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4 Pharmaceutical Quality System

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Q01: What are the benefits of implementing a Pharmaceutical Quality System (in accordance with ICH Q10)?

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The benefits are:

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- Improved robustness of the manufacturing process, through facilitation of continual improvement through science and risk-based post approval change processes

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- Consistency in the global pharmaceutical environment across regions

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- Enable transparency of systems, processes, organisational and management responsibility

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- Clearer understanding of the application of a Quality System throughout product lifecycle

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- Greater assurance of consistent supply of pharmaceutical product to the patient

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- Opportunity to increase trust between industry and regulators and more optimal use of industry and regulatory resources.

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Q02: How does a company demonstrate implementation of PQS in accordance with ICH Q10?

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A company will demonstrate the use of an effective PQS through its documentation (e.g. policies, standards), its processes, its training / qualification, its management and its performance against pre-defined Performance Indicators [see ICH Q10 glossary on 'Performance indicator'].

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A mechanism should be established to demonstrate at a site how the PQS operates across the product lifecycle, in an easily understandable way for management, staff and regulatory inspectors, e.g. a quality manual, documentation, flowcharts, procedures. This can be enabled by knowledge management.

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Q03: What information and documentation of the development studies should be available at a manufacturing site?

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Scientific collaboration and knowledge sharing between pharmaceutical development and manufacturing is essential to ensure the successful transfer to production.

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Sufficient pharmaceutical development information (e.g. supporting information on design space, chemometric model, risk assessment) should be available at the manufacturing site to ensure the understanding of the basis for the manufacturing process and control strategy, including the rationale for selection of critical process parameters and critical quality attributes. This can be enabled by knowledge management.

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Q04: How is adherence to ICH Q10 in the product lifecycle assessed?

Aspects of a company's quality system can be evaluated at any point of the product life cycle via internal and external audits. Regulatory inspections will normally assess the PQS at the manufacturing site. However in the event that specific development information in relation to an application for an marketing authorisation raises issues that cannot be addressed through such an inspection it may occasionally be necessary to evaluate this at the development site. This does not preclude any regional requirements for site inspections.

- 319 **Q05: Is it necessary to describe the PQS in a regulatory submission?**
320 No, however relevant elements of the PQS, such as change control and
321 deviation management may be described as part of the control strategy as
322 supporting information.
- 323 **Q06: Will there be ICH Q10 certification?**
324 There will not be a specific ICH Q10 inspection and certification
325 programme.
- 326 **Q07: How should the implementation of the design space be evaluated**
327 **during inspection of the manufacturing site?**
328 Inspection should verify that manufacturing operations are carried out
329 within the Design Space. The inspector in collaboration with the assessor
330 where appropriate should also verify successful manufacturing operations
331 under the Design Space and that movement within the Design Space is
332 managed within the company's change management system [see ICH Q10,
333 chapter 3.2.3b].
- 334 **Q08: What should be done if manufacturing operations run inadvertently**
335 **outside of the Design Space?**
336 This should be handled as a deviation under GMP. For example
337 unplanned 'one-off' excursions occurring as a result of unexpected events,
338 such as operator error or equipment failure, would be investigated,
339 documented and dealt with as a deviation in the usual way. The results of
340 the investigation may contribute to the process knowledge.
- 341 **Q09: Who should review and approve the Design Space?**
342 The Design Space is proposed by the applicant and is reviewed and
343 approved by the regulatory agency assessor [ICH Q8, chapter 2].
344 Information from the assessment of the design space can be shared with
345 the inspectors to facilitate verification of its implementation at the
346 manufacturing site.
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- 348 **5 ICH new quality guidelines impact on GMP inspection**
349 **practices**
- 350 **Q01: How will product related inspections differ in an ICH Q8, Q9 and**
351 **Q10 environment?**
352 In the case of product related inspection (in particular pre-authorisation)
353 depending on the complexity of the product and/or process there could be
354 a need for greater collaboration between inspectors and assessors for
355 example for the assessment of development data. The inspection would
356 normally occur at the proposed commercial manufacturing site and there
357 is likely to be greater focus on CQAs and CPPs.
- 358 **Q02: How will system related inspections differ in an ICH Q8, Q9 and Q10**
359 **environment?**
360 The inspection process will remain the same. However upon the
361 implementation of ICH Q8, Q9 and Q10 inspections will have greater
362 focus on how the PQS facilitates the use of e.g. Quality Risk Management
363 methods, implementation of design space and change management [see
364 ICH Q10, annex 1].
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6 Software solutions

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Q01: With the rapid growth of the new science and risk based quality paradigm coupled with the IWG efforts to facilitate globally consistent implementation of Q8, Q9, and Q10, a number of commercial vendors are now offering products that are being marketed as 'ICH compliant solutions' or ICH Q8, 9 & 10 Implementation software, etc. Is it necessary for a pharmaceutical firm to purchase these products to achieve a successful implementation of these ICH guidelines within their companies?

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No. The ICH Implementation Working Group has not endorsed any commercial products and does not intend to do so. ICH is not a regulatory agency with reviewing authority and thus does not have a role in determining or defining 'ICH compliance' for any commercial products. While there will likely be a continuous proliferation of new products targeting the implementation of these ICH guidelines, firms will need to carry out their own evaluation of these products relative to their business needs

平成 20 年 12 月 1 日

関係 各位

ICH Quality Implementation Working Group
厚生労働省代表委員
日本製薬工業協会代表委員

「ICH Q8、Q9 及び Q10 ガイドラインの運用に関する質疑応答集（案）」に関する
ご意見の募集について

関係の皆様方におかれましては、日頃より、日米 EU 医薬品規制調和国際会議（ICH）の活動にご理解とご協力を賜り、誠にありがとうございます。

ICH では、平成 17 年以降、Q8：製剤開発、Q9：品質リスクマネジメント、Q10：医薬品品質システム、の各ガイドラインが採択され、また、先般のブリュッセル会議（11 月 8 日～13 日）では、Q8（R1）：製剤開発ガイドライン付属書が運営委員会において承認されました。さらに、これらのガイドラインを適切に運用するための明確でより詳細な説明を提供することを目的として Quality Implementation Working Group on Q8, Q9 & Q10（Q-IWG）が設立され、現在、種々の活動を計画し、順次実施しているところです。

今般、Q-IWG では標記の質疑応答集（Q&A）（案）を作成し、関係の皆様より広くご意見を募集することとなりました。つきましては、本案に関してご意見いただけます場合には、下記によりご提出くださいますようお願いいたします。皆様からいただいたご意見については、今後の活動における参考とさせていただきます。なお、ご提出いただいたご意見に対する個別の回答はいたしかねますので、その旨ご了承願います。

記

1. 募集期限

平成 21 年 1 月 12 日（月）必着 （翌日以降は受け付けいたしません）

2. 提出方法

添付の回答様式（電子ファイル）にご意見、変更案等をご記入の上、電子メールにファイルを添付して、『Q-Trio Q&A 意見』の件名で、以下の電子メ

ールアドレス宛にご提出ください。ファクシミリ、郵送及びお電話によるお問い合わせ又はご意見のご提出はお受けできかねますので、あらかじめご了承ください。

電子メールアドレス： Q-IWG@pmda.go.jp

3. ご意見をご提出いただくにあたって

ご意見は、以下の3つの分類に従い、Q&A案の該当箇所を明記してご記入ください。また、それぞれのご意見・ご提案の重要度をC（重要）又はM（軽微）に区別して該当欄に記入してください。さらに、ご意見・ご提案の背景又は参考となる情報についてもご記入いただければ幸いです。なお、本Q&A（案）は、Q8、Q9、Q10ガイドラインにより導入された新たな概念の理解を促進し、即時実践することを目的として作成されるものであり、当該ガイドラインの改訂や追加の概念の導入を意図したものではありません。

● 記載整備に関すること

Q&A案で誤記や表現の間違い等があれば、ご指摘ください。変更案も併せてご記入ください。

● Q&A案に対するご意見

Q&A案について、わかりにくい点や補足すべき点があれば、ご指摘ください。改善案も併せてご提案ください。

● 追加のQ&Aのご要望

追加で記載すべきQ&Aがあれば、ご要望の理由とQ&Aの例をご提案ください。

ご意見等は日本語又は英語のいずれでご記入いただいても結構です。個人の場合は氏名・所属を、団体・法人の場合は団体名又は法人名を記載してください。なお、個人又は団体・法人の属性（名称を含む）に関する情報以外は公開することもありますので、あらかじめご了承ください。

以上

**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 <ul style="list-style-type: none"> ▪ 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 <ul style="list-style-type: none"> ▪ 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	<p>Session I: Introduction to ICH Quality Guidelines and Link to GMP</p> <p>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.</p> <p>Moderator:</p> <ul style="list-style-type: none"> ▪ Dr. Mark Paxton, Associate VP, International Regulatory Affairs, PhRMA (United States) <p>Part A: Role of ICH Quality Guidance Documents In Advancing Life Sciences in the APEC Region</p> <p>Speaker:</p> <ul style="list-style-type: none"> ▪ Mr. Mike Ward, Manager International Programs Division, Therapeutic Programs Directorate, Health Canada (Canada) <p>Part B: Linking ICH Quality Guidelines to GMP</p>

DRAFT: September 3

	<p>Speakers:</p> <ul style="list-style-type: none"> ▪ 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) <p>Part C: Question & Answer Session with the panelists</p>
11:30 – 1:30	Lunch Break
1:30 – 3:00	<p>Session II : Challenges and Opportunities of ICH Q8</p> <p>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.</p> <p>Moderator:</p> <ul style="list-style-type: none"> ▪ Dr. Jianhua Ding, Director, Pharmaceutical Division, Department of Drug Registration, State Food and Drug Administration (China) <p>Part A: A Regulatory Perspective</p> <p>Speaker:</p> <ul style="list-style-type: none"> ▪ Dr. Susanne Keitel, Head of Pharmaceutical Quality Division, Federal Institute for Drugs and Medical Devices (Germany) <p>Part B: An Industry Perspective</p> <p>Speaker:</p> <ul style="list-style-type: none"> ▪ Dr. Paul Stott, Associate Director, Research and Technology, Product Development, AstraZeneca (United States) <p>Part C: Question & Answer Session with the panelists</p>
3:00 – 3:30	Refreshment Break

DRAFT: September 3

3:30-5:00	<p>Session III: Challenges and Opportunities for ICH Q9</p> <p>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.</p> <p>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.</p> <p>Moderator:</p> <ul style="list-style-type: none"> ▪ Dr. Yuppadee Javroongrit, Drug Control Division, Food and Drug Administration, Ministry of Public Health (Thailand) <p>Part A: A Regulatory Perspective</p> <p>Speaker:</p> <ul style="list-style-type: none"> ▪ Dr. Jacques Morenas, Assistant Director, French Agency for the Safety of Health Products (AFSSAPS) & Chairman of PIC/S,(France) <p>Part B: An Industry Perspective</p> <p>Speaker:</p> <ul style="list-style-type: none"> ▪ Dr. Thomas Schultz, Director, Regulatory Sciences, Johnson & Johnson (United States) <p>Part C: Question & Answer Session with the panelists</p>
6:00 - 8:00	<p>Networking Reception/Dinner Carnation Room, Grand Intercontinental Hotel</p>

DRAFT: September 3

Day Two

Friday, September 14	
10:00 – 11:00	<p>Session IV: Pharmaceutical Quality Systems for ICH Q10</p> <p>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.</p> <p>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.</p> <p>Moderator:</p> <ul style="list-style-type: none"> ▪ Dr. Mark Paxton, Associate VP, International Regulatory Affairs (United States) <p>Part A: A Regulatory Perspective</p> <p>Speakers:</p> <ul style="list-style-type: none"> ▪ 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	<p>Part C: An Industry Perspective</p> <p>Speakers:</p> <ul style="list-style-type: none"> ▪ 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	<p>Session V: Developing and Regulating Biotech Products in a "Risk-Based Environment"</p> <p><i>Description:</i> 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.</p> <p>Moderator:</p> <ul style="list-style-type: none"> ▪ Dr. Stephen W. Cook, Vice President Regulatory Affairs, Asia Pacific, GlaxoSmithKline Pte Ltd (Singapore) <p>Part A: A Regulatory Perspective</p> <p>Speakers:</p> <ul style="list-style-type: none"> ▪ Dr. Blair Fraser, Director, Food and Drug Administration (United States) <p>Part B : An Industry perspective</p> <ul style="list-style-type: none"> ▪ Dr. Elaine Esber, Executive Director, Vaccine Division, Merck (United States) <p>Part C : Question & Answer Session with the panelists</p>
3:30 – 4:00	Concluding Comments and Adjournment
3:30-4:00	<ul style="list-style-type: none"> ▪ 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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National Institute of Health Sciences,
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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

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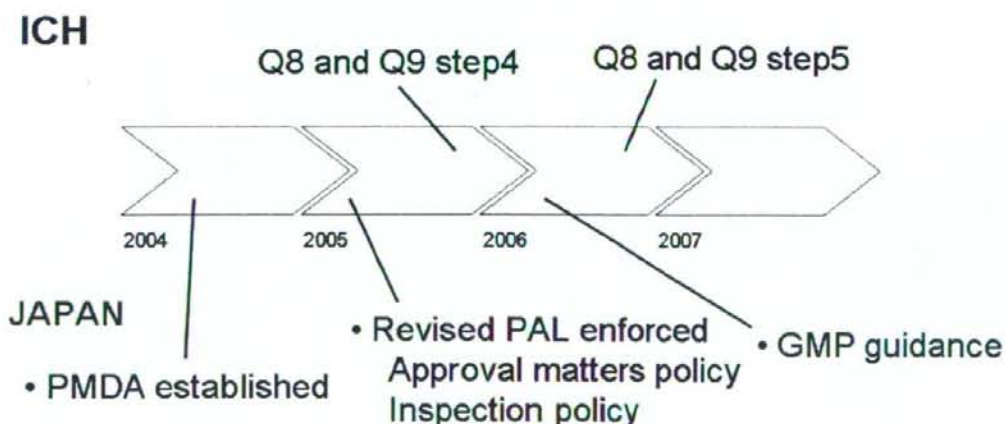
MHLW's Expectation to ICH

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

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 CD 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)

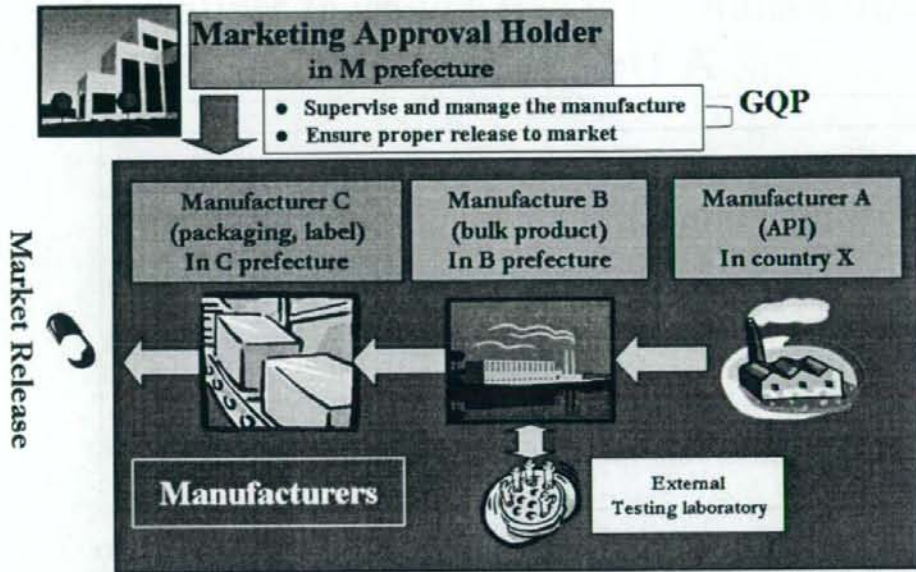
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1. MAH's responsibility for quality management (GQP)

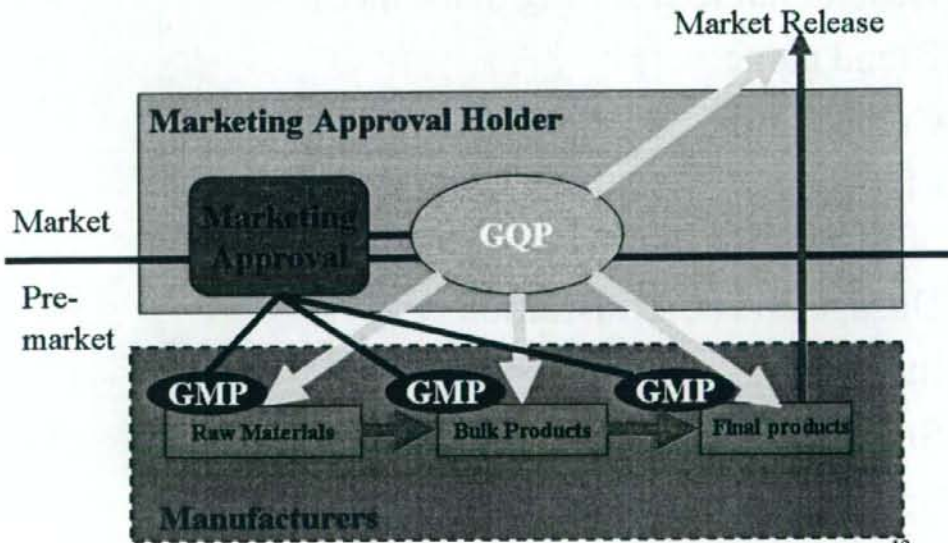
- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.

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.

13

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.

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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

16

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	

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Application Form after the Enforcement of Revised Pharmaceutical Affairs Law

