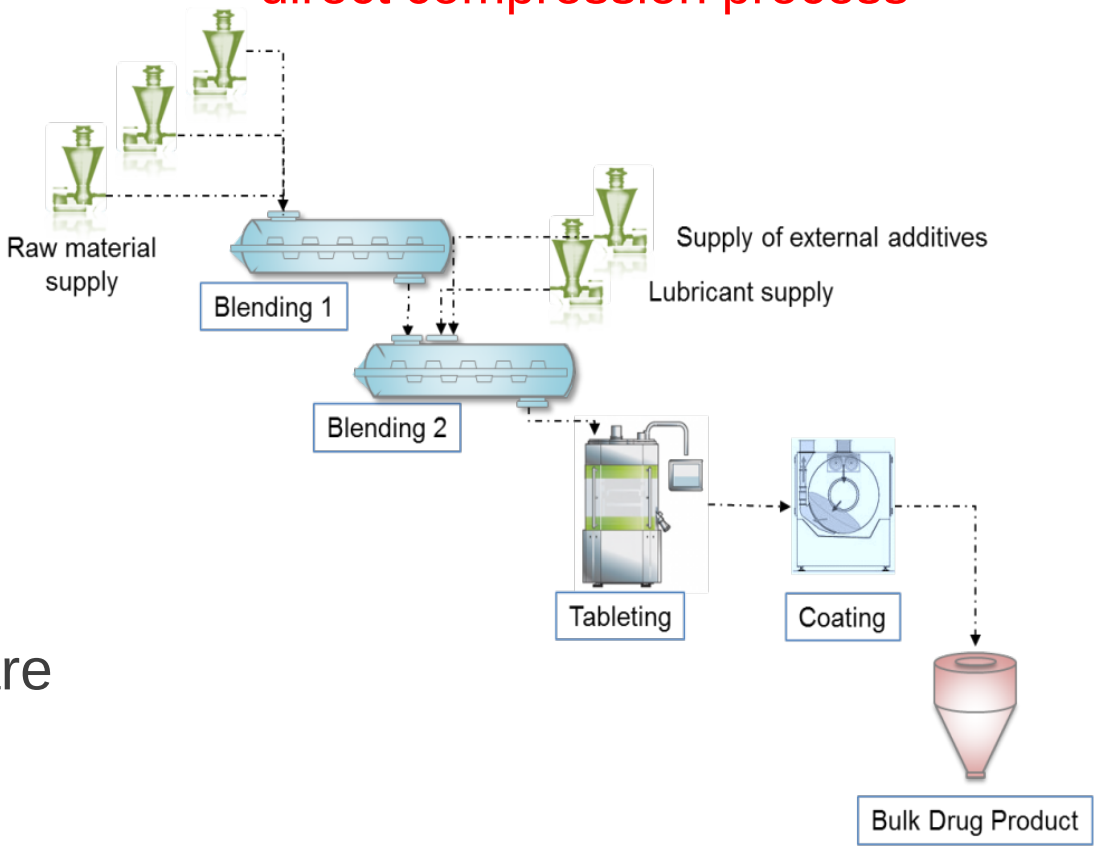
Process Dynamics

- Knowledge of process dynamics is important to maintain a state of control in CM. Specifically, understanding the impact of transient events helps to identify risks to quality and to develop an appropriate control strategy.
- Process dynamics could be characterized by determining properties such as residence time distribution (RTD) to understand how output material quality is impacted by transient events.

Residence Time Distribution (RTD) model

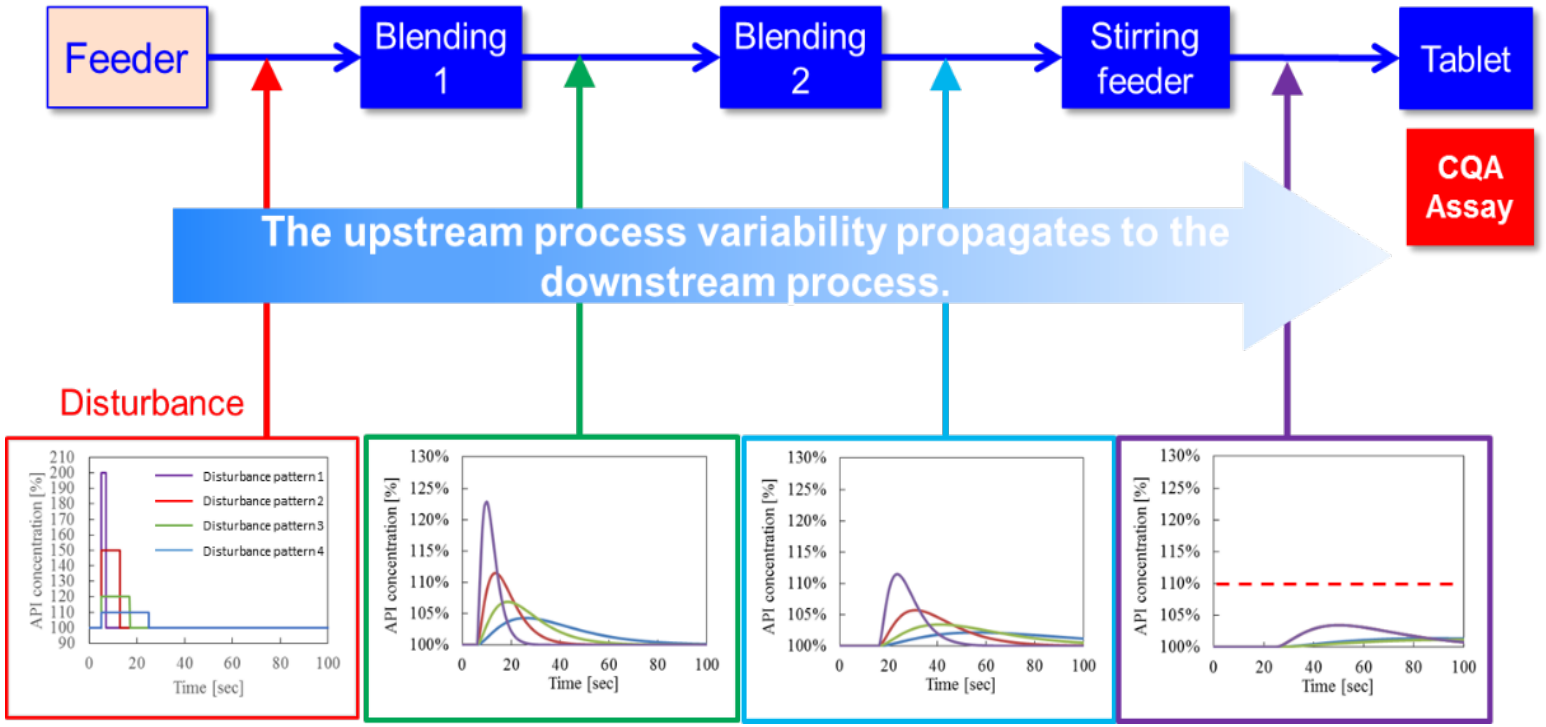
- The RTD model is a well-known theory in reaction engineering and can provide information about material flow and component concentration within the reactor.
- In the continuous direct compression process, the RTD model enhances the understanding of how the API and each excipient component flow to the blender and of how they are blended.

Schematic diagram of the continuous direct compression process



Reference: Asian Journal of Pharmaceutical Sciences 16, 253-262, 2021

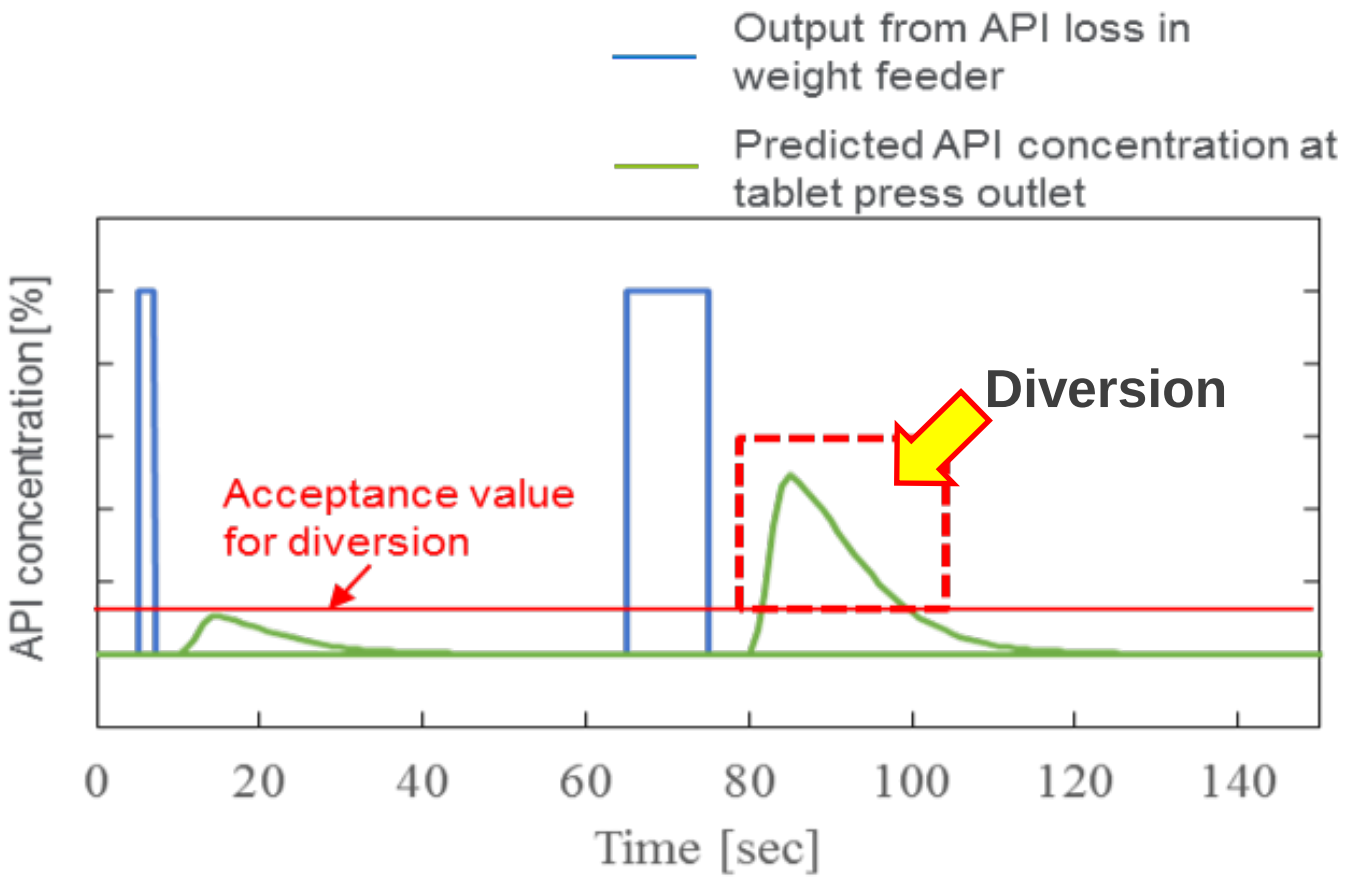
Variations of the Loss-In-Weight (LIW) feeder and a step-by-step image of each process



It is possible to predict how the variation caused by the LIW feeder continues the process, how it affects the quality of the final drug product, and how to set the acceptable range of variation of the LIW feeder.

Reference: Asian Journal of Pharmaceutical Sciences 16, 253-262, 2021

A process control image based on the API concentration predicted by RTD



Using the RTD model, the magnitude and length of acceptable variation of the LIW feeder can be established from its impact on the CQA of Assay and can be incorporated into the control strategy of the continuous direct compression process.

Diversion Strategy

Reference: Asian Journal of Pharmaceutical Sciences 16, 253-262, 2021

Current Status

- July, 2021: Step1 sign-off & Step2a/2b endorsement
- July, 2021~December, 2021: Regional Consultations
- November, 2022: Step4

ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Draft version

Endorsed on 27 July 2021

Currently under public consultation

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PMDA Experiences with CM

- Some CM products have approved in Japan.
  - Eli Lilly: Verzenio® Tablets (abemaciclib) 50mg, 100g, and 150mg
  - Janssen Pharmaceutical K.K.: Tramcet® Combination Tablets (tramadol hydrochloride, acetaminophen)
  - GSK: Duvroq® Tablets (daprodustat) 1mg, 2mg, 4mg, 6mg
  - Eisai: Tazverik® Tablets (tazemetostat) 200mg
  - Shionogi: Xofluza® Tablets (baloxavir marboxil) 10mg, 20mg
  - Pfizer: Cibinqo ® Tablets (abrocitinib) 50mg, 100mg, 200mg

    ⋮

Regulatory harmonization and convergence

- It is necessary for pharmaceutical industries to make similar regulatory decisions globally.

- The ICH is among the most effective ways of harmonizing regulatory decisions. → ICH Q13

- Are the ICH guidelines (ICH Q13) enough to achieve true harmonization?

- In addition, we also need to consider regulatory convergence.

Reference: Matsuda Y, Global Regulatory Landscape. AAPS PharmSciTech. 2019; 20(1)

Expectations in the future

- CM can potentially be a standard of drug manufacturing in the pharmaceutical industry.
  - Many regulatory agencies, including PMDA and US FDA, strongly support the implementation of CM technology.
  - CM is the necessary technology to realize Industry 4.0（a concept given to the current trend of automation and data exchange in manufacturing technologies)
  - CM can innovate the manufacturing and distribution of pharmaceuticals.

CM will be a benefit for everyone.

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Acknowledgements

Ask