The landscape of continuous manufacturing in Japan

(日本における連続生産の取組み状況)

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What is the continuous manufacturing?

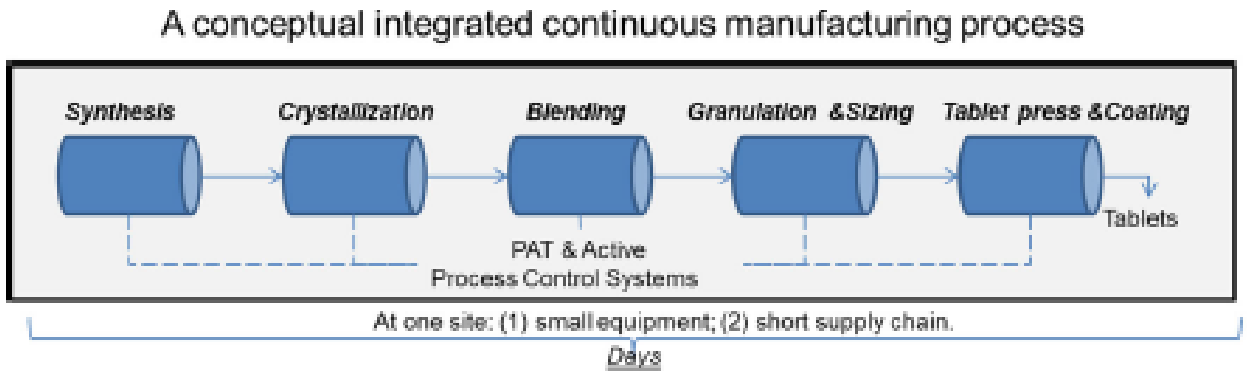
- A harmonized definition of continuous manufacturing (CM) in a pharmaceutical area has not been provided yet.
- However we consider it as・・・

CM is a manufacturing method in which raw materials or their blended materials are entered continuously in the manufacturing process throughout the duration of the process, and products are produced continuously through the manufacturing.

(連続生産とは、製造プロセスが稼働している期間中、連続的に原料又はそれらの混合物を製造工程内に供給し、生産物を継続的に生産する方法である。)

Question

- How many manufacturing processes should be integrated for CM?



Lee S. and Woodcock J. et al., *J Pharm Innov* (2015) 10:191-199

Why is CM so focused?

- Does the batch manufacturing have some problems?

- No. the batch manufacturing is still working well in pharmaceutical area.
- However we expect the CM to bring us additional opportunities.

Opportunities by CM

- Realization of flexible manufacturing
  - Production in response to demand
- Detectability of poor quality product
  - Prevention of drug shortage problem
- Prevention of waste
  - Promotion of Green chemistry
  - Cost reduction

and so on

Expectation to bring innovation

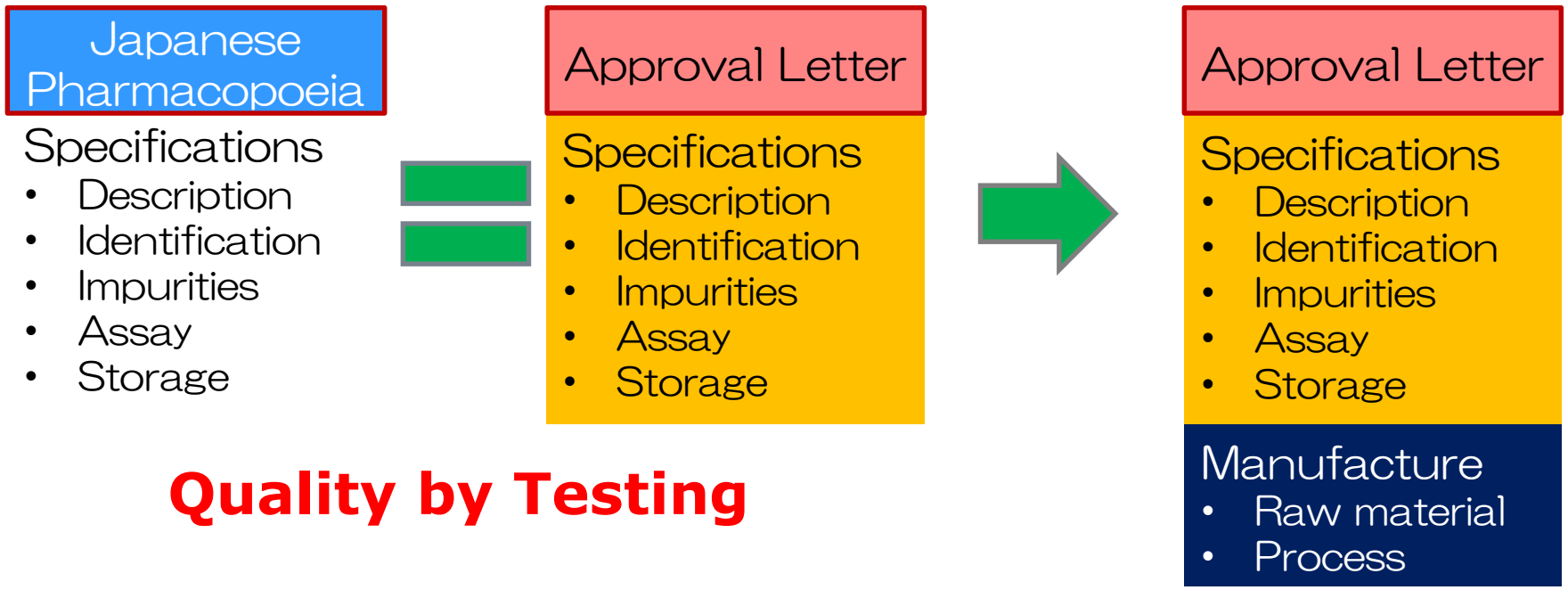
Why now?

- CM is not new technology in other area, such as petroleum refining, food processing, but in pharmaceutical area…

⇩ **New Paradigm**

- Now it is ready for new technologies by both regulators and pharmaceutical companies.

The Change of quality control in Japan



Quality by Testing

Quality by Design

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 (ICH Q8(R2))

（事前の目標設定に始まり、製品及び工程の理解並びに工程管理に重点をおいた、立証された科学及び品質リスクマネジメントに基づく体系的な開発手法。）

QbD provides us an opportunity to discuss on new technology/control strategy and it facilitates us to take flexible control strategy.

Regulatory expectations for CM

- Our expectations for pharmaceutical quality are the same in between CM and Batch Manufacturing.
- However we expect that CM is a key enabler for modernization of pharmaceutical manufacturing to improve
  - Agility
  - Flexibility
  - Robustness

  in the manufacture of Pharmaceuticals

Messages for CM by US FDA

- No regulatory hurdles for implementing CM
  - Both the Agency and industry are gaining experience
- Recommend early and frequent discussion with the Agency during CM development
  - **Emerging Technology Program** should be utilized for early FDA-Industry interactions even before the drug molecule is identified
- Process understanding is key to identifying product quality risks and developing a robust control strategy
- A robust control strategy for a CM process can include a combination of different scientific approaches
- FDA supports the implementation of CM technologies using science and risk-based approaches

＊Referring from a presentation by Dr. Sau(Larry) Lee at DIA CMC Workshop, 2017

Messages for CM by EMA

- Regulators are supportive of innovative pharmaceutical manufacturing.
- Current regulatory framework is adequate to allow CM. No specific guidelines currently available, but existing GL's are supportive.
- CM offers advantages over batch manufacture.
- Complex dossiers? Level of detail commensurate with impact on the commercial manufacturing process and control strategy.
- Regulators need to understand the product and process development, manufacturing and process control strategy (and decision making).
- Stick to ICH terminology. Provide clear definition for in-house terms when unavoidable.
- Early dialogue with regulators to ensure there is a mutual understanding.

＊Referring from a presentation by Dr. Peter Richardson at DIA CMC Workshop, 2017

Messages for CM by PMDA

- PMDA agrees to US FDA's and EMA's messages.
- PMDA is also supportive of innovative pharmaceutical manufacturing such as CM.
- PMDA believes that there are no regulatory hurdles for implementing CM.
- PMDA recommends industries to have early and frequent discussions with PMDA during CM development.

To facilitate CM in Japan

Innovative Manufacturing Technology Working Group (IMT-WG)

- Has been established in PMDA since July, 2016.
- Purpose
  - To establish PMDA's perspective on the latest technologies of pharmaceutical quality control
  - To propose a new regulatory framework for the pharmaceutical quality control by the new technologies
  - To draft guidelines
- Members
  - Senior Scientist (for Quality); Dr. Yoshihiro Matsuda
  - From Office of New Drugs
  - From Office of Manufacturing/Quality and Compliance
  - From Office of Generic Drugs
  - From Office of Cellular and Tissue-based Products
  - From Office of Regulatory Science

IMT-WG Activities for Continuous Manufacturing (CM)

- IMT-WG had face-to-face meetings with US FDA in 2016 and EMA in 2017.
- IMT-WG visited continuous manufacturing sites of chemical substance and product.
- IMT-WG joined some quality consultations regarding CM across multi-offices in PMDA.
- IMT-WG has good collaboration with a national research project on pharmaceutical quality control.

Japan Agency for Medical Research and Development (AMED) sponsored study group

- Study on quality control techniques in a new development and manufacturing change of pharmaceutical

  （医薬品の新規開発と製造変更における品質管理手法に関する研究）

  - It was started on August 15th , 2016.
  - Purpose:
    - To facilitate the smooth introduction of the CM in Japan by addressing issues of the CM together with industries, regulators and academia and by sharing our knowledge.
  - Members:
    - PMDA (assessors, GMP inspectors)
    - National Institute of Health Science (researchers)
    - Universities
    - Industries (Daiichi-Sankyo, Eisai, Sumitomo Dainippon Pharma, Chugai, GSK, Janssen, MSD etc.)

CM Research Outcome

A Points-to-consider document.

- We focused on 4 topics by following inputs from The Japan Pharmaceutical Manufacturers Association (JPMA) members.
  - Control Strategy
  - Batch Definition
  - Process Validation
  - Stability Testing

http://www.nihs.go.jp/drug/section3/AMED_CM_PtC.pdf

A provisional draft document for CM

- PMDA Views on Applying Continuous Manufacturing to Pharmaceutical Products for Industry (provisional draft) was published in March 30, 2018.
  （医薬品の連続生産を導入する際の考え方について（暫定案））
- This provisional draft document was developed by Innovative Manufacturing Technology Working Group (IMT-WG) at PMDA, based on the point-to-consider document.

https://www.pmda.go.jp/rs-std-jp/standards-development/cross-sectional-project/0018.html

Introduction (1)

- This document includes some views on applying Continuous Manufacturing to pharmaceutical products at this time point, which are compiled within the limited practical experience that the IMT-WG has. The contents of this document should be reviewed according to the future experience and accumulated knowledge. Therefore, it is submitted as a provisional draft. This provisional draft was prepared by anticipating the following cases, (1) through (2).

（本文書は、PMDA革新的製造技術ワーキンググループとして、限られた実務経験の中で現時点での連続生産を導入する際の考え方を取りまとめたものであり、その内容は今後の経験や知識の蓄積に応じて適宜、見直されるべきものであることから、暫定案として提示した。なお、この暫定案は以下の（1）～（2）の事項を想定し作成したものである。）

Introduction (2)

(1) It is intended for solid oral dosage forms (tablets, etc.) manufactured using drug substances (small-molecule compounds) produced by chemical syntheses.

（化学的合成法により製造される原薬（低分子化合物）を用いて製造する経口固形製剤（錠剤等）。）

(2) An ideal production state is achieved. For example, manufacturing equipment is filled up with required amount of raw materials and then raw materials are being supplied.

（理想的な製造状態。例えば、製造装置内に必要量、原料が充填され、供給され続けている状態など。）

Introduction (3)

- In addition, this document does not cover matters for GMP controls.

  (なお、本文書はGMP上の管理に関する事項を取りまとめたものではない。)

- Actual application of Continuous Manufacturing to individual products may require the control of their quality attributes and manufacturing processes, as well as the considerations according to the level of knowledge and understanding of these quality attributes and manufacturing processes. Therefore, the utilization of the PMDA's face-to-face consultation services with the PMDA review division is advised.

  (実際の個別品目における連続生産の導入については、品質特性及び製造工程並びにこれらに関する知識・理解の程度に応じた検討が必要となる可能性があるため、適時適切に対面助言などを利用し、担当審査部と相談すること。)

Control Strategy (1)

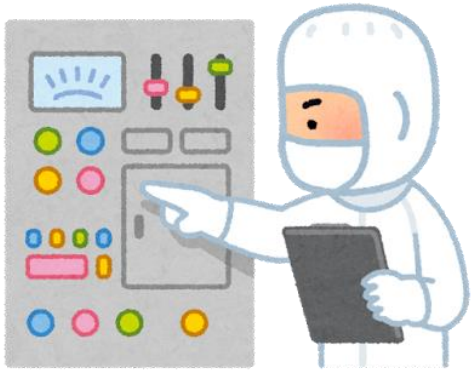
- For establishing a control strategy for commercial production during the developmental phase of pharmaceutical products, there is no fundamental difference between the Batch Manufacturing and Continuous Manufacturing in terms of factors to ensure Critical Quality Attributes (CQA) of the final products, such as quality attributes of the raw materials and intermediate products, specifications of the products, process parameters, and in-process controls (except for process dynamics which is mentioned below).

  (医薬品の開発段階では、商用生産に向けた管理戦略を構築する上で必要となる最終製品の重要品質特性（CQA）を保証するための要素（使用原材料、中間製品等の品質特性、製品規格、工程パラメータ、工程内管理等）は、後述する動的特性の要因を除き、バッチ生産と連続生産で本質的な違いはない。)

Control Strategy (2)

- It is necessary to take into consideration the specific factors that have not been anticipated during Batch Manufacturing, through the qualification of equipment or devices to be used in Continuous Manufacturing, regarding their characteristic factors.

  (連続生産に使用する機器・設備の特性要因を含めた検証を行うことにより、バッチ生産時では想定されなかった特有の要素も考慮する必要がある。)



Control Strategy (3)

- Beneficial control strategy for Continuous Manufacturing
  (連続生産で有益な管理戦略)
  - In Continuous Manufacturing, the process inputs, i.e. material attributes of raw materials could change along with the progression of the Continuous Manufacturing process, which may impact the quality of the product or intermediate product. Therefore, more flexible handling could be required compared to the traditional Batch Manufacturing, such as the adjustment of process parameters according to the changes in the material attributes.

    (連続生産では製造プロセスが連続的に進行するため、入力変数である原料の物質特性が製造プロセスの進行とともに変動しうることにより製品・中間製品の品質に影響を与える可能性があることから、物質特性の変動状況に応じて工程パラメータを調整するなど、従来のバッチ生産に比べてより柔軟な対応が必要とされる。)

Control Strategy (4)

Performance based Approach

- Differing from the process control using fixed process parameters, the control method that can achieve the desired product quality by adjusting process parameters as per the control strategy according to any changes that occur during processing based on measuring and assessing quality of the final or intermediate products in real time using PAT, etc..

  (固定された製造工程パラメータによる製造管理とは異なり、たとえばPAT等を用い、製品、中間製品等の品質をリアルタイムに測定／評価し、工程稼働中に生じる変動に応じて、管理戦略に従って製造工程パラメータを調整することで、目的とする製品品質を達成するための管理手法。)

For the achievement

- Need to understand the "Process Dynamics"
- Need to ensure the "State of Control"
- Need to consider the "Fit for Purpose"

Control Strategy (5)

- Process Dynamics（動的特性）
  - Traceability of the input materials based on the residence time distribution and effects of expected changes on the quality of the downstream products.

    （滞留時間分布に基づく投入された原料のトレーサビリティ及び想定された変動が下流工程の品質に及ぼす影響。）
- State of Control（管理できた状態）
  - A condition in which the set of controls consistently provides assurance of continued process performance and product quality (ICH Q10)

    （管理の組み合わせが継続する製造プロセスの稼働性能及び製品品質について恒常的な保証を提供する状態。（ICH Q10）。）
- Fit for Purpose
  - A risk based weighting of the control strategy based on potential impact on product quality.

    （製品品質への潜在的影響に応じた、リスクに基づく管理戦略の重みづけ。）

Control Strategy (6)

- Understanding of process dynamics （動的特性の把握）
  - Understanding of process dynamics (including start-up, hold and shut-down) includes the understanding of the traceability of the raw materials introduced into the process based on the Residence Time Distribution (RTD) and the understanding of the effects of anticipated changes on the quality of downstream products.

    (動的特性の把握（製造開始時、製造中及び製造終了時を含む）とは、例えば滞留時間分布（RTD）に基づく投入された原料のトレーサビリティの理解、想定される変動が下流工程の品質に及ぼす影響の把握が該当する。)
  - Before introducing Continuous Manufacturing, it is necessary to establish a robust control strategy that comprehensively covers the entire manufacturing process and demonstrate that a "State of Control" is maintained.

    (連続生産の導入に当たっては、製造工程全体を包括した頑健な管理戦略を構築し、「管理できた状態」が維持されていることを示す必要がある。)

Control Strategy (7)

- Tools
  - PAT tools (including soft sensors possibly)
  - A Residence Time Distribution (RTD) model
- The control strategy needs to be evaluated individually. Therefore PMDA recommends establishing an early dialogue with regulators during the development stage of Continuous Manufacturing.

  (管理戦略については個別の評価が必要となることから、早い段階からPMDAと相談することが望まれる。)

Batch Definition (1)

- There is no difference in the definition of "Batch" between Batch Manufacturing and Continuous Manufacturing. However, the concept of batch size is different.

  (ロットの定義自体には、バッチ生産と連続生産の間で違いはない。ただし、ロットサイズの考え方は異なると考える。)

- Definition of Batch (or Lot)
  - "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." (ICH Q7)

    (「規定された限度内で均質と予測できる、一つの工程又は一連の工程で製造された原材料等の特定の量。連続製造の場合には、ロットは製造の規定された画分に相当する。ロットサイズは、特定の量又は特定の時間内に製造された量と定義される。バッチともいう。」)

Batch Definition (2)

- Concept of Batch (or Lot) Size（ロットサイズの考え方）
  - The batch (or lot) size in Continuous Manufacturing can be specified based on any of the following aspects:

    （連続生産のロットサイズは、具体的には以下のいずれかに基づき規定されると考える。）

    (1) The run time and the processing speed（稼働時間及び処理速度）

    (2) The volume of material produced（製造量）

    (3) The feed amount of raw materials（原材料の仕込み量）
- In Continuous Manufacturing, parameters can be modified within a validated range. These parameters include run time, processing speed, volume of material produced, etc. The uniformity of a batch can be ensured by maintaining a "State of Control" through the control based on mathematical models and/or the continuous monitoring with PAT, etc.

  (連続生産では、バリデーションにより検証された範囲内でパラメータを変更することが可能となる。例えば、稼働時間、処理速度、製造量などが該当する。ロットの均質性は、数学的モデルに基づく管理やPATによる連続モニタリング等により「管理できた状態」を維持することで保証されると考える。)

Validation (1)

- As is the case in Batch Manufacturing, validation for Continuous Manufacturing needs to be implemented in accordance with the validation standards. For Continuous Manufacturing, it is important to validate the following:

  (連続生産を適用した場合であっても、バリデーション基準に基づきバリデーションを実施することが必要である。連続生産適用時においては、特に下記について検証することが重要である。)

  (1)Process performance and quality attributes during Continuous Manufacturing are consistently maintained in a "State of Control" by the pre-established control strategy.

  (あらかじめ設定された管理戦略により、連続生産中の製造プロセス稼働性能及び品質特性が恒常的に「管理できた状態」にあること。)

  (2)Based on the dynamics of how raw materials or intermediates flow through the process, chronological changes in quality between batches as well as within a batch remain within an acceptable range.

  (原料・中間体の動的特性を踏まえ、ロット間のみならず、ロット内における経時的な品質の変動が許容範囲内にあること。)

Validation (2)

- Batch size and the number of batches for process validation
  (プロセスバリデーションのロットサイズ及びロット数)
  - Basically, as in the Batch Manufacturing, process validation needs to be performed using the production batch size at the production scale, repeated with at least 3 batches or performed with an equivalent method to ensure the repeatability.
    (プロセスバリデーションは、バッチ生産方式と同じく、再現性の確保の観点から原則、実生産規模での製造ロットサイズとし、3ロットの繰り返し又はそれと同等以上の手法により行う必要がある。)
  - Validation design that introduces the idea of continuous process verification may be possible in some cases.
    (継続的工程確認(Continuous Process Verification)の考えを導入したバリデーションデザインが可能な場合もある。)
  - The batch size of a product to which Continuous Manufacturing is applied should be established before being manufactured by the manufacturer.
    (連続生産方式を適用する品目におけるプロセスバリデーションのロットサイズは、予め製造前に製造者が設定するものである。)

Validation (3)

- Specifically for CM
  - The batch size should be established by taking into consideration the operability of manufacturing equipment in a longer operation time and the effects of accumulated substances on manufacturing equipment.

    (長時間稼働させた場合の製造装置の作動性、製造装置への物質の蓄積の影響等を考慮してロットサイズを設定する必要がある。)

Therefore

This process validation should be repeated with at least 3 batches or performed with an equivalent or superior method.

(3ロットの繰返し又はそれと同等以上の手法によるプロセスバリデーションを実施する必要がある。)

Validation (4)

- Validation on changes for an approved product in switching from the Batch Manufacturing to Continuous Manufacturing

  (バッチ生産方式にて既に承認取得している製品を連続生産に切り替える場合の変更時のバリデーション)

  - Basically, this will be handled in the same manner.

↓

Process validation needs to be performed using the production batch size at the production scale, repeated with at least 3 batches or performed with an equivalent method to ensure the repeatability.

(プロセスバリデーションは、再現性の確保の観点から原則、実生産規模での製造ロットサイズとし、3ロットの繰り返し又はそれと同等以上の手法により行う必要がある。)

Stability Testing (1)

- Size of the primary batch（基準ロットのロットサイズ）
  - In Continuous Manufacturing, the batch size can be varied by changing the operating time of the manufacturing process within the validated range. Therefore, unlike Batch Manufacturing, in the case of Continuous Manufacturing, it is especially important to ensure that products are being manufactured with the equivalent quality regardless of any time point they are sampled from in the manufacturing process.

    (連続生産では、製造工程の稼働時間などをバリデートされた範囲内で変更することでロットサイズを変更することが可能となる。したがって、バッチ生産時とは異なり、連続生産時では、生産スケールに応じた保証よりも、製造時のどの時点からサンプリングされても同等の品質のものが製造できることの保証を行うことが特に重要となる。)

Stability Testing (2)

It is required to ensure a "State of Control," scientifically proving that chronological changes are within an acceptable range in quality due to transient disturbances or failures in equipment performance.
(「管理できた状態」を保証し、一過性の外乱や設備の稼働に不具合が生じたこと等による経時的な品質の変動が許容範囲内にあることを科学的に保証することが求められる。)

Stability Testing (3)

- Number of primary batches（基準ロット数）
  - Even in Continuous Manufacturing, the basic idea for the number of primary batches needed is the same as that in Batch Manufacturing. Basically, at least three batches are required according to ICH Q1A [R2].

    (連続生産を適用した場合でも、必要な基準ロット数の基本的な考え方はバッチ生産と違いはなく、「安定性試験ガイドラインの改定について」（平成15年6月3日付け医薬審発第0603001号）（ICH Q1A(R2)）に従い、3ロット以上が必要となる。)
  - It is necessary to record information on the sampling points (spot, time etc.) used for the primary batch, as the batch size of the primary batch itself may vary.

    (基準ロット自体のロットサイズが異なることも想定されることから、基準ロットとしてサンプリングしたサンプリングポイント（箇所、時間等）についての情報も記録しておく必要がある。)

Next step (1)

- We prepared the "State of control in continuous Pharmaceutical manufacturing" document by the AMED sponsored study group.

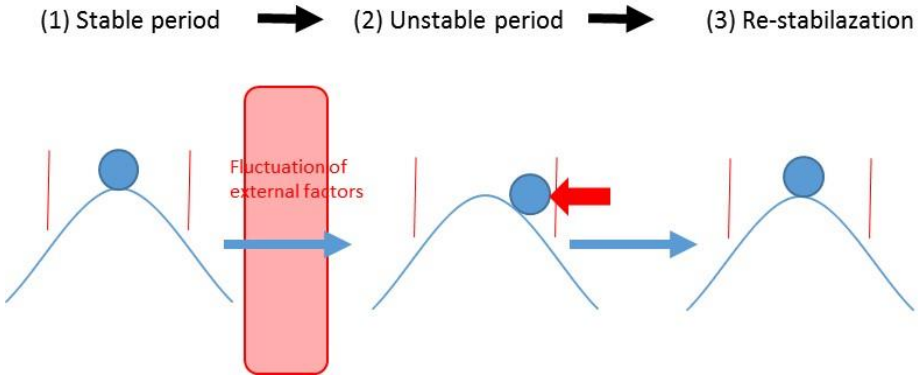
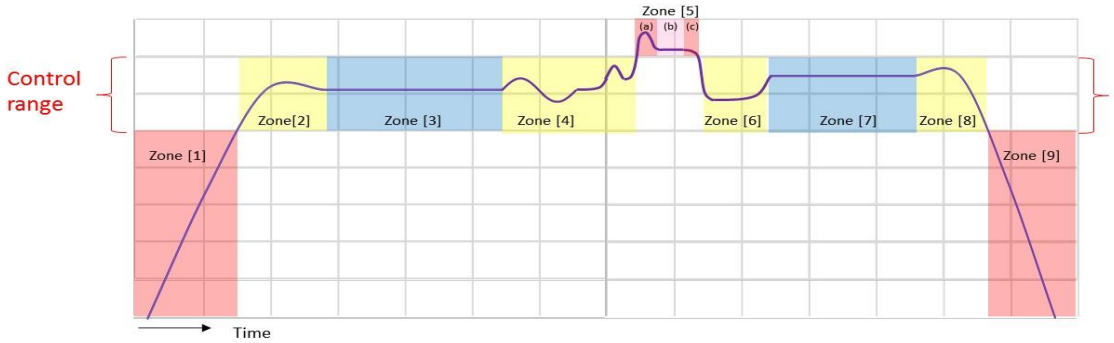


Figure 1: Conceptual diagram depicting State of Control
(Note: The red belt indicates the control range and the red arrow indicates designed control.)

Next step (2)

- A relationship between State of Control and Steady State.



Zone	[1]	[2]	[3]	[4]	[5]			[6]	[7]	[8]	[9]
Description of condition	Startup (Condition where control range is not yet achieved)	Startup (Condition where control range is achieved but is unsteady)	Steady state	Condition within the control range despite the fluctuation of external factors	(a)Deviation from the control range (b)Condition where steady state is achieved but which is still out of control range (c)Condition shifts to the unsteady and is still out of control range			Condition which is unsteady after recovery of the control range	Steady state with different values from Zone 3	Condition within the control range despite commencement of shutdown procedure	Shutdown (Deviation from the 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
Diversion out of line	Y	Y/N	N	Y/N	Y	Y	Y	Y/N	N	Y/N	Y

Figure 2: Conceptual diagram depicting relationship between "Steady State" and "State of Control"
(Y: Yes, N: No, Y/N: Yes or No)

AMED Study Group Members

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