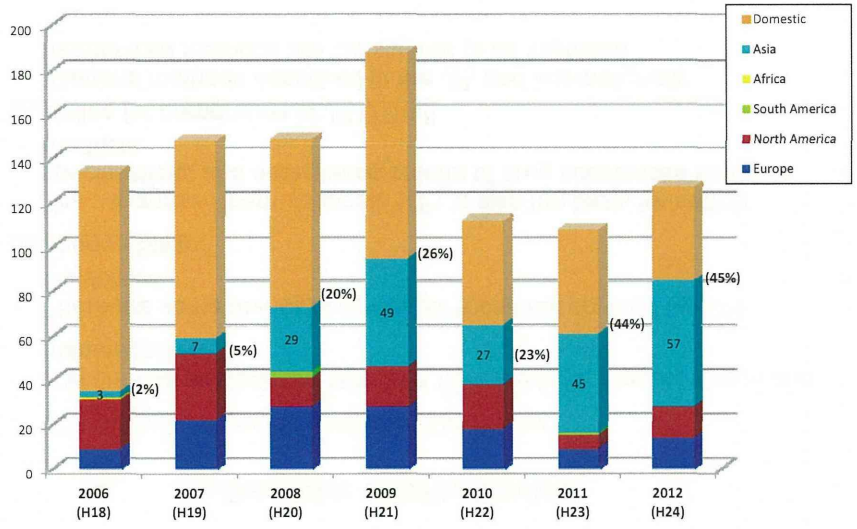
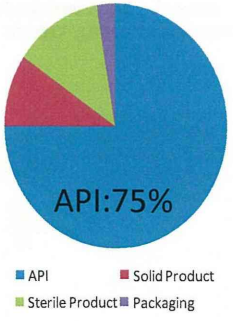
Number of domestic and foreign on-site inspections: Annual changes by area



Summary of GMP inspections for generic products

(April, 2006 - March, 2013)

Category	EU	North America	Central and South America	Asia	other	Total
Sterile drugs, Biological products	81	8	4	53	13	159
Solid Products	32	1	1	81	3	118
APIs (chemicals)	300	29	4	594	2	929
Packaging site Testing labs	16	4	3	7	2	32
Total	429	42	12	735	20	1238



The number of manufacturing sites that the PMDA inspects

As of March 2013

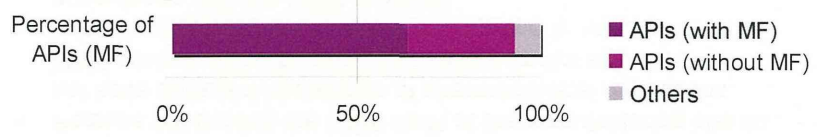
- Foreign manufacturing sites
  - Accredited sites: 2639
    Asia (excluding Japan) and the Middle East: 1075 (drugs: 917, quasi drugs: 158)
    Europe: 1058 (drugs: 984, quasi drugs: 74)
    North America, Central and South America, Africa, Oceania: 506 (drugs: 443, quasi drugs: 63)
  - Manufacturing sites where accreditation is not required (API intermediates, APIs made from food products or other industrial products, etc.): Approximately 300 (approximate figure)

Foreign manufacturing sites: Approximately 3,000

- Domestic manufacturing sites
  - Sites inspected by the PMDA (facilities licensed by the Minister): 137
    Biological products: 114
    Radiopharmaceuticals: 19
  - Sites related to new drugs (facilities licensed by the prefectural governor; sterile drugs, general, etc.): Approximately 350 (approximate figure)

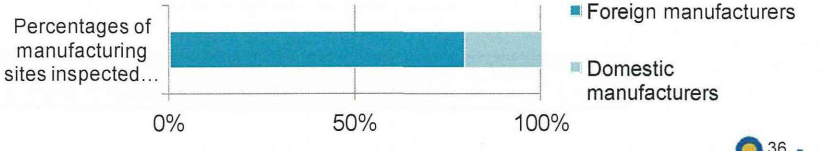
Domestic manufacturing sites: Approximately 500

The percentages of APIs, etc. in inspections for renewal of GMP certificates (periodic) by the PMDA



A majority of the inspections are through in-country caretakers of MF

80 %



Problems with in-country caretakers

- Lack of communication
  - In-country caretakers sometimes do not correctly understand the actual situation of manufacturing control and quality control. Therefore, the situation is not reflected in the MF.
  - Changes in a manufacturing site are sometimes not conveyed to the in-country caretaker of MF in a timely manner.
  - Lack of explanation to the manufacturing site about the pharmaceutical regulations in Japan.
- Lack of knowledge of the pharmaceutical regulations, GMP control, manufacturing technologies, and/or science

Problems with marketing authorization holders

- Lack of capability to manage suppliers
  - Marketing authorization holders sometimes do not understand the situation of GMP control at the manufacturing site and do not carry out GMP audits there themselves, leaving the audit to the in-country caretakers of MF.
  - Persons conducting the GMP audit at the manufacturing site do not have sufficient knowledge of pharmaceutical regulations, GMP control, manufacturing technology and/or science.
  - In some cases, a manufacturer is not properly selected in accordance with the GMP standard.
  - Insufficient guidance on GMP controls through supplier audits for the manufacturing site.

Basis for Quality Review

- ICH Guidelines are the basis for NDA review.
  - ICH Q8 and Notification #0210001 form basis for product design and manufacturing
- There are some domestic guides for those not covered by ICH Guidelines.

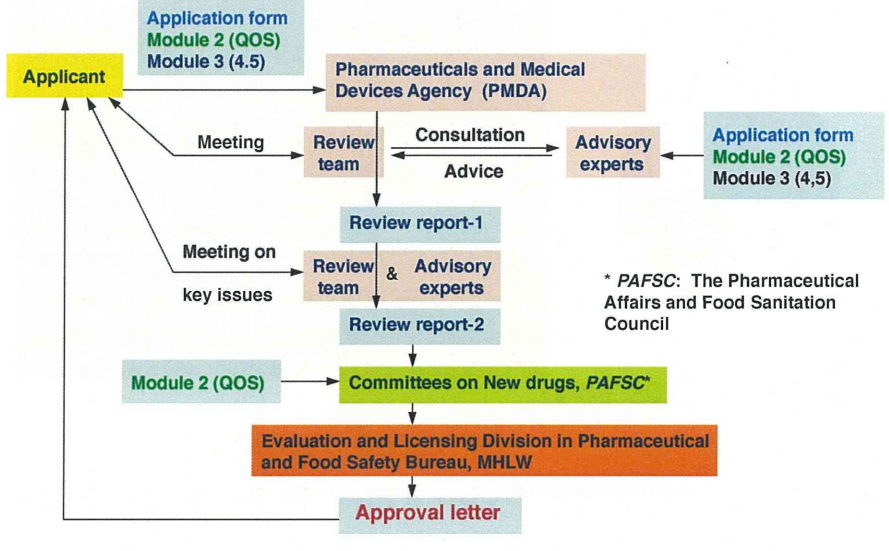
Seizouhou Sisin

- The Japanese Pharmacopoeia (JP) is also the basis for setting specifications and acceptance criteria of drug substances and drug products.

Guideline for preparation of JP17Draft

- "General methods described in the JP, and internationally harmonized methods are considered to be validated."

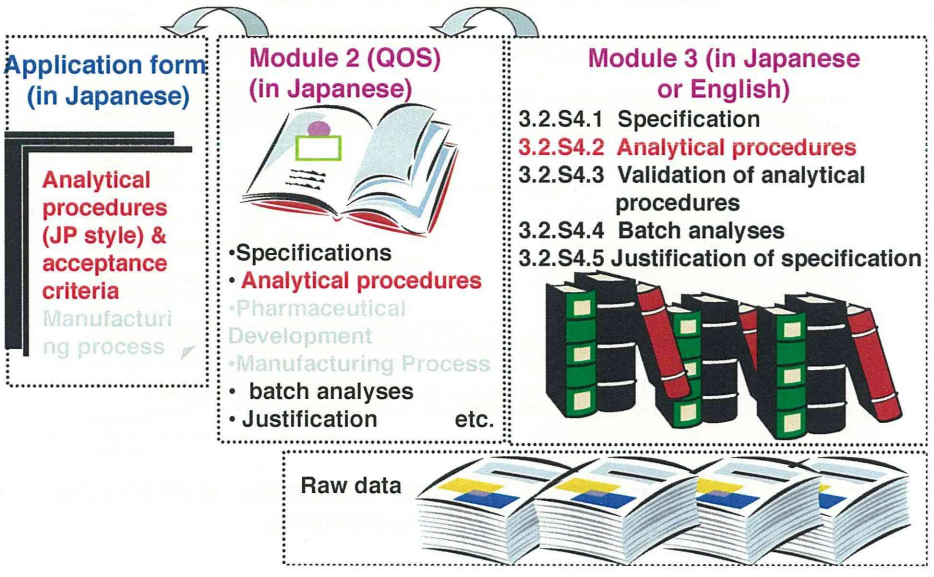
Flowchart of Reviewing Process



Role of Module 2

- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
  - Reviewers evaluate Module 2 and then narrow down into Module 3, 4, or 5 when they need more detailed information.
  - Module 1 and 2 together with reports written by reviewers are evaluated in Pharmaceutical Affairs and Food Sanitation Council.

Relationship between Application Form and CTD Documents



Mockup of Japanese QoS

- Old Version was published by Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation in July 2002
- Mock shows an example of description for each module 2 section and just a reference for an applicant to prepare QoS.
- **NEED more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8 and the revised PAL.**

  By 2006-2008 MHLW "Approval matters" study group

  Minimal approach (Risk Assessment step is included)

  Enhanced approach/Quality by Design approach (SAKURA Tablet case study), which became a basis of ICH QIWG training material

SAKURA Tablet case study development -History-

- Announcement to form a new study group

  (also at ISPE/PDA /FDA Q8 Q9 workshop in Washington 2006) – different approach from FDA, EMA-) over 20 industry participants
- General discussion on QbD in 2006
- Based on the data provided by AstraZeneca, total story with DS, RTRt is constructed in 2007.
- Published for comments at NIHS web site. Finalized the P2 mock and approval letter in 2008
- ICH QIWG took the case study for the training material in 2009-2010. MSD provided the API part.

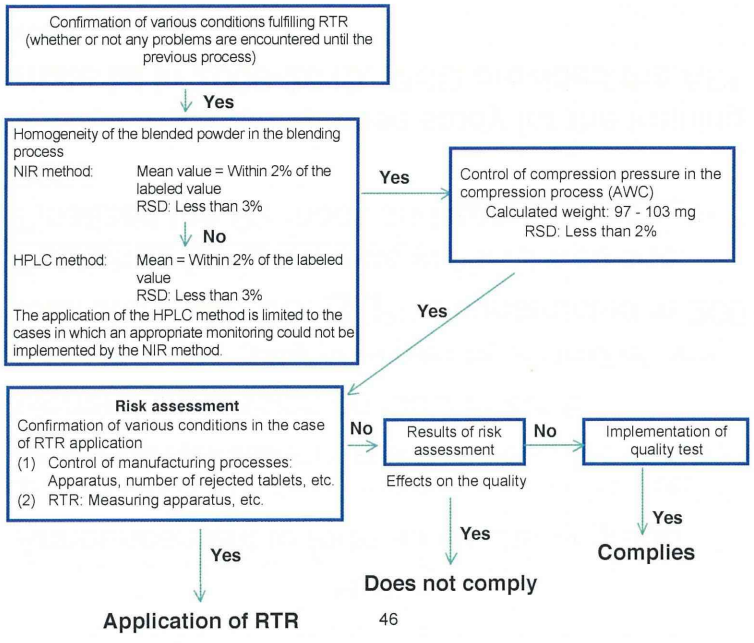
Relationship between Sakura Tablet Manufacturing Process and RTR Process Parameters

Manufacturing process	Procedure
Material	Drug substance and excipients
First step	Blending
Second step	Blending 2 (Magnesium stearate)
Third step	Compression
Fourth step	Film coating
Fifth step	Packaging

RTR proposal (1) : Content uniformity
Blending step : Drug substance content uniformity
Compression step: Monitoring of compression pressure

RTR proposal (2) : Dissolution test
Drug substance particle size
Mg stearate-specific surface area
Mg stearate blending time
Compression pressure

RTR proposal (3) : Assay
Blending step : Content of drug substance blended
Compression step: Mass measurement



Application Form for Sakura Tablet
Mock-Up for the Manufacture Method, Specifications, and Test Methods

- **[Manufacturing method]**
- [Range of manufacturing process]:
  Manufacture, packaging, labeling, storage, and testing of Sakura Tablet
- Critical steps
- <First Step> Blending process
- <Second Step> Second blending process
- <Third Step> Compression process
- <First Step> Blending process
- Blend 30 w/w% amokinol, 53 w/w% calcium hydrogen phosphate hydrate, 10 w/w% d-mannitol, and 5 w/w% sodium starch glycolate. Determine the blending end point according to [Process control 1]. [Process control 2]
- <Second Step> Second blending process
- To the mixture obtained from the First Step, add 2 w/w% magnesium stearate relative to the composition of the Sakura Tablet, and blend the mixture using a tumbling mixer for 1 - 15 min.
- <Third Step> Compression process
- Compress the mixture obtained from the Second Step at 6 - 10 kN using a rotary tableting machine (with a punch of 6 mm in diameter) [Process control 3]
- <Fourth Step> Coating process

- <Fifth Step> Packaging, labeling, and storage processes
- [Control item in the Second Step (Raw material)]
- Specific surface area of magnesium stearate (Brunauer, Emmett, and Teller (BET) method)
- [Process control 1]
- Relative standard deviation: Less than 3% (near-infrared (NIR) method)
- When the blending homogeneity is tested on the basis of the test method (NIR method) as determined by the uniformity of dosage units **(RTRT) of [Specifications], the relative standard deviation is less than 3%.**
- [Process control 2]
- Content: 98 - 102% (high-performance liquid chromatography (HPLC) method)
- When the content is tested on the basis of the test method (HPLC method) as observed in the assay method (RTRT) of [Specifications], the content is 98 - 102%.
- [Process control 3]
- When the mean weight of the tablet (following compression) is measured, the content is observed to be 100 ± 3 mg.

Application Form for Sakura Tablet
Mock-Up for the Manufacture Method, Specifications, and Test Methods

- [Specifications]
- [Test name: Uniformity of dosage units **(RTRT)**
- [Specifications]
- This test is performed as a real-time release test, which is subsequently set as the release specification.
- The homogeneity of the blend in the blending process <First Step> and the tablet weight in the compression process <Third Step> conform to the designated process control values.
- Note: The homogeneity of the blend in the blending process <First Step> is tested according to the following test method.
- The test is performed by Near-infrared Spectrophotometry (NIS) using the probes in the diffuse reflection mode through a borosilicate plate glass from the exterior of the operating blending equipment, by which the uniformity of the blend is determined by the relative standard deviation of the assay values at 6 consecutive points.
- (Equation 2)
- Operating conditions:
- **Measurement method:** **Diffuse reflectance**
- **Light source:** **High-energy air-cooled NIR source**
- **Detector: High-sensitive InGaAs detector**
- Scanning range: 7500 - 4000 cm-1
- Scanning frequency: 16-fold
- Resolution: 8 cm-1
- Conditions for the pretreatment of spectrum: Multiplicative Scatter Correction (MSC)
- Analytical method: Partial least squares (PLS)
- System suitability:
- System performance:
- When the content is measured using the blending powder in which the content of the drug substance has been verified to be approximately 100% according to a control evaluation procedure, this content is 98.0% - 102.0% according to the labeled amount.
- In the present study, the following calibration and validation processes are performed; further, a calibration curve obtained for the periodic revalidation implemented is used, if necessary.
- Calibration:
- A minimum of 5 samples that are to be used are prepared in the range of 70% - 130% of drug substance relative to the labeled amount, containing the excipients in the same excipient ratio as that of Sakura Tablet. The pretreatment of the spectrum uses MSC, and the analysis is done by constructing a calibration curve by PLS.
- Validation:
- The calibration curve obtained is validated using the production lots that reflect the commercial production.
- Periodic revalidation:
- The calibration curve is validated using commercial production lots at appropriately predetermined intervals.
- The control evaluation procedure to be used for the system suitability, calibration, and validation testing follows the assay method (RTRT) used in HPLC provided in the [Specifications] section.

Application Form for Sakura Tablet
Mock-Up for the Manufacture Method, Specifications, and Test Methods

- **[Specifications]**
- [Test name] Uniformity of dosage units
- [Specifications]
  This test can be substituted with the uniformity of dosage units test (RTRT), which is a real-time release test and is not conducted at the time of release.
- **At a time-point at which the manufacturing procedure has been changed, if the content uniformity test is performed according to the following method until the verification for each process control procedure is entirely completed, it is observed to comply with the designated specifications.**
- **Further, if the RTR is not applicable in a particular case in which the effects of the quality of Sakura Tablets have been verified in the results of risk assessment, and if the content uniformity test is performed according to the following method in such a case, it is observed to comply with the designated specification.**
- Take 1 Sakura Tablet, add 50 mL of a mixture of acetonitrile and water (1:1) into it, and shake the mixture until the tablet disintegrates. Sonicate the resultant solution for 10 min, and add a mixture of acetonitrile and water (1:1) into it to make its volume exactly 100 mL. Filter this solution through a membrane filter (pore size, 0.45 μm), and use the filtrate as the sample solution. Separately, accurately weigh approximately X.XX g of amokinol reference standard, and dissolve it in a mixture of acetonitrile and water (1:1) to make the volume of the solution exactly *V* mL. Measure exactly 5 mL of this solution, add a mixture of acetonitrile and water (1:1) to make the volume exactly 100 mL, and use this solution as the standard. Perform the test with the sample and standard solutions as directed under the Ultraviolet-visible Spectrophotometry, using a mixture of acetonitrile and water (1:1) as the control; thereafter, determine the absorbance - A_T and A_S - of the sample and standard solutions at 284 nm.

PMDA Experience with QbD

Approvals with QbD in Japan

2008	2009	2010	2011	2012	2013
3	3	2	11	11	6

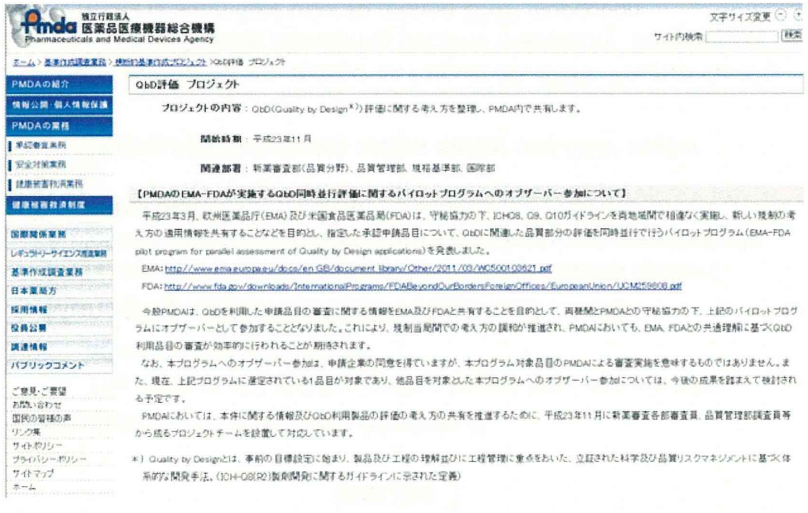
As of July 2013

Consultations with PMDA on QbD

2007	2008	2009	2010	2011	2012	2013
1	0	2	2	4	3	2

(As of July 2013)

EMA-FDA QbD Pilot Program
PMDA participated in as observer



What we PMDA learnt from our experience

- Our concerns about QbD applications are basically the same as FDA and EMA.
- There will be no great differences in the evaluation of QbD approaches among FDA, EMA and PMDA.
- Regulatory actions for the evaluation might be a little different because the regulatory framework of each regulatory agency is different.

Issues 1

- Module 2 (J-QOS) and Module 3
  - The content of J-QOS is getting larger. How can we take advantage of J-QOS?
- Managing application form (approval letter)
  - Is regulatory commitment (future change control system) written in the application form qualitatively and quantitatively adequate?
  - Distinguishing between review matter and GMP matter

GMP standards are revised on August 30, 2013. Product Quality Review/Stability Monitoring became mandatory. Summary of PQR is submitted prior to routine GMP inspection

Issues 2

- How to deal with Minor Changes in US and Type IA variation in EU
  - There are only two types of regulatory actions possibly taken in Japan
    - Partial change
    - Minor change (Notification)
  - Other choice
    - No statement of change in application form

Post-authorisation procedure

Risk of Changes	Japan	US	EU
High	Partial change (Application for approval of variation)	Major change (Prior approval supplement)	Type II variation (Application for approval of variation)
Moderate	Minor change (Notification within 30 days after implementation or shipping)	Moderate change 1)Supplement-changes being effected (CBE) in 30 days	Type IB variation (Notification before implementation and MAHs must wait a period of 30 days)
		2)Supplement-changes being effected (CBE)	Type IA_{IN} variation (Immediate notification)
Low		Minor change (Annual report)	Type IA variation (Notification within 12 months after implementation)

History & Legal Status of JP

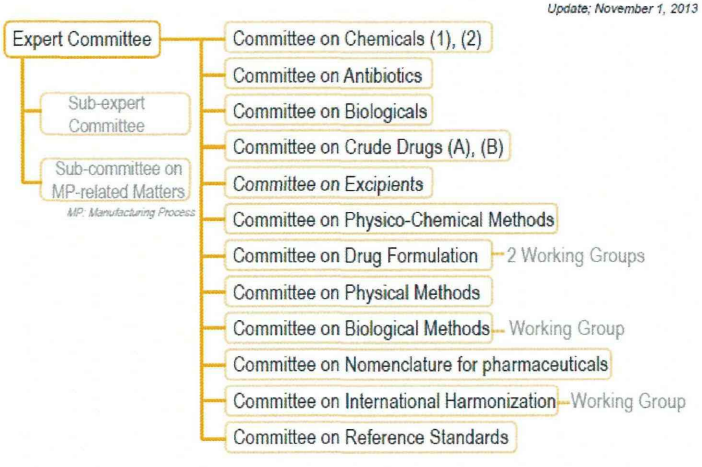
- JP is published by the Japanese Government

  The Ministry of Health, Labour and Welfare Ministerial Notification
- First published on June 25, 1886 and implemented on July 1, 1887
- In accordance with the provisions of Article 41-1 of the Pharmaceutical Affairs Law (PAL) of Japan

  *To standardize and control the properties and quality of drugs, **the Minister** shall establish and publish JP, after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC)*

System of Establishing Japanese Pharmacopoeia

Organization of JP Expert Committees



Main Policies on the Preparation of JP17

1. Providing all drugs essential for health care and medical treatment
2. Improving quality by positive introduction of latest science and technology
3. Promoting internationalization
4. Timely updating and revising as necessary and facilitating smooth administrative operation
5. Ensuring transparency in process and disseminating JP

Formulation and manufacturing process dependent issues

Conclusion

- Pharmaceutical Development, Standard Setting and Manufacturing must work together
- Likewise Reviewer(Assessor), JP and GMP must work together

添付資料6

QbD/リアルタイムリリースの現状と将来展望
-公的試験規格を適用する場合の諸問題-

Interphex Japan 2013 Seminer　Jul.11, 2013

国立医薬品食品衛生研究所　香取典子

トピックス

- RTRtと局方規格
  - リアルタイムリリース試験(RTRt)とは
  - 局方規格とRTRt規格の比較
  - 薬局方の製剤均一性(UDU)
  - PQRIワークショップにおける議論
- 各国の提案、動向
  - 米国PhRMAの提案
  - EPの提案
  - FDAの提案
  - USPの動向
  - 日本薬局方の対応

RTRTと局方規格

トピックス

- RTRtと局方規格
  - リアルタイムリリース試験(RTRt)とは
  - 局方規格とRTRt規格の比較
  - 薬局方の製剤均一性(UDU)
  - PQRIワークショップにおける議論
- 各国の提案、動向
  - 米国PhRMAの提案
  - EPの提案
  - FDAの提案
  - USPの動向
  - 日本薬局方の対応

Q8(R2)付録1. 異なる製剤開発手法（抜粋）

側面	最小限の手法 Minimal Approaches	より進んだQbD手法 Enhanced, Quality by Design Approaches
総合的な製剤開発	• 主に経験的 • 変量を一つずつ検討する開発研究が多い	• 体系的で、物質特性及び工程パラメータの機構的理解を製剤のCQAに関連づける • 製品及び工程を理解するための多変量実験 • デザインスペースの設定 ・ PATツールの利用
工程管理	• 主に継続か中止かを判断するための工程内試験 • オフライン分析	• 適切なフィードフォワード及びフィードバック管理を伴うPATツールの利用 • 承認後の継続的改善努力を裏付けるための工程操作の解析及び傾向づけ
製品規格	• 管理するための基本手法 • 申請時に得られているバッチデータに基づく Quality by Tests	• 総合的な品質管理戦略の一部 • 関連する支持データに基づいた目的とする製品性能に基づく Quality by Design

Q8(R2)製剤開発とQ9リスク管理

分類	Q8の呼び方	製剤開発	リスク管理	品質保証
今までの方法	最小限の手法 (minimum approach)	経験的	対症的	経験に基づいた製造、試験により品質を保証
新しい方法	より進んだQbD手法 (enhanced approach)	科学的	予防的	実験計画法(DoE)や多変量解析などの統計学や最先端の分析技術の上に立って品質を保証

クオリティ・バイ・デザイン(QbD):
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。
デザインスペースの設定 ・プロセス解析工学（PAT）ツールの利用など。

プロセス解析工学
Process Analytical Technology（PAT）

'A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.'

ICH Q8(R2)

最終製品の品質保証を目標として原材料や中間製品/中間体の重要な品質や性能特性及び工程を適時に(すなわち製造中に)計測することによって、製造の設計、解析、管理を行うシステム

PATの実例

- NIRによる含量測定
- NIRによる水分測定
- NIRによる混合均一性確認
- ラマン分光法による確認試験
- テラヘルツ分光によるコーティング厚測定

非破壊、インライン測定

リアルタイムリリース試験
Real Time Release testing (RTRt)

'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.'

ICH Q8(R2)

工程内データに基づいて，工程内製品及び／又は最終製品の品質を評価し，その品質が許容されることを保証できること。
通常，あらかじめ評価されている物質（中間製品）特性と工程管理との妥当な組み合わせが含まれる。

トピックス

- RTRtと局方規格
  - リアルタイムリリース試験(RTRt)とは
  - 局方規格とRTRt規格の比較
  - 薬局方の製剤均一性(UDU)
  - PQRIワークショップにおける議論
- 各国の提案、動向
  - 米国PhRMAの提案
  - EPの提案
  - FDAの提案
  - USPの動向
  - 日本薬局方の対応

局方規格とRTRt規格の比較

Item	Pharmacopoeia	RTRt
Sample size	Small (≤30)	Large(≥100) Large-N
Batch Distribution	Unknown	Known
Nature of Drug (pharmacological or pharmaceutical)	Not considered	Considered

PATとUDU (Uniformity of Dosage Units)

- ICHで調和されたJP，USP，EPの製剤均一性(UDU)の薬局方収載規格は，サンプルサイズとして1段階目 n=10，2段階目 n=30(10+20)投与単位を基本とした2段階試験
- 適否の判定は，含量の平均と標準偏差から判定値を計算し，判定値が限度を超えない場合を適合とする計量試験と，限度値を外れる投与単位の数で判定する計数試験の組合せ

- PAT導入時問題となるのは計数試験で，ICH調和案では表示量から25%を超える偏差を示した投与単位が1個でもあると不適(ZTC: Zero Tolerance Criteria)となる
- サンプルサイズの大きいPATでは1回の試験でこの外れ値を示す言わば不良品が出現する確率は，サンプルサイズが大きくなるほど無視できない頻度となっていく

ICHで調和された薬局方の製剤均一性（UDU: Uniformity of Dosage Units）規格

JP16 6.02 製剤均一性試験法

判定基準

計量試験（parametric）:

判定値 = $|M - \overline{X}| + ks$

判定係数: k = 2.4 (n=10) step 1

k = 2.0 (n=30) step 2

計数試験（nonparametric）:

c2（許容個数） = 0 (±25%、n=30) step 2

ZTC : Zero Tolerance Criteria

PQRIワークショップにおける議論

「新しい製造パラダイムにおける意思決定のためのサンプルサイズに関するワークショップ」

米国製品品質研究所 (PQRI) 主催、FDA、AAPS共催（Sep. 2011）

議論の要点

- RTRTへの適用の際もっとも問題になるのはZTC（Zero Tolerance Criteria）である。サンプルサイズが大きくなればoutlierが出現することは避けられないため、ゼロではない判定基準（outlierの許容個数：c2）が必要である。
- 正規性の検定について – ロットは、基本的には正規分布していることが求められるが、真の目的はoutlierの存在比率を見積もることであり、単純に正規性の検定を行うことは意味がない。（含量のばらつきが小さい場合には、検定を行うと非正規と判定されやすくなる）
- 出荷後の管理 — 市販後の収去試験等では通常のサンプルサイズを用いるので、この場合の合格率を考慮しないと市販後に不適となるリスクが大きくなる。
- 後発品について – RTRtで承認された先発品に対し、後発品がどのように試験規格を設定するかは今後の課題である。

◦ 各国の提案、動向

トピックス

- RTRtと局方規格
  - リアルタイムリリース試験（RTRt）とは
  - 局方規格とRTRt規格の比較
  - 薬局方の製剤均一性（UDU）
  - PQRIワークショップにおける議論
- **各国の提案、動向**
  - **米国PhRMAの提案**
  - EPの提案
  - FDAの提案
  - USPの動向
  - 日本薬局方の対応

PhRMAの提案した2つの判定法

Large-N(2006)とModified Large-N(2009)

含量の偏差が±15%を超えるサンプルの数を規定する。

ZTCを避ける

Table 1. Acceptance Values For the Large-N and Modified Large-N Test

Sample Size	Large-N Acceptance Value	Modified Large-N Acceptance Value
100	4	3
250	11	7
500	23	15

Modified Large-Nの設定根拠：Nの3.0%を計算し，整数値に切り捨て，許容限度値（c）を規定する。例えば，Nが250の場合，250錠の3.0%は7.5であり，これを切り捨ててcを7とする。

Large-N and Modified Large-NのOC曲線

Large-N　　Modified Large-N

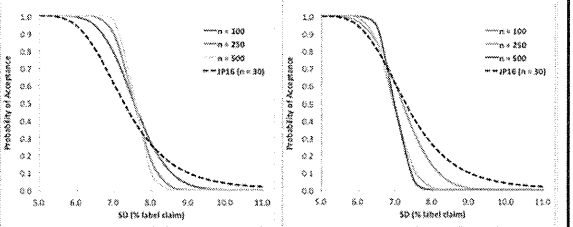


Fig. 2 OC curves of UDU tests recommended by PhRMA