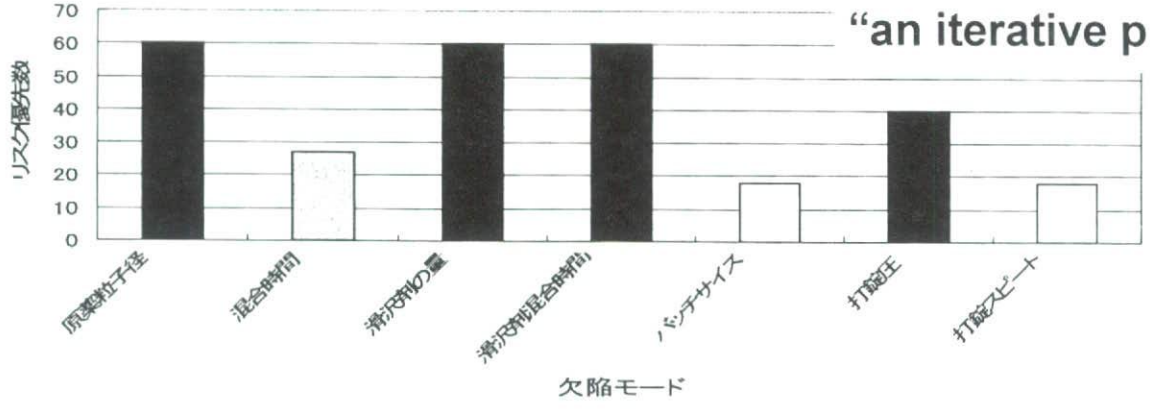
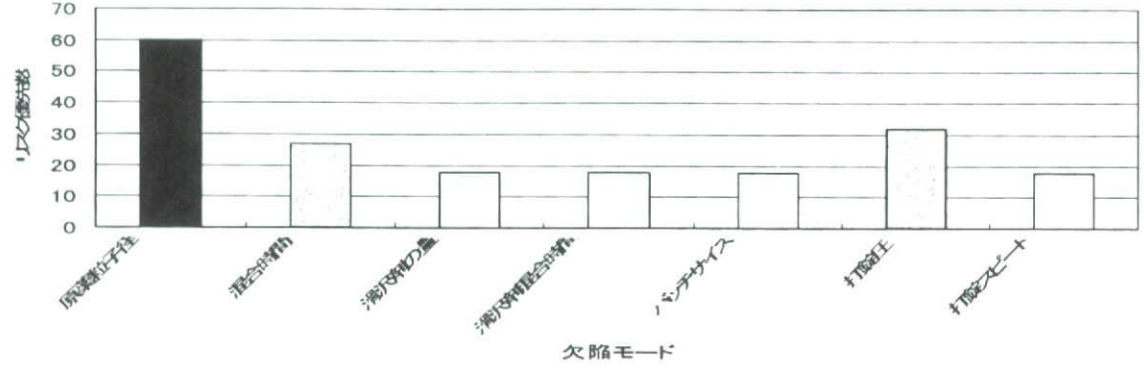
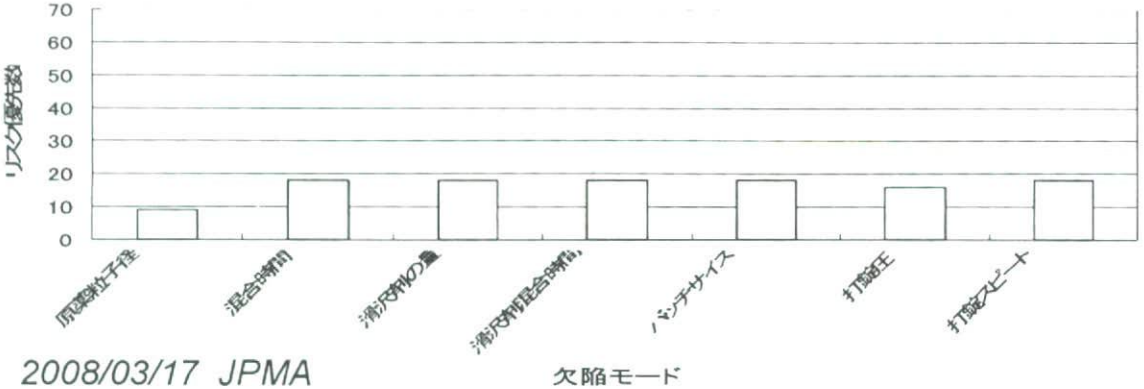
“an iterative process of QRM”／Q8(R1)



製造工程開発前
（処方確定後）



製造工程開発後



管理戦略後

Mock CTDの内容

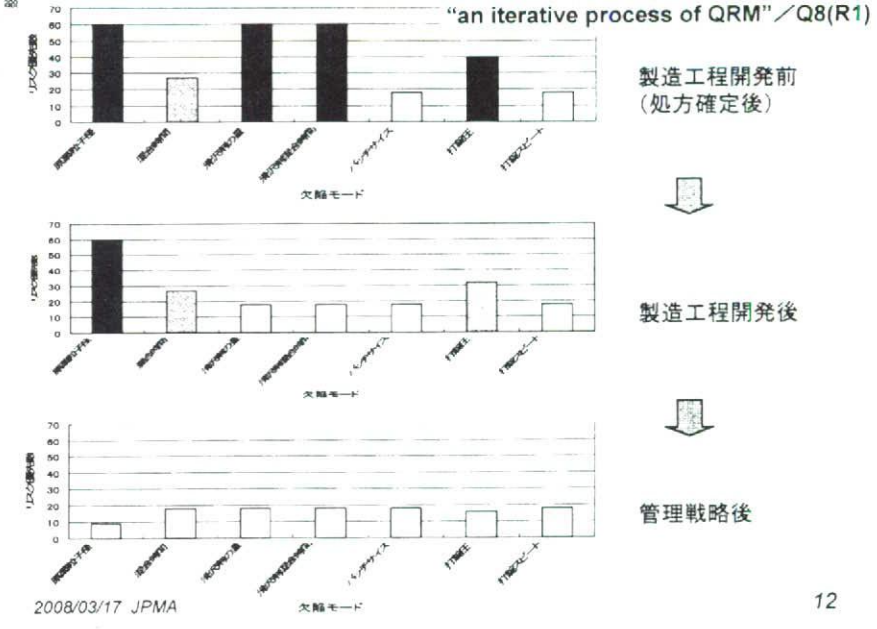
- 仮想製剤品名：サクラ錠
- Target Product Profile（標的製品プロファイル）
  - 即放性フィルムコート錠
- 原料特性（原薬）
  - 生物薬剤学的製剤分類（BCS）クラス2（溶解性が低く、透過性が高い）
- 製剤特性
  - IVIVC（in vitro/in vivo相関）がとれているものとする ⇒ 溶出試験で確認

Mock CTDの構成

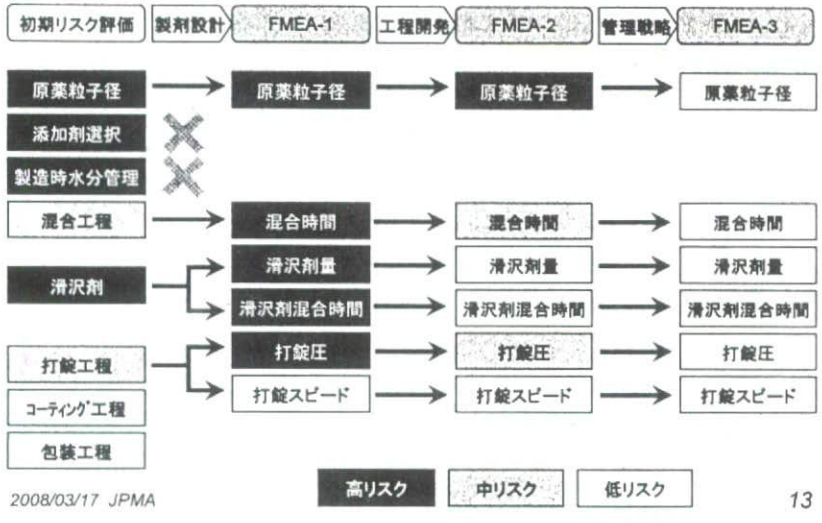
- 2.3.P.1 製剤及び処方
- 2.3.P.2 製剤開発の経緯
  - 2.3.P.2.1 製剤成分
    - 主成分の特性 ⇒ BCSクラス2
  - 2.3.P.2.2 製剤
    - 標的製品プロファイル
    - 初期リスク評価（Design Risk Assessment）
    - 製剤処方及び製造工程のリスク評価： FMEA-1
    - 製造工程の開発経緯
    - 実験計画（高リスクの欠陥モード）
    - 評価法の開発（IVIVC）
    - 品質特性への影響評価
    - 製造工程開発後のリスク評価： FMEA-2
    - デザインスペース
    - 管理戦略
    - 管理戦略適用後のリスク評価： FMEA-3

Mock CTDストーリー展開

標的製品プロフィール
↓
初期リスク評価
↓
製剤処方及び製造工程のリスク評価
↓
製造工程の開発
↓
品質に及ぼす影響の評価
↓
製造工程開発後のリスク評価
↓
デザインスペース
↓
管理戦略
↓
管理戦略適用後のリスク評価



Mock CTDストーリー展開： QRM



今後の予定

- 分科会報告書
  - 10ページ程度の報告書本部にモックCTDを資料として添付
  - 今年度中に完成
- 今後の展開： 第1分科会
  - 4月に公表して広く意見を求める予定（意見聴取期間：3ヶ月）
  - IWGに成果物として提案

DRUG INFORMATION ASSOCIATION

44TH Annual Meeting

Boston 2008

Establishing Design Space and Control Strategy: MHLW sponsored Study Group's approach

Kimiya Okazaki, Ph.D.
Director
Global CMC Japan
Pfizer Japan Inc.

pfizer

Contents

- CMC regulatory environment in Japan
- MHLW sponsored Study Group for QbD
- Model drug product as an example
- Establishing Design Space and Control Strategy: Summary and Next Step

Contents

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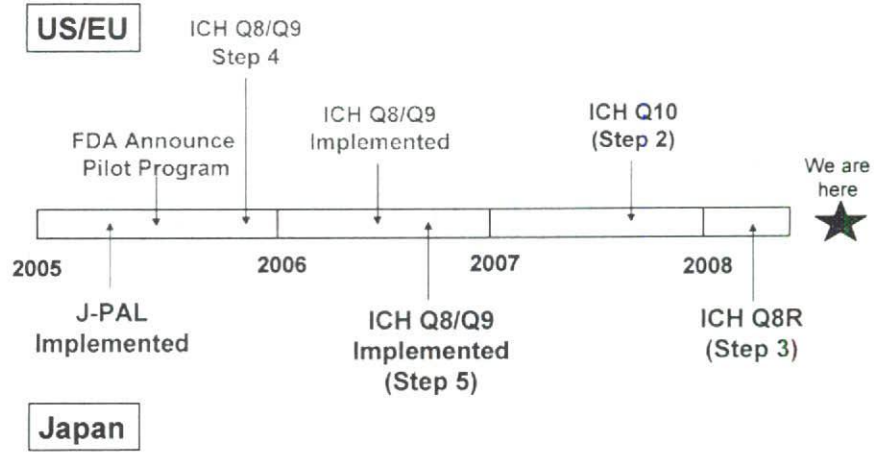
J-PAL & ICH Q8/9 implemented



Contents

- **MHLW sponsored Study Group for QbD**
- [illegible]
- [illegible]

MHLW sponsored Study Group for QbD kicked-off 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 and Quality by Design (QbD) in Japan.
- ✓ Provide an example (mock) of Application Form and P2 section in Quality Overall Summary.

Three sub-groups are formed.

'Design Space' sub-group in the Study Group

Theme: Establishing Design Space in critical steps

1. Clarify and understand the terminology in Q8
2. Identify issues, e.g. scale-effect, to apply Design Space (DS) on commercial production
3. Discuss regulatory flexibility of DS for post-approval change management
4. Create model product as an example (P2 mock)

Key Factors for Establishing Design Space
- Scale Effect on Manufacturing -

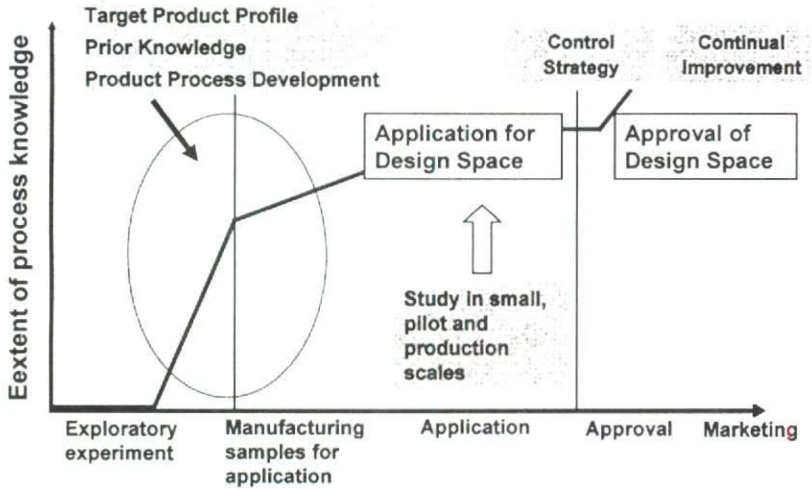
Case A: where DS established would not be affected by scale difference

Case B: where DS established could be extrapolated to different scales

Case C: where DS established could not be extrapolated to different scales and commercial production

Case D: where DS established would be required to change at commercial production due to other factors rather than scale effect

Design Space in the flow of development



Contents

- Model drug product as an example

Study on Model Drug Product as an Example for 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)

Strength
- 30 mg

Route of administration
- Oral

Model Drug Product: 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

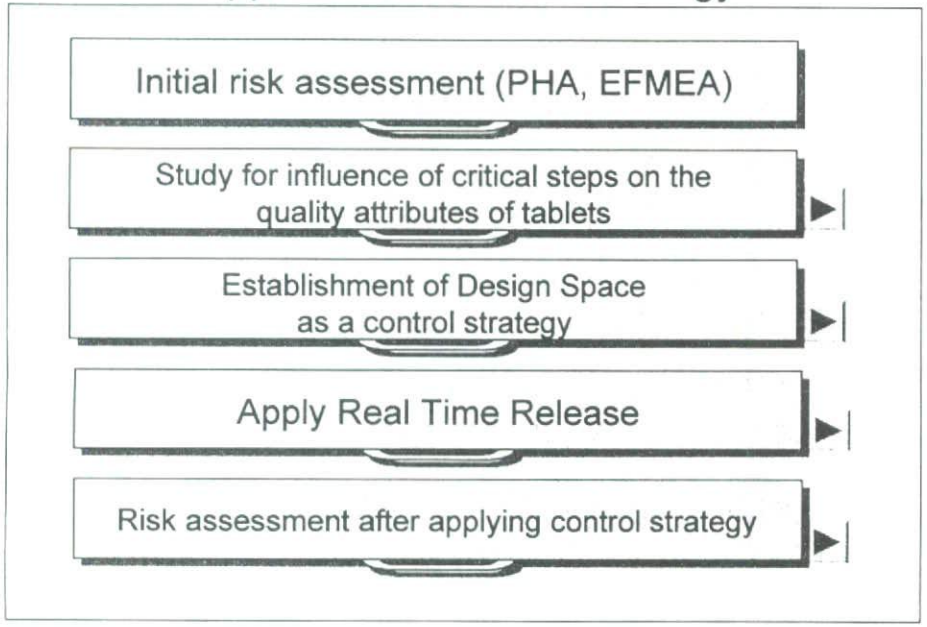
Overview of Strategy for Pharmaceutical Development of Sakura tablet

1. Establishment of target product profile and initial risk assessment
2. Risk assessment of manufacturing processes
3. Identification of critical steps and study for influence of critical steps on the quality attributes of tablets
   - Influence of particle size of drug substance on the dissolution and *in vivo* absorption performance of drug product
   - Lubrication process
   - Tabletting process
   - Blending process and uniformity of powder for tabletting process

Overview of Strategy for Pharmaceutical Development of Sakura tablet (cont' d)

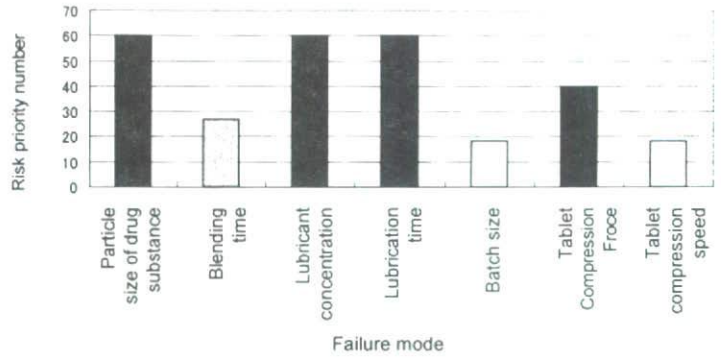
4. Study for establishment of DS as a control strategy
5. Study for establishment of Real Time Release (RTR) in critical steps
6. Risk assessment after applying the control strategy

Approach for Control Strategy



Risk Assessment of Drug Product and Manufacturing Processes

High-risk: Particle size of drug substance, lubricant concentration, lubrication time, and tablet compression force



Study for Influence of Critical Steps on Quality Attributes of Tablets

Influence of particle size of API (BCS2) on *in vivo* absorption performance and dissolution

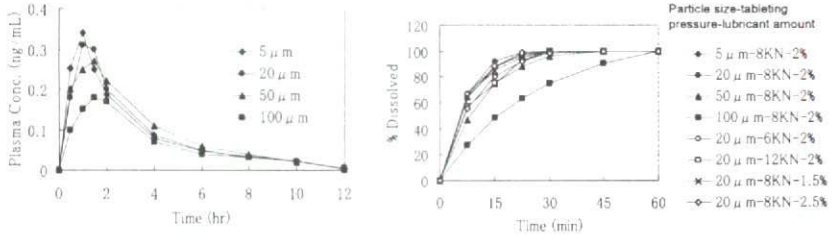


Fig. *In vivo* absorption performance and dissolution profile shown in the range of 5 to 100 um

Study for Influence of Critical Steps on Quality Attributes of Tablets (cont' d)

Study for lubrication process

- Lubricant concentration and lubrication time changed for three levels:
  - ✓ Influence on dissolution and tablet hardness
  - ✓ Tablets manufactured under any conditions showed comparable dissolution
  - ✓ Reduction in tablet hardness with increasing lubricant concentration and extending lubrication time

⇩

- These parameters do not markedly influence dissolution and tablet hardness.

Study for Influence of Critical Steps on Quality Attributes of Tablets (cont' d)

Study for tabletting process

The process parameters are controlled for mean weight of tablets and tablet compression force (6 -10 KN).

Number of rotations of tablet compressing machine	Compression force (KN)	Drug product uniformity test	Dissolution rate for 30 min. (%)	Tablet hardness (N)	Tablet strength (F-strength, Friability%)
40rpm	6	2.2	97	90	0.5
	8	1.9	95	109	0.3
	10	1.7	85	131	0.1
	12	2.4	75	159	0.1
80rpm	6	3.6	97	81	0.6
	8	3.7	97	104	0.4
	10	3.1	86	123	0.1
	12	3.8	73	141	0.1

Study for Influence of Critical Steps on Quality Attributes of Tablets (cont' d)

Experiment No.	Condition	Blending time (min.)	Rotation speed (rpm)	Blender	Particle size D90 (μm)
1	Variation	2	10	V	10
2	Variation	16	10	V	50
3	Variation	2	30	V	50
4	Variation	16	30	V	10
5	Variation	2	10	Drum	50
6	Variation	16	10	Drum	10
7	Variation	2	30	Drum	10
8	Variation	16	30	Drum	50
9	Standard	9	20	V	30
10	Standard	9	20	Drum	30
11	Standard	9	20	V	30
12	Standard	9	20	Drum	30

Blending time controlling by In-line NIR:
to manufacture powder with target blending uniformity

Establishment of Design Space as a Control Strategy

- The Design Space of this product was established by combination of input variables, process parameters, and final product specifications as a control strategy.

✓ **Input variable:**

- Particle size of API most affected on dissolution, and target dissolution was obtained by controlling the particle size in range of 5 to 20 um.

Establishment of Design Space as a Control Strategy (cont' d)

✓ **Process parameter:**

- Tablet compression force affected on tablet hardness.

⇩

- **Blending process of powder, lubricant blending process and tabletting process were defined as critical steps.**

Establishment of Design Space as a Control Strategy (cont' d)

- **Blending process of powder:**

  RSD of blending uniformity at < 6% controlling by NIR

- **Lubricant blending process:**

  Blending time of 1 to 15 min does not affect on dissolution and tablet hardness

- **Tabletting process:**

  Tablet compression force of 6 to 10 KN

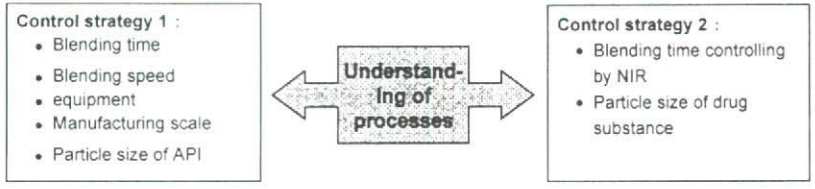
Establishment of Design Space as a Control Strategy (cont' d)

- Correlation between dissolution and *in vivo* absorption was confirmed over the range of 5 to 50 um.
- Low possibility that tablet compression force will affect on the quality attributes of tablets.

⇩

- Opportunity for Real Time Release by controlling blending uniformity by NIR with no influence by equipment and manufacturing scale

Establishment of Design Space as a Control Strategy (cont' d)



✓ **Control strategy 1:**
- Many parameters depend on equipment and manufacturing scale

✓ **Control strategy 2 employed:**
- Opportunity for Real Time Release (RTR) by using NIR

Control Strategy for Finished Product (RTR 1)

Dissolution

- Particle size of API affects on dissolution.
- Controlling appropriate particle size can achieve an intended quality attribute.

⇩

✓ **Dissolution test can be skipped as a release test.**

Control Strategy for Finished Product (RTR 2)

Content Uniformity

- Controlling blending uniformity by NIR can assure content uniformity of tablets.
- Monitoring tablet compression force of each tablet can assure content uniformity in tabletting process.

⇩

✓ **Content Uniformity test can be skipped as a release test.**

Control Strategy for Finished Product (RTR 3)

Assay

- Content of blended powder in blending process and mean weight of tablets after tabletting can assure content of the API in finished product.

⇩

✓ **Assay can be skipped as a release test.**

Control Strategy for Finished Product

Real Time Release

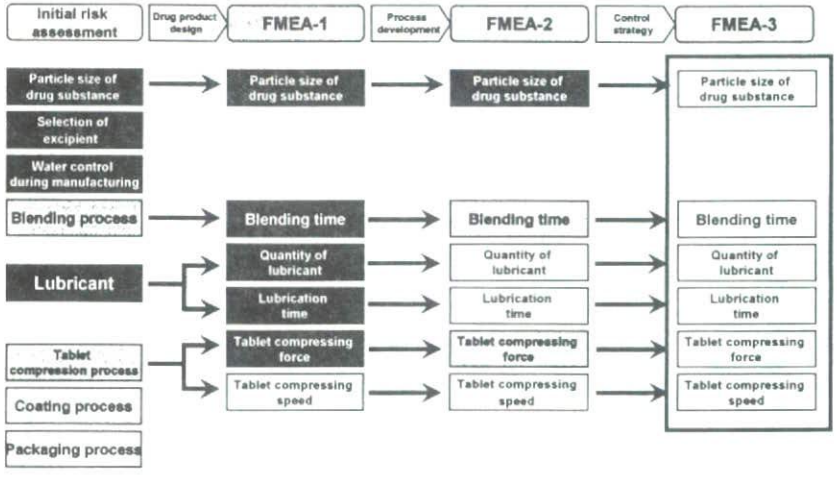
- Monitor and control particle size of API, blending uniformity and tablet compression force

⇩

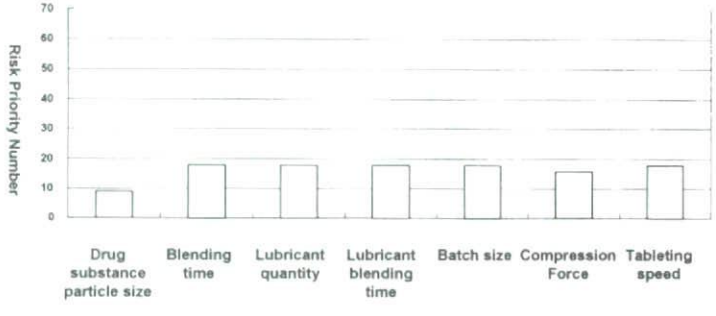
✓ **Dissolution, Content Uniformity and Assay can be skipped as release tests.**

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

Flow of Pharmaceutical Development and Risk Assessment



Risk assessment after applying control strategy

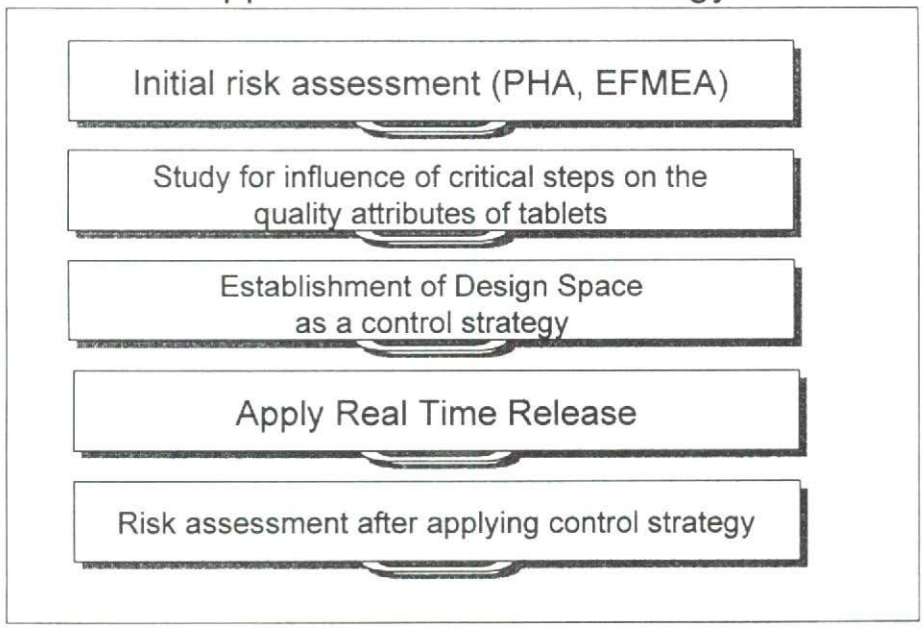


Results of FMEA Risk Analysis for Sakura Tablet after Control Strategy Implementation

Contents

- [illegible]
- [illegible]
- **Establishing Design Space and Control Strategy: Summary and Next Step**

Approach for Control Strategy



Summary 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
- Tablet compression force will not affect on the quality attributes of tablets.

⇩

- Controlling blending uniformity by NIR for Real Time Release

Summary 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: *Case A***

Next Step

✓ **P2 mock will be released for public comments on the web.**

✓ **Continue to study for establishing DS and control strategy in Case B, C and D.**

✓ **Establish clear link between manufacturing description in Application Form (module 1) and P2 mock under QbD approach with J-PAL.**

✓ **Create a mock of Application Form....**

Acknowledgement

Ryuta Asada	Pharmaceutical and Medical Devices Agency
Makoto Kikoshi	Kyowa Hakko Kogyo Co., Ltd.
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Yoshio Nakano	Eli Lilly Japan K.K.
Kazushige Hibi	AstraZeneca K.K.
Yukio Hiyama	National Institute of Health Sciences
Hirokazu Matsunaga	Takeda Pharmaceutical Company Limited
Tetsu Yamada	Otsuka Pharmaceutical Co.,Ltd.

DIA
DRUG INFORMATION ASSOCIATION

44TH
Annual Meeting

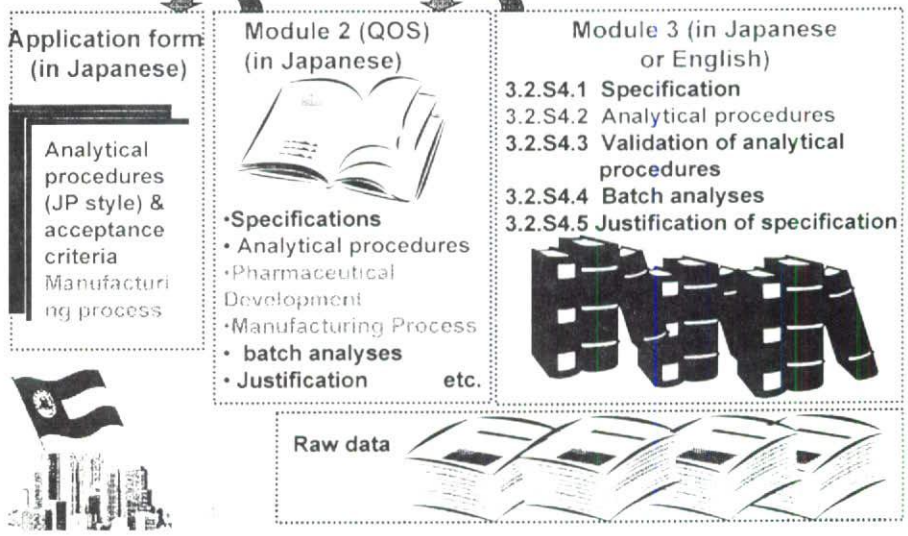
Boston 2008

Topics of Real Time Release in Japanese Regulation

Mockup of Japanese QOS

Tatsuo Koide
Division of Drugs
National Institute of Health Sciences,
MHLW, Japan

Relationship between Application Form and CTD Documents



MHLW Health and Labour Sciences Research Grant

- **2006-2008 MHLW "Approval matters" study group began to discuss new QOS and AF**
  - Encourage more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8.

-Three sub-themes (according to Q8)

1)Enhanced approach
  a) Design space
  b) RTR
2)Minimum (Baseline or Traditional) approach
3)Design space" in formulation

Real Time Release (RTR) as Approved Matters

- Application Form should include the essential elements of RTR when applicants have control strategies including RTRs in lieu of specification of final products.
- Specification with test method would not go away because of need for stability test, equipment breakdown, calibration and later evaluations.

Mockup of Japanese QOS and Application Form

Discussion Point:

1. Inclusion of RTR in application dossier
   (site and severity of failure mode and control procedures)
2. Measures for specifications and test methods in the case of RTR
3. Decision tree of RTR implementation (Application Form)

Relationship between RTR proposed based on risk assessment results and drug product specifications/test methods

Test		Test method	Specifications
Appearance		Visual inspection	White plain tablet
Identification test	UV-visible spectrum	UV-visible spectrophotometry (acetonitrile/water mixture (1:1))	Compare the spectrum from the test sample with that from the reference standard: both the test sample and reference standard exhibit the similar intensity of absorption at the same wavelength.
Purity test	Related substances	Liquid chromatography (absolute calibration method)	Individual related substance: Not more than 0.2% Total related substances: Not more than 1.0%
Content uniformity		UV-visible spectrophotometry (acetonitrile/water mixture (1:1))	Conforms to the requirements for homogeneity of drug products (content uniformity)
Dissolution test		Apparatus: Paddle method Test solution: 0.1% sodium lauryl sulfate Volume of test solution: 900 mL Rotation speed: 50 rpm Assay: Liquid chromatography (Absolute calibration method)	Dissolution (%) after 30 minutes: Not less than 80% (Q)
Assay		Liquid chromatography (Internal standard method)	Content: 95.0 to 105.0% of the labeled amount

Proposal (1) for RTR:
Content uniformity
Blending process:
Drug substance content uniformity
Compression process:
Monitoring of compression pressure

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

Proposal (3) for RTR: Assay
Blending process:
Content of the drug substance blended
Compression process:
Mass measurement

Other quality control strategies such as that for change of manufacturing site and preparation of specimen for quality control test in stability test are considered to be necessary.

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

Checking of various conditions involved in RTR
(Is there any issue in the precedent processes?)

↓ Yes

Content uniformity monitoring during the blending process
Mean measured value = within ±2% of the labeled amounts
RSD: ≤1.0%

↓ Yes

Compression pressure monitoring during the compression process (AWC)
Weight-equivalent value: 97 to 103 mg
RSD: ≤1.0%

Yes ↓

Risk assessment
Various conditions required to apply RTR should be ensured (e.g., the presence of out-of-specification items, number of tablets to be removed)

→ **Application of RTR**

→ **Implementation of Content Uniformity Test**

Content Uniformity Test: Proceedings leading to RTR application

(Arguments under discussion)
(1) Should risk assessment be carried out before application of RTR?
(2) Should shipping test be carried out as a measure in the event of unanticipated issue during the process?

Call for comment and information on the draft QOS mock

The mock(draft) is released for public comments on the NIHS, Division of Drug Homepage.

http://www.nihs.go.jp/drug/DrugDiv-J.html (Japanese)

http://www.nihs.go.jp/drug/DrugDiv-E.html (English)

Please send your comments and information to the e-mail

E-mail : q8_g1pubc@nihs.go.jp

Application Form and revised QOS Mock will be released soon

Design Space Description and Submission in the Pharmaceutical Development Section of a Regulatory Filing-a MHLW Perspective

Tatsuo Koide
Division of Drugs
National Institute of Health Sciences,
MHLW, Japan

Outline of presentation

- Organization and work relationship within Ministry Health, Labour and Welfare (MHLW)

Outline of presentation

- Organization and work relationship within Ministry Health, Labour and Welfare (MHLW)
- Relationship between Application Form and CTD Documents
- MHLW "Approval matters" study
  Revision of Mockup of Japanese QOS

Organization and work relationship within MHLW

MHLW

Pharmaceutical and Food Safety Bureau
Pharmaceutical Affairs and Food Sanitation Council

Pharmaceuticals and Medical Devices Agency (PMDA)

Reviews and Related Operations
- Approval reviews of pharmaceuticals and medical devices GMP/QMS audits
- Re-assessment and re-evaluation
- Preparation of Japanese Pharmacopoeia etc

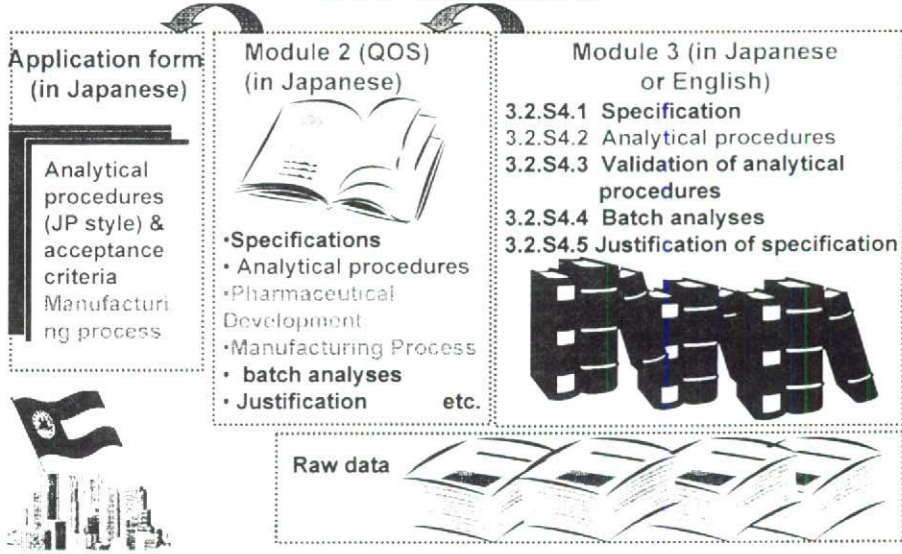
National Institute of Health Sciences (NIHS)

Major functions and responsibilities of this institute are:
- to conduct wide range of research works and tests to ensure quality, efficacy and safety of drugs, foods and other goods.
- to gather information and develop databases on the safety of chemicals in drugs, foods, etc.

Outline of presentation

- Relationship between Application Form and CTD Documents

Relationship between Application Form and CTD Documents



Application Form and Approval Matters

A Unique System in Japan

- Contents provided in the NDA application form are dealt with as "matters subject to approval."
- Contents described in approval letter are "legal binding" approval matters.

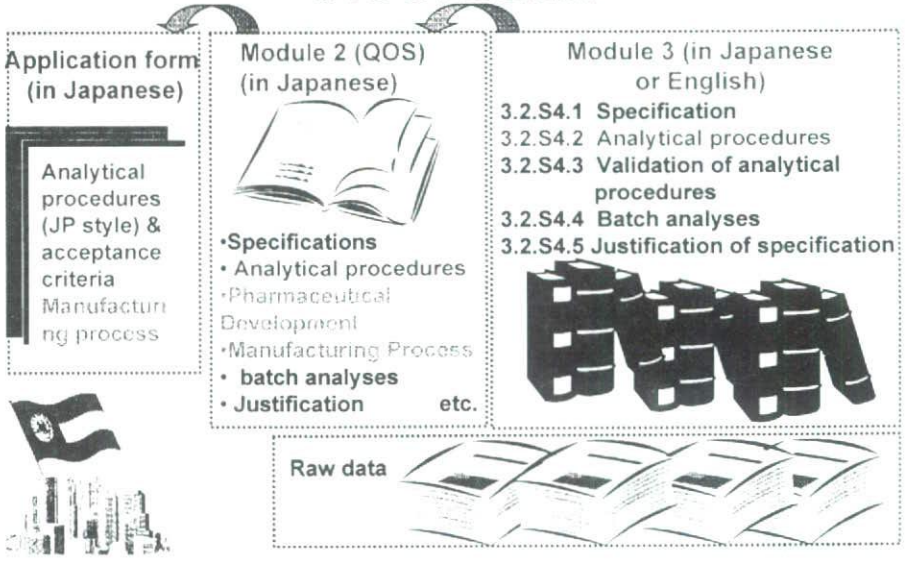
Approval Matters

- General name (for drug substance)
- Brand name
- Composition
- Manufacturing process, including control of materials
- Dosage and administration
- Indications
- Storage condition and shelf-life
- Specifications and analytical procedures

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 (in MHLW).**

Relationship between Application Form and CTD Documents



Outline of presentation

- MHLW "Approval matters" study

Health and Labour Sciences Research Grant

- **2006-2008 MHLW "Approval matters" study group began to discuss new QOS and Application Form**
- **The Study Group consists of regulatory and industry CMC experts led by Dr. H. Okuda of NIHS.**

Three sub-themes (according to Q8)

1)Enhanced approach
  a) Design space team
  b) RTR team

2)Minimum (Baseline or Traditional) approach

3)Design space" in formulation

Enhanced Approach Group

The study objectives are:

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

P2 mock(draft) is released for public comments on the web. (June 2008-)

P2 mock is being revised using the public comments. (Sep. 2008-)

Revision of Mockup of Japanese QOS

- Old Version was published in July 2002
  - Not include ICH Q8 concept
- Merely shows an example of description for each module 2 section and just a reference for an applicant to prepare QOS.
- Not covers all information required for each NDA

Outline of presentation

Revision of Mockup of Japanese QOS

Study on Model Drug Product as an Example for QOS 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)

Strength
- 30 mg

Route of administration
- Oral