Japanese Regulatory Workshop

September 26-27, 2007 | Washington, D.C.

AGENDA

Wednesday, September 26, 2007

1:30 p.m. – 2:40 p.m.

Opening Plenary Session

Moderator: Shigeru Hayashi, PhD; Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

1:30 p.m. – 1:40 p.m.
Welcome and Opening Comments
Robert L. Dana, Vice President, Quality and Regulatory Affairs, *PDA*

1:40 p.m. – 2:40 p.m.
Keynote Presentation
Yukio Hiyama, PhD, Chief, Third Section, Division of Drugs, *National Institute of Health Sciences*

2:40 p.m. – 3:00 p.m.
Break

3:00 p.m. – 4:30 p.m.

Plenary Session 2: Marketing Applications – Current and Future Thinking

Moderator: Speaker invited

This session will focus on the current and future state of applications for marketing new products under the Japanese Pharmaceutical Affairs Law, as well as how recent ICH Guidance might impact those submissions.

3:00 p.m. – 3:30 p.m.
Japanese Government Perspective
PDMA Speaker invited

3:30 p.m. – 4:00 p.m.
Industry Perspective – Quality by Design (QbD) Submission
Tom Garcia, Research Fellow, Regulatory CMC PharmSci, *Pfizer Global Reseach*

4:00 p.m. – 4:30 p.m.
Industry Perspective – Traditional Submission
Robert Fike, Vice President Global Regulatory Affairs Japans, *Wyeth Research*

4:30 p.m. – 4:50 p.m.
Panel Discussion and Q&A featuring afternoon speakers

4:50 p.m. – 5:00 p.m.
Closing Remarks
Moderator: Shigeru Hayashi, PhD, Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

Thursday, September 27, 2007

8:30 a.m.
Welcome and PDA Technical Report Briefing
Moderator: Robert Myers, President, *PDA*

8:30 a.m. – 10:00 a.m.
Plenary Session 3: GMP Inspections I
Moderator: Simon Golec, PhD, Senior Director, Women's Health, Global Regulatory Affairs, CMC, *Wyeth*

This session will provide an overview of the Japanese Pharmaceutical and Medical Device Agency's (PMDA) GMP inspection program.

8:30 a.m. – 9:15 a.m.
Overview of the PDMA GMP Inspection Program
Hirokazu Hasegawa, Director for GMP Inspection, Office of Compliance and Standards, *PDMA*

9:15 a.m. – 10:00 a.m.
GMP Inspections – Current trends and Inspectional Findings
Takashi Nagajima, GMP Expert, Office of Compliance and Standards, *PDMA*

10:00 a.m. – 10:15 a.m.
Break

10:15 a.m. – 11:45 a.m.
Plenary Session 4: GMP Inspections II
Moderator: Robert L. Dana, Vice President, Quality and Regulatory Affairs, *PDA*

This session will continue the discussion of GMP inspections by providing the industry perspective on the Japanese PDMA inspection program.

10:15 a.m. – 10:45 a.m.
Japanese Industry's Experience of PAI GMP Inspection by PMDA and FDA
Izumi Saito, *Shionogi Pharmaceutical Co Ltd.*

10:45 a.m. – 11:15 a.m.
Case Study-Quality by Design Submission in Japan
Todd M. Smith, Senior Manager, Quality Assurance, Asia-Pacific, *Merck and Co. Inc.*

11:15 a.m. – 11:45 a.m.
Panel Discussion and Q&A featuring morning speakers

11:45 a.m. – 12:30 p.m.
Workshop Wrap-up and Closing Remarks
Moderator: Shigeru Hayashi, PhD, Associate Research Fellow, Regulatory CMC Pharmaceuticals, *Pfizer Inc*

Science and Regulatory Studies at National Institute of Health Sciences

Yukio Hiyama
Chief, 3rd Section, Division of Drugs
NIHS, MHLW
Seminar at US FDA, October 2, 2007

Outline of presentation

- Organization and work relationship within MHLW
- Overview of NIHS
- Health Science Studies

Analytical Methods Development to support product development and manufacturing controls

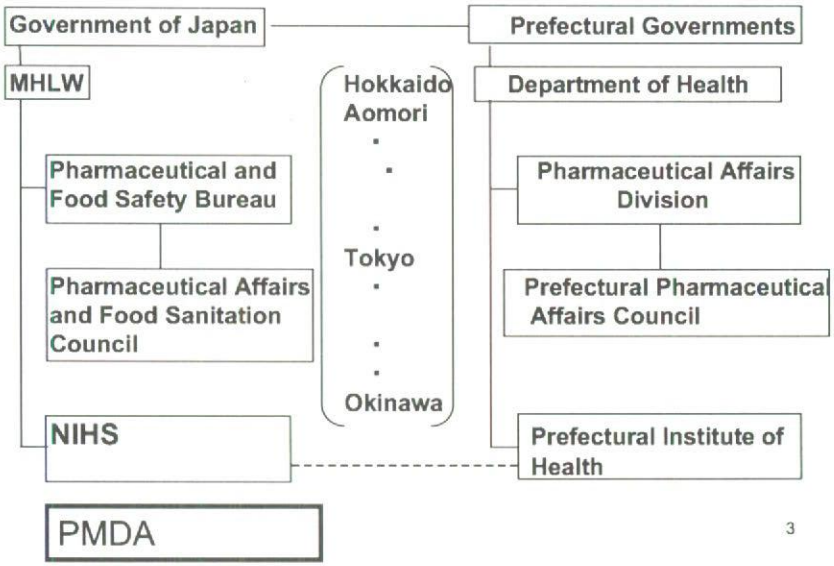
- Regulatory Sciences Studies

Quality System, GMP guidance, Tech Transfer
GMP inspection policy, guidance
Manufacturing process in Approval- ICH Q8
GMP policy for Clinical Supplies-Exploratory clinical trials

- Pharmaceutical Regulations, Review Process, JP
- Training program for GMP/QMS inspectors

Annual 5 week training course at N I Public Health

Relation of Central and Prefectural Pharmaceutical Administration



National Research Institutes of the MHLW

National Institute of Health Sciences (NIHS)

- Established in 1874 as the Tokyo Drug Control Laboratory / Rearranged on 2002.4.1/Updated on 2004/4/1
- Number of staff :
- Budget
- Major functions and responsibilities of this institute are:

1. to conduct wide range of research works and tests to ensure quality, efficacy and safety of drugs, foods and other goods.
2. (to evaluate drugs and medical devices applied for approval. Moved to PMDA)
3. to gather information and develop databases on the safety of chemicals in drugs, foods, etc.

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Organization of PMDA (est 2004)

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MHLW Grant (Health Science) study on Evaluation Methods for Pharmaceutical and Process Development (2004-2007)

- The needs-quality assurance based on science and risk management, gap between desired state and current status, rPAL and ICH
- The group structure- Industry, Academia and Government (NIHS) Joint

(Industry: Eisai, Fujisawa, Pfizer, Powrex, Shionogi, Santen and Tanabe 2004-2005 member)

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List of topics in the Health Science Program (2006)

Characterization of granulated powders by NIR (NIHS)
Characterization of freeze dried formulation by NIR (NIHS)
Water activity and microbiological preservative capability in non aqueous ophthalmic formulation (Santen)
Crystal morphology and dissolution characteristics (Toho University)
Potential application of Ultra Performance Liquid Chromatography for PAT (NIHS)
Rapid microbiological detection for solid dosage manufacturing controls (Pfizer)
Granulation mechanism by NIR imaging technique (NIHS)
Investigational methods for manufacturing deviations (Eisai)
Raman spectrometric application in API crystallization process (Tanabe)
Rapid content determination at tableting process (Astellas)
Identification of packaged clinical formulations by NIR (Shionogi)
Real time process control of coating process (Powrex)

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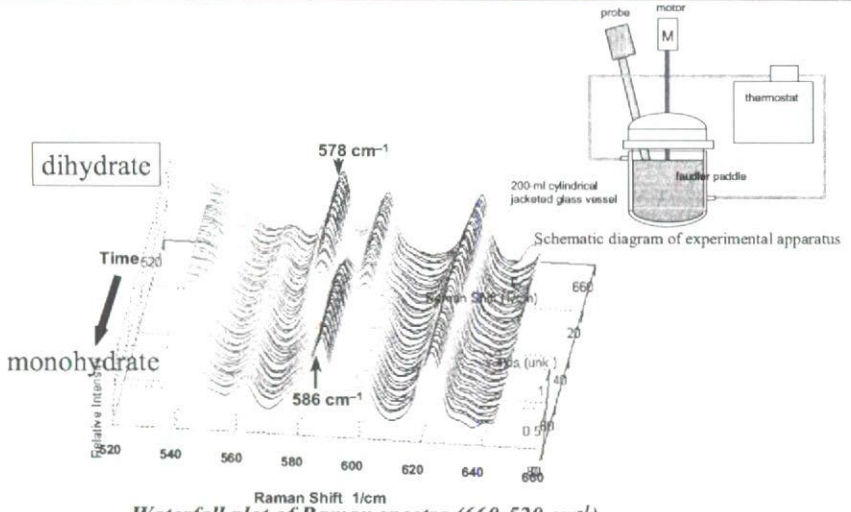
Application of Raman to Process Chemistry - Crystallization -



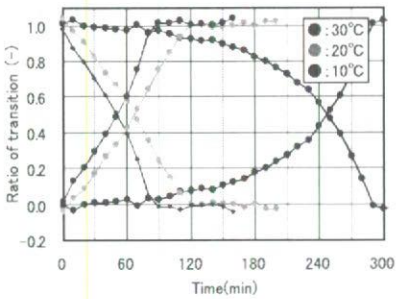
Schematic diagram of experimental apparatus

Waterfall plot of Raman spectra (660-520 cm^{-1}).

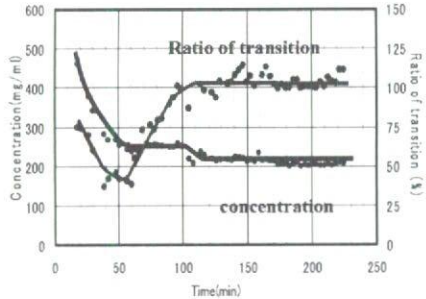
in situ monitoring of polymorphic transition was possible!

TANABE SEIYAKU CO.,LTD.

Application of Raman to Process Chemistry - Crystallization -



temperature vs transition rate



Ratio of transition and concentration in crystallization

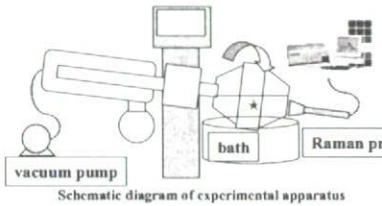
The kinetics and endpoint of polymorphic transition can be monitored easily!!

Both the ratio of polymorphic forms and concentration can be determined by PLS!!

Raman is effective as a process analytical technology tool

TANABE SEIYAKU CO.,LTD.

Application of Raman to Process Chemistry - drying -

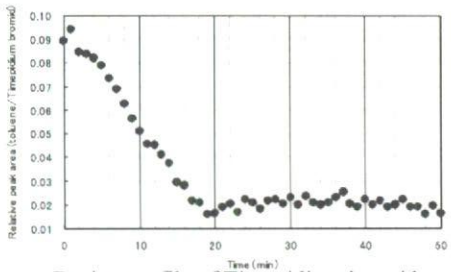


Schematic diagram of experimental apparatus

Solvent Wet cake
toluene(18.2%w/w) in Timepidium bromide

Drying Condition
in vacuum, the bath temperature of 40degrees

Raman probe
Non-contact Optics with working distances of 3 inches



Drying profile of Timepidium bromide

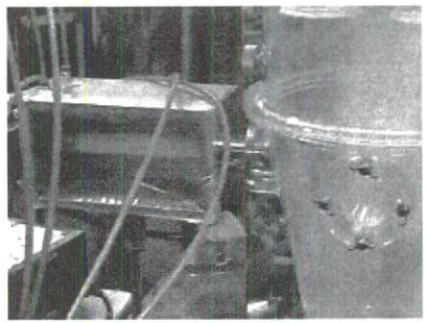
in situ monitoring through glass of drying was possible!

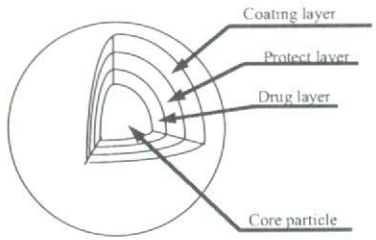
this method do not need braking vacuum for sampling

Raman is effective as a process analytical technology tool

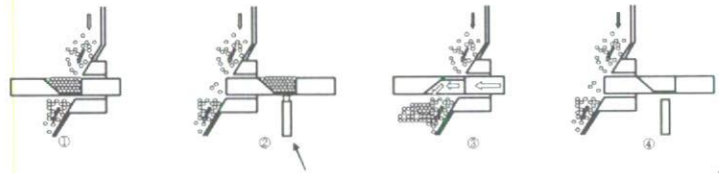
TANABE SEIYAKU CO.,LTD.

Real-time monitoring of coating performance
by NIR (POWREX)

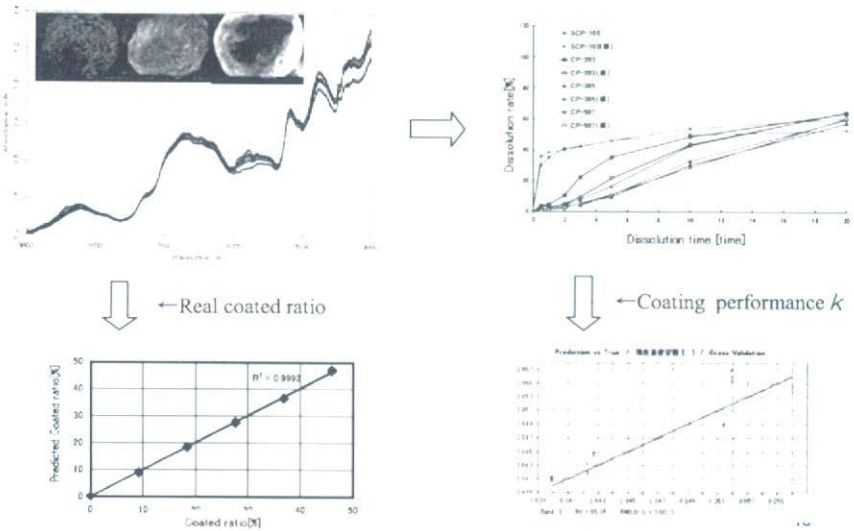




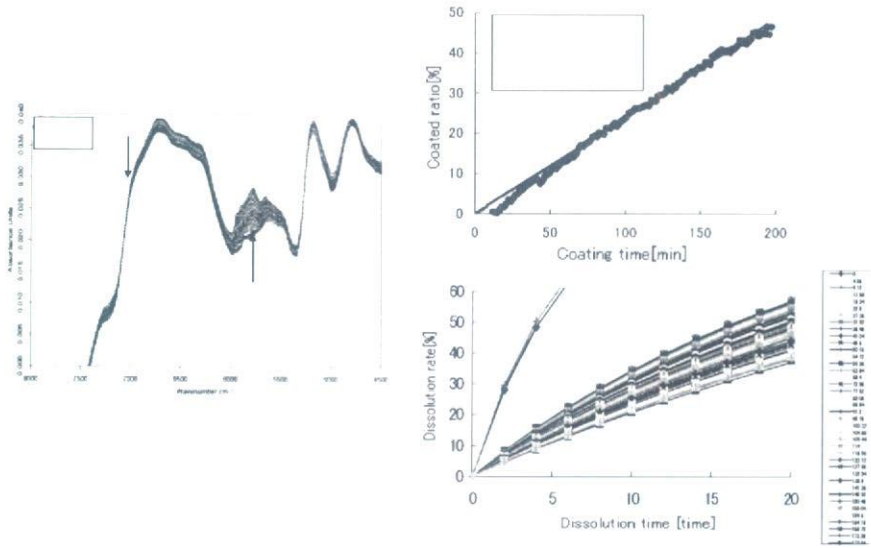
Particle coating



Prediction vs True by NIR (off-line)



Coated ratio/Coating performance (Real-time monitoring)



Granulation mechanism by NIR imaging (T.Koide, NIHS)

The wet granulation is commonly employed in Japan.

The purpose of this investigation:
To understand granulation mechanisms
To apply its results to pharmaceutical development and manufacturing process control

In this study, we analyzed high shear granulation by NIR imaging system where <u>chemical information at micron level</u> is available

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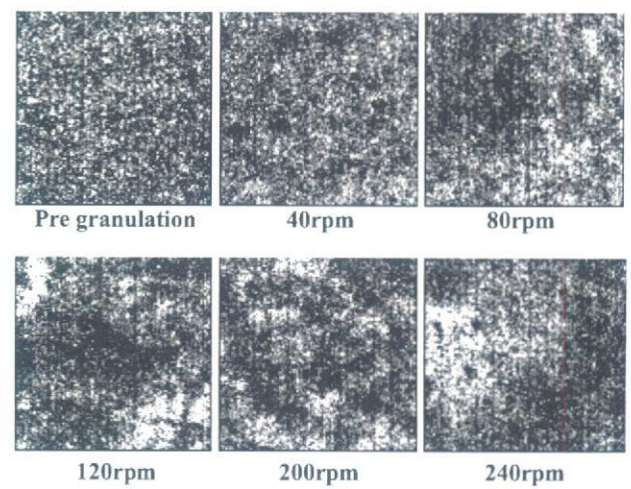
RBG Image by PLS2 (5 min granulation, hand pressed tablet)



RED: Ethenzamide, GREEN: Cornstarch, BLUE:Lactose
YELLOW: Ethenzamide+ Cornstarch

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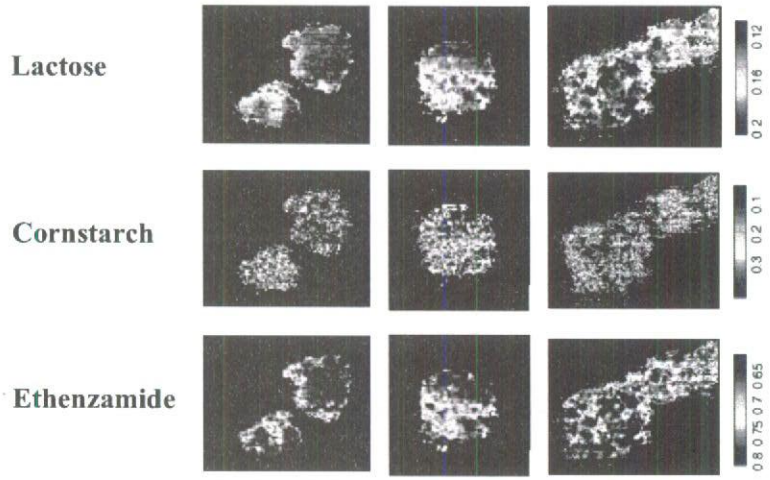
NIR Image of Granules by PLS2 (160rpm, 10 min granulation):



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 guideline
Revised PAL enforced	Q9 reached step 2	**2005** Inspection Policy
Inspection policy published	Q8 and Q9 reached step4	Skip Test guideline
2006	Q10 started	Inspection Checklist
Product GMP guidance	**2007**	**2006** Sterile process guideline
Sterile process guidance	Q10 reached step 2	**2008**
		P2 /application mock
		Change management system

Regulatory Science Studies

- Quality System, GMP guidance (2002-2004, 2005-2007)

QS, Regulations, Product GMP, Information Flow/Tech Transfer, Lab Control, Change Management

- GMP Inspection Policy, Manual(2003-2005, 2006-2008)

Policy, System Base, Inspection Check (Reference) list, Inspection Scenario (Key Questions)

- Manufacturing Process Commitment in Approval Letter

Survey, Technical Elements, Policy, Mock for AL and P2

- Clinical Supply GMP Policy

- Sterile Manufacturing GMP guidance

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 CTD based application
4. Consolidation of the Legal Positioning of GMP
5. Revision and Consolidation of GMP standards

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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.

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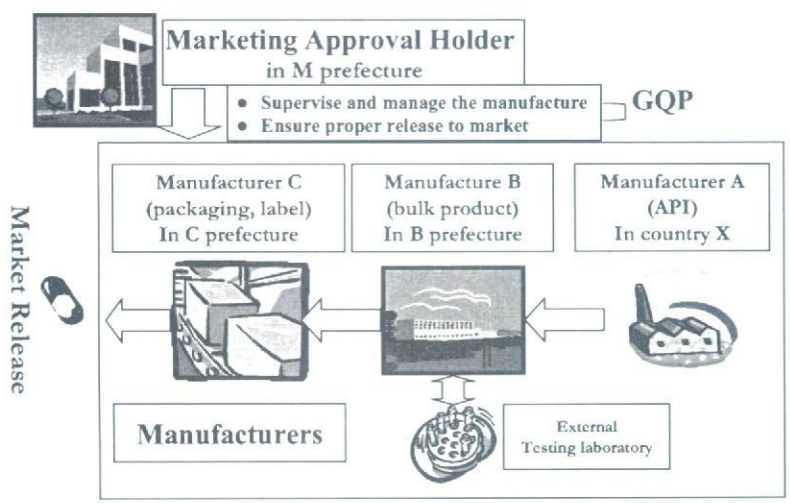
Marketing and Manufacturing



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

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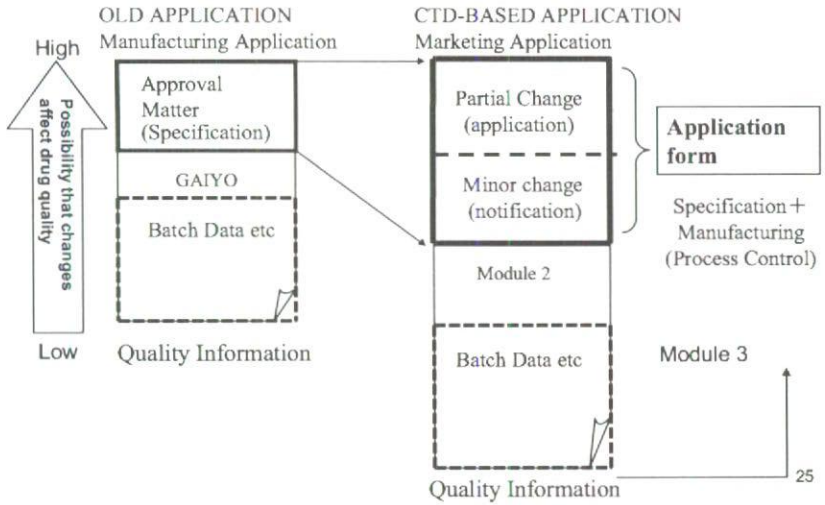
Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



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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

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Approval Letter

- **No change:**
  - **Approval letter system**
- **Changes:**
  - **From manufacturing approval to marketing approval**
  - **Requirement of detailed description in application form regarding manufacturing process and control**
    Encourage industry to better control quality of products
    Link review/assessment and INSPECTION
  - **Introduction of a notification system pertaining to minor change**
    Effective regulatory system

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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

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Matter Subject to Approval under Revised Pharmaceutical Affairs Law

(Chemical drug substance and drug product)

- Manufacturing site
- Manufacturing method

  Detailed information about:
  - Manufacturing process and process control
  - Control of material
  - Container-closure system

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Matter to Be Described in Application Form -Drug Products-

- **All processes from raw material(s) to packaging process**
  - **A flow diagram of manufacturing process including:**
    - **Raw materials**
    - **Charge-in amount**
    - **Yield**
    - **Solvent**
    - **Intermediate materials**
    - **Process parameter (e.g. Target Value and Set Value)**
  - **A narrative description of manufacturing process**

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Narrative Description of Manufacturing Process

- **Matters needed for assuring the quality consistency should be selected**
- **Quantities of raw materials, critical processes, process control, equipment, process parameter (speed, time, temp., pressure, pH, etc)**
- **Test and acceptance criteria of critical step and intermediate**
- **Identity and specification of primary packaging material (or manufacturer and type number of the packaging material)**

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Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - the evaluation methods which was approved at the time of previous submission might be invalid.
- Change in materials of primary packaging component
- Change in matters for aseptic manufacturing
- Change in specification of intermediate product in case that the test is performed instead of release test of final drug product

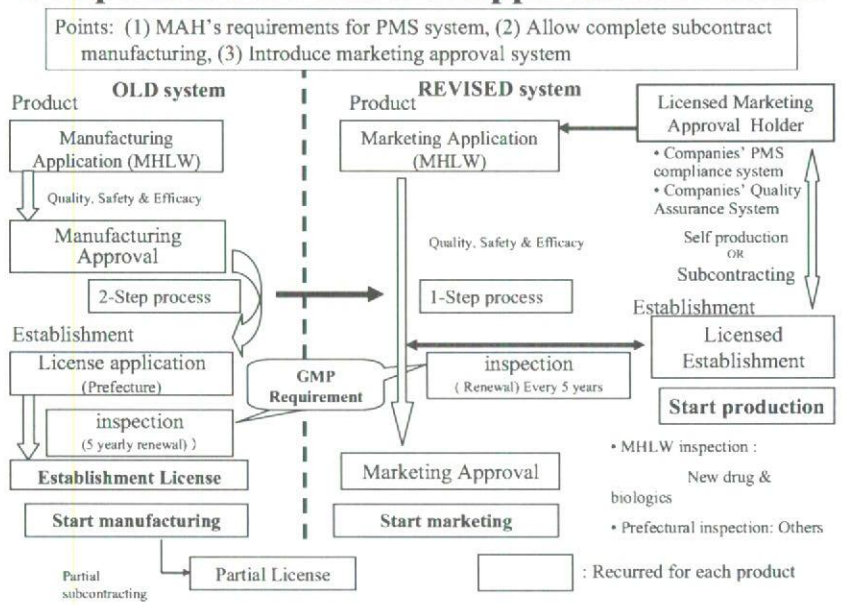
Distinctions between Partial Change Approval Application and Minor Change Notification

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	

4. Consolidation of the Legal Positioning of GMP

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

Comparison Flowcharts of Approval and License



GMP/QMS Inspection for Foreign Sites

- GMP/QMS* inspection for foreign manufacturing facilities started in 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)

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

Change by notification and Q8 Design space

	Minor Changes by Notification	Design Space
Scope	Changes of approval matters do not require reviewer's assessment	Space by input/process variables demonstrated to provide assurance of quality
Areas not applicable	Excipient range Principle of "critical" unit operations	No limitation(?)
Regulatory procedures	Notification within 30days from the change (market release date)	Region dependent Regulator will not evaluate changes within DS for pre-approval purpose
If/when deviation happens	(Target/set value) May be usable if deviation investigation supports	Discard the batch

Basis for Quality Review

- ICH Guidelines are the basis for NDA review.
- ICH Q8 and Notification #0210001 form basis for product design and manufacturing
- There are some domestic guides for those not covered by ICH Guidelines.

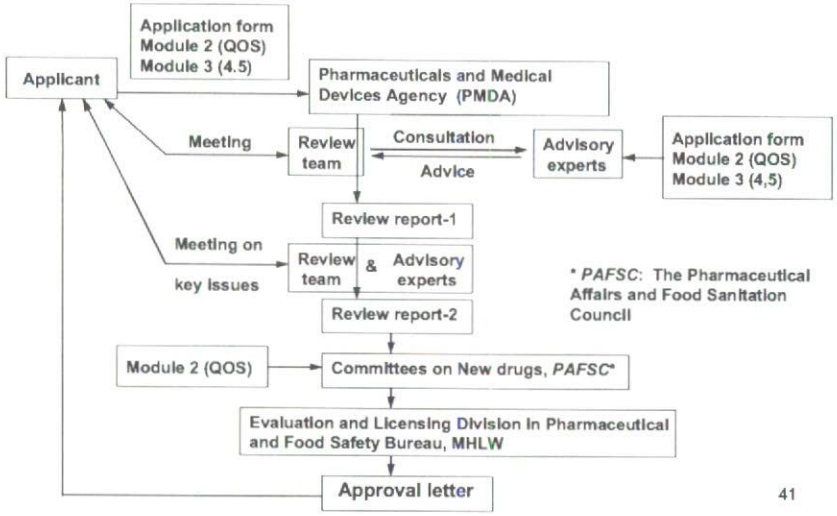
Seizouhou Sisin

- The Japanese Pharmacopoeia (JP) is also the basis for setting specifications and acceptance criteria of drug substances and drug products.

Guideline for preparation of JP16 Draft, *March 2007*

- "General methods described in the JP, and internationally harmonized methods are considered to be validated."

Flowchart of Reviewing Process



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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.

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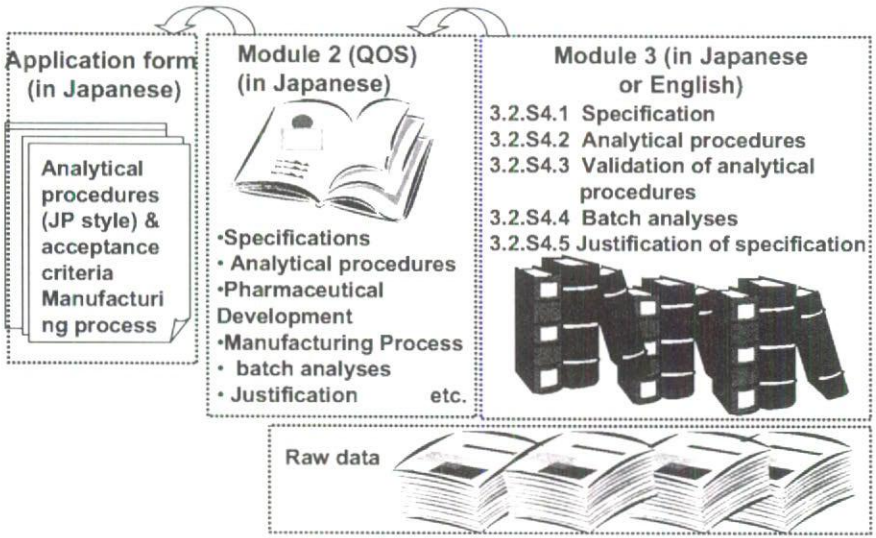
Relationship between Application Form and CTD Documents



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**

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History & Legal Status of JP

- JP is published by the Japanese Government

  The Ministry of Health, Labour and Welfare Ministerial Notification
- First published on June 25, 1886 and implemented on July 1, 1887
- In accordance with the provisions of Article 41-1 of the Pharmaceutical Affairs Law (PAL) of Japan

  *To standardize and control the properties and quality of drugs, **the Minister** shall establish and publish JP, after hearing the opinion of the Pharmaceutical Affairs Food Sanitation Council (PAFSC)*

Various Roles and Characteristics of JP (1)

Official, Public and Transparent Standards for ensuring Quality of Pharmaceuticals

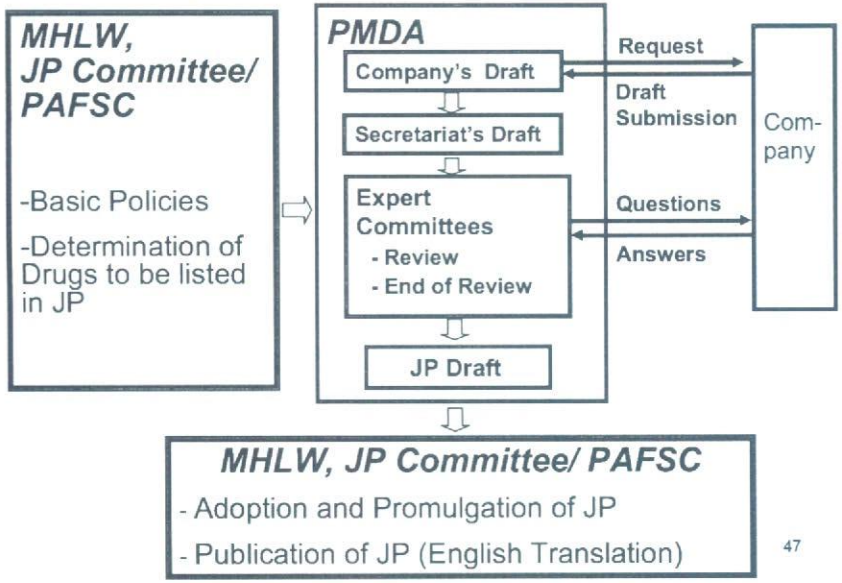
For Pharmaceutical Administration

- Standards of Quality Assessment of the Approval of New Entities and Quality Assurance for Pharmaceutical Vigilances

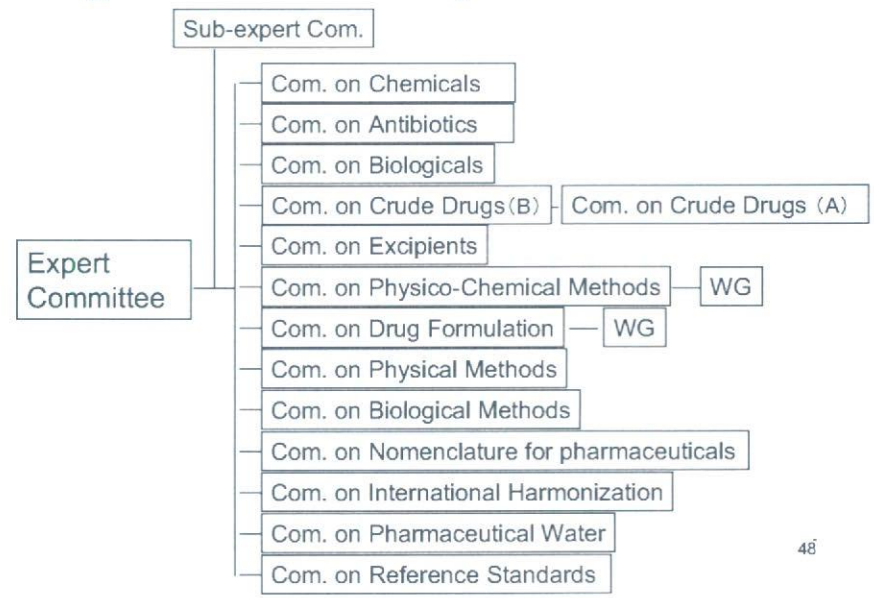
For Pharmaceutical Industry

- Scientific and Technical Standards that are to be Referenced in Drug Development

System of Establishing JP



Organization of JP Expert Committees



Schedule of JP Publication

The Japanese Pharmacopoeia Fourteenth Edition (JP14)
Published on March 2001

Supplement I to JP14
Published on December 2002
Supplement Ⅱ to JP14
Published on December 2004

Main Policies on the Preparation of JP15
November 2001 and December 2002
Guidelines for preparation of JP15 Draft
December 2002

The Japanese Pharmacopoeia Fifteenth Edition (JP15)
Published on March 2006

Supplement I to JP15
To be Published on September 2007
Supplement Ⅱ to JP15
To be published on March 2009

Main Policies on the Preparation of JP16
August 2006
Guidelines for preparation of JP16 Draft
March 2007

The Japanese Pharmacopoeia Sixteenth Edition (JP16)
To be published on March 2011

GMP/QMS training for Inspectors at National Institute of Public Health

- Annual 5 week course for Prefectural and PMDA inspectors and their technical support staff in Wako, Saitama-30 students, several trainees from Review Div of PMDA
- Program

1st week, Regulations, Overview of Development, Analytical Validation, Sterile Product Development /Manufacture
2nd week, Filter/Air, API Development/Manufacture, Medical Devices, 2 day Plant Tour
3rd week, Medical Devices, Solid Dosage Development/Manufacture, Manufacturing Equipment
4th week, Biologics, Drug Information, Inspection Methods, Day Inspection (four sites)
5th week, Report writing, Presentation

- Faculty and Lecturers

8 faculty members to establish program and conduct inspection exercise (NIPH-1, NIHS-3, NIID-1,PMDA-3)
MHLW, NIHS, PMDA, Industry

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Current Japanese Regulations and Implementation of ICH Q8-Q10

Shintaro TOBIISHI
Office of Compliance
Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare (MHLW)

Yukio HIYAMA
Chief, 3rd Section, Division of Drugs
National Institute of Health Sciences,
MHLW
JAPAN

Presentation Outline

- Pharmaceutical Affairs Law (PAL)
- Approval and Licensing system under PAL
- Review and Inspection
- Relationship between MHLW and PMDA
- MHLW's expectations and ICH vision
- Commitment of Manufacturing Process as Approval Matters
- Roles of ICH guideline

Pharmaceutical Affairs Law (PAL)

Points on 2002 revision of the PAL

- **Fortification of post-marketing safety measures**

→ **Concept of Marketing Approval Holder(MAH)**

- **Revision of the approval and licensing system**

→ **Focus to "Marketing Approval" rather than "Manufacturing Approval"**

Responsibility of MAH under PAL - as prerequisites for license of MAH -

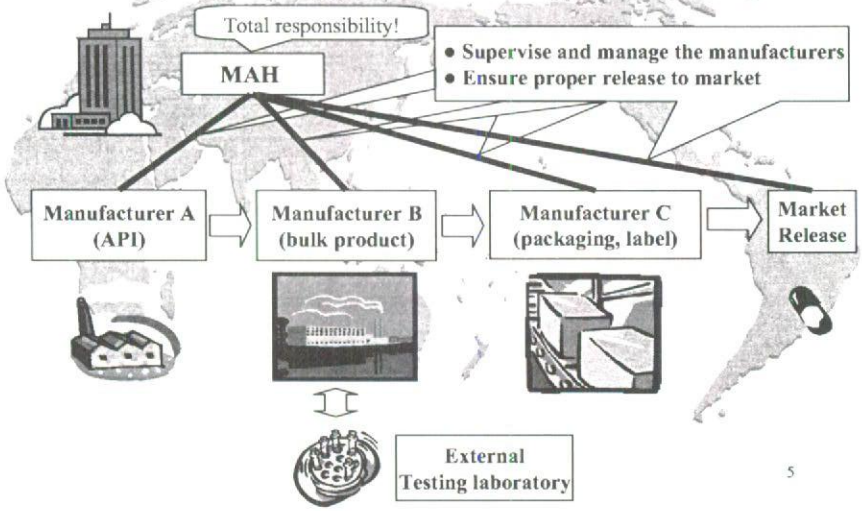
- MAH must comply with GQP for its License.

*GQP: Good Quality Practice
Rules for quality assurance operations

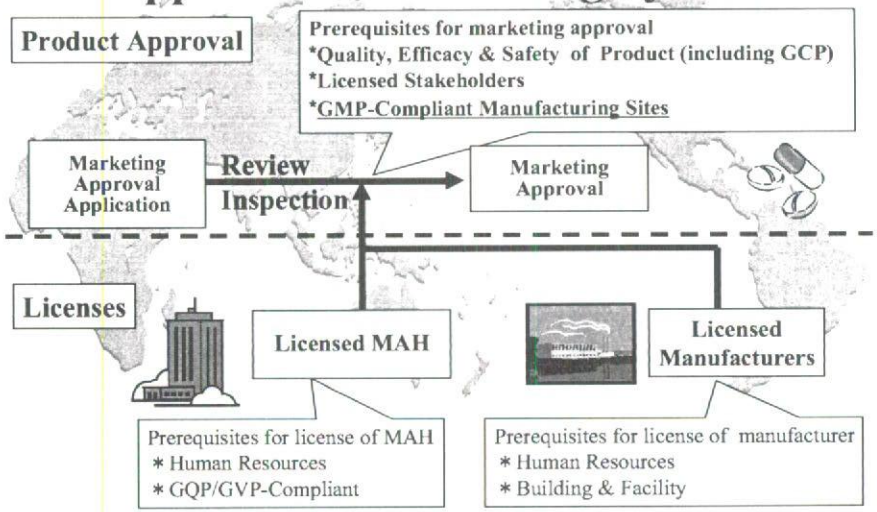
- MAH must comply with GVP for its License.

*GVP: Good Vigilance Practice
Rules for post-marketing safety management

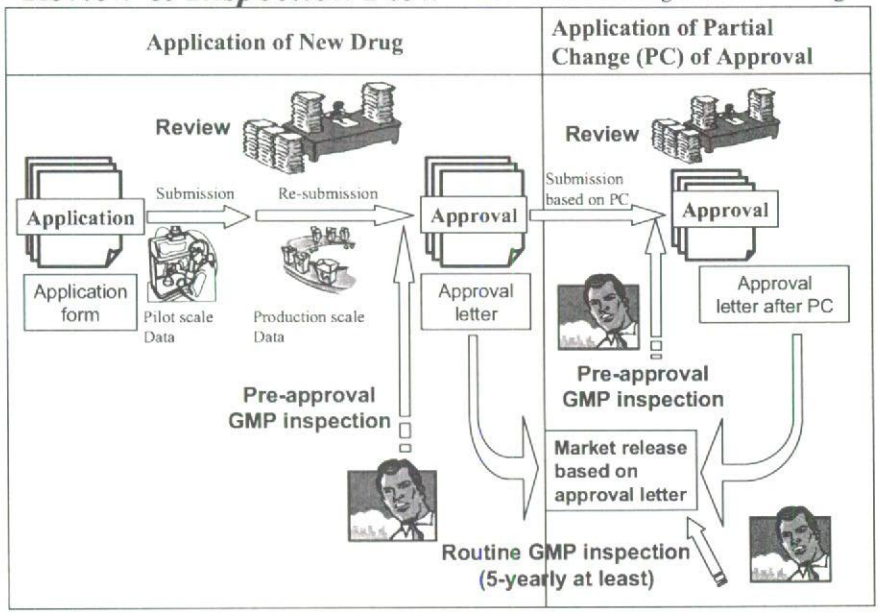
Responsibility of MAH based on GQP



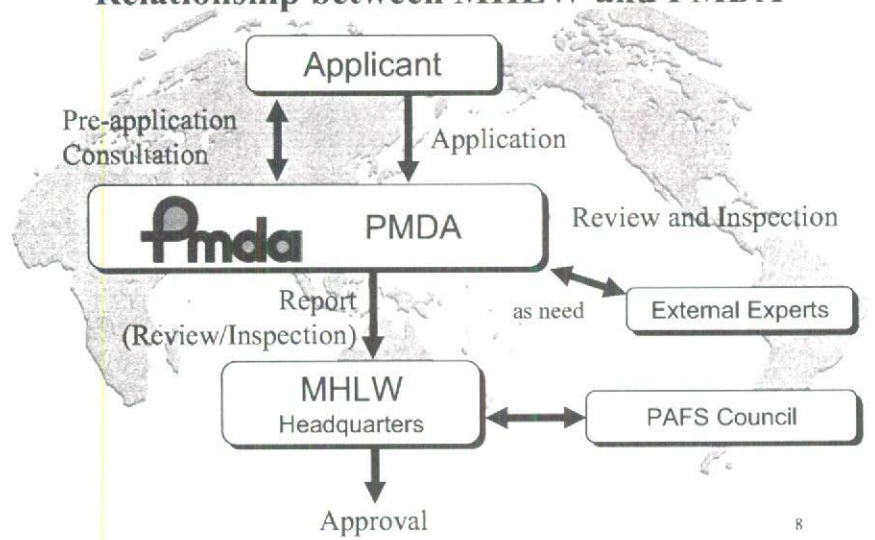
Approval and Licensing System



Review & Inspection Flow



Relationship between MHLW and PMDA



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) and Q8R reached step 2 .)

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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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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	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
	Q8R reached step 2	Change management system

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

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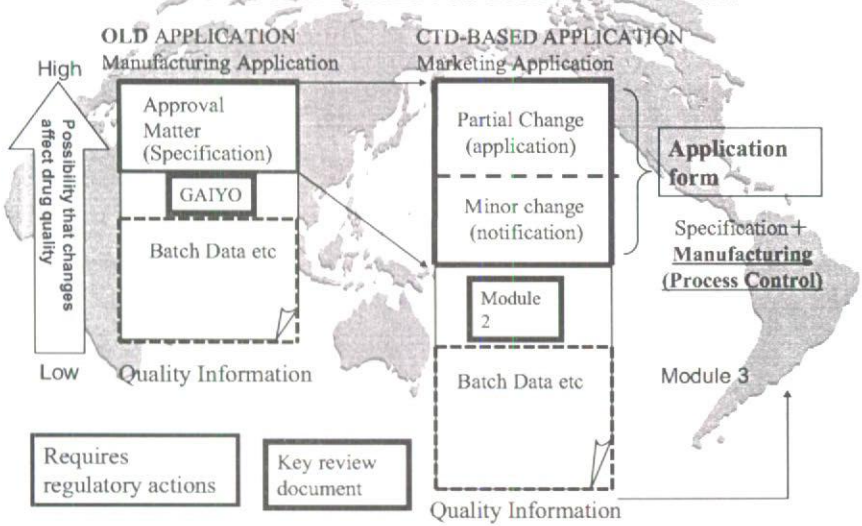
Application Form after the Enforcement of Revised Pharmaceutical Affairs Law



Approval Matters Policy

Notification from Director of Evaluation and licensing division, 0210001 February 10, 2005

- Manufacturing Process: Principles and end points of the critical manufacturing steps with key operational parameters of commercial scale are approval matters. Principle and quality end point for each manufacturing step are 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

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Examples of Matter Subject to a Partial Change Application

- Change in principle of unit operation of critical process: matter subject to approval
  - the evaluation methods which was approved at the time of previous submission might be invalid.
- Change in materials of primary packaging component
- Change in matters for aseptic manufacturing
- Change in specification of intermediate product in case that the test is performed instead of release test of final drug product

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