て纏めた。この過程で、QbD のコンセプトを取り入れて分析法が開発された場合における、分析法開発に関する報告書の内容について議論した。分析法の開発に際して事前に設定される性能、分析法プロファイルや、開発中に得られる知見を基に行われるリスクマネジメントの要素を報告書に記載することにより、分析法に関する知識を第三者と共有することが容易になり、有効に活用することが可能になると期待される。また、分析法の性能を日常の運用の中で検証することを目的に、システム適合性試験を管理戦略として位置づけることにより、分析法が意図した目的に適う性能を維持しているかを、より確実に検証することが可能となった。

ICH Q8, Q9, Q10 及び Q11 で示されている、QbD のコンセプトを分析法の開発に取り入れることにより、より頑健な分析法を体系的に開発することが促進され、それを文章化することによって、分析法に関する知識及び重要な特性やパラメータに関する知識の移転が可能となることが示唆されたものと考える。本研究では、主として分析法の開発時における QbD コンセプトの適用について検討してきた。今後は、QbDコンセプトに基づき設定された分析法が運用されるなかで蓄積される知識や経験を活用しつつ、分析技術の進歩に応じた分析法の円滑な変更及び改良を検討することが望まれる。

E-3. 管理戦略に関する研究

本厚労科学研究では、ICH Q8 以降新たに出現した用語の中から、管理戦略という用語が「医薬品のライフサイクルを通じた品質確保と改善」を実現する上で特に重要な keyword と考え、用語の定義の解釈を中心に医薬品ライフサイクルにおける管理戦略の役割について検討を行ってきた。その結果、管理戦略の定義を検討する過程で、その解釈について研究班内で議論された用語「ongoing process verification(日常的工程確認)」と「重大性(severity)」について本研究で解説を行った。本研究ではこれらの議論について、ICH ガイドラインにおける管理戦略および関連用語の概説として取り纏めた。

添付資料

1. Ad-hoc Meeting of the MHLW-sponsored QbD Study Group 要旨
2. "Sakuramil" S2 Mock 発表資料
3. Expectation for QbD and PAL (Pharmaceutical Affairs Law) in Japan based on experiences in regulator and industry 発表資料
4. GSK's QbD approach
5. サクラ開花錠P2モック パブコメ募集における代表的なご指摘とその対応
6. サクラ開花錠 P2 モック
7. サクラ開花錠 P2 モック英語版
8. Analytical QbD を適用した分析法開発研究報告書の事例(案)
9. ICH ガイドラインにおける管理戦略および関連用語の概説

参考文献

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline, Pharmaceutical Development Q8(R2), Step 4. 2009.
2. 平成20年度厚生労働科学研究. 品質に関する概括資料 P2 モックアップ(記載例). 2009.
3. 医薬品製造開発・承認審査の確実かつ効率的なプロセス構築に関する研究 第 1 分科会 承認申請書. 製剤製造方法、規格及び試験方法欄のモックアップ(記載例). 2010.
4. 平成 24 年度厚生労働科学研究補助金分担

研究報告書. 医薬品のライフサイクルを通じた品質確保と改善に関する研究-製剤のライフサイクルにわたる品質保証に関する研究-. 2013.
5. 平成 25 年度厚生労働科学研究補助金分担研究報告書. 医薬品のライフサイクルを通じた品質確保と改善に関する研究-製剤のライフサイクルにわたる品質保証に関する研究-. 2014.
6. Implications and Opportunities for Applying QbD Principles to Analytical Measurements ; Position paper from EFPIA ADS and PhRMA ATG. Pharm. Tech., 34 (2), 52, 2010
7. FDA Guidance for Industry, Process Validation: General Principles and Practices, January 2011
8. Lifecycle Management of Analytical Procedures: Method Development, Procedure Performance Qualification, and Procedure Performance Verification, Pharmacopeial Forum, vol 39 (5)
9. 松田嘉弘;Informal Quality Discussion Group、第 30 回 ICH 即時報告会、東京(2014.7)
10. Robert A. Lionberger, Sau Lawrence Lee, LaiMing Lee, Andre Raw, and Lawrence X. Yu., "Quality by Design: Concepts for ANDAs", The AAPS Journal, Vol. 10, No. 2, June 2008, pp268-276.
11. James NM, Holly B, Buffy L, Hudson C, Steven L, Hung-Ren HL, et al. "Attribute Based Design Space: Materials-Science- Based Quality-By-Design for Operational Flexibility and Process Portability", J Pharm Innov., vol.6, 2011, pp.193–201.
12. Lawrence X. Yu, Gregory Amidon, Mansoor A. Khan, Stephen W. Hoag, James Polli, G. K. Raju, and Janet Woodcock, Understanding Pharmaceutical Quality by Design, The AAPS Journal, July 2014, Volume 16, Issue 4, pp 771-783.
13. Monica L.Dumont, Mark R.Berry, Beverly Nickerson, "Probability of passing dissolution acceptance criteria for immediate release tablet", Journal of Pharmaceutical and Biomedical Analysis 44 (2007) 79-84
14. 戦略の本質, 野中郁次郎、他(日経ビジネス人文庫)日本経済新聞出版社

F. 健康危険情報

なし

G. 研究発表

誌上発表

- 香取典子、坂本知昭、小出達夫、「日本薬局方における品質試験と製造工程管理:プロセス解析工学(PAT)と新たな品質パラダイム」、レギュラトリーサイエンス学会誌、4(2)、177-187(2014)

口頭発表

- 香取典子、日本の PIC/S 加盟によるインパクトー公的試験機関に求められる変化ー、ファームテックジャパンセミナー、東京、2014 年 11 月

H. 知的財産権の出願・登録状況

なし

Ad-hoc Meeting of the MHLW-sponsored QbD Study Group

14:00 – 16:30 on April 9th, 2014

@ PMDA Conference Room (Rm # 26 of 14 F)

Agenda as of March 1st

Time	Topic	Who
14:00-14:15	Opening & Introduction	N. Katori, NIHS ALL
14:15-14:45	New P2 Mock "Sakura-Kaika Tablet"	K. Okazaki, GSK
14:45-15:15	"Sakuramil" S2 Mock	S. Nagayama, Pfizer
15:15-15:30	Break	
15:30-16:00	– Expectation for QbD and PAL (Pharamceutical Affairs Law) in Japan based on experiences in regulator and industry – GSK's QbD approach	M. Nasr, GSK L. Wylie, GSK
16:00-16:30	Open discussion – Based on implementation to date, what are the current technical gaps? – Based on implementation to date, is there a need for more ICH activity to facilitate and speed up implementation? – Continuous manufacturing: awareness, current global activities and regulatory gaps – Other focus area?	ALL
16:30	Closing	Y. Hiyama, NIHS

Attendes

QbD Study Groups' member:

NIHS, PMDA CMC reviewers and Inspectors, Daiichi-Sankyo, Astellas, Takeda, Shionogi, Eisai, Dainippon Sumitomo , Ono, Chugai, Pfizer, AstraZeneca, GSK

Ad-hoc Meeting of the MHLW-sponsored QbD Study Group

1. QOS P2 Mock: "Sakura-Kaika Tablet"

By Kimiya Okazaki (GSK)

Critical Material Attribute (CMA)

- Critical Material Attribute (CMA) has been once suggested but rejected at early ICH because the ICH-WG did not want to introduce a new terminology. ICH-WG resorted the term and replaced to "Drug Product CPP".
- The presentation raises some key issues. Looking at a bigger picture, you are suggesting a different definition of Design space. Design space that relies more on product quality and material at the end of manufacture (time-attribute based design space) versus process-related design space. It was not supported at the early stage of QbD but I think it is time to revisit.

Background of Sakura-Kaika Tablet Mock

- Quality endpoint criteria (品質終点基準) is similar to the concept suggested in this mock.
- Sakura-kaka tablet is a mock, therefore is still merely a concept. However, it is created on the basis of the latest review experience at PMDA, and their ways of thinking are reflected. There are strong reasons behind the suggestions in the mock.
- Yes, the view of GMP inspection is also incorporated.

QMS

- We need to differentiate between what need to be done to assure the quality of a product *in the file* and an implementation *at the site* to bring the product quality as described in the file. You can have flexibility to some of the process parameters and that need to be documents in QMS for the inspection.
- The industry is also saying we cannot do QbD unless we have a robust QMS. It is a prerequisite.
- What we are trying to revisit is this; you have variable inputs, but still you have flexibility in the process obtaining fixed outputs by attribute-based Design space.

2. QOS Sakuramil S.2 mock

By Satoshi Nagayama (Pfizer)

3 cases relating to Edge of Failure (EoF)

- You need to look at the relationship with that process parameter to other process parameters because there are examples where you could have 3 process parameters and EoF for one will never happen because the other two will together behave such way. We have to be careful too prescriptive about EoF.
  The other thing is you may never find an EoF for some of the PPs by RA or even by DoE.
  There has to be some accommodation in terms of partial change or major change.
- Although you perform investigation wide enough at small scale to find EoF, how would you reflect it in the production scale? I think you should base the criticality on the production scale. Should look at by efficacy and safety and is not necessarily at EoF.

Q: The difference between Case A, B and C are the distance from the EoF? Case C is insensitive?
A: Yes, correct

Q: PQS, process design and characterization whether those three elements are treated the same way in the risk assessment standpoints? Or, process design element is prioritized?
A: Tough question, not answered.

Q: In Case A, is this a true EoF or an edge of an investigated range? This is a CPP but if we can expand the EoF and if we wanted to make regulatory change, is the parameter can be handled as a minor change item?
A: We assume it as a true EoF so it is easy to explain them as 3 cased but I understand in the real world it is difficult to find the true EoF. In this mock, we wanted to focus on process criticality.

3. QbD Expectations in Japan – Personal Observations

By Moheb Nasr (GSK)

4. GSK's QbD Approach

By Lindsay Wylie (GSK)

Three comments from R. Nosal.

1) Identification of CQAs

The majority of CQAs come from QTPP but I also think they also come from in-use and patient compliance. Patients do not take drugs having different looking which is an issue for safety and efficacy as well as other attributes.

2) Use of criticality

I like the designation by GSK because there are certain attributes and parameters we will not have definitive information but we will have a strong probability that they are unlikely to be critical. We want to make sure they are continually evaluated through risk assessment and through life cycle.

3) Product life cycle

In most of companies, we do risk assessment when we do change management. The concern I heard from the regulators is what happens 10 years after approval when you made 50 different major changes to the product. You need to carry all of those changes because Knowledge management is now a part of change management system – this is another consideration we have to talk about. This is more about inspector-type (GMP) of evaluation than a review-type of evaluation.

Differentiation of minor change pp and pp with no impact

- The definition we have at API study group is whether it is statistically related to CQA or not.
- I agree apart from the realistic ranges. How much ranges need to be studied and what ranges need to be looked at. We can apply statistical relation but it is difficult to be black and white.
- Theoretically speaking, if you stretch a range enough, there might be an impact. We need to find a balance where we have a determination based on science and experience rather than being challenge the range that never happen.

Key Process Parameter (KPP)

- Pfizer has no longer use KPP now?
- Internally we have but in regulatory submissions we no longer use it.
- Need to consider regulatory filing with a consideration of a product life cycle. Now it is very difficult to reverse the judgment once it is found to be critical but later found to be non-critical. This is same for Application Form in Japan and the other markets.

Question is - does it really matter what is non-critical/critical if we have right Control strategy and internal controls? Which is important – a good file or a good product?

Edge of failure

- I would like to focus on the "detectability of failure" (i.e. bioequivalent). If a process parameter fails, we do not know what impact occurs to the product quality. If you do not have detectability, then some important measures have to be set for process controls or by specification.
- Agree. What the industry is trying to find is can we predict.
- What we are trying to achieve through QbD, is what we are going to discuss at ICH Workshop in June.

Process Validation

- In Japan, it is expected to complete process validation at the time of PAI. I think this is a problem. In US (and will be starting in EU), there is a program called "break-through designation". The concept is

to take a risk of not understanding everything but to take a benefit of the drug and deliver the drug as early as possible to the patients in need.

Although Japan wants the same drug, we cannot deliver it due to this hurdle of not approving the product until PAI is completed. It is not patient-focused. I would like PMDA to consider it.

Note that break-through designation is clinically-driven program but there will be some impact to CMC as well.

Q: As per break-through designation, is there similar program in Japan?

A: No but the information is shared by FDA.

QbD products in US and EU

- Among your marketed products, how much of those went through QbD approach?
- Very small in number. Prospectively and retrospectively we have done QbD approaches when we make changes.
- Then, what would you do for the existing products developed with non-QbD approach?
- Need to look at risks of each product whether do we need to do full QbD assessment. In case of Pfizer, assume there are 600 molecules translated to various products. Of those, about 70 to 80 are undergone either prospective/retrospective QbD. Reasons are driven by the business (i.e. need for understanding the process better in order to reduce the number of deviations or to optimize the process).
- Similar at MSD. About 10% are undergone either prospective/retrospective QbD - science risk based approach.
- For line extension, I think you should consider thinking in a QbD ways to be successful.
- Some QbD principles can be applied to all products. Risk assessment is something needs to be performed to all products.
- The reasons I asked the question is because we are trying to transform JP.

Generic company

- How is that QbD change the way the Generic industry in Japan improve the quality of the regulatory submissions?
- We had a QbD training a couple years ago in Japan. Most of generic companies did not attend – they do not see any value for using QbD approach.

Use of Module 3

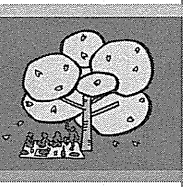
- QOS in Japan is not a summary – a lot of discussions in M3 are translated into Japanese. Now, emerging market is becoming more important and also regulatory expectations outside ICH is increasing. There may be a better way of using module 3 to create one QOS that can be submitted everywhere. It has to be a QOS – not module 3 translated into Japanese.
- One of the benefits of QOS is that it can be a reviewer-friendly dossier.
- The other benefit for QOS is it can be revised during review whereas Module 3 cannot.

Comparability Protocol

- Japan is also applying comparability protocol once PIC/S is agreed.
- Comparability protocol is not related to PIC/S. We receive information and we understand the concept but we do not have a plan so far.

End

QOS P2 Mock: "SAKURA-KAIKA Tablet"



April 9th, 2014
@ MHLW-sponsored QbD Study Group Meeting

Kimiya Okazaki, GSK Japan
On behalf of SAKURA-KAIKA Tab Sub-Team

Contents

- MHLW-sponsored QbD Study Group
- QOS P2 Mock: SAKURA Tablet
- New P2 Mock: SAKURA-KAIKA Tablet
- Challenge in practical terminology
- Globalisation & Regulatory Challenges

MHLW-sponsored Study Group for QbD started in December 2006:

The Study Group consists of regulatory and industry CMC experts led by Dr. H. Okuda of NIHS.

The study objectives are:

- ✓Show framework of efficient implementation for the concept of Q8-Q11 and Quality by Design (QbD) in Japan
- ✓Provide an example (mock) of Application Form and P2 section in Quality Overall Summary

API and Drug Product QbD groups are formed.

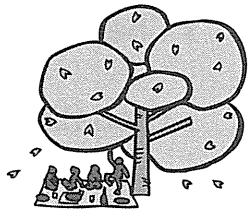
What were Achieved!!

QbD Study Group 1st Generation: 2006 - 2008

- SAKURA Tablet P2 Mock – ICH-Q IWG Training Material
- COMMON Tablet (Traditional) / YOKOZUNA Tablet P2 Mock

QbD Study Group 2nd Generation: 2009 -

- SAKURAMIL API S2 Mock
- *SAKURA-KAIKA Tablet P2 Mock (ongoing)*



1st Gen: SAKURA Tablet P2 Mock

Brand name
- Sakura Tablets

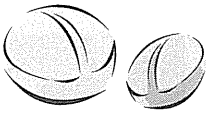
Generic name of API
- Amokinol (BCS class2)

Company name
- Moshi Pharma Co., Ltd.

Dosage form
- Tablets (film-coated immediate release tablets)
- Direct compression process employed

Strength
- 30 mg

Route of administration
- Oral



Formula of SAKURA tab 30 mg

Purpose of combination	Specification	Name of ingredient	Sakura tablet 30mg, in one tablet (100mg)
Active ingredient	Separate specification	Amochinol	30 mg
Diluent	JP	Calcium hydrogen phosphate hydrate	appropriate amount
Diluent	JP	D-mannitol	10 mg
Disintegrant	JP	Sodium starch glycolate	5 mg
Lubricant	JP	Magnesium stearate	2 mg
Coating agent	JP	Hypromellose	2.4 mg
Polishing agent	JP	Macrogol 6000	0.3 mg
Colorant	JP	Titanium oxide	0.3 mg
Colorant	JPE	Iron sesquioxide	trace amount

Approach for Control Strategy

Initial risk assessment (PHA, FMEA)

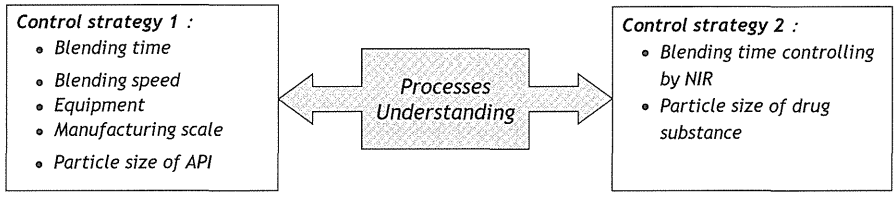
Study for influence of critical steps on the quality attributes of tablets

Establishment of Design Space as a control strategy

Apply Real Time Release

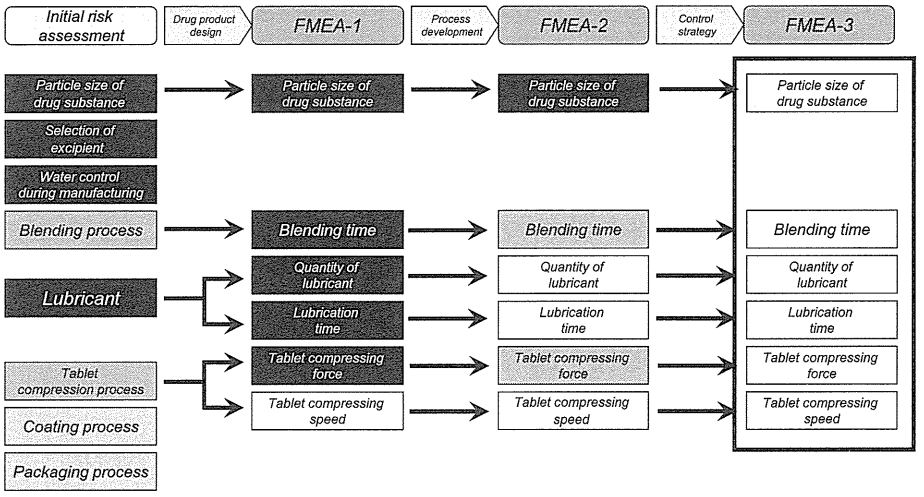
Risk assessment after applying control strategy

Establishment of Design Space as a Control Strategy

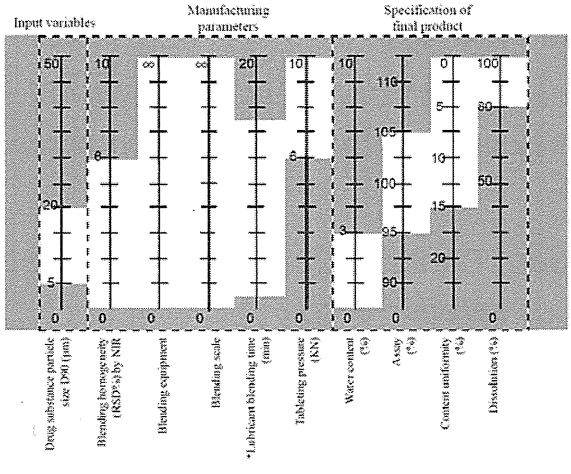


- ✓ **Control strategy 1:**
  - Many parameters depend on equipment and manufacturing scale
- ✓ **Control strategy 2 employed:**
  - Opportunity for Real Time Release (RTR) by using NIR

Flow of Pharmaceutical Development and Risk Assessment



Design Space of SAKURA Tab



*: Design space will be established after process validation in the commercial scale

Figure 2.3.P.2.3-8 Design Space of Sakura Tablet

Summary of SAKURA Tab - 1

- *Particle size of API affected on dissolution*
- *Blending process, lubricant blending process and tabletting process were defined as critical steps*

⇩

- *Correlation between dissolution and in vivo absorption over the range of 5 to 50 um of particle size of API*
- *Tablet compression force will not affect on the quality attributes of tablets.*

⇩

- *Controlling blending uniformity by NIR for Real Time Release*

Summary of SAKURA Tab - 2

Real Time Release

- *Monitor and control particle size of API, blending uniformity and tablet compression force*

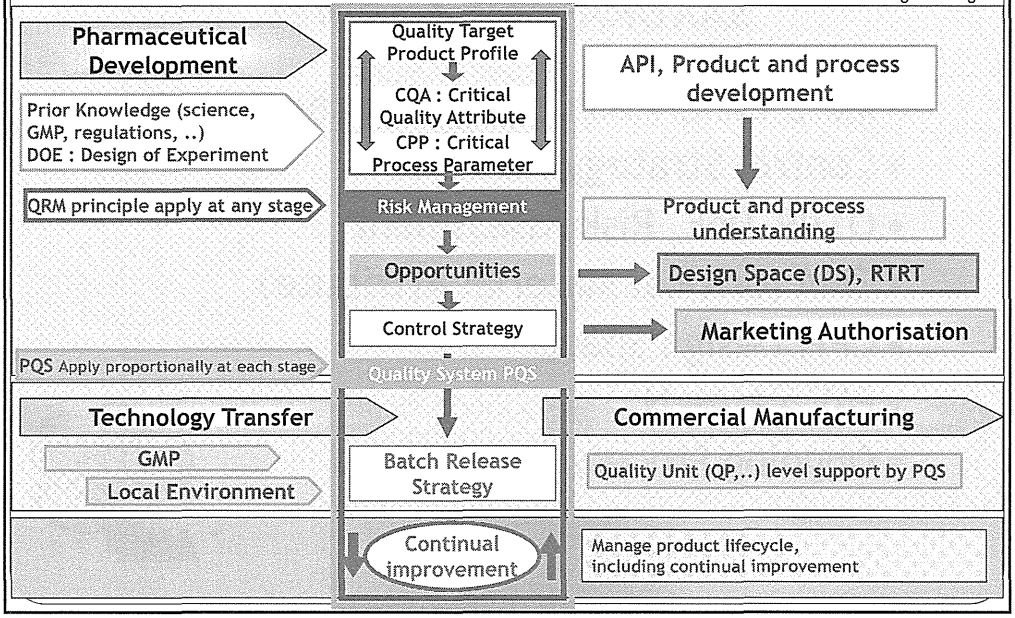
⇩

✓ *Dissolution, Content Uniformity and Assay can be skipped as release tests.*

✓ *Each process parameter was confirmed to be independent from manufacturing scale.*

More enhanced approach beyond SAKURA Tab

From ICH-IWG Training Package



2nd Gen: SAKURA-KAIKA Tablet

Brand name
- Sakura-kaika Tablets

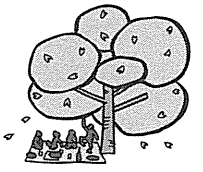
Generic name of API
- Prunus (BCS class2)

Dosage form
- Tablets (film-coated immediate release tablets)
- *Fluidized bed granulation process employed*

Strength
- 20 mg

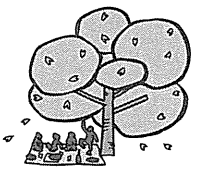
Route of administration
- Oral

Storage condition
- 3 years at room temperature



Points to consider for developing SAKURA-KAIKA Tablet

- More enhanced QbD approach
- Control Strategy for RTRT
- QTPP, DoE, Risk Assessment
- CMA (Critical Material Attribute)
- CPP, Design Space
- PAT, Large-N
- Ongoing Process Verification



Control Strategy for RTRT - 1

ICH Q8(R2)

Design Space *- "The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality."*

Real Time Release Testing *- "The ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls."*

Questions!!

- ✓ *Are " Process Parameters" essentially needed to establish the elements of Design Space?*
- ✓ *Should Design Space be essentially verified at a commercial production scale?*
- ✓ *What is a relation between RTRT and Design Space?*

Control Strategy for RTRT - 2

Post-approval CMC regulatory action (major change) may be required when blending mixer or tablet compression machine is changed?

Example of Design Space of "SAKURA Tablet":
<<Dissolution test by RTRT in AF>>

Dissolution (%) = 108.9 - 11.96 ×log10 (d(0.9)) drug substance particle size - 7.556 × 10-5 × specific surface area of magnesium stearate - 0.1849 × lubricant blending time - 3.783×10-2 × compression pressure

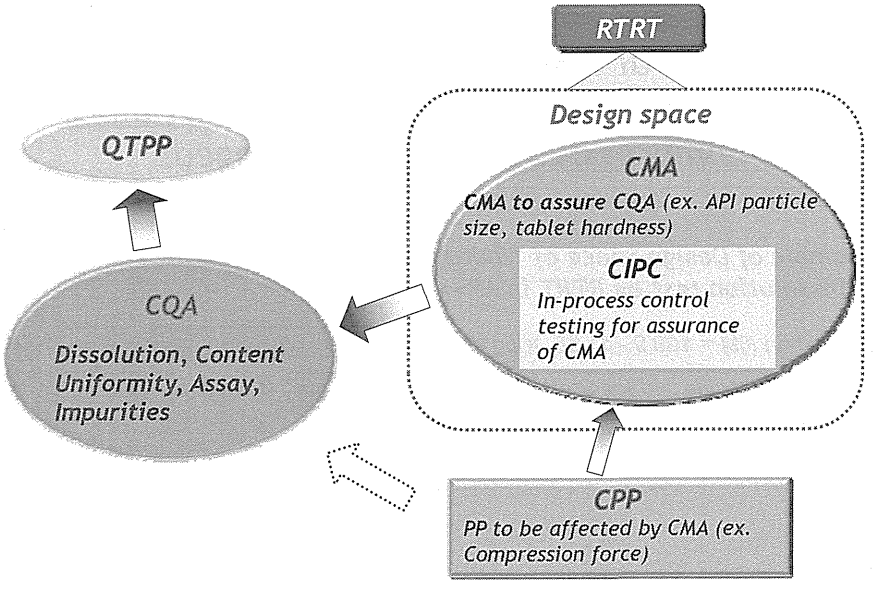
Process Parameter
Material Attribute

Control Strategy for RTRT - 3

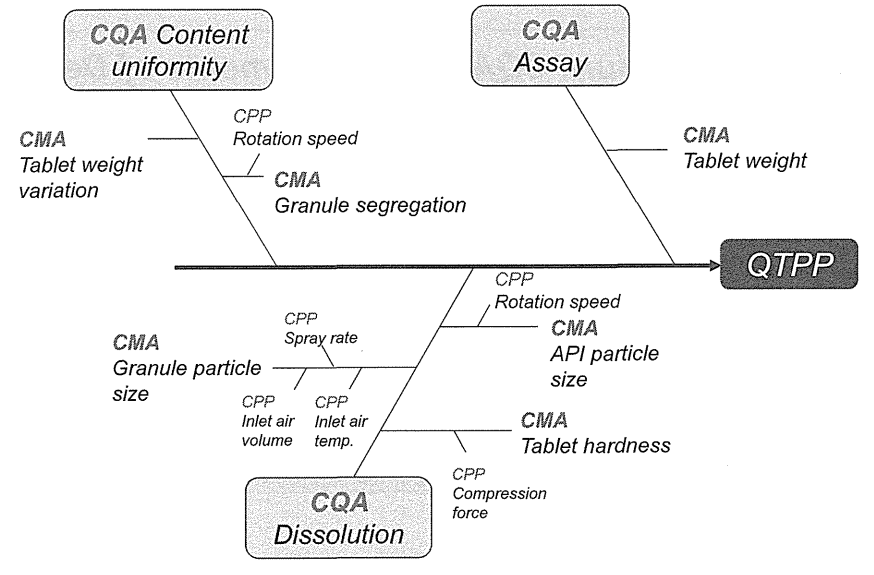
In order to assure CQAs, could elements of Design Space and RTRT be directly linked excluding any impacts of variety of process parameters?

CMA (Critical Material Attribute) under applying RTRT could be "Input Variables" to develop Design Space based on ICH Q8.

Control Strategy for RTRT - 4

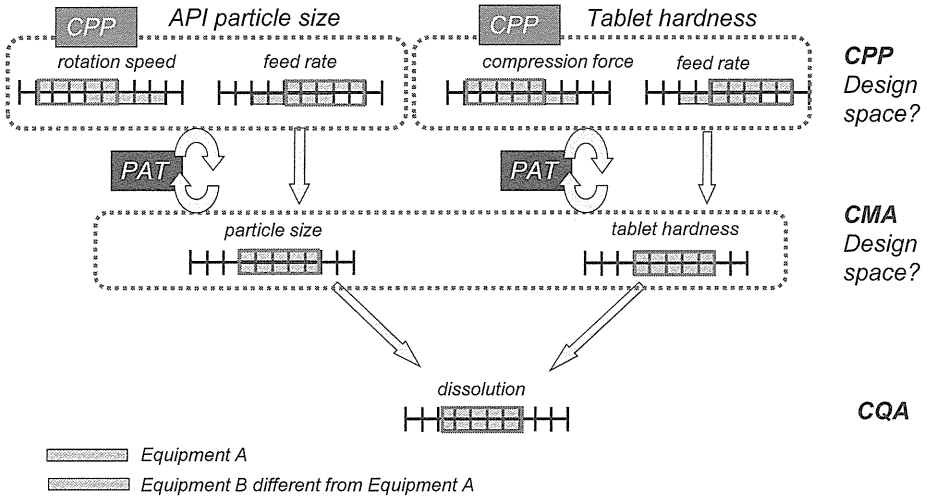


Relation in QTPP, CQA, CMA and CPP

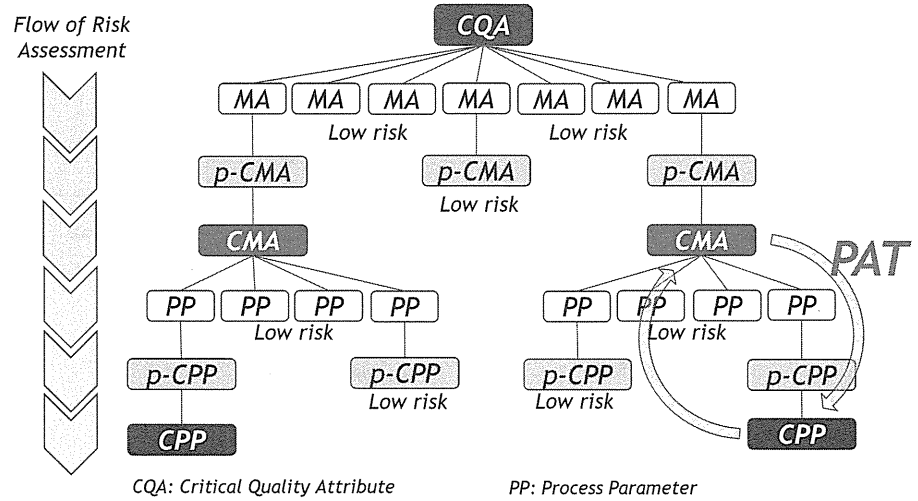


Control Strategy for RTRT - 5

Ex: Tablet dissolution to be affected by API particle size and tablet hardness only



Control Strategy for RTRT - 6



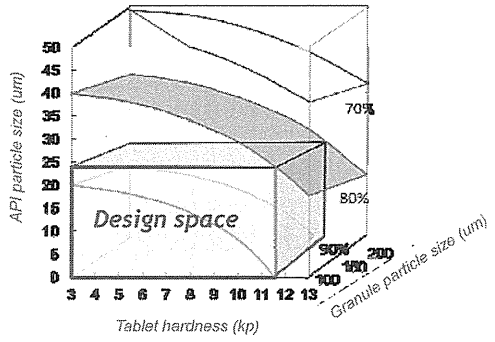
CQA: Critical Quality Attribute
MA: Material Attribute
CMA: Critical Material Attribute
p-CMA: Potential Critical Material Attribute

PP: Process Parameter
CPP: Critical Process Parameter
p-CPP: Potential Critical Process Parameter

Design Space Development - 1

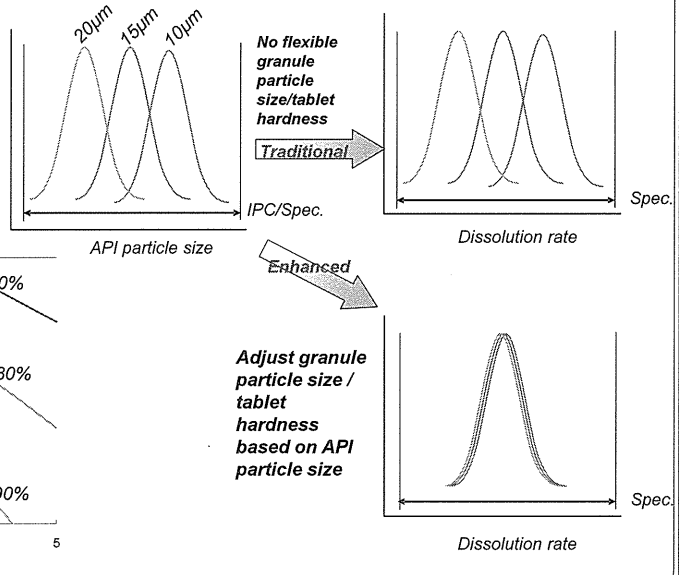
Based on risk assessment for dissolution CQA, if the risk factors would be API particle size, tablet hardness and granule particle size,

1. *Conduct DOE at a pilot scale, then establish "numerical formula (model)" tentatively based on statistical analysis*
2. *Conduct validation for the "model" at a commercial scale at the timing of technology transfer*
3. *Verify the "model" which can meet the criteria expected*



Design Space Development - 2

Feed / Forward Process for Dissolution rate



Large-N applied for Uniformity of Dosage Unit

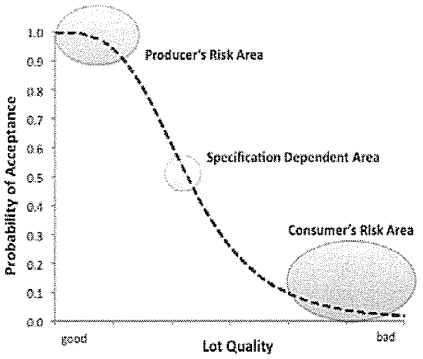
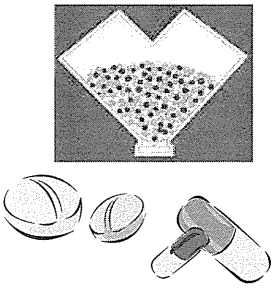


Fig. 1. A typical OC curve showing test characteristics



Sampling

- Sampling plan for Tablets
  - Tablets samples taken uniformly across batch
  - 10 tabs x 20 points (200 tablets) during compression run
- Drug Content of Tablets
  - Drug concentration by NIR and Weight Uniformity determined on same tablet samples
- Criteria for Large-N counting test for UDU: see next slide