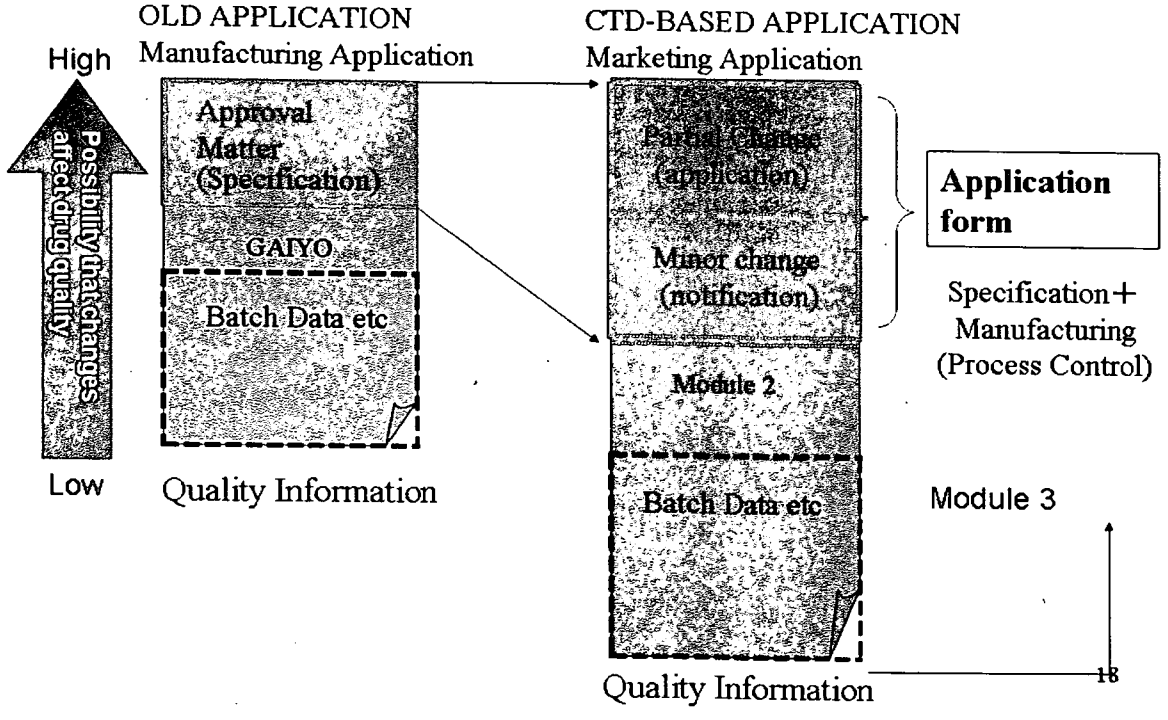
Distinctions between Partial Change Approval Application and Minor Change Notification

Partial Change Approval Application	Minor Partial Change Notification
Change in the principle of unit operation of critical process	Process parameter to control the quality endpoint criteria
Change in process control criteria as quality endpoint criteria	

17

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



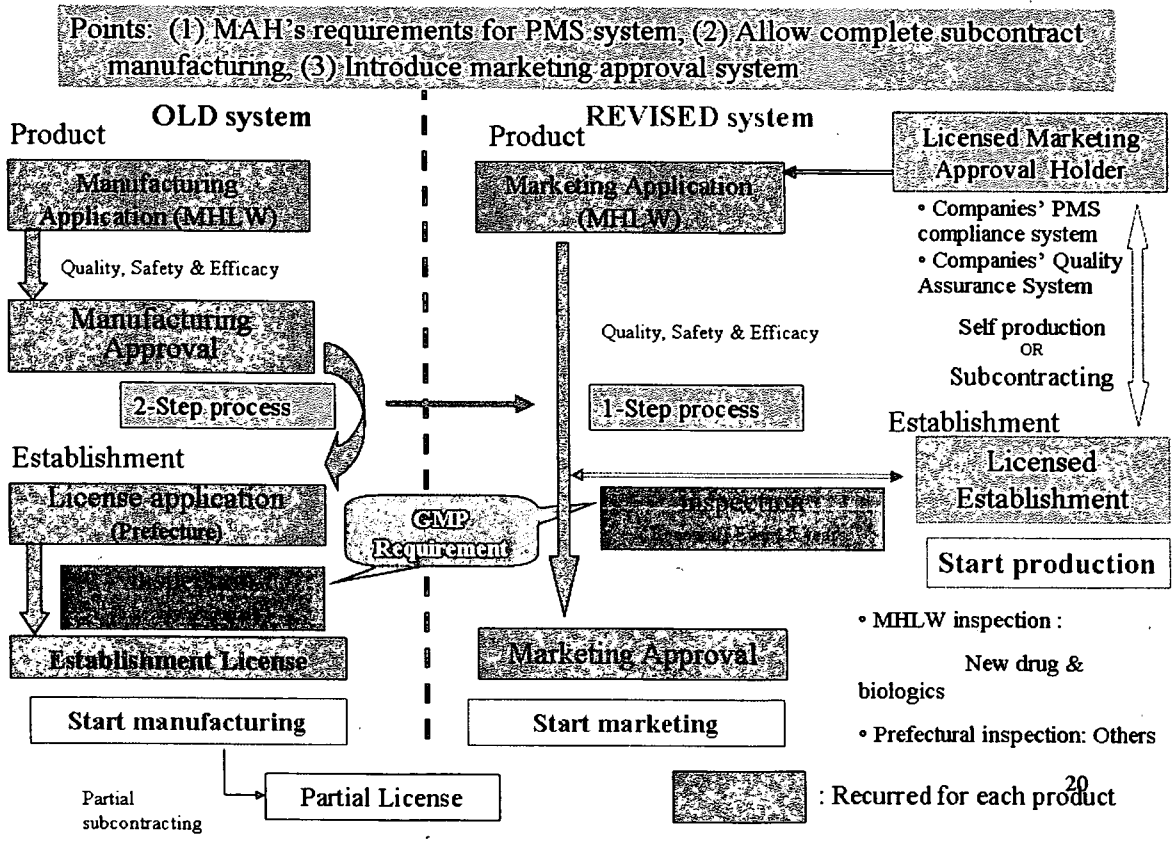
18

4. Consolidation of the Legal Positioning of GMP

- **Became a requirement for product approval**
- GMP inspection **prior to approval**, and periodical GMP inspection in post-marketing phase
- GMP inspection **at the time of application for partial change(pre-approval required) of the approval matters**
- GMP inspection **at foreign sites**

19

Comparison Flowcharts of Approval and License



20

GMP/QMS Inspection for Foreign Sites

- GMP/QMS* inspection for foreign manufacturing facilities started since April, 2005.
  - MRA*: Document check only for pharmaceuticals except sterile products and biologics
  - MOU*: Document check only for Pharmaceuticals
- Number of facilities inspected (~July. 2007)
  - Pharmaceuticals: 75
  - Medical devices: 24

QMS*: Standards for Manufacturing Control and Quality Control for Medical Devices and In-vitro Diagnostic Reagents; MRA* Japan-EU Mutual Recognition Agreement (API: out of scope); MOU* Memorandum of Understanding between Japan and Australia, Germany Sweden, Switzerland)

21

Number of Foreign Facilities inspected by PMDA (~July.2007)

	Europe	North America	Central/ South America	Asia	Others	Total
Sterile products/ Biologics	17	21	0	2	0	40
Oral solid etc	1	7	0	0	0	8
API (Chemical)	10	6	1	3	1	21
Packaging, Labelling, Storage and Laboratory	0	6	0	0	0	6
Total	28	40	1	5	1	75

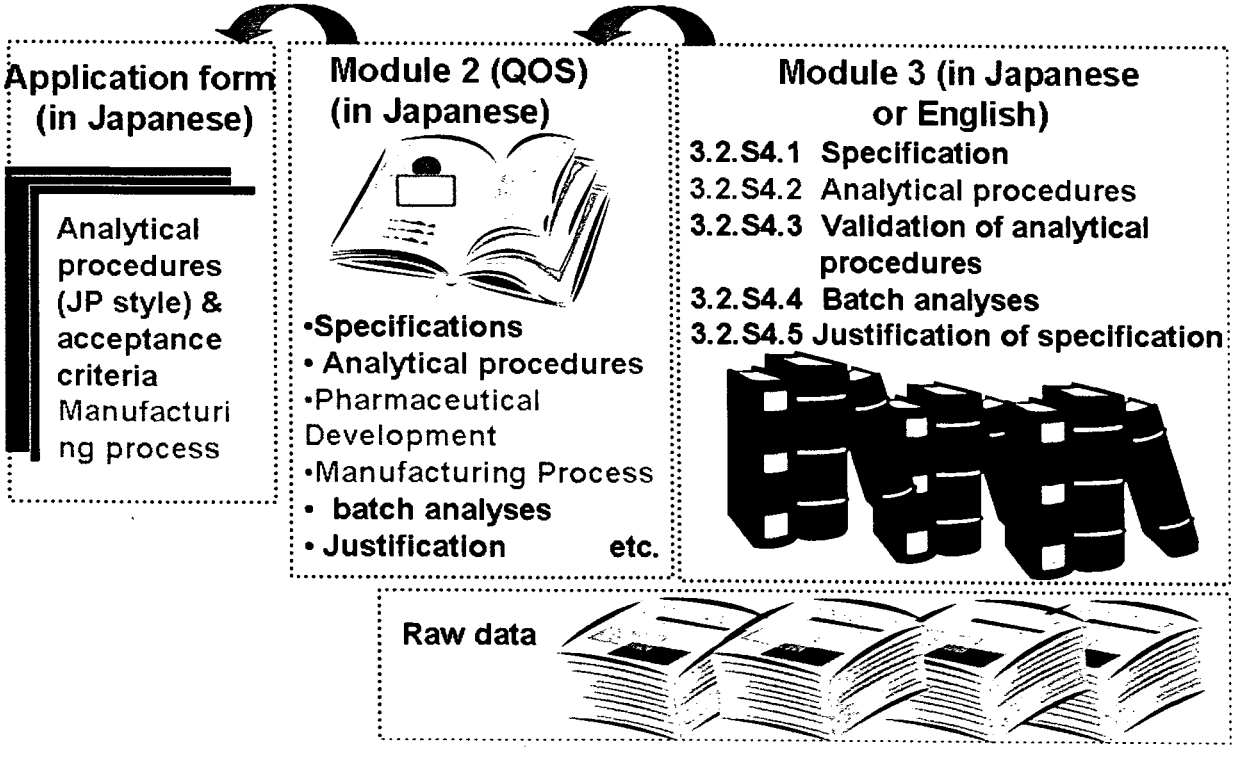
22

Role of Module 2

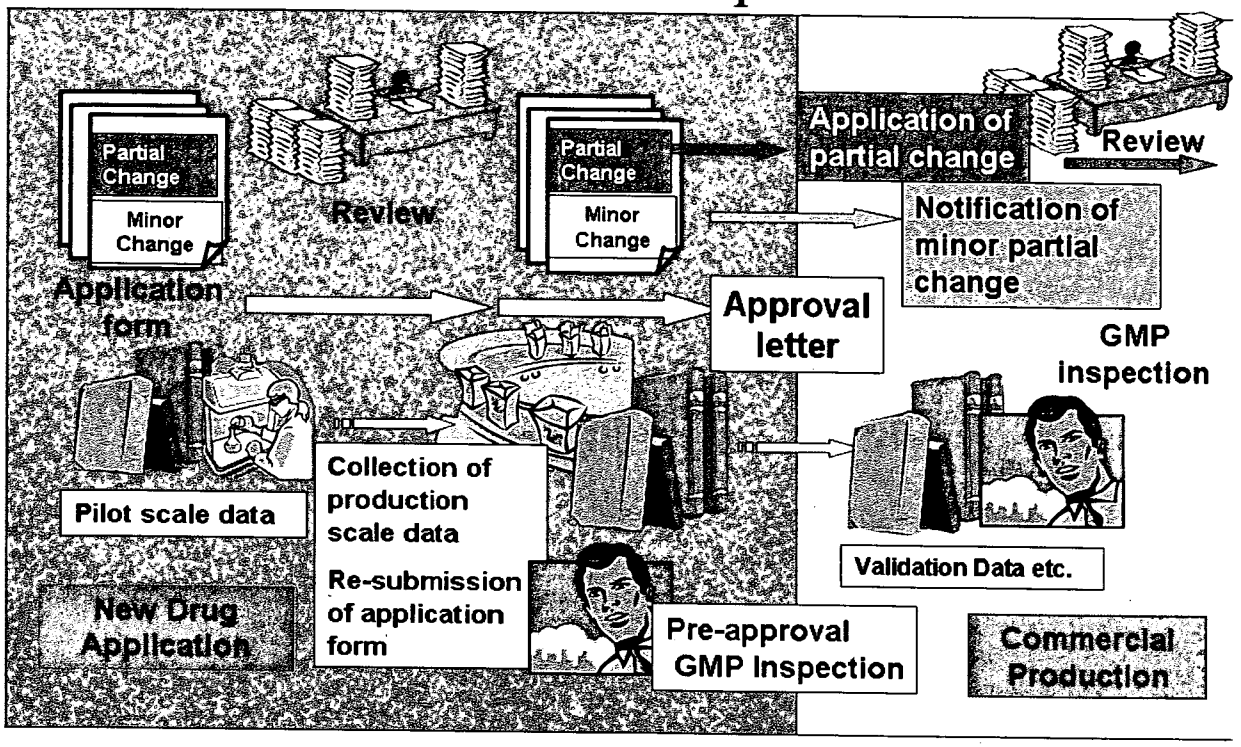
- Module 2 bridges NDA Application Form (approval matters) and Module 3
- Module 2 is one of the key review documents
  - Reviewers evaluate Module 2 and then narrow down into Module 3, 4, or 5 when they need more detailed information.
  - Module 1 and 2 together with reports written by reviewers are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

23

Relationship between Application Form and CTD Documents



Framework for Review and Inspection



Challenges when implementing rPAL regulations with ICH Q8

- Baseline expectations need to be clarified

"At minimum(identify risks and risks controlled)" expectations do not seem to be traditionally submitted in Japanese NDA. With "traditionally" submitted contents, it is difficult to sort out pre-approval matters, minor change matters.← expect Q8(R) address this

- Range for excipients as a design space: scientific basis, description in approval letter←under consideration with "approval matters" study group
- Design spaces with interacting multi-variables and with interacting unit operations:description in approval letter←see industry's creativity
- Real time release:process and facility dependence ←Need final scale data to justify. Specification with test method would not go away because of need for later evaluations including generics

26

Revision Mockup of Japanese QoS

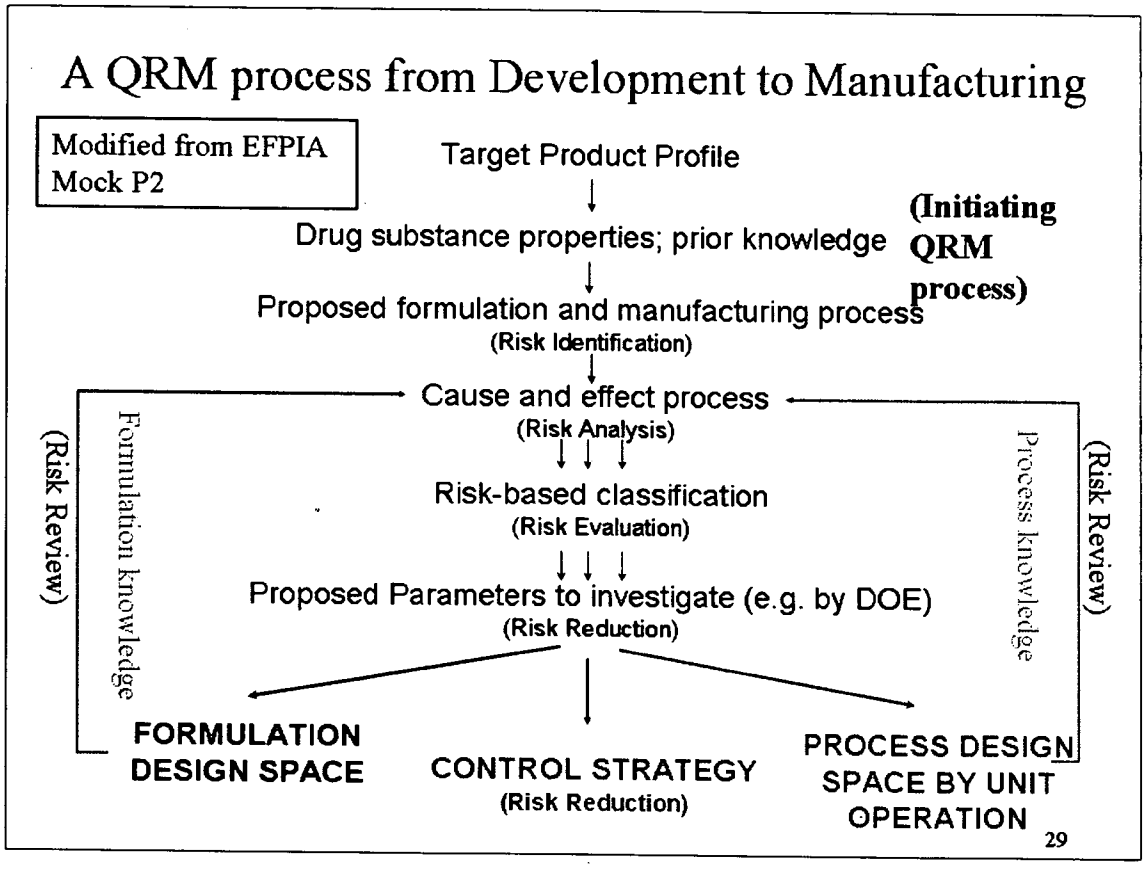
- Old Version was published by Pharmaceutical Manufacturers Association of Tokyo, Osaka Pharmaceutical Manufacturers Association and Japan Health Sciences Foundation in July 2002
- Merely shows an example of description for each module 2 section and just a reference for an applicant to prepare QoS.
- Not covers all information required for each NDA, nor shows acceptance criteria for each categories.
- **NEED more description on pharmaceutical development and on justification of manufacturing process according to ICH Q8 and the revised PAL.←2006-2008 MHLW "Approval matters" study group**

27

Opportunities by Q9

- Integration to Industry's Pharmaceutical Quality Systems
  (ICH Q10 will address this area)
- Integration to Regulatory Authorities' work process (e.g. QS for GMP inspectrate)
- Integration to Guidance Development and Pharmacopoeia Policy (Government and Industry joint effort)

28

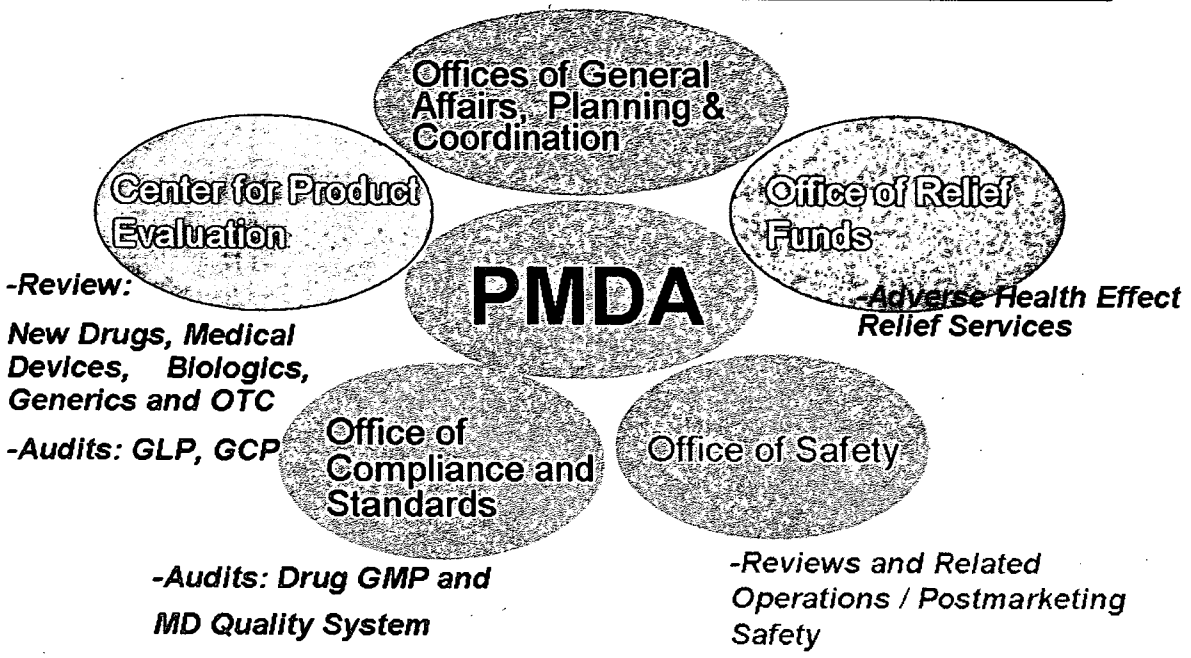


6. Establishment Pharmaceuticals and Medical Devices Agency (PMDA)

- Reviews and Related Operations
  - Approval reviews of pharmaceuticals and medical devices GMP/QMS audits to assess pharmaceutical and medical device facilities, processes, and quality management systems
  - Re-assessment and re-evaluation based on Pharmaceutical Affairs Law etc.
- Post-marketing Safety Operations
- Adverse Health Effect Relief Services

30

Organization of PMDA

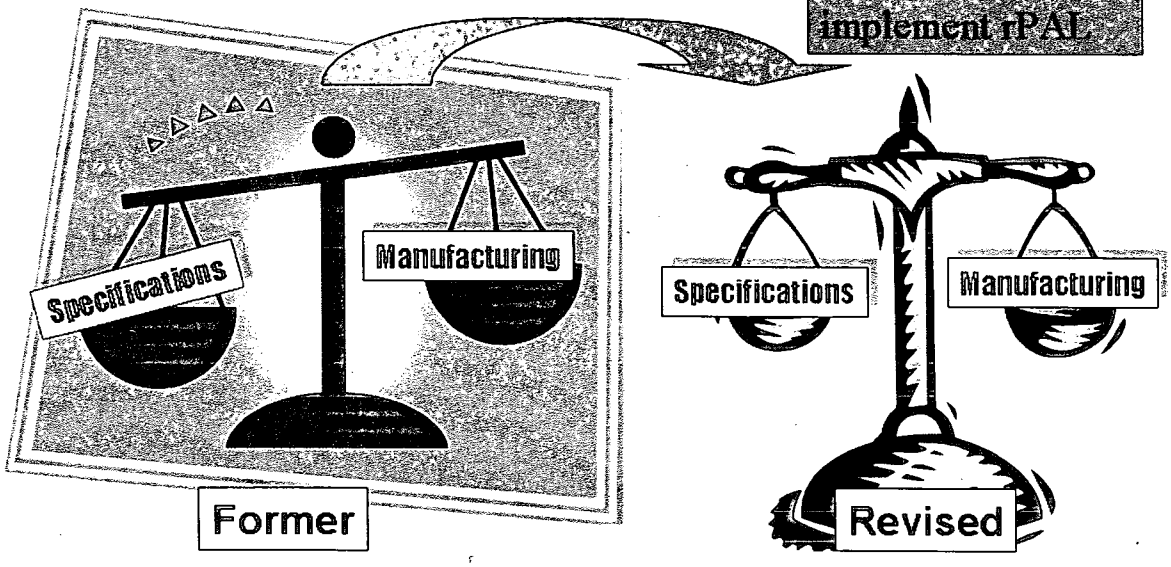


31

Balance between "Specification" and "Control of Manufacturing"

- Implementation of ICH-CTD (July, 2003)
- Revision of Pharmaceutical Affairs Law (April, 2005)

ICH Q8, Q9&Q10 Help us to implement rPAL



Deepen Understanding on ICH Q10

Japan PDA

1

Overview of ICH Q10 -Table of Contents-

2

Management Responsibility

2. MANAGEMENT RESPONSIBILITY
Leadership is essential to establish and maintain a company-wide commitment to ...

2.1 Management Commitment
i) Senior management has the ultimate responsibility to ensure ... , and that responsibilities and authorities are defined, ...

◆Discussion Point:

- What positions or governance do 'Management' and 'Senior Management' refer to?
- What are the scope of work and roles of 'Management' and 'Senior Management?'

3

Management Responsibility

2.5 Internal Communication
i) Management should ensure appropriate communication processes are established and implemented within the organization.
ii) Communications processes should ensure the flow of appropriate information between all levels of the company.
iii) Communication processes should ensure the escalation of certain product quality and pharmaceutical quality system issues to appropriate levels of management in a timely manner.

◆Discussion Point

How do GMP organization and management communicate with each other regarding quality?

- Scope: What is the level of management?
- Subjects: existing products, investigational products, development products, etc.
- Frequency: periodically, only on the occurrence of problems, or both?
- Means: meetings, reports, etc.

4

CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

3.2 Pharmaceutical Quality System Elements
ii) Corrective Action and Preventive Action System (CAPA)
The pharmaceutical company should have a system ... CAPA methodology should result in product and process improvements and enhanced product and process understanding.

◆Discussion Point
Is there any system to feed back troubles occurred at manufacturing sites to development department?

5

CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

3.1 Lifecycle Stage Goals
i) Pharmaceutical Development
The goal of pharmaceutical development activities is ... meet the needs of patients, healthcare professionals, regulatory authorities and internal customers. ...

3.2 Pharmaceutical Quality System Elements
iv) Management Review of Process Performance and Product Quality
(1) The management review system should include:
(i) Measures of customer satisfaction such as customer complaints and recalls;

◆Discussion Point:
- How is customer satisfaction surveyed?
- When is the survey conducted?
- How are the results fed back to manufacturing and development departments?

6

CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

2.3 Quality Planning

v) Key performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate.

4.1 Management Review of the Pharmaceutical Quality System
Management should have a formal process for reviewing ...
The review should include:
ii) Assessment of Key Performance Indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, ...

◆Discussion Point

- In what items are Key Performance Indicators set in each production lifecycle? What indicators are set as KPI?
- Are there any ways of thinking or methods to set parameters?

7

CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

Are KPIs set for the items below in each stage of the production lifecycle?
Are there any other items for which KPIs are set?

<table>
<tr><th></th><th>Development</th><th>Technology Transfer</th><th>Manufacturing</th><th>Product discontinuation</th></tr>
<tr><td>Process Performance & Product Quality</td><td rowspan="3">Percentage of fulfillment of simulation product aims

Percentage of success of scale-up

Percentage of NDA approval, Delay from Schedule</td><td rowspan="3">Schedule, Cost

The number of changes of scope or design</td><td>The number of OOS, deviations, rejected lots, complaints, recalls</td><td>The number of complaints, recalls</td></tr>
<tr><td>CAPA System</td><td>Schedule
Effects of actions</td><td></td></tr>
<tr><td>Change Management</td><td>Percentage of failure decreasing, cost reduction after changing

Schedule</td><td></td></tr>
<tr><td>Management review of Process Performance & Product Quality</td><td colspan="4">Is timely management review of above-mentioned items conducted?
(review of management review)</td></tr>
</table>

8

CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

2.2 Quality Policy

i) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

ii) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.

iii) The quality policy should be communicated to and understood by personnel at all levels in the company.

iv) The quality policy should be reviewed periodically for continuing effectiveness.

◆Discussion Point

- What is the appropriate frequency by 'reviewed periodically?'
- Which division is the 'senior management' that plans and approves the quality policy? Who is the final approver?
- Is the scope of communicating the quality policy pre-fixed? Are outsiders, such as stockholders, included? How is the policy communicated?

9

PHARMACEUTICAL QUALITY SYSTEM

1.1 Implementation of ICH Q10 throughout the product lifecycle should facilitate ...

1.2 Scope

This guideline applies to pharmaceutical drug substances and drug products, including biotechnology and biological products, throughout the product lifecycle.

◆Discussion Point
'throughout the product lifecycle'

Which stage is specifically the development stage in the lifecycle?

10

PHARMACEUTICAL QUALITY SYSTEM

1.3 ICH Q10 thereby serves as a bridge between the regional requirements, helping industry and regulators achieve harmonization of the pharmaceutical quality system throughout the lifecycle of a product.

◆Discussion Point

What kind of things are feasible as 'a bridge between the regional requirements?'

11

添付資料8　2007年12月　製剤機械技術研究会・医薬品品質フォーラム合同シンポジュウムプログラム

第8回 製剤機械技術・第7回医薬品品質フォーラム 合同シンポジウム

プ ロ グ ラ ム

メインテーマ:『ICH製剤開発(Q8)及び品質リスクマネジメント(Q9)の具体的課題事例とガイドラインの適用について』

総合司会 : 水本 隆雄(アステラス製薬)
日　時 : 平成19年12月7日(金) 9:30～18:00
場　所 : グランシップ静岡 交流ホール(6階)

9:40～10:10	ICHｶﾞｲﾄﾞﾗｲﾝQ8の概略と展望　ICH専門家会議から(MHLW、JPMA)	≪ 座長 ≫ 小嶋 茂雄 (医薬品総合機構) 国立医薬品食品衛生研究所　奥田 晴宏 大日本住友製薬株式会社　石川 英司
10:10～10:40	ICHｶﾞｲﾄﾞﾗｲﾝQ9の概略と展望　ICH専門家会議から(MHLW、JPMA)	≪ 座長 ≫ 小嶋 茂雄 (医薬品総合機構) 国立医薬品食品衛生研究所　檜山 行雄 エーザイ株式会社　松村 行栄
10:40～11:00	ICHQ8Q9ガイドラインに関するアンケート	≪ 座長 ≫ 小嶋 茂雄 (医薬品総合機構) 三菱ウエルファーマ株式会社　長友 章文
	【Q8関連の具体事例】	
11:15～11:45	原薬製造におけるQuality by Design	≪ 座長 ≫ 寺田 勝英 (東邦大学薬学部) 大日本住友製薬株式会社　中村 明彦
11:45～12:10	厚生労働科学研究班からの事例課題発表－ QbDアプローチⅠ:重要工程におけるデザインスペースの設定並びに Control Strategy としての Real Time Release(仮題)	≪ 座長 ≫ 寺田 勝英 (東邦大学薬学部) ファイザー(株)・武田薬品工業(株)　岡崎公哉・松永浩和
12:10～12:30	厚生労働科学研究班からの事例課題発表－ QbDアプローチⅡ:添加剤処方量の幅に関するフレキシビリティ(仮題)	≪ 座長 ≫ 寺田 勝英 (東邦大学薬学部) グラクソ・スミスクライン(株)　丸山俊夫
	【Q9関連の具体事例】	
13:15～13:45	無菌医薬品製造と無菌操作法におけるリスクマネジメント	≪ 座長 ≫ 板井 茂 (静岡県立大学薬学部) アステラス製薬株式会社　片山 博仁
13:45～14:15	Q9教育資料からの事例	≪ 座長 ≫ 板井 茂 (静岡県立大学薬学部) 持田製薬工場株式会社　實田 哲仁
14:15～15:00	GMP監査における品質リスクマネジメントの応用	≪ 座長 ≫ 檜山 行雄 (国立医薬品食品衛生研究所) スイス ロッシュ社　Dr. S Roenninger
	【関連分科会討論】	
15:15～16:00	Q8関連分科会	(司会) 宮嶋 勝幸(奥羽大学) (記録) 田村 繁樹(アステラス製薬)、小出 達夫(国立衛研)
16:10～16:55	Q9関連分科会	(司会) 加藤 晃良(エーザイ) (記録) 實田 哲仁(持田製薬工場)
17:05～17:25	厚生労働科学研究班からの事例課題発表－ ベースラインアプローチに関する事例紹介(仮題)	≪ 座長 ≫ 板井 茂 (静岡県立大学薬学部) 武田薬品工業株式会社　大河内 一宏
17:25～17:55	総合討論　各分科会からの発表とまとめ	宮嶋 勝幸(奥羽大学)、加藤 晃良(エーザイ)

シンポジウム前日に Dr.S Roenninger 氏を囲み、座談会を計画しています。座談会参加希望者は別途お申し込み願いします。

○ 座談会日時/場所　:平成19年12月6日(木) 15:00～17:00 グランシップ静岡 ／ 交流ホール(6F)にて

○ 座談会テーマ　:「Q9リスクマネジメントツールと応用事例座談会:リスクマネジメント ツールの使い方」

ICHガイドラインQ9の概略と展望
ICH専門家会議から

エーザイ㈱ 信頼性保証本部
コーポレートQA部
松村 行栄
国立医薬品食品衛生研究所
薬品部
檜山行雄

2007年12月7日
第8回製剤機械技術 第7回医薬品品質フォーラム
合同シンポジウム

Q9文書の経緯

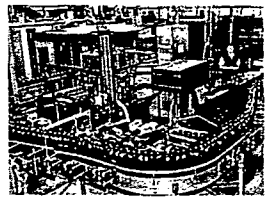
大阪
2003年11月

ロンドン
2004年3月

ワシントン
2004年6月

横浜
2004年11月(Step 2)

意見聴取
2005年3月



シカゴ
2005年11月(Step 4)

2006年 9 月、薬食審査発第0901004号、
薬食監麻発第0901005号発出

品質リスクマネジメントに関するガイドライン

リスクマネジメントの原則は、多くの産業活動や行政活動、及びこれらの企業を規制管轄する機関において有効に活用されている。

医薬品の品質においても、品質リスクマネジメントは、効果的な品質システムにおける重要な構成要素であるということが明らかになりつつあることから、本ガイドラインが制定された。

（1）本ガイドラインは、医薬品の品質の様々な側面に適用できるリスクマネジメントの原則及び手法の具体例を示したものであること。これらの側面には、原薬、製剤、生物由来医薬品及びバイオテクノロジー応用医薬品（製剤、生物由来医薬品及びバイオテクノロジー応用医薬品への原料、溶剤、添加剤、包装及び表示材料の使用を含む）のライフサイクル全般における、開発、製造、配送、査察及び承認申請／審査が含まれる。

（2）本ガイドラインは、その他のICH品質ガイドラインとは独立しているものの、それらを支持し、また承認申請者と規制当局において使われている既存の品質管理の実践、要求事項、基準、ガイドライン等を補完するものであること。製剤開発については、平成18年9月1日付け薬食審査発第0901001号厚生労働省医薬食品局審査管理課長通知「製剤開発に関するガイドライン」を参考にされたい。

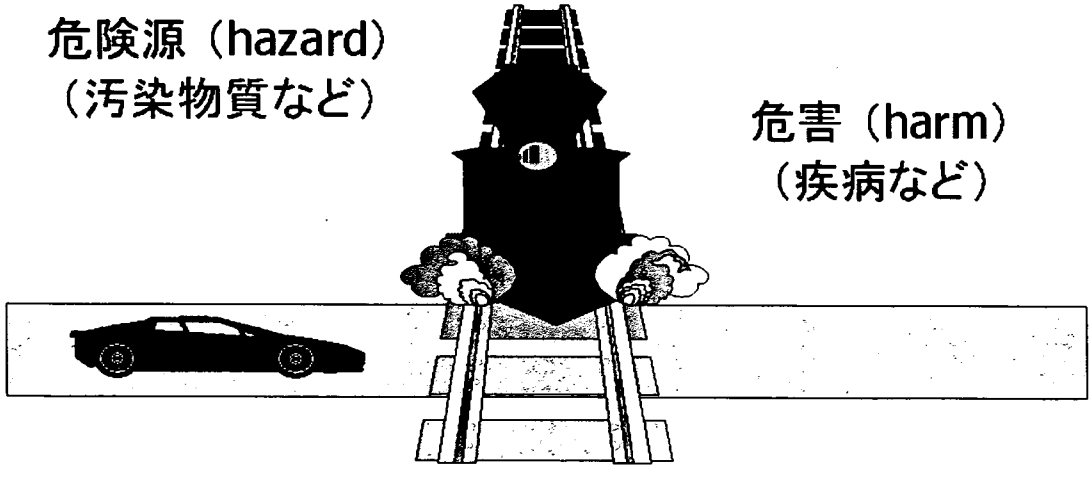
（3）本ガイドラインは、現行の規制要件を超え新たな要件を創出するものではないこと。

発出後の日本における取り組み

- ブリーフィング・パック（日本語版）の公開（4月）
- 説明会の開催
  - 製薬協（7月）
  - 東西合同局方／技術研究常任委員（8月）
  - その他
- 解説書の出版
  - 製薬協：PDF版のWeb掲載（3月）
  - ファームテク ジャパン（4月）
  - 製薬協：会員向け資料配布（7月）

リスク

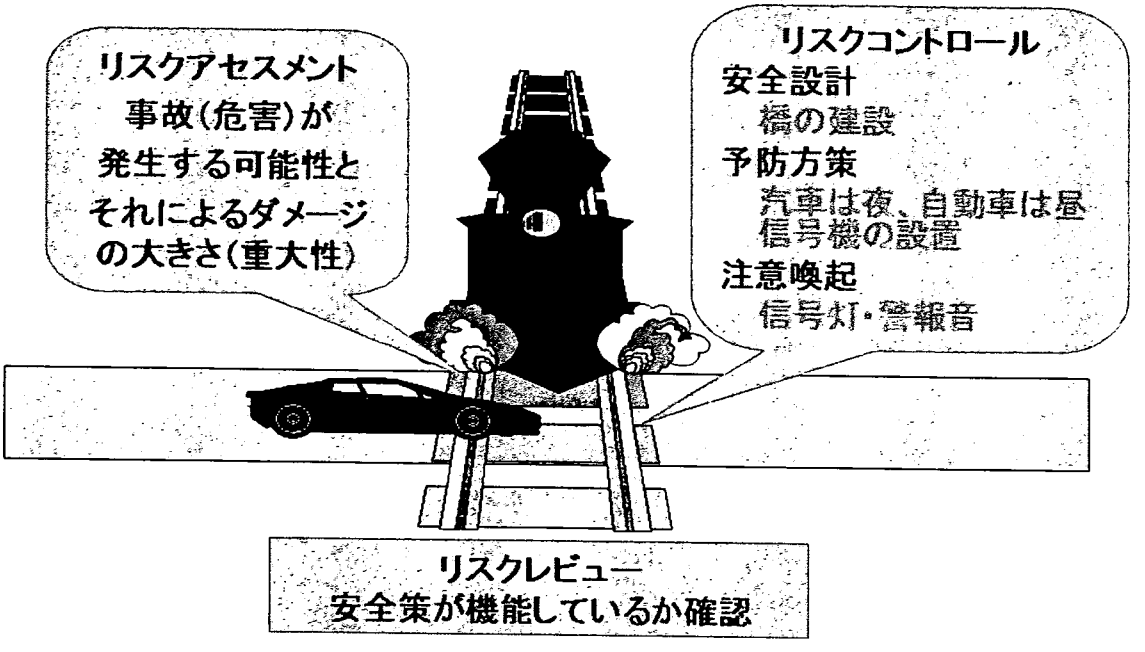
危険源（hazard）
（汚染物質など）



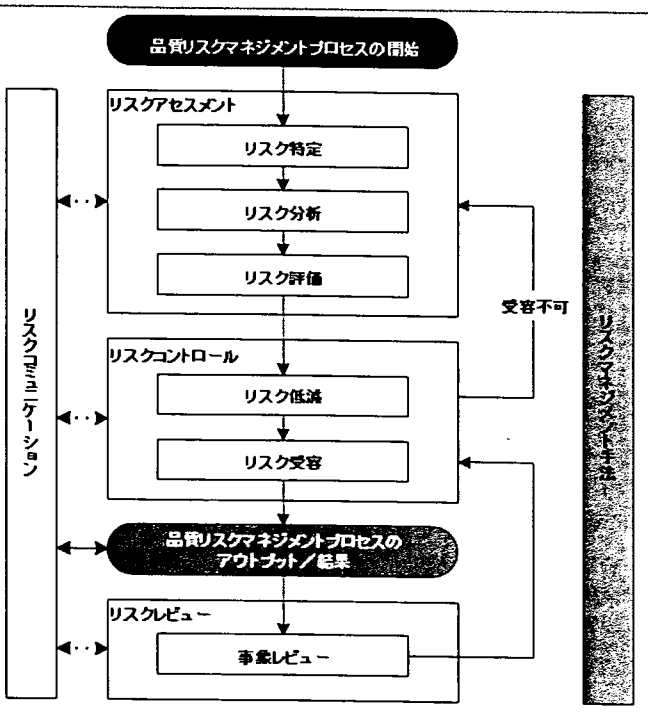
危害（harm）
（疾病など）

リスク（risk）
（危害の発生する可能性と重大性）

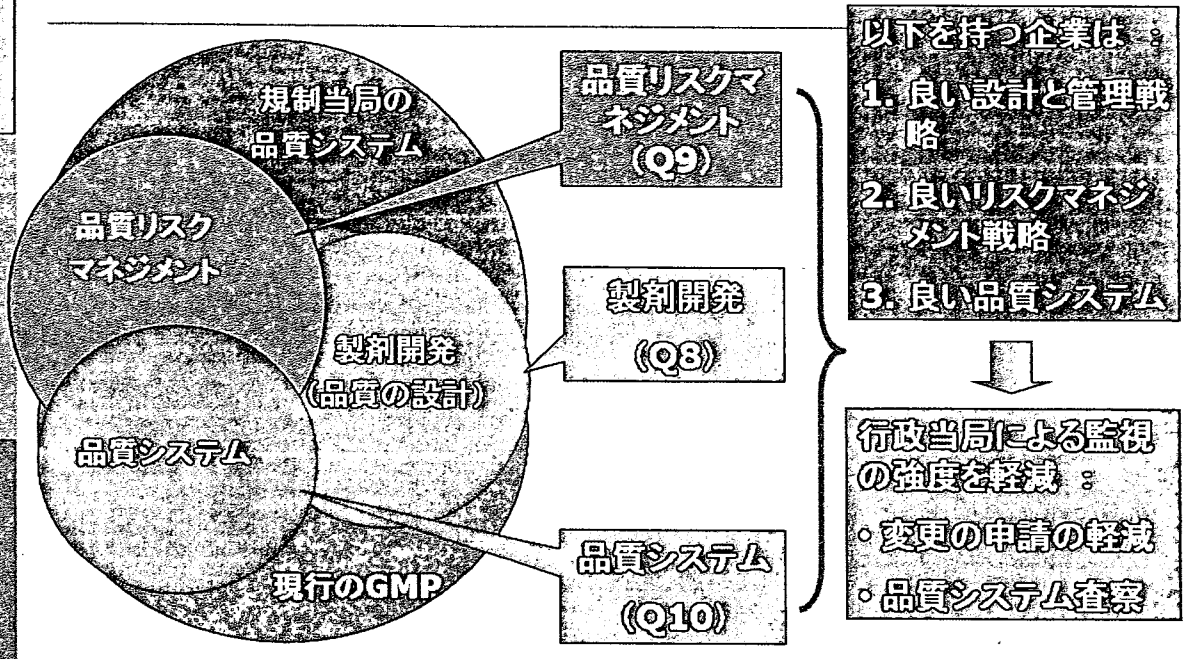
リスクマネジメント



一般的なQRMのプロセス



将来の医薬品の品質システム（企業のビジョン）



QRMで何を先ず実施するか？

既存の品質システムに品質リスクマネジメントを統合するよう推進すること

- 独立した部署を設置しないこと
- 実践のコーディネートと資源配置
- 優先； 小さなところから開始し、行うに従って学ぶこと