5. 用語 (3): ISO-9000に基づくICH Q10定義

- 医薬品品質システム： 品質に関して製薬企業を指揮し管理するマネジメントシステム。⇒ICH Q10で一般的に製薬企業において管理される品質システムを言う場合に用いている。ICH Q10の文書そのものを指す場合は、ICH Q10または本ガイドラインと呼ぶ。
- 上級経営陣： 企業又は製造サイトを最高レベルで指揮及び管理する人（々）。⇒ISO9000-2005でいうトップマネジメントに相当するが、企業規模や人数等に対応できる訳語とした。社長、品質保証担当役員、工場長、総括製造販売責任者等を指す。品質システムを適用する組織や企業組織体系により、個々の企業が定義する。

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5. 用語 (4): ICH Q10の定義

- 変更マネジメント： 変更を提案、評価、承認、実施及びレビューする体系的アプローチ。⇒GMPでいう“変更管理”より広い概念で用いられる。個別の変更のみを指すのではなく変更全体の管理。
- 達成のための手法 (Enabler)： 目標を達成するための手段を提供するツール又はプロセス。⇒1.6章に規定されている。“製品知識管理”と“品質リスクマネジメント”。
- 外部委託活動 (Outsourced Activities)： 委託者との契約下において、受託者により実行される活動。⇒GMP上の委託製造より広い概念。
- 製品実現 (Product Realisation)： 患者、医療従事者、規制当局（販売承認の遵守を含む）及び内部顧客のニーズを満たす適切な品質特性を有する製品の達成。 ⇒1.5章に規定されている。
- 品質目標 (Quality Objectives)： 品質方針及び戦略を測定可能な活動に変えるための手段。 ⇒達成できたかどうか測定可能な、具体的なターゲットを示したもの。通常、各レビュー期毎に見直す。
- 管理されている状態 (State of Control): 管理の組み合わせが継続するプロセス稼動性能および製品品質について恒常的な保証を提供する状態⇒“管理されている状態”を確立し、維持することが重要。

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5. 用語 (5): ICH Q8, ICH Q9によるもの

ICH Q8によるもの

- デザインスペース： 品質を確保することが立証されている入力変数（原料の性質など）と工程パラメータの多元的な組み合わせと相互作用。

ICH Q9によるもの

- 品質： 製品、システム、又は工程に係る本質的性質の組み合わせが要求事項を満たす程度。
- 品質リスクマネジメント： 製品ライフサイクルを通じて、医薬品の品質に係るリスクについてのアセスメント、コントロール、コミュニケーション、レビューからなる系統だったプロセス。

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別表1 科学及びリスクに基づく薬事的アプローチに対して今後見込まれる機会

- 規制のプロセスを増強する今後見込まれる機会。
- 実際の規制のプロセスは各極で決定される。

場面	今後見込まれる機会
1.GMPとの適合	遵守— 現状維持
2., 3., 4. ICH Q8,Q9,Q10の組み合わせ	薬事的アプローチに関する機会が増大する（次のｽﾗｲﾄﾞに記載）

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別表 1

Q9＋Q10	Q8＋Q9	Q8＋Q9＋Q10
•当局の査察についてリスクベースの取り組みの使用を増大する	•科学に基づく医薬品の品質評価の促進 •プロセスバリデーションへの革新的取り組みを可能とする •リアルタイムリリースの仕組みの確立	•当局の査察についてリスクベースの取り組みの使用を増大する •科学に基づく医薬品の品質評価の促進 •科学およびリスクベースの承認後変更プロセスを最適化し、イノベーション及び継続的改善の利点を最大化 •プロセスバリデーションへの革新的取り組みを可能とする •リアルタイムリリースの仕組みの確立

53

ISO 9001 (2000)

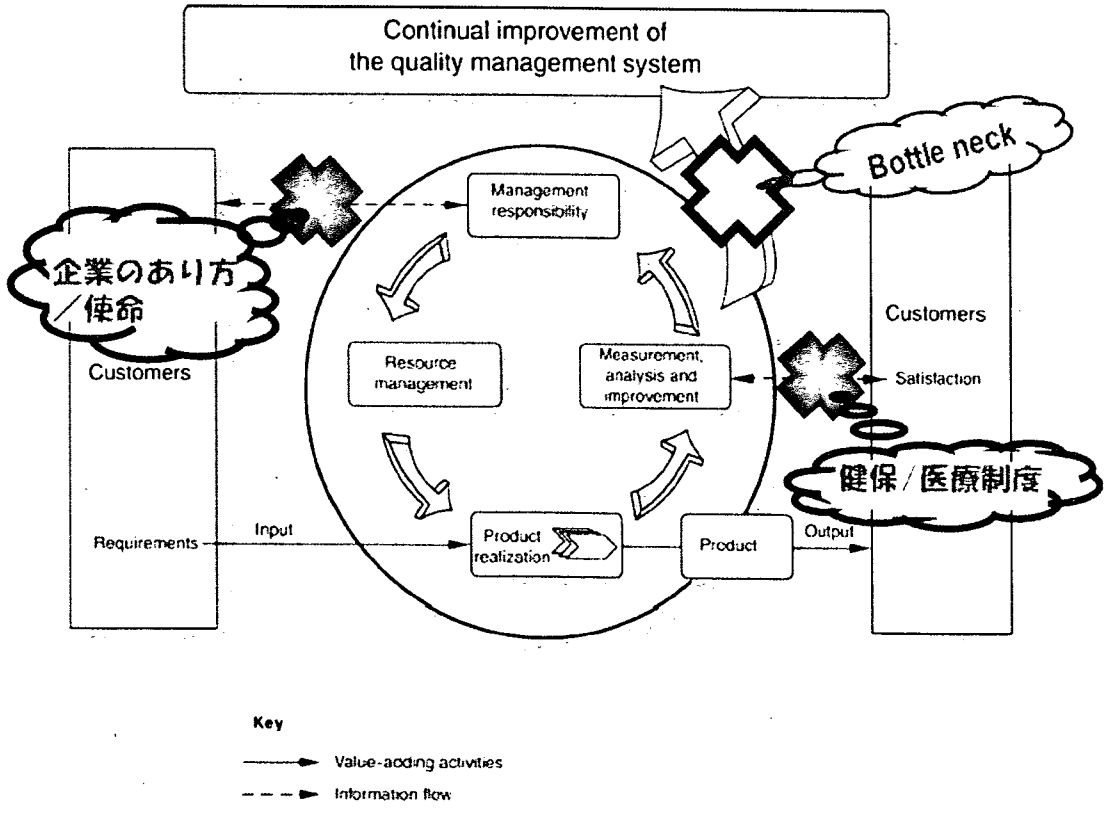

Figure 1 — Model of a process-based quality management system

日本企業の体質

希薄な社会的ミッション

顧客の軽視（医師の介在）

未成熟な株主との関係（村上ファンド）

自律性/自浄作用の欠如（類似事案の頻発）

拝金主義（勝ち組 v.s.負け組み）

モラルハザードの可能性（団塊世代、非正社員化）

55

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of QRM, and the effectiveness of the PQS. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1.

Regulatory processes will be determined by region.

業界：ＰＱＳのデモンストレーション
当局：ＰＱＳレベルの確認/評価

結果としての薬事規制への適用範囲および程度は当局の専管事項

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Q10の意味

組織内に対するGovernanceの改善、および組織外に対するAccountabilityの強化という利点について、適正に総合的な認識が必要。

Optionalなので実施しないと何も得られない。

年次レビューおよび**CAPA**と連動した Management Review の実効性が今後の鍵。

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Q10への期待

- Q10に記述されたモデルを使い、現存のシステムを評価し、その改善に役立ててほしい
- 特に注目して欲しいところ
  マネジメントレビュー
  製品知識管理

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展望

- 短期的なニーズ

「科学とリスクマネジメント」に基づいた品質システムーすでにQ8(製剤)およびQ9は発効しているが、原薬のプロセス開発のガイドラインが必要

- 中期　長期

薬事法改正により欧米制度とcomparableとなり、日本の審査・査察が注目される。一方、新制度の「現実」が認識されはじめた。

さらなる国際調和の機会が認識されつつある。

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- ICH Q10今後の予定
- 1. 『「ICH Q10:医薬品品質システム」に関するご意見・情報の募集について』を平成19年7月13日に通知
- 2. 平成19年10月1日パブリックコメント締め切り
- 3. パブリックコメント締め切り後、
- ①ICH専門家会議へ持って返るべき意見・論点
- ②日本国内での課題
- ③翻訳の問題
- をMHLWとJPMAで整理
- 4. ①を平成19年末頃めどにICH専門家会議に報告
- 5. 他の極からの課題がそろったところで、3極がそれらに対する対応を提案し、平成20年2～4月ごろに電話会議を開催
- 6. 平成20年5～6月ごろのアメリカにおけるICH専門家会議でSTEP4を目指す
- 7. 平成20年秋ごろ、ガイドラインの翻訳を完成させ、パブリックコメントに対する回答も併せて国内通知をする。

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Part of APEC Life Sciences Innovation Forum Projects

DRAFT PROGRAM
APEC LSIF

First ICH Quality Guidelines Q8, Q9, Q10 Seminar

Opportunities and Challenges Related to Implementation

September 13-14, 2007

Seoul, Korea
COEX Conference Center

DRAFT: September 3

Day Zero

Wednesday, September 12, 2007	
6:30 – 8:30	Registration and Opening Night Reception • Participate in BioKorea 2007 Reception for all the Participants of BioKorea 2007

Day One

Thursday, September 13, 2007	
9:00 – 10:00	Registration and Check-In
10:00 – 10:30	Welcome and Opening Remarks • **Dr. Yong Heung Rhie,** President, Korea Health Institute Development Institute • **Dr. Kyeong Ho Lee,** President of Inje University, APEC LSIF Leadership (Korea) • **Dr. Pakdee Pothisiri,** Commissioner of the National Counter Corruption Commission, Former Secretary General of the Food and Drug Administration, Thailand, APEC LSIF Leadership (Thailand)
10:30 – 11:30	**Session I: Introduction to ICH Quality Guidelines and Link to GMP** ***Description:*** All drug manufacturers within the ICH regions are expected to adhere to current good manufacturing practices (cGMPs). While each of the three regulatory authorities within the ICH regions have similar cGMP requirements, there are some differences in both approaches to inspections and implementation of cGMPs. The ICH quality guidelines are intended to augment cGMP requirements for many aspects of both drug development and manufacturing models. The earlier quality guidelines focused on specific quality aspects of drug substances and products, whereas the latter guidelines -- specifically ICH Q8-Q10 -- taken together, address new models of drug development and quality assurance. ***Moderator:*** • **Dr. Mark Paxton,** Associate VP, International Regulatory Affairs, PhRMA (United States) **Part A: Role of ICH Quality Guidance Documents In Advancing Life Sciences in the APEC Region** ***Speaker:*** • **Mr. Mike Ward,** Manager International Programs Division, Therapeutic Programs Directorate, Health Canada (Canada) **Part B: Linking ICH Quality Guidelines to GMP**

	Speakers: ▪ **Dr. Dong sup Kim,** Director of Drug Evaluation Department, Korea Food and Drug Administration (Korea) ▪ **Dr. Tony Webber,** President of Management Committee, Queensland Clinical Trial Network, Professor Emeritus, Queensland University of Technology (Australia) **Part C: Question & Answer Session with the panelists**
11:30 – 1:30	**Lunch Break**
1:30 – 3:00	**Session II : Challenges and Opportunities of ICH Q8** ***Description:*** The Pharmaceutical Development section as detailed in ICH Q8 provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. ICH Q8 also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided. ***Moderator:*** ▪ **Dr. Jianhua Ding,** Director, Pharmaceutical Division, Department of Drug Registration, State Food and Drug Administration (China) **Part A: A Regulatory Perspective** ***Speaker:*** ▪ **Dr. Susanne Keitel,** Head of Pharmaceutical Quality Division, Federal Institute for Drugs and Medical Devices (Germany) **Part B: An Industry Perspective** ***Speaker:*** ▪ **Dr. Paul Stott,** Associate Director, Research and Technology, Product Development, AstraZeneca (United States) **Part C: Question & Answer Session with the panelists**
3:00 – 3:30	**Refreshment Break**

3:30-5:00	**Session III: Challenges and Opportunities for ICH Q9** ***Description:*** The manufacturing and use of a drug product, including its components, necessarily entails some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product quality should be maintained throughout the product lifecycle such that the attributes that are important to the quality of the drug product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. In addition, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight. The purpose of ICH Q9 is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, by both regulators and industry, regarding the quality of drug substances and drug products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements. ***Moderator:*** ▪ **Dr. Yuppadee Javroongrit,** Drug Control Division, Food and Drug Administration, Ministry of Public Health (Thailand) **Part A: A Regulatory Perspective** ***Speaker:*** ▪ **Dr. Jacques Morenas,** Assistant Director, French Agency for the Safety of Health Products (AFSSAPS) & Chairman of PIC/S,(France) **Part B: An Industry Perspective** ***Speaker:*** ▪ **Dr. Thomas Schultz,** Director, Regulatory Sciences, Johnson & Johnson (United States) **Part C: Question & Answer Session with the panelists**
6:00 – 8:00	**Networking Reception/Dinner** **Carnation Room, Grand Intercontinental Hotel**

DRAFT: September 3

Day Two

Friday, September 14	
10:00 – 11:00	**Session IV: Pharmaceutical Quality Systems for ICH Q10** ***Description:*** ICH Q10 establishes a new ICH tripartite guideline describing a model for an effective quality management system for the pharmaceutical industry, referred to as the Pharmaceutical Quality System. ICH Q10 describes one comprehensive approach to an effective pharmaceutical quality system that is based on ISO concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current GMP requirements is optional. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model. ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate innovation and continual improvement and strengthen the link between pharmaceutical development and manufacturing activities. ***Moderator:*** ▪ **Dr. Mark Paxton,** Associate VP, International Regulatory Affairs (United States) **Part A: A Regulatory Perspective** ***Speakers:*** ▪ **Dr. Yukio Hiyama,** Chief, Third Section Division of Drugs, National Institute of Health Sciences (Japan) ▪ **Dr. Ian Thrussell,** Senior Medicines Inspector, Medicine Control Agency (United Kingdom)
11:00 – 11:30	**Refreshment Break**
11:30 – 12:30	**Part C: An Industry Perspective** ***Speakers:*** ▪ **Dr. Mark Paxton,** Associate VP, International Regulatory Affairs (United States)

DRAFT: September 3

	Part D: Question & Answer Session with the panelists
12:30 – 2:00	**Lunch Break**
2:00 – 3:30	**Session V: Developing and Regulating Biotech Products in a "Risk-Based Environment"** ***Description:*** Many biotechnologically derived products represent new risks to patients that are quite different from those associated with products made with synthesized small molecules. Although the probabilities associated with the occurrence of adverse events are often still being estimated, the severity of many of these events can be substantial when compared to small molecule drugs. Moreover, many of the large molecule substances derived from biotechnology processes have inherently greater variability in structure, and in some cases, composition. Thus, while the principles outlined in ICH Q8-Q10 are equally applicable to these unique products, the character and measures used to estimate risk and subsequently, quality assurance, can be quite different. This session is intended to provide an overview of some of the challenges associated with applying the quality guidelines to biotech products. ***Moderator:*** ▪ **Dr. Stephen W. Cook**, Vice President Regulatory Affairs, Asia Pacific, GlaxoSmithKline Pte Ltd (Singapore) **Part A: A Regulatory Perspective** ***Speakers:*** ▪ **Dr. Blair Fraser,** Director, Food and Drug Administration (United States) **Part B : An Industry perspective** ▪ **Dr. Elaine Esber**, Executive Director, Vaccine Division, Merck (United States) **Part C : Question & Answer Session with the panelists**
3:30 – 4:00	**Concluding Comments and Adjournment**
3:30-4:00	▪ **Mr. Mike Ward,** Manager, International Programs, Therapeutic Products Directorate, Health Canada (Canada) ▪ **Dr. Kyung Won Jang**, Senior Researcher, Head of trade and international cooperation Team, Department of Drug Industry Promotion, Korea Health Industry Development Institute (Korea)

ICH Harmonisation and Japanese Pharmaceutical Regulations

APEC LSIF ICH Quality Guidelines Q8 and Q9
Challenges of Implementations
COEX, Seoul, September 13-14, 2007

Yukio Hiyama
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1

Presentation Outline

- Pharmaceutical Affairs Law (PAL) changes, ICH discussion and MHLW studies
- Quality Regulations under the Revised Pharmaceutical Affairs Law
- Commitment of Manufacturing Process as Approval Matters and Role of ICH Q8, Q9 and Q10

2

The 2003 ICH Quality Vision

Industry parties and regulatory authorities of the ICH Quality met in Brussels in July 2003 and agreed on the ICH Quality vision "A harmonised pharmaceutical quality system applicable across the lifecycle of the product emphasizing an integrated approach to risk management and science".

In order to develop a modern pharmaceutical quality system, discussions on two topics, 1) Pharmaceutical Development (Q8) and 2) Quality Risk Management (Q9) started. The guidelines on the two topics were published in 2006 in the three ICH regions.

(Pharmaceutical Quality System (Q10) reached step 2 in May, 2007.)

3

MHLW slide at 2003 workshop 14/15

Expected Outcome

For Industry

- Establishment of quality management system from development to post-marketing

For regulatory authority

- Improvement of the approval review system by integration of the review and the GMP inspection
- To concentrate on higher risk products
- The establishment of effective, efficient, and streamlined quality regulation

4

From MHLW slides at 2003 Work Shop

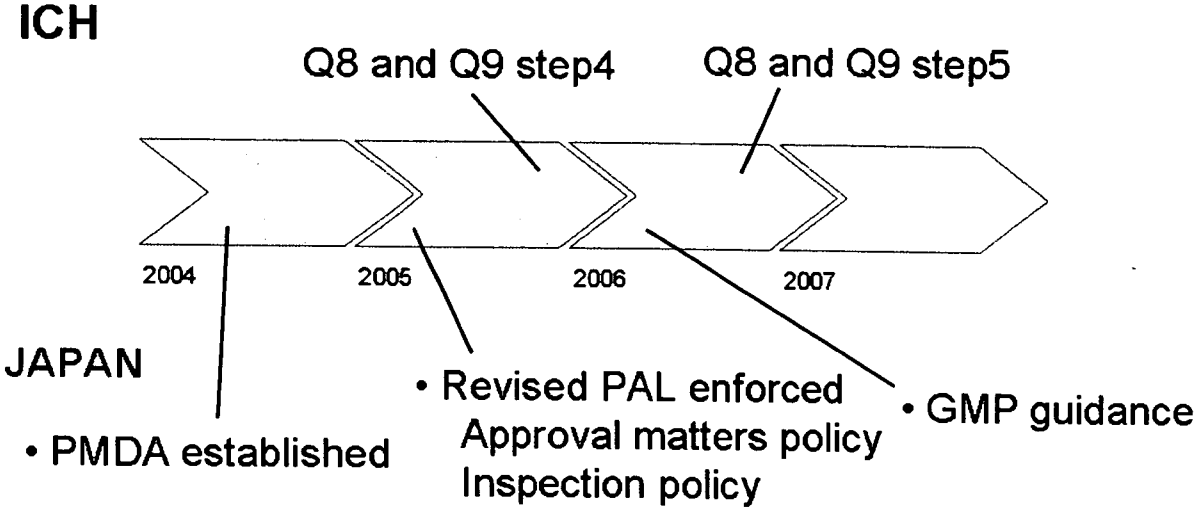
MHLW's Expectation to ICH

Comprehensive approach for quality management

- Throughout the product life cycle
  - From development to post-marketing
- Includes;
  - Risk management
  - Technology transfer
  - Change control, etc.

5

ICH and Quality regulation in Japan



6

Pharmaceutical Affairs Law(PAL), ICH Q8/Q9/Q10 and MHLW Grant **Regulatory Science** Studies

PAL regulation changes	ICH discussion	Regulatory science groups
2002	**2002**	**2002**
Revised PAL published	CTD Q&A	QS/GMP guidance
	2003	**2003** CTD mock
2004	GMP workshop in Brussels	Approval matters
PMDA established	Q8 and Q9 started	Inspection Policy
New GMP standards	**2004**	**2004**
2005	Q8 reached step 2	Approval matters
Approval matters policy	**2005**	GMP guidelines
Revised PAL enforced	Q9 reached step 2	**2005** Inspection Policy
Inspection policy published	Q8 and Q9 reached step4	Skip Test guidance
2006	Q10 started	Inspection Checklist
Product GMP guidance	**2007**	**2006-2008**
	Q10 reached step 2	P2 /application mock
		Change management system

Revision of the Pharmaceutical Affairs Regulation (effective April 2005)

- ***Revision of the Approval and Licensing System***

  = From Manufacturing (or Importation) Approval/License to Marketing Authorization

- ***Enhancement of Post-marketing Measures***

  = To clarify the Market Authorization Holder's (MAH) responsibility of the safety measures as well as quality management (GVP, GQP)

8

Revision of the Quality Regulation

1. **MAH's* responsibility for the Quality management** * Marketing Authorization Holder
2. **Requirement Changes in Approval Matters**
3. Drug Master File system to support CTD based application
4. **Consolidation of the Legal Positioning of GMP**
5. Revision and Consolidation of GMP standards

---

6. Establishment of Pharmaceuticals and Medical Devices Agency (PMDA)

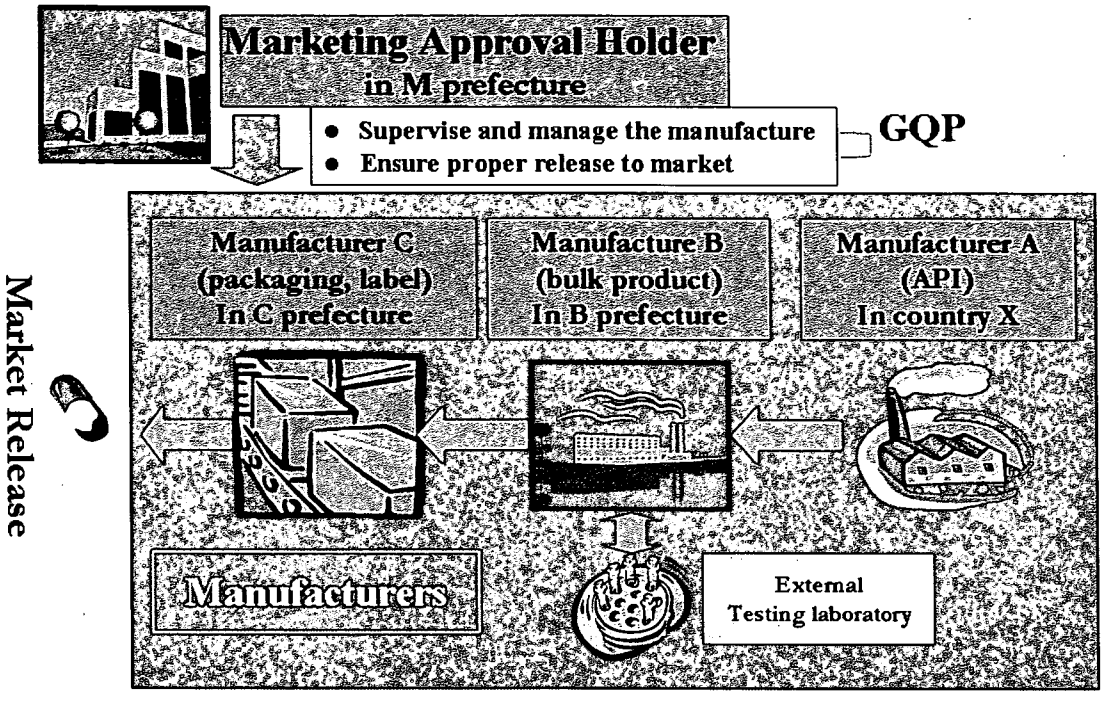
9

1. MAH's responsibility for quality management (GQP)

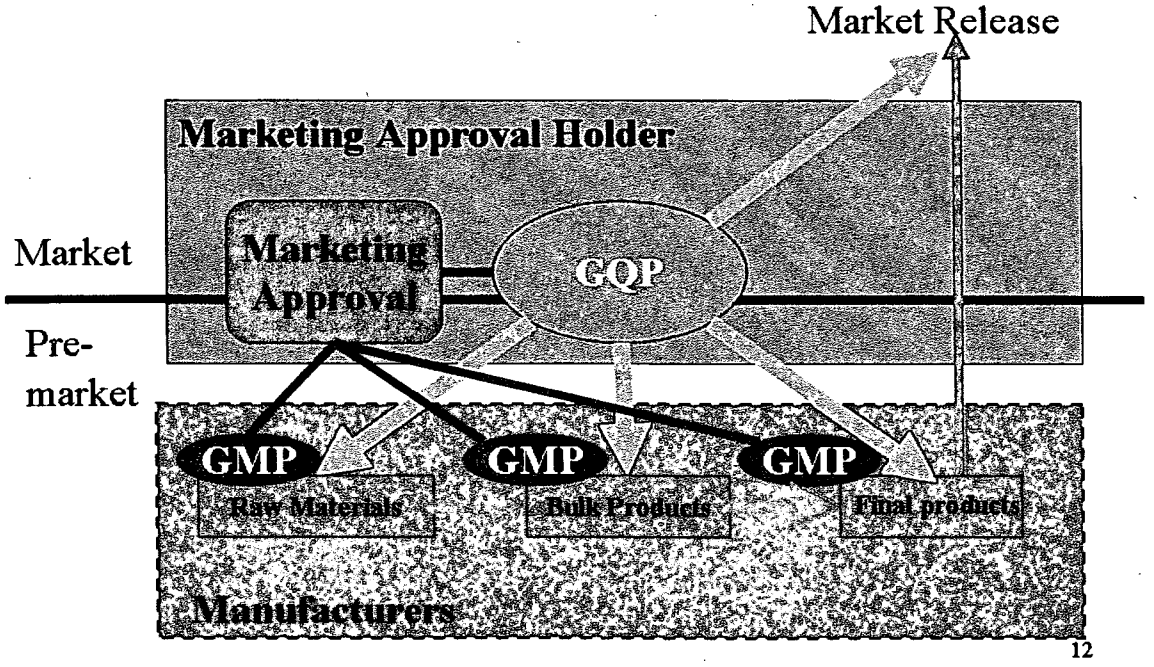
- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.

10

Marketing and Manufacturing



Good Quality Practice (GQP)



2. Manufacturing Process Commitment Application Form and Approval Matters- A Unique System

- 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.

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Approval Matters

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

14

Approval Matters Policy

Notification from Director of Review Management, 0210001
February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale will become approval matters. Principle and quality end point for each manufacturing step will be subject to pre-approval review.
- In-process procedure is pre-approval matter if it replaces final specification test.

15

Approval Matters Policy (continued)

- A pilot scale manufacturing processes may be submitted at Application.
- The commercial scale processes will be subject to Pre-approval GMP inspection and the commercial scale must be described in the approval.
- Pre-approval vs. notification classification may be determined through the review process

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