PMDA perspective on Continuous Manufacturing

Yoshihiro Matsuda, Ph.D.
Senior Scientist for Quality
PMDA

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DIA

Introduction of PMDA

Headquarters, Tokyo

- Name : Pharmaceuticals and Medical Devices Agency
- Date of Establishment : In April 2004
- Established as an Incorporated Administrative Agency

Kansai branch

Hokuriku branch

https://www.pmda.go.jp/english/index.html

Regulatory authorities for drugs and medical devices

PMDA

- Scientific review for drugs and medical devices
- Consultation on clinical trials etc.
- Inspection (GCP, GLP, GMP, QMS etc.)
- Supporting MHLW's activities

MHLW

- Authorization of applications
- Publication of guidelines
- Supervision of PMDA activities

PMDA: Pharmaceuticals and Medical Devices Agency
MHLW: Ministry of Health, Labour and Welfare

Flowchart of Reviewing Process

① Submission

② Review Report

The Pharmaceutical Affairs and Food Sanitation Council

MHLW
Ministry of Health, Labour and Welfare

③ Approval

Why is Continuous Manufacturing (CM) drawing attention?

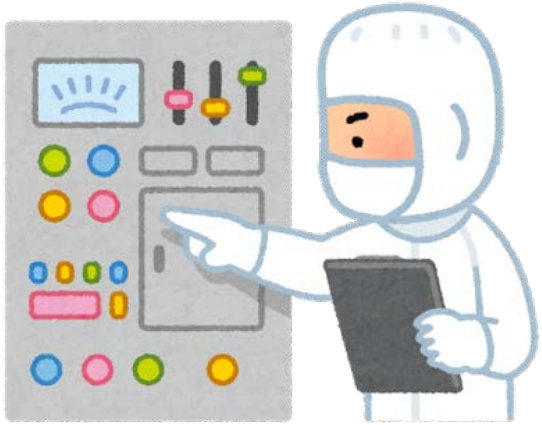
- Are there any problems with conventional Batch Manufacturing (BM)?

- 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

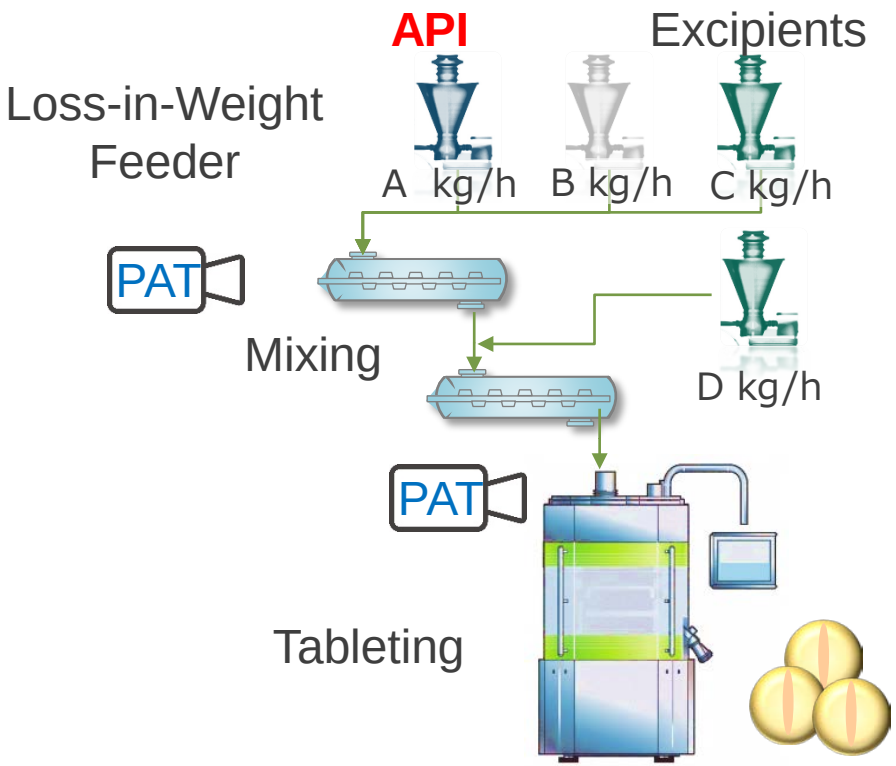
- Flexible manufacturing
  - Production in response to demand
- Detectability of poor-quality products
  - Prevention of drug shortage problems
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

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 to control CM specific matters?

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

- Controls
  - Traditional off-line testing
  - Models
    - NIRS (Chemometric models)
    - Process models (Mechanistic models)
    - Multivariate Statistical Process Control (MSPC), etc.

Specialized teams for CM at the EMA, FDA and PMDA

- EMA
  - Process Analytical Technology (PAT) team
- US FDA
  - Emerging Technology Team (ETT)
- PMDA
  - Innovative Manufacturing Technology Working Group (IMT-WG)
  - AMED research group for small molecule
    - Study on quality assurance of pharmaceutical CM
  - AMED research group for large molecule
    - Study on quality control strategies for the practical application of CM of biopharmaceuticals

AMED: Japan Agency for Medical Research and Development

PMDA's Milestones

- PMDA IMT-WG
  - PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft)

    https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0018.html
- AMED research group
  - Document: "Points to Consider Regarding Continuous Manufacturing"

    http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf
  - Document: "State of Control in Continuous Pharmaceutical Manufacturing"

    http://www.nihs.go.jp/drug/section3/AMED_CM_CONTROLST.pdf
  - Approach to establishment of control strategy for oral solid dosage forms using continuous manufacturing

    Chemical and Pharmaceutical Bulletin 69(2), 211-217, 2021
  - Control strategy and methods for continuous direct compression processes

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

State of Control

- “State of control” means a condition in which a change remains within the control range under the predetermined control even if the condition changes over time due to the fluctuation of external factors.

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

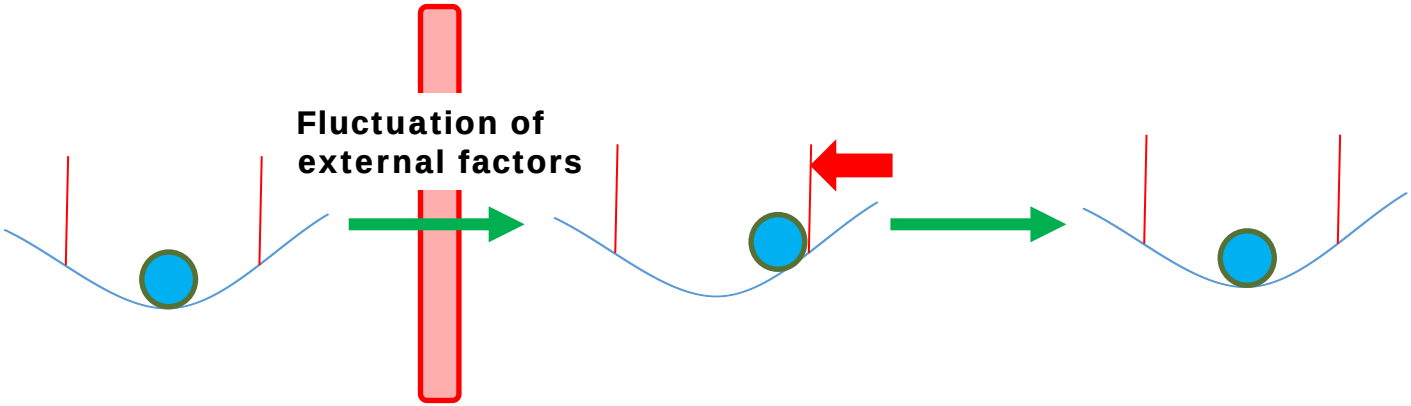


Figure : Conceptual diagram depicting the State of Control
(Note: The red belt indicates the control range and the red arrow indicates the designed control.)

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

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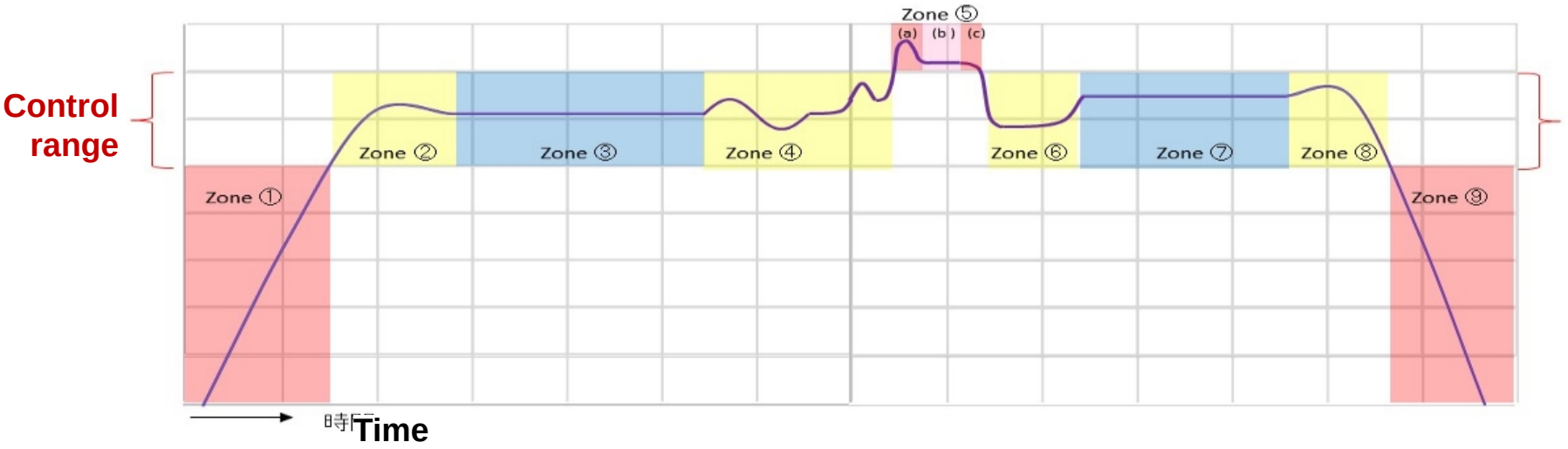
Concept of the Relation between “Steady State” and “State of Control”



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

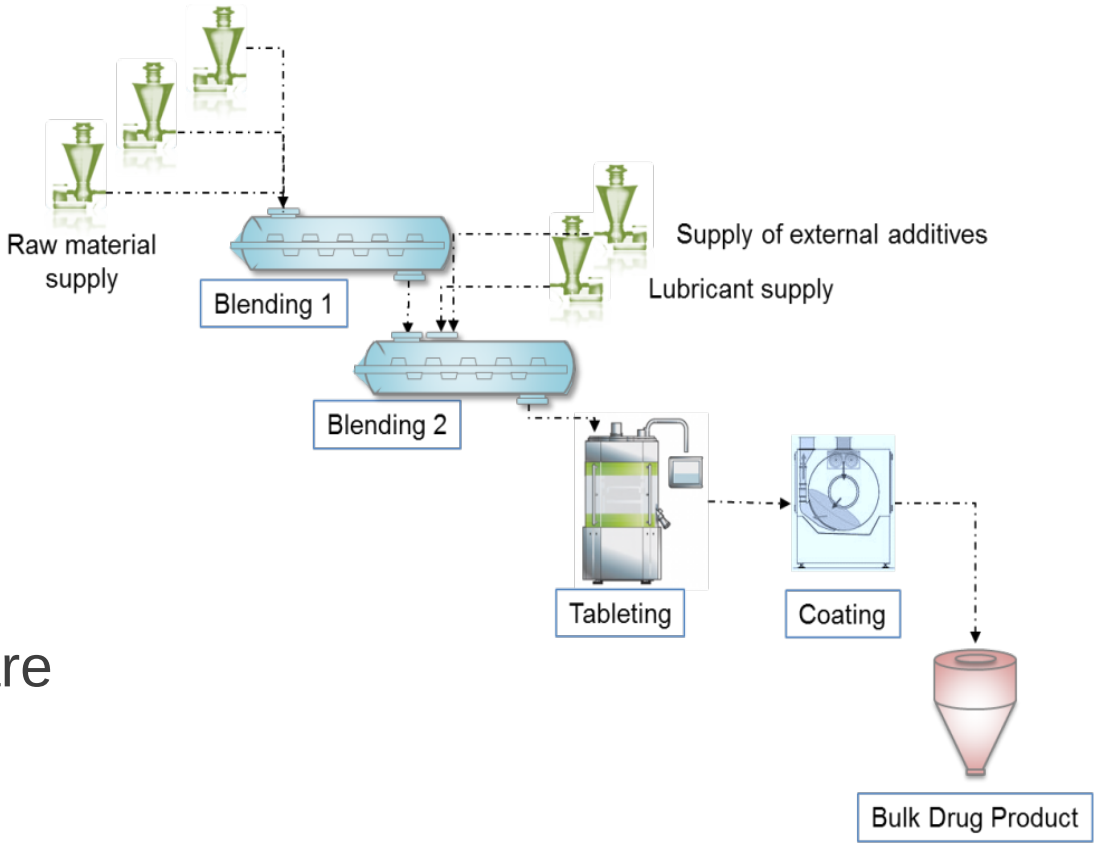
(Y: Yes, N: No, Y/N: Yes or No)

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

An Example of a Process Model:
Residence Time Distribution (RTD) model

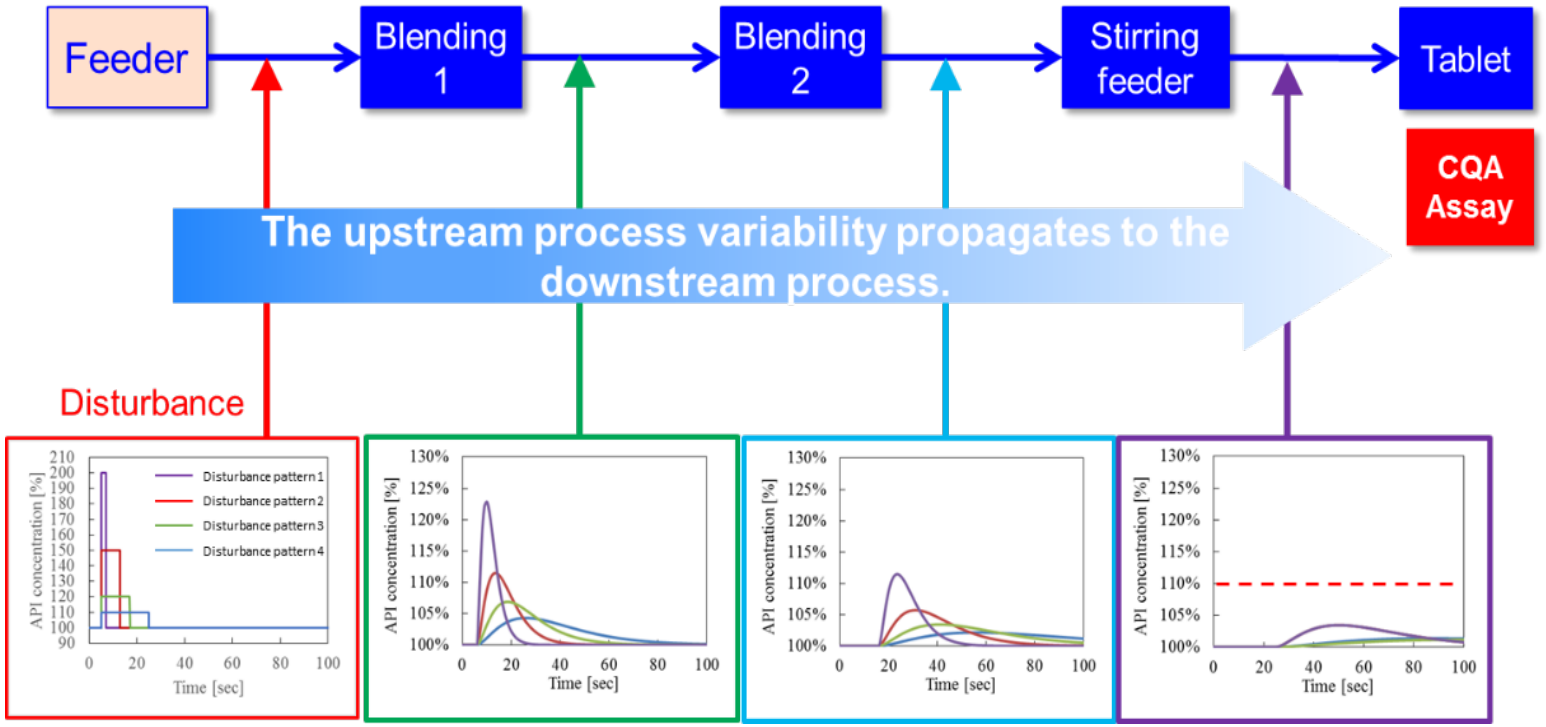
- The RTD model is a well-known theory in reaction engineering and can provide information about material flow and component concentration within the reactor.
- In the continuous direct compression process, the RTD model enhances the understanding of how the API and each excipient component flow to the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

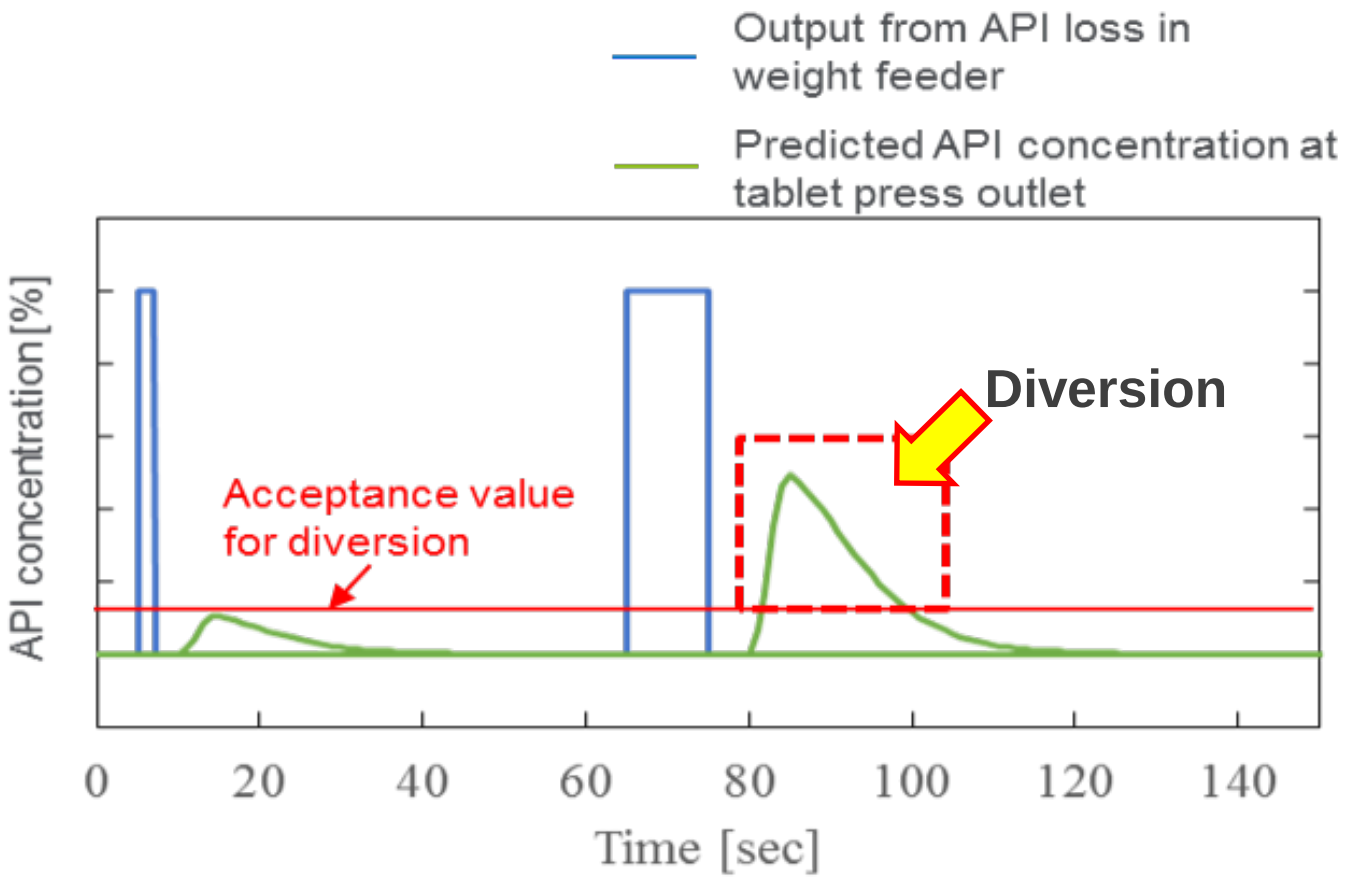
Variations of the Loss-In-Weight (LIW) feeder and a step-by-step image of each process



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

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

    ⋮

Example case of Approval in Japan（1）

独立行政法人 医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

× 画面を閉じる
文字サイズ 標準 大 特大

一般名	アブロシチニブ

販売名	製造販売業者等	添付文書	患者向医薬品ガイド／IF／くすりのしおり	RMP	RMP資材	
					医療従事者向け	患者向け
サイバインコ錠50mg／サイバ …	製造販売元／ファイザー株式会社	PDF(2021年12月13日) / HTML	患者向医薬品ガイド G サイバインコ錠50mg／サイバインコ錠100mg／サイバインコ錠200mg 2021年11月作成 インタビューフォーム F1 サイバインコ錠50mg／サイバインコ錠100mg／サイバインコ錠200mg くすりのしおり くすりのしおり一覧	○	適正使用ガイド	サイバインコを服用されるアトピ …

重篤副作用疾患別対応マニュアル				
	消化性潰瘍	無顆粒球症（顆粒球減少症、好中球減少症）	薬剤性貧血	薬物性肝障害
	血小板減少症	血栓症（血栓塞栓症、塞栓症、梗塞）	間質性肺炎	

承認情報公知申請への該当性に係る報告書	承認年月日等	報告書	申請資料概要	備考
	2021年09月27日	審査報告書	申請資料概要	既存治療で効果不十分なアトピー性皮膚炎を効能・効果とする新有効成分含有医薬品

Cibinqo Tablets（abrocitinib）

Reference:
https://www.pmda.go.jp/drugs/2021/P20211011001/672212000_30300AMX00443_A100_1.pdf

Example case of Approval in Japan（2）

2.2.2　製造方法

製剤は原料供給、混合、打錠、フィルムコーティング及び包装・表示からなる工程により製造され、原料供給から打錠までは連続生産技術により連続的に、その後のフィルムコーティング工程ではバッチ式で製造される。なお、[redacted]、[redacted]及び[redacted]工程が重要工程とされ、工程管理項目及び工程管理値が設定されている。

クオリティ・バイ・デザインの手法を利用し、以下の検討等により、品質の管理戦略が構築されている（表 3）。

- 重要品質特性の特定
- 品質リスクアセスメント、実験計画法に基づく重要工程パラメータの特定
- NIR と SS の混成法によるリアルタイムモニタリング

- In this example case, continuous manufacturing technology is used in the LIW feeding and tableting process.
- A real-time monitoring system consisting of a hybrid of Near InfraRed and Soft Sensor (NIR-SS) for IPC

Example case of Approval in Japan（3）

2.R.1　製剤の製造管理について

申請者は、連続的な工程を含めた製剤の均質な製造についての管理戦略は、以下の要素から構成されていると説明している。

① [redacted]の[redacted]が製剤品質に与える影響の評価による、製剤組成が製造中の変動に脆弱ではないこと及び目標とする製剤品質が得られる変動範囲の確認

② 原料ごとの[redacted]供給装置の[redacted]モニタリングによる、連続混合機への[redacted]速度及び[redacted]割合の制御（リアルタイム）

③ 連続混合機内の混合末の[redacted]制御に基づく混合均一性の確保（リアルタイム）

④ [redacted]モデル（②の[redacted]速度及び③の[redacted]設定値に基づく[redacted]濃度推定）による、混合機から排出される混合末中の[redacted]濃度の管理（リアルタイム）

⑤ [redacted]の混合末の NIR-SS 混成法による、原薬含量値のリアルタイムモニタリング及び不適合となる錠剤の除外（NIR が使用不可能な場合には、製造時間全体に亘り定期的にサンプリングした素錠のオフライン検査で含量及び製剤均一性を確認する）

⑥ 製造時間全体にわたり定期的にサンプリングした素錠の[redacted]及び[redacted]が設定範囲内であることの確認（オフライン）

⑦ フィルムコーティング後の製剤についての出荷判定試験（オフライン）

- Controlling parameter A speed and ingredient B mass balance of components into the continuous mixing equipment (RT)
- Ensuring uniformity of dosage units of the mixed powder in the continuous mixing equipment by controlling factor C (RT)
- RT monitoring of the drug substance concentration of the mixed powder by the hybrid NIR-SS model and diverting non-conforming material

Example case of Approval in Japan（4）

2.R.2　NIR-SS 混成法の使用について

製剤製造の均一性を管理するための[redacted]の[redacted]含量モニタリングには、NIR の [redacted] モデルをそのまま使用するのではなく、供給装置の[redacted]や混合機の[redacted]等の工程パラメータを入力変数として[redacted]モデルに基づく含量推定を行う SS を混成させた、NIR-SS 混成法が使用されている。

申請者は、NIR-SS 混成法を用いる点について、以下のように説明している。

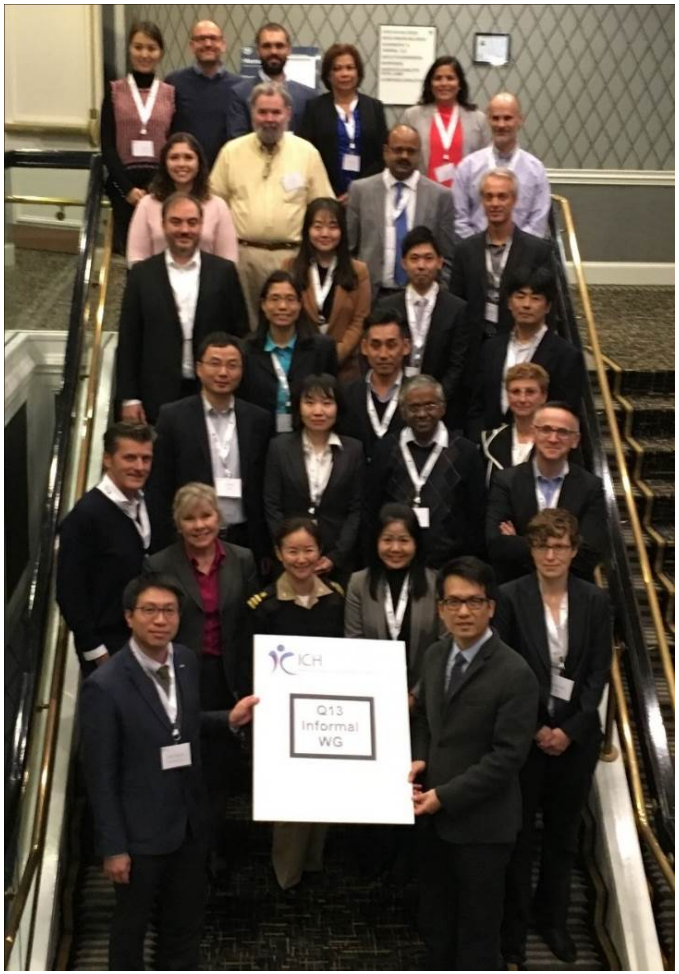
NIR に SS を混成する理由として、NIR の [redacted] モデルは、原料ロット等がモデルの頑健性に影響を及ぼし、結果として推定値に偏りが生じる可能性があるが、SS は入力変数による[redacted]モデルであるため、NIR において推定値に偏りを生じさせる因子の影響は受けず、混成の結果、より頑健な測定結果が得られると考えられる。

- Utilize the Hybrid NIR-SS model which performs content estimation. This model consists of NIR and process parameters of LIW feeders and mixing equipment.
- The SS is not affected by factors that bias estimates in NIR.

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
- NMPA, China
- PhRMA
- Swissmedic, Switzerland
- TFDA, Chinese Taipei
- IFPMA
- APIC
- IPEC
- National Center, Kazakhstan
- USP
- PIC/S
- EDQM



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

DIA

Regulatory harmonization and convergence

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

- The ICH is among the most effective vehicles of harmonization. → 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)

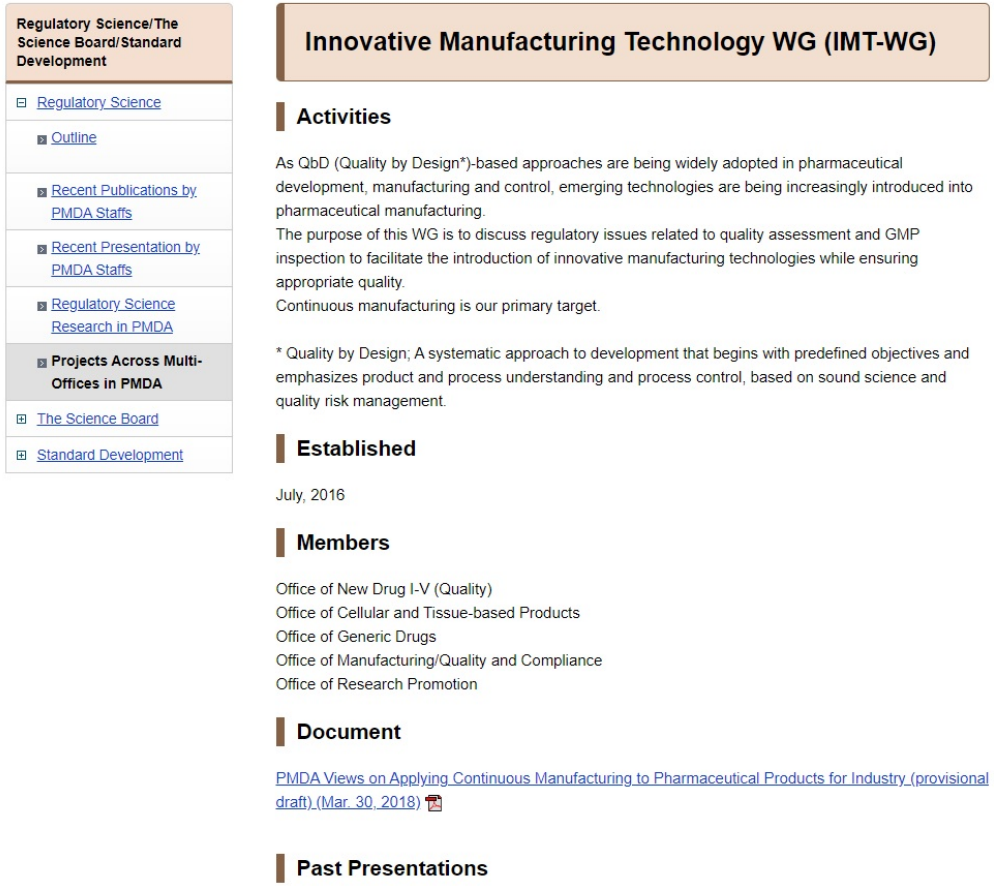
Expectations in the future

- 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.

DIA

How to stay up to date with PMDA



Regulatory Science/The Science Board/Standard Development

- Regulatory Science
  - Outline
  - Recent Publications by PMDA Staffs
  - Recent Presentation by PMDA Staffs
  - Regulatory Science Research in PMDA
  - **Projects Across Multi-Offices in PMDA**
- The Science Board
- Standard Development

Innovative Manufacturing Technology WG (IMT-WG)

Activities

As QbD (Quality by Design*)-based approaches are being widely adopted in pharmaceutical development, manufacturing and control, emerging technologies are being increasingly introduced into pharmaceutical manufacturing.
The purpose of this WG is to discuss regulatory issues related to quality assessment and GMP inspection to facilitate the introduction of innovative manufacturing technologies while ensuring appropriate quality.
Continuous manufacturing is our primary target.

* Quality by Design; A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Established

July, 2016

Members

Office of New Drug I-V (Quality)
Office of Cellular and Tissue-based Products
Office of Generic Drugs
Office of Manufacturing/Quality and Compliance
Office of Research Promotion

Document

PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft) (Mar. 30, 2018)

Past Presentations

This website will provide compiled information on domestic regulations applicable to pharmaceutical CM including:

- Presentation files
- Regulatory documents, etc.

https://www.pmda.go.jp/english/rs-sb-std/rs/0012.html

Ask