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ございません。

- 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 ▪ 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**

DRAFT: September 3

	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**

DRAFT: September 3

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
Chief, 3rd Section, Division of Drugs
National Institute of Health Sciences,
Ministry of Health, Labour and Welfare
JAPAN

E mail: hiyama@nihs.go.jp

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

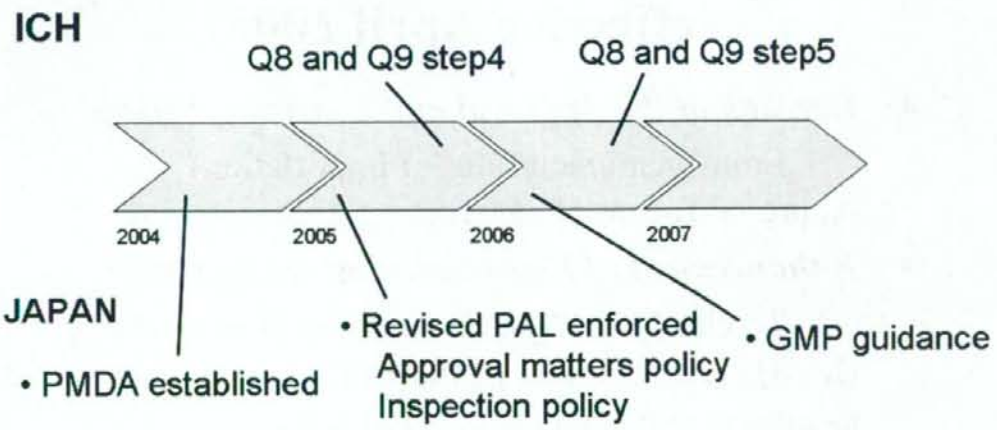
MHLW's Expectation to ICH

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)

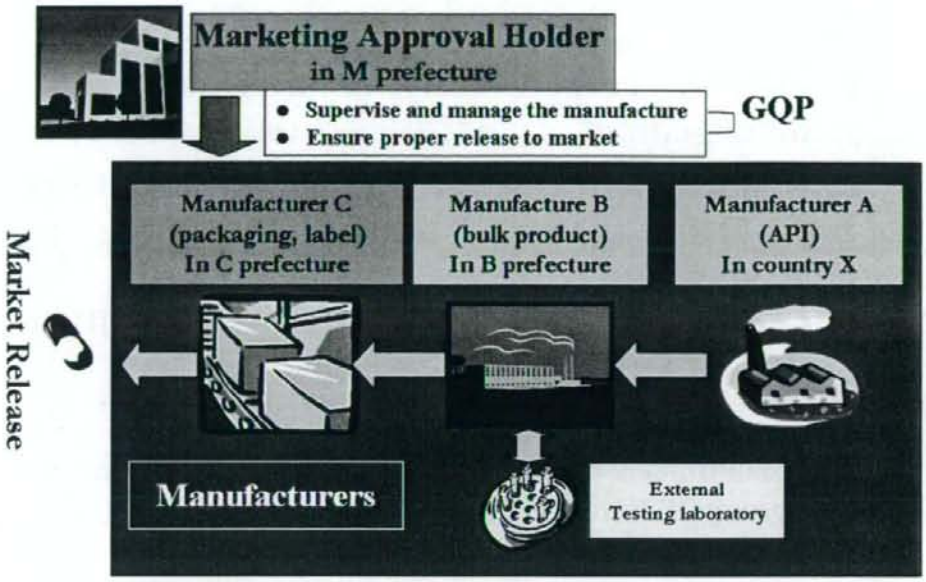
9

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

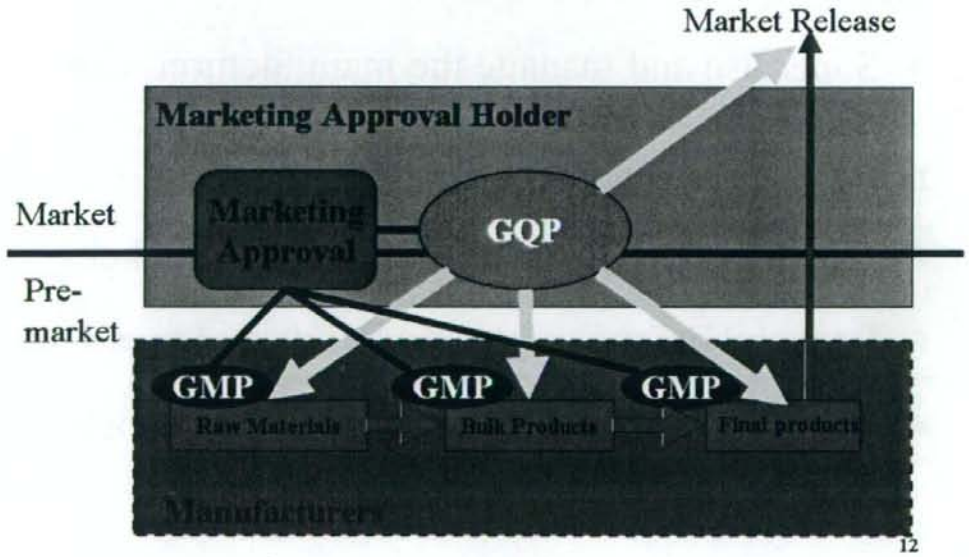
- Supervise and manage the manufacturer, and ensure the compliance with GMP of all manufacturing sites
- Ensure proper product release to the market
- Respond quickly with complaints and recall, etc.
- Conduct quality management based on post-marketing information, etc.

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.

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.

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

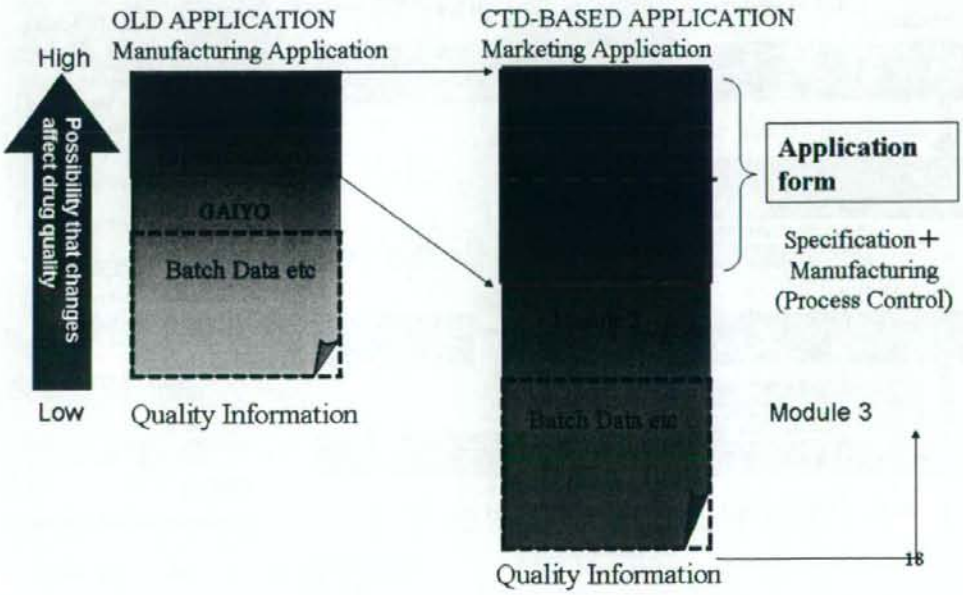
16

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	

17

Application Form after the Enforcement of Revised Pharmaceutical Affairs Law

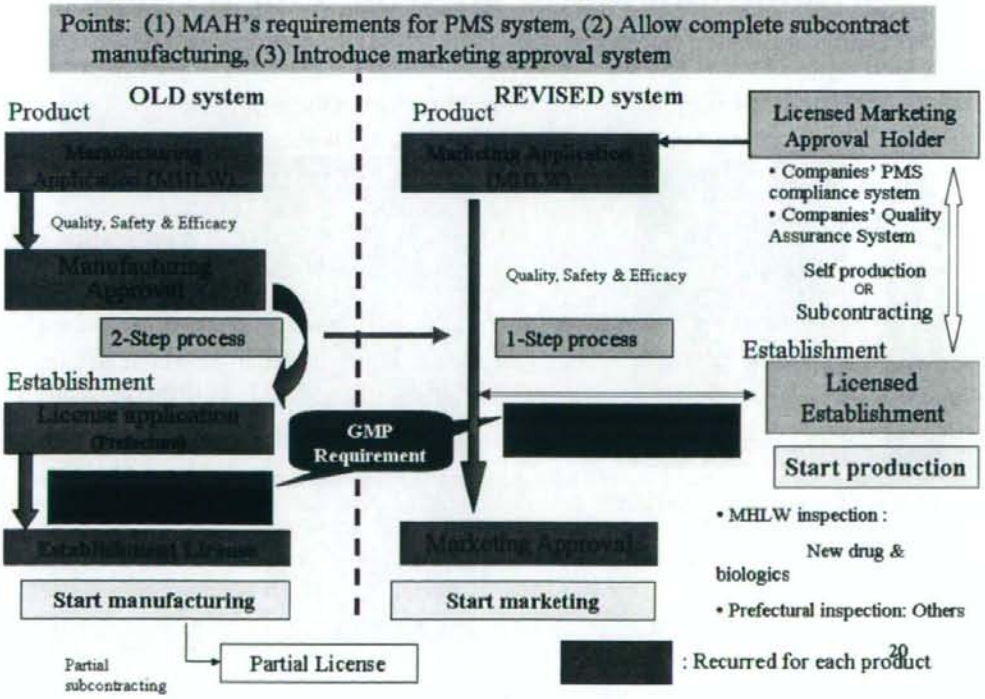


4. Consolidation of the Legal Positioning of GMP

- **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